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PAST ESA OFFICE BEARERS 1958-2008

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1960-62	C.W.Emmens		K.Harrison	K.Harrison
1962-64	K.Harrison		I.Thomas	I.Thomas
	C.W.Emmens (March 63)			
1964-66	B.Hetzel	V.Trikojus	I.Jarrett	I.Jarrett
1966-68	B.Hudson	V.Trikojus	R.Melick	I.Jarrett
1968-70	P.Taft	R.Cox	R.Melick	I.Jarrett
1970-72	I.Jarrett	K.Ferguson	T.J.Martin	L.Lazarus
1972-74	K.Ferguson	L.Lazarus	R.D.Gordon	L.Lazarus
1974-76	H.G.Burger	J.R.Turtle	S.Posen	C.J.Eastman
1976-78	S.Posen	J.P.Coghlan	P.E.Harding	C.J.Eastman
1978-80	J.P.Coghlan	C.J.Eastman	R.G.Larkins	J.W.Funder
1980-82	C.J.Eastman	J.W.Funder	D.P.Cameron	G.L.Warne
1982-84	J.W.Funder	R.G.Larkins	R.C.Baxter	G.L.Warne
1984-86	R.G.Larkins	D.P.Cameron	R.C.Baxter	D.M.Hurley
1986-88	D.P.Cameron	R.C.Baxter	S.J.Judd	D.M.Hurley
1988-90	R.C.Baxter	S.J.Judd	J.R.Stockigt	D.J.Handelsman
1990-92	J.R.Stockigt	J.A.Eisman	G.W.Tregear	D.J.Handelsman
1992-94	D.J.Handelsman	P.J.Fuller	R.L.Prince	D.J.Topliss
1994-96	P.J.Fuller	R.L.Prince	G.P.Risbridger	D.J.Topliss
1996-98	D.J.Topliss	R.J.Rodgers	G.P.Risbridger	M.S.Lewitt
1998-00	R.J.Rodgers	J.D.Zajac	K.K.Y.Ho	M.S.Lewitt
			B.J.Waddell (May 99)	
2000-02	K.K.Y.Ho	B.J.Waddell	B.Canny	C.Coulter
2002-03	B.Canny	J.D.Zajac	R. Cuneo	C.Coulter
2004-06	J.D. Zajac	L. Bach	M. McLean	V. Clifton
2006-08	L. Bach	M. McLean	V. Clifton	D. Phillips

SOCIETY SECRETARIAT - ENDOCRINE SOCIETY OF AUSTRALIA

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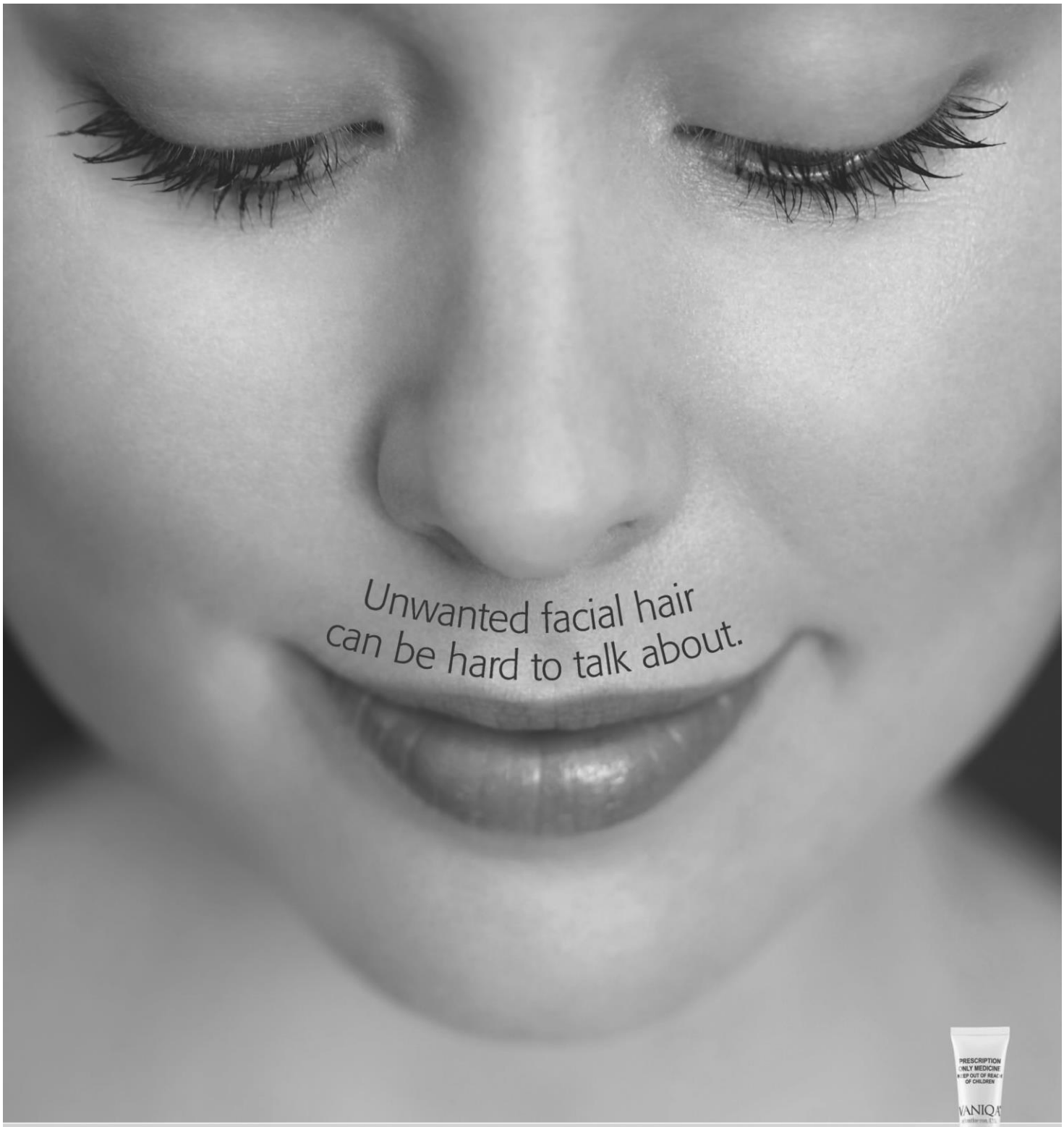
1st May – 3rd May 2009
Ettalong Mantra Resort
www.esaseminar.org.au

ESA Clinical Weekend
21st August – 23rd August 2009
Barossa Novotel Resort
www.esaclinicalweekend.org.au

Combined ESA/SRB Annual Scientific Meeting
23rd August – 26th August 2009
Adelaide Convention Centre
www.esa-srb.org.au



Unwanted facial hair (UFH) can be a delicate, often distressing topic to raise for women who struggle with it. Vaniqa is the only topical prescription cream to slow the growth of unwanted facial hair in women. Visible results may be seen as early as 4-8 weeks.[1] For further information, email Vaniqa@csl.com.au

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KEITH HARRISON MEMORIAL LECTURERS

1964	Kenneth Ferguson
1965	Geoffrey Harris
1973	Albert Renold
1974	Paul Franchimont
1975	William Odell
1976	John Landon
1977	Hugh Niall
1978	Samuel Yen
1979	John Shine
1980	Ronald Swerdloff
1981	Sidney Ingbar
1982	Jens Rehfeld
1983	Philip Lowry
1984	Fernand Labrie
1985	Michael Berridge
1986	Michael Thorner
1987	Lynn Loriaux
1988	Axel Ulrich
1989	Hiroo Imura
1990	Iain McIntyre
1991	Eli Adashi
1992	Jan-Ake Gustafsson
1993	Eberhard Nieschlag
1994	Allen Speigel
1995	Natalie Josso
1996	Gregory Mundy
1997	M.Geoffrey Rosenfeld
1998	Ken Korach
1999	Henry Burger
2000	Pierre Chambon
2001	Jack Martin
2002	George Chrousos
2003	Derek LeRoith
2004	Bruce McEwen
2005	Richard Pestell
2006	William Crowley
2007	Gerard Karsenty
2008	Colin Ward

NOVARTIS JUNIOR INVESTIGATOR AWARD

The Novartis Junior Award is awarded annually to a member who is a postgraduate student or recent post-doctoral student, for the best original paper at the Annual Scientific Meeting.

1976	Kathryn Rich & Peter Fuller
1977	David Kennaway
1978	David Healy
1979	George Werther
1980	Rebecca Mason
1981	Yvonne Hodgson
1982	David Hurley
1983	Carolyn Scott
1984	David James
1985	Guck Ooi
1986	Marie Ranson
1987	Lora Hutchinson
1988	Vasilious Papadopoulos
1989	David Phillips
1990	Sharon Gargosky
1991	Marie-Christine Keightley & Helen Maclean
1992	Fiona Young
1993	Emma Ball
1994	Vicki Clifton
1995	Michael Downes & Sylvia Lim-Tio
1996	John Walsh
1997	Bu Yeap
1998	Julie Joyner
1999	Renea Jarred & Helena Teede
2000	Jeremy Smith
2001	Stephen Heady
2002	Patrick McManamny
2003	Sophie Chan
2004	Esme Hatchell
2005	Agnes Kovacic & Amy Au
2006	David Macintyre
2007	Marrianne Elston

ESA CSL BIOTHERAPIES BRYAN HUDSON CLINICAL ENDOCRINOLOGY AWARD

The ESA CSL Biotherapies Bryan Hudson Clinical Endocrinology Award will recognize the best clinical research presentation at the Annual Scientific Meeting by an active member of the Endocrine Society of Australia early in their career. It will be made on an annual basis.

2004	Sonia Davison
2005	Carolyn Allan
2006	Jui Ho
2007	Morton Burt

ESA / IPSEN INTERNATIONAL TRAVEL GRANT

2003	Emma Ball
2004	Gordon Howarth, Sophie Chan and Vincenzo Russo
2005	Stuart Ellem
2006	Kevin Pfleger and Erosha Premaratne
2007	Lisa-Marie Atkin, Elspeth Gold and Michael Stark

SERVIER AWARD

The Servier Award is awarded for the best published work in the previous year by a member of the Society within 5 years of award of higher degree.

1991	Sharon Gargosky
1992	Peter Stanton
1993	Janet Martin
1994	Chen Chen
1995	Timothy Crowe
1996	Jun-Ping Lui
1997	Liza O'Donnell
1998	Stephen Twigg
1999	Dan Lee
2000	Fraser Rogerson
2001	Karen Kroeger
2002	Susan Fanayan
2003	Jenny Gunton
2004	Peter Liu
2005	Simon Chu
2006	Renea Taylor
2007	Kirsten McTavish

HONORARY LIFE MEMBERS

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Dr H.D. Breidahl
Prof James B Brown
Prof Henry G Burger
Dr R.A. Burston
Prof Donald P Cameron
Prof John P Coghlan
Prof Alex Cohen
Dr.Ron I Cox
Prof David Curnow
Dr Ewan Downie
Prof David De Kretser
Prof C J Eastman AM
Dr K.A. Ferguson
Prof John W Funder
Prof R.D. Gordon
Dr Ian B Hales
Dr Philip Harding
Prof Basil Hetzel
Dr Brian Hirschfeld
Dr Ivan G Jarrett
Assoc Prof. Stephen Judd
Prof Richard G Larkins
Prof Leslie Lazarus
Dr T.B. Lynch
Prof Ian McDonald
Prof T John Martin
Dr Len Martin
Dr F.I.R. Martin
Dr Ian C A Martin
Dr Roger Melick
Prof Solomon Posen
Prof Marilyn Renfree
Prof T.J. Robinson
Prof Rodney Shearman
Prof Alfred W Steinbeck
Prof Jim Stockigt
Prof R. Strang
Prof Pincus Taft
Dr Ian D Thomas
Prof Prof Victor Trikojus
Emeritus Prof John R Turtle
Prof R. Vines
Dr A.L. Wallace
Prof Norman Wettenhall
Prof F. H Wilson
Prof Marelyn Wintour-Coghlan
Dr K.N. Wynne

CONFERENCE ORGANISING COMMITTEES

The Local Organising Committee
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Deputy Convenor: David Phillips (ESA),
Darryl Russell (SRB), Duangporn Jamsai (ESA & SRB), Sarah Meachem (ESA & SRB), Mary Wlodek (ESA), Helen MacLean (ESA), Emma Hamilton (ESA)

ESA Program Organising Committee
Helen MacLean (chair), Warrick Inder, Mathis Grossmann, Carolyn Allan, Vince Russo, Brian Oldfield, Greg Anderson,
The Program Committee thanks those members who assisted in reviewing the abstracts.

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INVITED PLENARY SPEAKER PROFILES 2008

2008 Harrison Lecturer

Dr Colin Ward - Colin Ward's research interest, since the early 1990s, has been on the structure and function of members of the insulin and epidermal growth factor receptor families. Prior to that he worked on: the structure and function of influenza virus coat proteins (haemagglutinin and neuraminidase); the structure of plant virus proteins and their use in virus identification and classification; insect proteases; parasitic helminth metabolic pathways and recombinant veterinary vaccines against viruses, bacteria and intestinal parasites. He is a former Assistant Chief and Deputy Chief of the CSIRO Division of Protein Chemistry and Biomolecular Engineering. He was the Lemberg Medallist and Lecturer for ASBMB in 2007 and the Leach Medallist and Lecturer (Lorne Protein Conference) in 2001.

Professor John Bilezikian - John P. Bilezikian, MD is professor of medicine and pharmacology at the College of Physicians and Surgeons, Columbia University, in New York. He also is chief of the Division of Endocrinology, and director of the Metabolic Bone Diseases Program at Columbia-Presbyterian Medical Center in New York City. Dr. Bilezikian is editor-in-chief of the Journal of Clinical Endocrinology & Metabolism. During the course of his professional career, Dr. Bilezikian has authored more than 425 publications which reflect his investigative initiatives and interest in endocrinology and metabolic bone diseases. Recognized both nationally and internationally as a spokesperson in the field of metabolic bone diseases, Dr. Bilezikian has served on numerous panels and has received many awards. His major research interests include clinical investigation of metabolic bone diseases, in particular, osteoporosis and primary hyperparathyroidism, and biochemical mechanisms of the hormones that regulate calcium metabolism.

Professor Shigeaki Kato - Kato obtained PhD in 1988 from the University of Tokyo, and became independent at the Institute of Molecular Cellular Biosciences (IMCB), the University of Tokyo from 1996, and became professor at 1998. Kato was awarded by many organizations; Fuller Albright award from American society of bone and mineral research (ASBMR) in 1998, and the international prize from Austrian SBMR. He has also been leading a research group supported by JST, as CREST / SORST (1997-2004), and ERATO (2004~).

Dr Lynnette Nieman - Dr. Nieman is a Senior Investigator, Associate Director of the Inter-institute Endocrinology Training Program, NICHD-NIDDK and Chief of the Endocrinology Consultation Service at the NIH Clinical Center. She completed her internship, residency and a chief residency position in internal medicine and a year as an endocrine fellow at the SUNYAB affiliated hospitals before joining NICHD as a medical staff fellow in 1982. She has been with NIH since that time. From 1991 to 2001 Dr. Nieman served as the Clinical Director, NICHD, overseeing the clinical care of the institute's patients and ensuring compliance with regulations regarding human subjects research. Dr. Nieman is also an active clinical investigator, with special expertise in disorders of hypercortisolism, and development of antiprogestins as therapeutic agents. She is the author or co-author of more than 225 publications and has sponsored three investigational new drug applications to the FDA.

Professor William Young Jr - Dr. Young received his MD degree in 1978 from Michigan State University. He trained in internal medicine at William Beaumont Hospital, Royal Oak, Michigan, and in endocrinology and metabolism at Mayo Clinic, Rochester, Minnesota. He has been a member of the staff at Mayo Clinic since 1984. Dr. Young is a member of The Endocrine Society, American Association of Clinical Endocrinologists, American Society of Hypertension, and Council of Science Editors. He is the associate editor for the *Journal of Clinical Endocrinology and Metabolism*, senior editor for *Clinical Endocrinology*, and editor of the *Mayo Clinic Endocrinology Update Newsletter*. He is the recipient of multiple education awards. Dr. Young's clinical research focuses on primary aldosteronism and pheochromocytoma. He has published over 200 articles on endocrine hypertension and adrenal and pituitary disorders. He has presented at over 200 national and international meetings and he has been an invited visiting professor for more than 80 medical institutions.

PREFACE

This supplement to the 2008 Annual Scientific Meeting arose as a part of the 50th anniversary celebrations of the ESA. It became apparent early on in the process that the corporate knowledge of the Society needed collation; in many cases this was not readily accessible and sometimes resided entirely in the neural matter of some of our long-standing members. Hence it is hoped that this compendium will be a solid foundation on which to build an appropriate electronic archive, regularly updated, about who and what the Society represents. My thanks to Phil Harding, Skip Martin, Roger Melick and colleagues, who put together the Society's history for the first 25 years. This was published in the 25th anniversary proceedings in 1982 and appears below with only minor editing. With the later sections covering the second 25 years, again Phil provided much insight, along with much assistance from Ivone Johnson, Leon Bach and others too numerous to name. It should also be recorded that the ESA Presidents over the last 25 years and many members, including our Honorary Life Members, provided much of the detail following, particularly with the biographies.

I regard this as a continually evolving work, so if parts of the document are factually incorrect or if you can help fill the inevitable holes in our knowledge, please contact the Secretariat. We also thank the Australian Academy of Science for their support of the 50th anniversary Annual Scientific Meeting, and have included in the biographical details those Fellows of the Academy who have contributed especially to the field of endocrinology.

Honorary Secretary, ESA
August 2008

THE FIRST 25 YEARS: 1958-1982

Origins

The very first moves towards the formation of the Endocrine Society of Australia occurred in May 1957, when Keith Harrison of the Royal Prince Alfred Hospital, Sydney, and Bryan Hudson of the Alfred Hospital, Melbourne, discussed the possible formation of an association of physicians interested in diabetes and metabolism. By the time of the first meeting of the Diabetic Association of Australia – later to become the Diabetes Federation of Australia – considerable further discussion had occurred. At this meeting in Sydney on October 14-15, a scientific programme was presented and an interim committee subsequently set up to explore the formation of a society for the study of diabetes and endocrinology. Ewen Downie, Bryan Hudson and Pincus Taft of Melbourne, Basil Hetzel of Adelaide and Keith Harrison considered the questions of membership and draft constitutions and the relationship the new body would have with the Royal Australasian College of Physicians. In February 1958, a letter was circulated inviting all those interested in the formation of an Endocrine Society to attend a meeting at the BMA Hall, 135 Macquarie Street, Sydney, on June 2.

Sixty-nine persons attended this first meeting, chaired by Ewen Downie. The report of the interim committee was accepted and there was unanimous agreement that the Society should be formed. After the passage of a further motion that 'All present here this afternoon who desire to become members shall in fact become members', the acting secretary (Bryan Hudson) read out the names of eighty persons who had expressed interest in becoming members. It was agreed that these, together with twelve others added at the meeting, should be considered as original members of the Society; seven further names were added subsequently, leading to ninety-nine Foundation Members of the Society.

Later in the meeting, some amendments were made to the draft Constitution which had been circulated. Perhaps the most important of these related to the naming of the Society. In draft, the constitution referred to the Endocrine Society of Australasia. As it transpired that New Zealand colleagues had not been consulted, and as 'Australasia' was felt to be 'a fighting word in New Zealand', the name 'Endocrine Society of Australia' was agreed.

The first council, elected at this meeting, consisted of E. Downie, J. Bornstein and H.P. Taft (Victoria), K. Harrison, T.J. Robinson and C.W. Emmens (NSW), R. Hawker (Queensland) and B.S. Hetzel (SA). At the first Council meeting the following day, Ewen Downie was elected President and Pincus Taft Secretary/Treasurer. It was resolved to circulate the proceedings of the Scientific Meeting, to advise the medical press of the formation of the Society, and to hold the 1959 meeting in Adelaide.

Constitutions and Controversies

The initial draft constitution circulated in 1957 reflected the fact that the interim Committee was composed of physicians working in the field of Endocrinology. It proposed that there be three types of members: medical, scientific and honorary life members. Annual meetings were to be held each year in association with the College of Physicians meeting and members were to be encouraged to present material of clinical interest to the College, whereas matters of scientific or technical interest were to be presented to the Society itself. There was criticism of these provisions on the general ground that they differentiated between scientific and medical members and might prejudice one of the Society's stated objectives, namely 'to bring together physicians and scientists for scientific discussions and demonstrations'. C.W. Emmens, T.J. Robinson and others argued for revision of these arrangements. On the one hand it was felt that holding meetings in conjunction with the College of Physicians might limit scientific representation, particularly from other states; on the other, that meetings held in conjunction with ANZAAS might not be well attended by clinicians. As a result of this debate, the constitution was redrafted prior to the meeting of June 2, 1958, so as to provide for ordinary and honorary life member only and for some flexibility in the selection of meeting venues.

In the original Constitution, it was specified that members should hold a degree in either science or medicine. By 1970 it was felt that this was inappropriate and the Annual General Meeting passed a Constitutional amendment that 'anyone working in a relevant field and showing an interest in Endocrinology and Metabolism should be considered for membership'.

At various times the suggestion arose that special interest groups to be formed within the Society. In 1967, Professor Emmens wrote to the Council to ask whether a section of Reproduction and Fertility could be set up within the Society and it was decided that papers on this subject should be encouraged and grouped together in the programme. Unaware of these moves, another group went ahead and formed a separate Society which became the Australian Society of Reproductive Biology (now the Society for Reproductive Biology, SRB). The two Societies have of course remained closely associated and continue to hold their meetings in parallel with a joint organizing committee. In 1975 an attempt was made to differentiate areas of interest by means of a constitutional amendment '…to establish within the Society one or more chapters of the Society each having its primary object the advancement of knowledge…in a particular branch or branches of endocrinology'. This amendment, which came a year after the founding of the Australian Diabetes Society (ADS), was defeated.

The question of State representation has been a constitutional problem from time to time. In 1970 the legality of council was called into question as Dr. Ron Cox had moved from Adelaide to Sydney and thereby reduced the number of states represented on Council from four – as specified by the constitution – to three. The matter was finally settled honourably with Dr. Jarrett from Adelaide being appointed to fill the rest of Dr. Cox's term and Dr. Cox being asked to attend by invitation; members of the thus legalized Council were asked to approve all previous actions of the illegal Council by mail. The problem surfaced again when Endocrinology spread into previously unexplored geographical regions, necessitating a constitutional amendment to define the Australian Capital and Northern Territories as 'states' as far as the Society was concerned.

Early Scientific Meetings

The First Scientific Meeting was held on June 3, 1958, the day after ESA was formed. The papers presented included:

R.I. Cox; Pregnane-3α : 17α : 20α-Triol and related steroids.

W. Hamilton-Smith; Liver disease and virilism.

B.S. Hetzel & J.S. Charnock; A comparison of the metabolic effects of salicylate and hydrocortisone in man

I.D. Thomas, T.H. Oddie & F.F. Rundle; Thyroxine hormone flow in euthyroid subjects with high iodine uptake rates

June B. Shoath; The estimation of urinary 17 ketosteroids: an appraisal of current methods

R. Melick & P. Taft; Observations of body hair in old people

Peter Hall; Neurohypophysial function

R.W. Hawker & P.A. Robertson; Some properties of an oxytocic substance in blood extracts

For this first meeting, there was no call for abstracts, no programme committee and no referees' reports. For the second meeting in 1959, Pincus Taft, the Secretary, circulated the Notice of Meeting which, in relation to submitted papers said 'Members desiring to read papers at this meeting are requested to notify the Secretary by 1st March 1959 and to enclose a precis of 400 to 500 words suitable for circulation to members in the Society's Proceedings. This will facilitate circulation of these Proceedings soon after the meeting'. Members were also requested to forward their annual subscription of 2 guineas ($4.40). By comparison with average weekly earnings, today's subscription remains modest. The 1959 meeting was the first to be threatened with disruption by an airline strike, thus establishing something of a tradition. It is recalled that the Secretary and others from Melbourne decided to travel by train which they left at Murray Bridge to complete the journey by taxi so as to arrive on time; thereby being missed by the local organizers who had gone to meet the train. The Presidential address that year

was given by Ewen Downie on the subject of oral hypoglycaemic compounds, with ten papers presented by other members of the Society.

Puberty, Adolescence and Maturity

The second meeting in Adelaide in 1959 saw twelve new members admitted. C.W. Emmens was appointed as the Society's official representative to the International Society of Endocrinology and the Asia-Oceania Congress, which were both to meet for the first time within the subsequent year. In 1960, when Professor Emmens was President, a plenary session was held with the College of Physicians in Melbourne and in the following year the annual meeting was held in conjunction with the ANZAAS meeting. By this time, a number of medical scientific societies were flourishing in Australia and liaisons were established with The Australian Biochemical Society, the Genetic Society of Australia, The Australian Society of Microbiology, The Australian Physiological Society and the Australian Society of Plant Physiologists, with agreements to circulate meeting dates and programmes between these various societies. In 1962, it was decided that there should be a Presidential Address every second year and that in the intervening years the Society should invite a visiting speaker. It is interesting to compare this arrangement with the numbers of visiting speakers at the Society's current meetings. On March 6, 1963 the then President of the Society, Dr. Keith Harrison died, and C.W. Emmens was installed as President for the remainder of Dr. Harrison's term. Because of Dr. Harrison's death in office, the constitution was amended to allow for a Vice-President and it was decided that the guest lecturer for 1964 be called the Keith Harrison Memorial Lecture, to be given by Ken Ferguson. This has of course now become an annual event and remains the highest scientific award of the Society.

In 1959, C.W. Emmens had been one of the few Australians to attend the inaugural Asia and Oceania Congress of Endocrinology at Kyoto, Japan. At the request of Council, he applied successfully for the Second Congress to be held in Sydney in 1963. The credibility and reputation of the Endocrine Society of Australia were established both nationally and internationally by the successful holding of this Congress at a very early stage of the Society's history. It was opened by Lord Casey, the Governor General, on Tuesday May 28, 1963 and continued until Monday June 3. A total of 96 papers were included and there were symposia on fertility regulation, thyroid secretion, hormonal response to the environment, protein hormones and growth, and steroid hormone assay. The society was actively involved in the organization of subsequent Asia Oceania Congresses in Manila (1967), Auckland (1971), Chandigarh (1974), Singapore (1978) and Tokyo in 1983.

By 1966, the Society had grown substantially to a strength of 180 members. It had nominated its first Honorary Life Member – Dr. Ewen Downie, the first President. In response to a suggestion for a Summer School in Endocrinology, the 1968 Council decided that it would instead arrange a Seminar in Melbourne in early 1969, with a widely based programme, a registration fee, and a contribution from Society funds - $300 on this occasion. This was the beginning of the Seminar Programme which has continued ever since, interrupted only by International meetings being held during the same year. By this stage, the inevitable increase in Society business had occurred – anyone who has served on Council will be able to testify to the length of these meetings – and it was decided that council meetings should be held twice a year in association with the Seminar and Annual Scientific Meetings. Council also ruled that Councillors' travel expenses should be paid only to the interim meeting and not to the Annual Scientific Meeting. It is of interest to note that first-class fares were paid in the earliest days of the Society, the arrangement being changed to economy in 1965. At some point, all payments to Council members to attend meetings of the Society were ceased. The 1970 Council Election was the first to be contested, the Society by then having grown to over 250 members.

Pituitary Gland Collection in Australia

The early years of the Society coincided with the beginnings of pituitary gland collection. In the late 1950s glands were being collected by Drs. Melick and Bornstein in Melbourne and Dr. Vines in Sydney, with some growth hormone being extracted from the Sydney glands at CSIRO Prospect. In Melbourne, the initial batch of acetone-dried material was sent to Merck Sharp and Dohme in New Jersey for growth hormone (GH) extraction but little biological activity was finally obtained. Collaboration with the College of Pathologists resulted in a more extensive collection programme being set up in Melbourne with glands being contributed from Brisbane. By 1962, F.I.R. Martin was active in the collection programme which had increased, with pituitaries arriving from other areas such as New Zealand. From the resulting acetone processed material, Kevin Catt was preparing growth hormone and Jim Brown gonadotrophins. The first patient to receive follicle-stimulating hormone (FSH) was treated in 1963 and conceived in the third cycle. Over the subsequent five years, Jim Brown processed 9,000 pituitaries, producing over 11,000 ampoules of FSH from acetone dried glands using an ethanol extraction procedure. The residues from this process were further extracted by Kevin Catt and found to have satisfactory GH activity. The supply of FSH obtained was sufficient for Australian requirements and pituitaries were processed for Halifax, Nova Scotia and Singapore as well as New Zealand. In Melbourne, there were supplies sufficient for treatment of all anovulatory women being seen as well as some 20 men. In 1964 the Victorian Pituitary Group began to assess applications for supplies of GH to treat short stature. At about the same time, a meeting was convened by the CSIRO, CSL, AMA, RCOG and RACP. This meeting ultimately resulted in the formation of the Human Pituitary Advisory Committee on which the Society was originally represented by C.W. Emmens and subsequently, from late 1965, by Les Lazarus who became secretary to the Committee and then its Chairman.

In 1966, CSL started to process frozen glands while the Melbourne Group continued with their acetone drying procedure until 1968. By that stage, Dr. Lazarus reported that 5,000 glands per year were being collected and that 25 patients were being treated with GH and 56 with FSH. In 1970, the collection was 8,000 glands per year; 65 patients were being treated with GH and 109 with FSH as a result of which there had been 45 pregnancies. All those involved regard these early days as having been most exciting, of course being unaware of the potential dangers of pituitary extracts that later emerged.

Publication of the Proceedings

The question of publishing the Society's abstracts was first discussed at the 1960 Council meeting. In 1962, it was agreed to publish the Constitution and the Membership List of the Society in the form of a booklet and the 1982 volume of the Proceedings was the next occasion on which the Membership was published. For the 1965 and 1966 meetings, the abstracts were prepared by offset printing. The Medical Journal of Australia published the abstracts in 1967 and 1968, but was unable to allocate sufficient space for them in subsequent years. The Journal of Endocrinology had quoted the equivalent of $440 to publish the abstracts and this was regarded as too expensive. A separate booklet was therefore published and a subcommittee formed to discuss the feasibility of a Journal; their conclusion was that this would be too costly and their recommendations resulted in the first issue of the Proceedings in its present form being published for the 13th Annual Meeting in 1970. In 1975, the Seminar Meeting abstracts were published together with the annual meeting for the first time.

THE SECOND 25 YEARS: 1983-2008

Research Highlights

No history of Endocrinology can hope to encompass all the significant research advances in this field that has continually evolved over the course of fifty years or more. Nevertheless, some highlights in this second 25 years of the Society that heavily featured efforts by Australians and members of ESA are worth recording. These include the contributions of Geoff Tregear and Hugh Niall that led to the sequencing of PTH, relaxin and other peptides. Subsequently the full characterisation of relaxin at the Florey made relaxin almost an Australian hormone. Similar claims could also be made to the purification and characterization of the inhibin, activin and follistatin family by the groups led by Henry Burger and David de Kretser. While leading efforts were made at the same time by the Sugino group in Japan and Wylie Vale's group at the Salk, the reputation of the Melbourne groups in this field is undisputed. The identification of PTHrP as a cause of tumour hypercalcaemia by Jack Martin's group is another highlight of Australian endocrinology. Other notable efforts include the endocrinological advances leading to IVF and assisted reproductive procedures and Australia's profile in the ongoing use of stem cells and their application in endocrinology and related applications. The face of research in general has undergone a quantum shift from the initial purification of hormones and their early clinical use through to today's science which has benefited enormously from the Human Genome project and often features a global assessment of hormone action through array technology and bioinformatics and the potential contemplation, not even able to be envisaged 25 years ago, of individual gene therapy for patients.

Annual Scientific Meetings

The scheduled Annual Scientific Meeting (ASM) of the Society, held annually since the first meeting in 1958, has undergone some subtle but significant changes over recent years. There was a long-standing tradition of holding the meetings in the September AVCC common week, which enabled them to be held at University venues with all the joys of undergraduate college accommodation, shared bathrooms, narrow beds and no heating coupled with draughty inadequate lecture theatres and vast halls. There was a move initially to hotels with chandeliers, but over recent years with the growth of the Society, the ASM is held in major purpose-built convention centres. In so doing, the meetings moved away from the University break, which was initially fiercely fought by a number of University academics who felt that their commitments during term would preclude them attending the meetings. Some other 'notable' reminiscences include the 2001 ASM on the Gold Coast, where a forklift setting up the trade display ran over a junction box and brought down the computer network, leading to unexplained chaos in the various meeting rooms as to why none of the projectors were working. That meeting also coincided with the 9/11 terrorist attack in the US. One of the plenary lecturers, Domenico Accili from New York, had spent the whole night watching the catastrophe and trying to contact family and colleagues. After asking for a moment of silence with extreme dignity, he then proceeded to dazzle the delegates with an outstanding lecture. The Society has also moved in recent years to a 'seamless' system of meetings with other societies such as the SRB, ADS and the Australian and New Zealand Bone and Mineral Society (ANZMBS). The ASM also features electronic abstract submissions and registrations with one conference organizer, one trade display, etc. This progressed and improved each year and ESA has used the same company for its conference Secretariat since 2001.

A major achievement was the Society's successful bid to host the 2000 International Congress of Endocrinology (ICE) meeting. That process heavily relied on people like John Eisman, Rob Baxter and David Handelsman and their colleagues in Sydney. Ultimately and, somewhat ironically, the process came down to a shoot-out between Beijing and Sydney as it had for the Olympics, and again the outcome was the same. It is fair to say the Chinese were not happy. The Congress had 3500 registrants and there were 18 associated Satellite Meetings in Australia

and New Zealand. Within Australia it generated 62 radio or news items, 53 newspaper articles, 32 on-line news items, 20 television interviews and three articles for general practice journals. Overseas coverage was not monitored but ten international media representatives covered the Congress. As well as increased international profile, the meeting returned a profit of $260,000 to ESA!

As well as the ASM, the Society has run its annual Seminar Meeting since the instigation of these meetings in 1969. In the mid 90s, for instance, there was a series of colourful seminar meetings including three at the Lake Hume Resort in Albury, chosen more for its central location to address Melbourne and Sydney rivalries, than for any other virtue. Subsequently, Roger Smith was charged with finding a central location and went for geography rather than demography and took everyone off to Alice Springs! He then ran a couple of very successful meetings in Canberra. The Albury meetings, however, marked the end of an era in that the seminar meetings had started out as a Gordon Conference/Laurentian Hormone Conference-type scientific meeting with two or three plenary lectures, usually including two overseas lecturers, followed by a symposium-style meeting with much time for discussion. After the Ayers Rock meeting, they moved to a more clinical update-type format offering substantial educational experience to registrars and continuing education to endocrinologists and other physicians. This has been enormously successful as reflected in both attendance and income, but some members were somewhat saddened to see the loss of the generalist scientific-style meeting that it was.

Another development of note at the ASM has been the instigation of the Taft Lectureship in 1994. Following Pincus Taft's death, his seminal influence on Australian clinical endocrinology was celebrated by inviting clinically oriented presentations to balance the Harrison Lecturer, which was increasingly and inevitably focused on the tremendous advances in basic research. The closer relationship with the Japanese Endocrine Society has been seen in the publication of the ASM proceedings as a supplement to the *Endocrine Journal* (2005-2007) and the Australia-Japan Lecture featuring a plenary speaker from Japan at the ASM. Another recent innovation is the neuroendocrinology interest group with a dedicated symposium held as part of the ASM. ESA has also recently expanded its portfolio of junior investigator awards by adding the Bryan Hudson Clinical Endocrinology Award to the longstanding junior investigator award which has been predominantly won by basic scientists. A number of travel grants are awarded annually to help junior members attend international meetings and visit overseas laboratories.

The needs of clinical endocrinology have not been forgotten by ESA. The clinical weekend, which has preceded the ASM since 1986, is a wildly successful combination of clinical presentations, updates by local and international experts, time for colleagues to catch up with each other and a dose of 'endocrine trivial pursuit' in most years. For many clinicians, this weekend has become the main focus of their interaction with the Society.

The Structure of the Society

While ESA has grown significantly since its inception with 99 Foundation members, it is a vibrant mixture of clinicians and other medical professionals in practice, clinicians in research and basic scientists in endocrinology and associated fields. Currently there are 899 members of the Society, including 689 full members, 138 student members, 21 retired members and 51 Honorary Life Members. It is worth noting that in 1982 the Society decided to confer Honorary Life Memberships on all its Foundation members who were still active members at the time. Since then, there has been a sporadic conferring of Honorary Life Membership to members who have provided outstanding service to the Society, with the intention to propose four members for consideration of Life Membership at the 2008 annual general meeting. Although some of the student members do not remain ESA members once their student training is complete, the Society actively encourages membership by a strategy where the registration costs to attend the ASM as a non-member is more than the total of the member rate combined with the annual membership fees. Another feature of tracking membership was developing the first membership database and publishing the membership directory (which was especially significant pre-internet), leading to today's online membership database containing relevant details of all our members including their fields of interest.

The tyranny of distance has always been an issue with ESA Council meetings and meetings via teleconference have been the norm for a number of years. Council meetings are held at roughly quarterly intervals, including a Council meeting held at the ASM and preceding the AGM. A recent chapter in the history of the ESA is the modernisation of the Secretariat, which moved from a nomadic model based around the location of the Honorary Secretary to a base at the Royal Australasian College of Physicians (Sydney) in 1999. The new structure with a dedicated Secretary has greatly improved the running of the Society's activities and communication to its members. Another recent development has been the reorganisation of Council with overlapping terms for Councillors and a President-elect. This is an important structural step to ensure that ESA is managed optimally without loss of corporate memory after each election.

Finances

The Society has undergone a major restructure in terms of financial management. This is particularly relevant given that the financial assets of the Society are currently around one million dollars. David Handelsman, first as Treasurer and then as President, undertook to stabilise and re-energise this part of the Society's activities. He developed a financial backing of at least twice the cost of the ASM outlays, achieving that and then exceeding this target partly courtesy of the ICE meeting profit in 2000. This ongoing financial stability has allowed the recent

initiation of the scholarship and post-doctoral awards given by ESA and also that of the increased number of travel awards, not only to attend the ASM but also to overseas meetings. This has been also been made possible in part by taking the bold step to invest more aggressively than previously, when all funds were held in bank accounts and term deposits. This was managed by previous Councils and Treasurers (David Handelsman and Cathie Coulter, in particular). While this has been of tremendous benefit, the financial position of the Society is thus subject to temporary fluctuations in stockmarket and share value, such as those related to 9/11 and the recent sub-prime mortgage fiasco in the US.

Supporting young members

A Society needs new members to survive and a discipline needs new members to thrive. As mentioned above, ESA has expanded its portfolio of junior investigator awards to encourage trainees to do excellent work and present it at our meetings. Travel grants assist them in attending ESA meetings as well as international meeting and laboratories. As mentioned above, ESA now provides a postgraduate research scholarship and a postdoctoral award to help junior members establish their research careers at a particularly vulnerable time. An important component of the 50th Anniversary celebration is the Rising Star Symposium, which honours four young members who have already made important contributions to endocrinology.

ASM Proceedings and Newsletters

The ASM Proceedings have remained essentially as they had been since the 1970s, but recently have moved to a larger page format, partly prompted by being published as a supplement to *Endocrine Journal*. This has created some debate in the membership, as the single bright colour scheme of the front cover changing year by year and the uniform size made it easy for the proceedings to sit on the office bookshelf. Many remember the famous (infamous?) 1999 proceedings that were distinguished primarily by the colour (pink) and the fact that it matched a now famous dress worn by Cathie Coulter, the then Editor of the proceedings - a fact she has never lived down. Newsletters are published twice a year, with the Newsletter Editor providing content to a professional graphic designer, with printing and mailing arranged off-site. This contrasts very much with earlier times when the newsletter was roneo'd from typed copy.

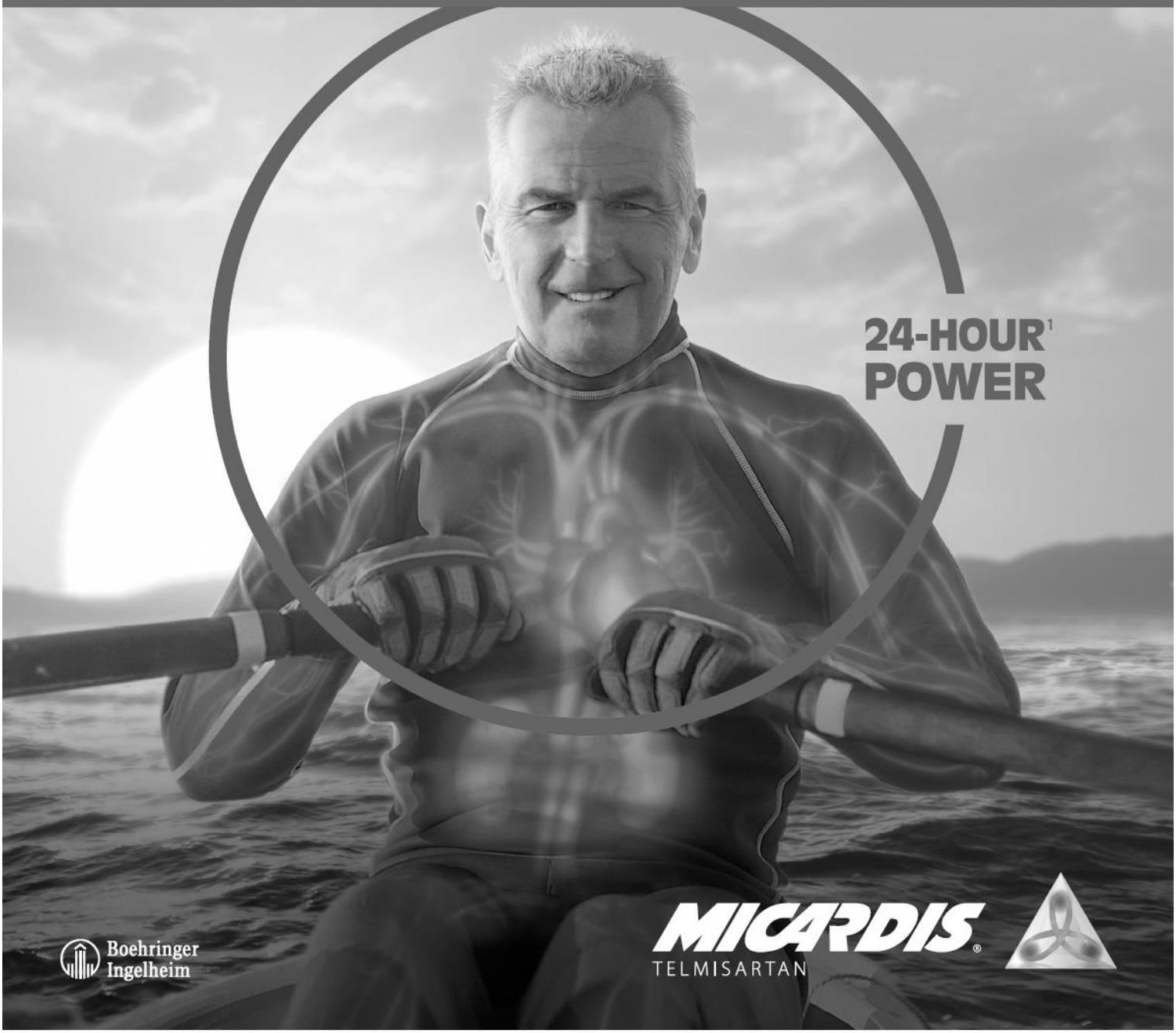
The Society Profile and its Relationship with the RACP

Importantly, ESA has evolved into a well-respected professional body where expert opinion is sought by Government bodies and other organizations. Previously this was on an *ad hoc* basis, but in the late 1980s there was a position created on Council with responsibility for Clinical Affairs, which has been continued to the present day. This acts mainly as a mechanism of liaison between ESA and RACP, but also occasionally has input into matters of particular concern to clinical endocrinologists. There have been reports commissioned from expert members of the Society covering topics such as the use of growth hormone in adults, androgen treatment of men (Med J Aust 2000; 172, 220-224), metformin to treat polycystic ovarian syndrome (Med J Aust. 2001; 174, 580-583), the use of postmenopausal hormone therapy by medical practitioners (with the RANZCOG and Menopause Society) and Vitamin D deficiency in Australia (with ANZBMS). These reports have been utilised by various Government agencies and Council regularly receives invitations to provide submissions to Government enquiries on various aspects related to endocrinology and clinical practice. Another aspect of ESA's professional relationship has been its involvement in curriculum development with the RACP.

Concluding Remarks

What has emerged, based on the solid foundation of its first 25 years of existence, is that the most recent 25 years of The Endocrine Society of Australia depicts a continually expanding, vibrant and healthy body of professionals, both clinicians and basic scientists, that represent the broad meaning of what it is to be an endocrinologist in Australia in the early years of the 21st century. This attests to the vision of the founding fathers of the Society at that fateful meeting on June 2, 1958, and how this has been built into a pillar of achievement by many, many members who have not stinted in their commitment to this Society. We are sure that Keith Harrison and Bryan Hudson would be amazed and proud at what ESA has become, but it could also have disappeared a long ago without the commitment of so many. One wonders what those who are preparing a history update for the 75th anniversary of the Society will make of the next 25 years we are about to experience, and how far the Organization will have come since 2008!

POWERFUL BP REDUCTIONS from Morning to Morning[1]



PBS information: General Benefit.

FULL PRODUCT INFORMATION IS AVAILABLE ON REQUEST FROM THE MANUFACTURER. PLEASE REVIEW THE FULL PRODUCT INFORMATION BEFORE PRESCRIBING.
Reference: 1. White *et al. Am J Hypertens.* 2004;17:347-353. Boehringer Ingelheim Pty Ltd. ABN 52 000 452 308, 85 Waterloo Road, North Ryde NSW 2113. ®Registered Trademark. **MICARDIS® (telmisartan) Tablets 40 mg and 80 mg. INDICATIONS:** Treatment of hypertension. **CONTRAINDICATIONS:** Hypersensitivity to any components of the product. Pregnancy. Lactation. Biliary obstructive disorders. Severe hepatic impairment. Rare hereditary conditions (fructose intolerance).* **PRECAUTIONS:** Primary aldosteronism; congestive heart failure; aortic/mitral valve stenosis; obstructive hypertrophic cardiomyopathy; ischaemic cardiovascular disease; renal artery stenosis, kidney transplant; patients whose vascular tone and renal function depend on the activity of the renin-angiotensin-aldosterone system; hepatic and/or renal impairment; combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics; volume and/or sodium deficiency; fructose intolerance, children. Interactions with Other Drugs: Other antihypertensive agents; digoxin; lithium, NSAIDs (including aspirin, COX-2 inhibitors and non-selective NSAIDs*), potassium-sparing diuretics, potassium supplements, other agents that may cause increased serum potassium levels. **ADVERSE REACTIONS:** headache, upper respiratory tract infection, diarrhoea, back pain, pain, influenza-like symptoms, sinusitis, erythema, syncope/faint, hypotension, bradycardia, abnormal hepatic function / liver disorder, renal impairment, hyperkalaemia, anaemia, eosinophilia, thrombocytopenia, weakness, dizziness, fatigue, angioneurotic oedema*, pruritus, rash, urticaria, others (see full PI). **DOSAGE:** Adults: 40 mg once daily. Increase to 80 mg once daily if necessary. The maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment. No dosing adjustment is necessary in the elderly or in patients with renal impairment, including those on haemodialysis. Telmisartan is not removed from blood by haemofiltration. In patients with mild to moderate hepatic impairment, dosage should not exceed 40 mg once daily. **PBS DISPENSED PRICE:** MICARDIS® 40 mg $20.02, MICARDIS® 80 mg $26.96. *Please note changes in Product Information. TH MIC FP 6/08 CSANZ

HONORARY LIFE MEMBERS OF ESA AND FELLOWS OF THE AUSTRALIAN ACADEMY OF SCIENCE WITH PROFILES IN ENDOCRINOLOGY

Robert C. Baxter

ESA member since 1977; awarded Life membership in 2004; elected to Australian Academy of Science in 2004.

Rob Baxter obtained his PhD in Biochemistry in 1973, and was awarded a DSc in 1990. His research has contributed to understanding both the regulation of normal tissue and body growth, and the aberrant cellular growth in cancer and overgrowth syndromes. Since 1994 Rob has been the Director of the Kolling Institute of Medical Research, after almost 20 years in the Department of Endocrinology, Royal Prince Alfred Hospital, headed by Professor John Turtle. He is a former President of ESA. National and international awards for his research include the Dale Medal of the British Endocrine Society (1993), the Wellcome Australia Medal (1994), the Lemberg Medal of the Australian Society for Biochemistry and Molecular Biology (1997) and the Ramaciotti Medal for Excellence in Biomedical Research (2002). He became a Fellow of the Australasian Association of Clinical Biochemists (FAACB) in 1987, and was elected a Fellow of the Australian Academy of Science in 2004. He is an ISI Highly Cited Researcher in Biology and Biochemistry with over 16,000 citations, and has given keynote plenary lectures at meetings in Australia, Europe, South America and the USA.

Alan W. Blackshaw

ESA foundation member (1958); awarded Life membership in 1982.

Alan graduated from the University of Sydney in Veterinary Science in 1948/49 and spent a formative 10 years in Veterinary Physiology with Professor C.W. Emmens understanding experimental design and analysis. They were very successful in the cryopreservation of human, ram and bull spermatozoa and gained a good knowledge of sperm physiology. Over a further 33 years in Physiology and Pharmacology at the University of Queensland, with nearly nine years spent as Head of Department, significant developments were made assessing the heat damage to spermatogenesis using qualitative and quantitative histology and histochemistry. Reproduction in micro- and mega bats, including seasonal changes in testosterone, and in fish (bream, whiting and barramundi) was also studied. The sperm of these three species were cryopreserved and those of the barramundi were successfully used in aquaculture. Studies in the behaviour of pigs and rams were conducted with his wife, Dr J.K. Blackshaw. Post-retirement, he has been involved in collaborative studies spanning pig embryo cryopreservation and transfer to the culturing of mud crabs (Scylla serrata).

Hal D. Breidahl

ESA foundation member (1958); awarded Life membership in 1982.

Hal Breidahl graduated in Medicine from the University of Melbourne in 1948 and his MD in 1952 following appointments at the Alfred Hospital. In 1953, he was the Flack Travelling Scholar at The Mayo Clinic soon after the Clinic was awarded the Nobel Prize for the discovery of cortisone. From 1954-56, he was at Hammersmith and King's College Hospital in the UK, including work in pregnancy diabetes and an insulin bioassay. On his return to Melbourne, Hal held various clinical appointments at the Royal Women's, Prince Henry's and Alfred Hospitals. He was appointed to the Diabetes and Metabolic Unit under Bryan Hudson and Joseph Bornstein and his position as Endocrinologist at the Queen Victoria Hospital allowed him to pursue his interest in diabetes in pregnancy. In 1974, in conjunction with John Turtle, he established the Australian Diabetes Society, becoming Foundation President (1974-76). He has held numerous Committee positions and given many plenary presentations and was the AMA representative on the Australian Standards Association. Hal retired from hospital positions in 1984 and began a practice in Frankston until his retirement in 1993. He regards the development of reliable diagnostic tests for diabetes and the means for home blood glucose testing as the most significant advances in this aspect of endocrinology.

James B. Brown AM

ESA member pre-1971; awarded Life membership pre-1992.

James Brown graduated with a Science degree from the University of Melbourne and then completed a PhD in Edinburgh. There he developed the first accurate clinical method for measuring oestrogen and progesterone in urine. These were foundation assays enabling insights into steroid production and metabolism in both human and animals, and were awarded Citation Classics. James was also involved in establishing biological standards for the gonadotrophins, which later became the basis for International Units for LH and FSH. He continued his research into the role of oestrogens in various cancers and was part of the team, along with Gregory Pincus, that led to the development of the contraceptive pill. Returning to Melbourne, in the 1980s James and his collaborators at the Royal Women's Hospital in Melbourne devised an ovarian monitor for home use that could detect changes in steroids by biochemically testing samples of a woman's urine. He also collaborated with John Leeton and Carl Wood leading to egg pick-up needed for IVF procedures and the now general use of gonadotrophins for causing

ovulation at an accurately, pre-determined time. He was made a Member of the Order of Australia (AM) in 2003 for service to medical science, particularly clinical research into womens health and reproductive issues and the development of the Home Ovarian Monitor.

Henry G. Burger AO
ESA member since 1965; awarded Life membership in 1992; elected to Australian Academy of Science in 1994.

Henry Burger is Emeritus Director of Prince Henry's Institute of Medical Research and Honorary Professorial Fellow, Faculty of Medicine, Monash University, Melbourne Australia. He is a practising clinical endocrinologist and a clinical investigator, whose major interests have been in reproductive endocrinology, specifically the physiology of the inhibins, the endocrinology of the menopause and the therapeutic use of androgens in women. He chaired the World Health Organization's Scientific Group on 'Research on the Menopause' in 1994 and is a Past President of the International and Australasian Menopause Societies. He is author or co-author of more than 560 publications. He has won a number of prizes and awards, including the Dale Medal of the British Endocrine Society, Distinguished Physician of the US Endocrine Society (1999) and the North American Menopause Society's 2000 NAMS/Wyeth Ayerst Perimenopause Research Award and the 2006 NAMS Leadership Award in Androgen Research.

Robin A. Burston
ESA foundation member (1958); awarded Life membership in 1982.

Bob Burston commenced his medical course at the University of Adelaide, finishing in 1944 with high honours. He then joined the Australian Imperial Forces (AIF) in January 1945, serving in Australia and finishing in Irian Jaya. He subsequently joined the British Occupational Force, and served 18 months in Japan. On returning to Australia, Bob decided to further his medical career and went to the UK to study, becoming a Fellow of the Royal College of Physicians of Edinburgh and later London. On returning to Adelaide, he also became a Fellow of the RACP, and practised as a specialist physician in diabetes. Bob pioneered the diabetic services at the Royal Adelaide Hospital and, was appointed honorary physician to The Queen Elizabeth Hospital and in 1980 established the first Diabetic Educational Centre in South Australia. He retired in 1987, having also made significant contributions to postgraduate education through various positions including at the University of Adelaide. Bob maintained his interactions with the military corps, including appointment as honorary physician to the Governor General of Australia in 1971 and being granted the title of Colonel and Honorary Colonel at various times. Bob passed away recently (2008) aged 87 years.

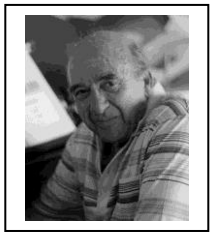
Donald P. Cameron AO
ESA member since 1966; awarded Life membership in 2003.
Don Cameron began his career in Endocrinology as the Registrar in the Diabetes and Metabolic Unit at the Alfred Hospital with Pincus Taft and Hal Breidahl. He joined Henry Burger as a Research Fellow at the Medical Research Centre at Prince Henry's Hospital, where Bryan Hudson and Kevin Catt were in the Department of Medicine. He worked on the clinical metabolism of human growth hormone involving, amongst other things, giving labelled growth hormone to himself and his colleagues! In 1969, he went to Geneva to the lab of Albert Renold, and in 1972 returned to Prince Henry's Hospital. He was appointed in 1977 as the Director of Endocrinology at Princess Alexandra Hospital in Brisbane, but before taking up the post, spent nine months at the University of Louvain in Brussels. He spent the next 20 years at the hospital before becoming Chair of the Centres for Health Research on the Hospital Campus for several years. He was Secretary of ESA from 1980-82, Vice-President from 1984-86 and President from 1986-88. He has also been heavily involved with the RACP for some years as well as NHMRC Committees. He continues to practice in Clinical Endocrinology and was made an Officer of the Order of Australia (AO) in 2000 for service to medicine, particularly in the fields of endocrinology and diabetes.

John P. Coghlan AO
ESA member since 1960; awarded Life membership in 1992.

John Coghlan studied Science at the University of Melbourne and completed his BSc in 1958, a MSc in 1960 and his PhD in 1964. He worked as a pre/post-doctoral fellow at Cornell University Medical School working on labelling of steroids and several periods working with James Tait and his wife Sylvia in the UK on steroids. In 1972 he was awarded a DSc from the University of Melbourne and became Deputy Director of the Howard Florey Institute in 1972, taking over as Director in 1990. His key research advances were in the routine measurement of steroid hormones using radioimmunoassays, assays for small non-antigenic peptides and compounds, understanding hormone production and blood pressure regulation and detection of specific gene products in complex organ systems. He has also held various senior posts such as Deputy Vice-Chancellor (Research) at the University of Melbourne (1987-90), is the Executive Director of the The Sir Robert Menzies Memorial Foundation to support excellence in medical and health research education and was Chairman of the Medical Research Committee of NHMRC (1988-90). He was made an Officer of the Order of Australia in 1997. John has been

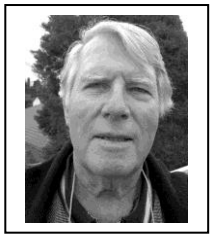
awarded the Dale Medal of the British Endocrine Society (1987) and has been invited speaker at many international scientific forums; he has published over 500 scientific papers and chapters.

Alex K. Cohen AO
ESA foundation member (1958); awarded Life membership in 1982.



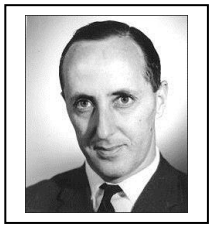
Alex Cohen graduated from the University of Adelaide in 1950 and was the inaugural Mortlock Research Fellow working with cortisone in idiopathic thrombocytopenic purpura (ITP). He worked at Hammersmith Hospital for a year before moving to the Diabetic Unit at King's College Hospital working with RD Lawrence. He then spent a year working with the first sulphonylurea, carbamazepine, in Edinburgh. Alex then spent time at the Thorndyke lab at Harvard studying alcohol hypoglycemia, which led to a MD being awarded by Adelaide University. After returning to Perth, he was one of the instigators of the Diabetes Research Foundation of WA in 1980. He remained President of the Foundation until 2007, served on the Diabetes Australia Board and was instrumental in obtaining funding for a chair in diabetes research. He has also been Chancellor of the University of Western Australia and was President of the RACP from 1992-94. Alex was made an Officer in the Order of Australia in 1995 in part for his contributions to the field of endocrinology.

Ron I. Cox
ESA foundation member (1958); awarded Life membership in 1982.



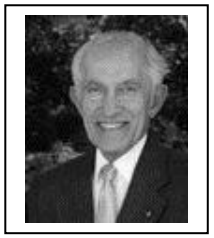
Ron Cox did a PhD in the Biochemistry department at Edinburgh University in 1952 with Guy Marrian looking at adrenocortical steroids. This was followed by a Fellowship with the NSW Cancer Council at University of Sydney in 1955. Research included studies on Congenital Adrenal Hyperplasia (pregnanetriol and pregnanetriolone), polycystic ovary syndrome, and the initiation of the concept of antioestrogens using synthetic stilboestrol analogues (with Cliff Emmens, Peter Claringbold and Len Martin). This work led others to the development of tamoxifen for use in breast cancer by commercial interests in the USA. He was appointed as Reader in Endocrinology at Adelaide University in 1962, and this was associated with a shift of his interests from steroids, prostaglandins and related compounds to monitoring treatments for ovulation induction and fertility enhancement. A return to Sydney in 1970 and to the CSIRO Division of Animal Physiology took Ron's work into endocrine patterns of the oestrous cycle and pregnancy in farm animals, often as a model for human studies. Using immunological techniques to form steroid specific antibodies, his research group proved it was possible to control ovarian function and fecundity in sheep. These procedures led to a number of commercial outcomes, including several patents and over 100 papers. Ron has participated in ESA during the formative period of the Society, served on Council from 1964-70 and was Vice-President from 1968-70.

David H. Curnow AO
ESA foundation member (1958); awarded Life membership in 1982.



After a Science degree from the University of Western Australia, David Curnow obtained a PhD from the University of London in 1950. He was appointed Head of the Department of Clinical Biochemistry in 1953 and retained this position until he became Head of Combined Clinical Biochemistry Services at the Queen Elizabeth 11 Medical Centre in 1974. David built an outstanding Department of Biochemistry at the Royal Perth Hospital with an international reputation. In 1968 he was appointed Foundation Professor of Clinical Biochemistry at the University of Western Australia but retained his post as head of department at the Royal Perth Hospital. In 1987, he was appointed an Officer in the Order of Australia for service to science, particularly in the field of clinical chemistry. He is co-author on over 90 scientific papers and was co-author of the text book *Metabolic Pathways in Medicine*. A number of his papers dealt with results from the Busselton Population Studies and he played an important role in the planning and execution of these studies. He passed away in 2004.

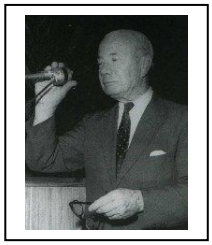
David M. de Kretser AC
ESA member since 1967; awarded Life membership in 2004; elected to Australian Academy of Science in 1996.



David de Kretser received his MBBS in 1962 from the University of Melbourne and his MD in 1969 from Monash University. From 1969-71 he was a Fogarty International Post-doctoral Fellow at the University of Washington in Seattle. He returned to Melbourne and had positions at Monash and Prince Henry's Institute before becoming Professor and Chairman of the Department of Anatomy at Monash in 1978. In 1991, he became founding Director of the Monash Institute of Reproduction and Development, now known as the Monash Institute of Medical Research. He also initiated and directed Andrology Australia, a Federal Government initiative first funded in 1999 to provide public and professional education in Men's Health. Practising as a physician in male infertility and andrology, he was involved in basic and clinical research in these fields. Together with colleagues, he isolated inhibin and follistatin and has been at the forefront of international research into the biology of these proteins and the activins. He has published over 400 papers in refereed journals. David was admitted as an Officer in the Order of Australia in 2000, made a Companion of the Order in 2006 and is a Fellow of the Australian Academies of Science and

Technological Sciences and Engineering. He retired as Institute Director in 2005 and since 2006 has been Governor of Victoria.

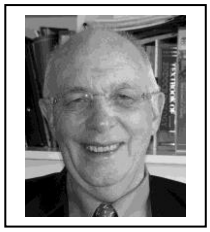
Ewen Downie



ESA foundation member (1958); awarded Life membership in 1965.

Ewen Downie completed his MBBS at the University of Melbourne in 1925 and his MD in 1929. He spent two years as a resident and registrar at the Alfred Hospital before working at St Bartholomew's Hospital in London with Sir Francis Fraser. Returning to Melbourne, Ewen was appointed Assistant to the Asthma Clinic at the Alfred, also developing an interest in diabetes, becoming Physician-in-Charge of the Hospital Diabetic Clinic in 1929. He also worked at the Baker Medical Research Institute on aspects of carbohydrate metabolism and in 1932 was awarded the Bertram Armytage Prize for medical research. He was Physician to out-patients (1932-41), honorary Physician to in-patients (1941-56) at the Alfred, sub-dean (1932-45) of the clinical school and a foundation Fellow (1938) of the Royal Australasian College of Physicians. In 1941, Ewen was appointed a major in the Australian Army Medical Corps and served in general hospitals in the Middle East (1941-42) and Australia (1942-44). He became dean of the Clinical School at the Alfred (1946-57) and also ran the diabetic and metabolic unit until 1962, which was subsequently named after him. He then took up a Foundation Chair of Medicine along with Bryan Hudson at the new Monash University in 1962. Ewen's contributions to the fields of metabolism, nutrition and diabetes earned him an international reputation, with his interest in diabetes and metabolism leading to the recognition of endocrinology as a sectional specialty in internal medicine and to the formation of ESA, of which he was first President (1958-60). He died in 1977, aged 75 years.

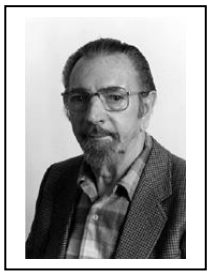
Cresswell J. Eastman AM



ESA member since 1967; awarded Life membership in 2003.

Creswell (Cres) Eastman is Clinical Professor of Medicine the University of Sydney and a practising Consultant in Endocrinology and Public Health. He has recently retired after 16 years as Director of the Institute of Clinical Pathology and Medical Research (ICP&MR) at Westmead Hospital and Director of the Western Sydney Area Pathology Service. He studied Medicine at the University of Sydney, graduating in 1965 and then receiving his MD in 1980. From 1996-2006 he was the Director of the NSW Division of Analytical Laboratories (DAL) that provides all public health analytical and forensic services for NSW. Before becoming Director of the ICPMR, he was Head of the Department of Endocrinology at Woden Valley and Royal Canberra Hospital (1975-9) and at Westmead in 1979. Cres was Treasurer (1974-78), Vice President (1978-80) and President (1980-82) of ESA and has also served on many RACP committees, particularly at state level. His research interests are focused predominantly in thyroidology, especially in the area of iodine deficiency disorders (IDD). He has directed major research and public health projects into IDD in the Asia-Pacific region and has coordinated multi-million dollar aid efforts in IDD. He is a Board Member of the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) and was appointed ICCIDD Regional Coordinator for the Asia Pacific Region in April 2002 and Vice Chairman in 2006.

Cliff W. Emmens



ESA foundation member (1958); awarded Life membership in 1982; elected to Australian Academy of Science in 1956.

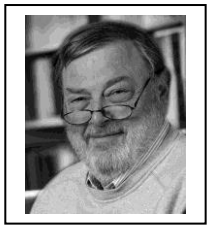
Cliff Emmens was born in London in 1913 and underwent training in endocrinology, culminating in a PhD, at University College, London. Before the Second World War, he developed bioassays for steroids and gonadotrophins and after the War he continued his career in the Medical Research Council, focusing on freezing protocols suitable for sperm. He became the Foundation Professor of Veterinary Physiology at the University of Sydney in 1948. As well as establishing and maintaining a vibrant department, Cliff was involved in the establishment of commercial freezing of bull semen and continued his interest in female endocrinology and the use of hormone bioassays. In the early 1950s, he was partly seconded to CSIRO to establish its Sheep Biology Laboratory at Prospect. Cliff was instrumental in many professional organisations, including President of ESA from 1960-62 and March 1963-64. He retired in 1978 and was awarded an Honorary DVSc in 1979. Cliff passed away in June, 1999.

Ken A. Ferguson

ESA foundation member (1958); awarded Life membership in 1982.

Ken Ferguson graduated in Veterinary Science from the University of Sydney in the 1940s and joined CSIRO. Because research degrees were not available in Australia at that time, he went to Cambridge to complete a PhD studying the role of the pituitary gland on wool growth of sheep. He continued this work on his return to Australia, defining the proteins in the pituitary by paper electrophoresis and ion exchange chromatography. This work was presented as part of the 19th Laurentian Hormone Conference (1963) and Ken was the first Harrison Plenary Lecturer for ESA in 1964. He retired from active research in 1972, leaving CSIRO as Director of the Institute of Animal and Food Sciences. He was also made a Fellow of the Australian Academy of Technical Sciences and Engineering (FTSE) in 1976 and is a Life Member of the Australian College of Veterinary Scientists.

John W. Funder AO



ESA member since 1967; awarded Life membership in 2003.

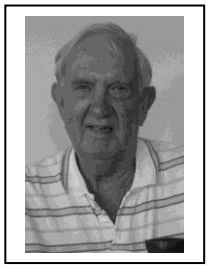
John Funder, or 'Funder' as he is almost universally known, was born in Adelaide but went to grew up in Melbourne, completing a BA and MBBS (1958-65) at the University of Melbourne. Thereafter, he did a PhD and MD at the Howard Florey Institute (1967-70). He then was a Resident at St Vincent's Hospital before spending two years as a National Heart Foundation Fellow at UCSF and then a year in Paris at L'Hospital Necker. Returning to Melbourne, Funder was a Senior Research Fellow at Prince Henry's Hospital from 1973-90, apart from a year in Paris as Visiting Professor (1976-77) and three months at Stanford. In 1990, he resigned as Senior Principal Research Fellow of the NHMRC to become Director of the Baker Medical Research Institute, a position he held until 2001. Currently he is a Senior Fellow of Prince Henry's Institute and has recently been appointed as Director of Research Strategy for Southern Health in Melbourne. He has also provided consulting for the pharmaceutical and philanthropic sectors. Funder has undertaken research into the role of hormones in heart failure and hypertension, particularly with respect to aldosterone and mineralocorticoid receptors, and has published more than 550 papers. He was made an Officer in the Order of Australia in 1998. He was on ESA Council for a number of years, including Treasurer (1978-80), Vice-President (1980-82) and President (1982-84). He sits on a number of scientific Editorial Boards and has been an invited speaker at numerous international scientific meetings, including the International Society of Endocrinology.

Richard D. Gordon AO

ESA member since 1966; awarded Life membership in 2003.

Richard (Dick) Gordon was Secretary of ESA (1972-74) and Council member from 1970-74 and 1976-78. Dick studied Medicine at the University of Queensland before he commenced training as an endocrinologist with Bryan Hudson in Melbourne, leading to his MD by thesis on the circadian rhythms of adrenocortical and renal function. While a Fulbright Scholar/ NIH Research Trainee in Endocrinology (1964-66) with Grant Liddle (who elucidated Cushing's syndrome, described Liddle's syndrome and ectopic hormone production by tumours), he described a diurnal rhythm for renin in continuously recumbent subjects and a role for the sympathetic nervous system in renin regulation. In Adelaide (1966-69), he described the reversibility by dietary salt restriction or low dose thiazide of Gordon's syndrome. On his return to Brisbane in 1970, he established endocrine services at Princess Alexandra and Greenslopes Hospitals and an Endocrine Hypertension Research Unit, which described angiotensin-responsive aldosterone-producing adenoma, Familial Hyperaldosteronism Type II and identified primary aldosteronism as the commonest potentially curable form of hypertension. Dick has published more than 200 peer-reviewed papers, with his current research focus on the genetics of autonomous aldosterone secretion. He also established the Queensland Hypertension Association in 1981 and was made an Officer in the Order of Australia in 1994 for services to medicine in the field of endocrine hypertension.

Ian B. Hales



ESA member since 1959; awarded Life membership in 1992.

Ian Hales was born in 1926 and having served in the Royal Navy in 1945-46, graduated in Medicine from the University of Sydney in 1950. He was a physician at the Royal North Shore Hospital, and Director of Nuclear Medicine and Endocrinology from 1970-85. He has published over 75 papers on thyroid function and disease. He was a past President of the Australian and New Zealand Society of Nuclear Medicine and became a member of ESA the year after its establishment.

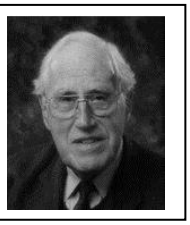
Philip E. Harding

ESA member since 1973; awarded Life membership in 2003.

Philip Harding trained in endocrinology in London with Victor Wynn and in Pittsburgh with James B. Field. He returned to Adelaide in 1973 and in 1976 was appointed Director of the Royal Adelaide Hospital Endocrine and Metabolic Unit. He was Honorary Secretary of the ESA from 1976-78 and subsequently continued as Editor of the Proceedings, and as Society archivist, for many years. He retired from institutional work in 2003 and continues part-time in private practice. Research interests have included hepatic insulin extraction and the relationship between diabetes control and gastric motility and most recently involvement in the National Iodine Nutrition Study.

Basil S. Hetzel AC

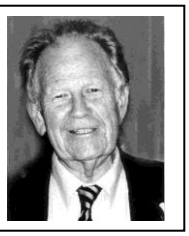
ESA foundation member (1958); awarded Life membership in 1982.



Basil Hetzel studied Medicine at the University of Adelaide and graduated with a MBBS in 1944. He filled various clinical postings at Adelaide Hospitals until 1949, when he was awarded a MD. In 1951, he began a Fullbright Fellowship in New York, where he worked on, amongst other things, correlating urinary cortisone output with stress levels. Then followed two years at St Thomas' Hospital in London where he studied the metabolic characteristics of aldosterone. He returned to Adelaide in 1956 and was heavily involved in the establishment of The Queen Elizabeth Hospital, with research interests being in circulating thyroid hormones and neonatal hyperthyroidism. A challenging break was his seven years as the Foundation Professor of Social and Preventative Medicine at Monash University (1968-75). Returning to Adelaide, he became Chief of he Division of Human Nutrition of CSIRO, retiring from this post in 1985 at the age of 63. Thereafter, he held the position of Executive Director of the International Council for Control of Iodine Deficiency Disorders (1986-95). This appointment reflects his long-standing interest in iodine deficiency disorders such as cretinism, neuromuscular disability and goiter, resulting in many trips to the developing world as a 'clinical ambassador'. Other appointments include Lieutenant Governor of South Australia (1992-2000) and Chancellor of the University of South Australia (1992-98). He has also written a very engaging book of his experiences, entitled *Chance & Commitment. Memoirs of a Medical Scientist*.

Brian Hirschfeld

ESA foundation member (1958); awarded Life membership in 1982.



Brian Hirschfeld was born in 1926 and after matriculation at Brisbane Grammar School, he withdrew from the quota in Medicine at the University of Queensland to enlist in the navy. He completed Medicine as a returned serviceman in December 1952. At Royal Brisbane Hospital, he had the good fortune to experience the mentoring of Professor Alf Steinbeck. Brian and Bernard Knapp established the Diabetic Clinic at Princess Alexandra Hospital. Brian owes much gratitude to Bernard and the other clinicians for putting up with his eccentricities! From 1956-59, he also was a medical consultant to the Electrical Industry in S.E. Queensland. Insight into the problems of employment, work and superannuation showed him that many of the problems for those with diabetes mellitus were created by the patient and professional advisors. In this area, the Society has made a tremendous contribution to diagnosis, therapeutics, teaching and research in this area with the aid of the patient.

Bryan Hudson AO

ESA foundation member (1958); awarded Life membership in 1982.

Bryan Hudson was born in 1923 and graduated in Medicine from the University of Melbourne after a shortened wartime course. From 1946-48 he was a resident at the Alfred Hospital. After a year studying pathology in Chicago and two years at St Mary's Hospital in London, Bryan returned to the Alfred. At the Baker Institute, he did a PhD studying melanocyte-stimulating hormone. Concurrently, he developed a clinical endocrinology service at the Alfred and became physician in charge at the newly opened Diabetic and Metabolic Unit. After a two year period studying steroid biochemistry in the US, he returned to become a foundation Professor of Medicine at Monash University in 1962. He developed an abiding interest in the endocrinology of the pituitary-testicular axis including during his appointment as Associate Director of the Howard Florey Institute and Medical Director of the Royal Southern Memorial Hospital. He was President of ESA from 1966-67 and on Council from 1961-68, was on the Council of RACP for many years and on the ISE Committee for a number of years, including as President. ESA has named its clinical endocrinology award after Professor Hudson recognizing his outstanding contribution to both clinical and basic endocrinology. Bryan was made an Officer of the Order of Australia in 1985.

David E. James

Elected to Australian Academy of Science in 2007.

David James is a Senior Principal Research Fellow with the NHMRC and Director of the Diabetes and Obesity Research Program at the Garvan Institute of Medical Research. He has spent his research career studying the link between insulin receptor signalling and glucose uptake into muscle and fat cells. While initially intending to study Medicine, David majored in Biochemistry at the University of New South Wales and then undertook a PhD at the Garvan. He undertook postdoctoral research at Boston University and then in St Louis, where he discovered and cloned insulin-regulated genes in muscle and fat cells. Since then, his research has focused on defining the signal pathways between insulin binding to its receptor and increased glucose uptake. In 1999, David was awarded the Glaxo Wellcome Medal recognising his contribution to his field, received the Australian Diabetes Society Kellion Award in 2007 and in that year was also made a Fellow of the Australian Academy of Science.

Ivan G. Jarrett

ESA foundation member (1958); awarded Life membership in 1982.

Ivan studied for his BSc at the University of Adelaide part-time while working as a cadet technician with CSIRO, completing his degree in 1939. His introduction to endocrinology began in 1946 when he realised that alloxan, a diabetogenic agent, could be applied to ruminant species, resulting in a successful experimental model and a number of visits to Harvard and lasting collaborations. In 1964, he was awarded a DSc from the University of Adelaide for his work on experimental diabetes and on the metabolic and endocrinological status of lambs. In 1972 he worked at the Brabraham Institute at Cambridge working on liver perfusions to study carbohydrate and fatty acid metabolism, and in 1978 as a Medical Research Professorial Fellow at Colorado State University at Fort Collins. He retired as Chief Scientific Officer of the CSIRO Division of Human Nutrition in 1980 after 41 years with that Organization, and then spent a number of years at the Queen Elizabeth Hospital in Adelaide as an Honorary Senior Research Fellow. Ivan was Secretary/Treasurer of ESA from 1964-66, Treasurer from 1966-70 and then President from 1970-72. Although long-distance travelling is now difficult, Ivan, at age 93, is very alert and maintains his own email account!

Stephen J. Judd OAM

ESA member since 1973; awarded Life membership in 2004.

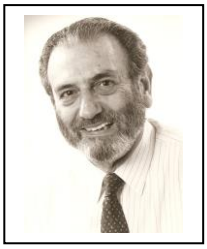
Stephen Judd graduated with MBBS from University of Adelaide in 1969 and completed his MD at the same University in 1979. He held a number of clinical positions at Queen Elizabeth Hospital, Adelaide, from 1969-73, moved to Sydney in 1974-76, before returning in 1977 to Flinders Medical Centre in Adelaide, where he is currently Associate Professor of Medicine. His research interests are the neuroendocrinology of chronic anovulation, particularly those related to changed energy status and fat metabolism. Between 1978 and 2002, Stephen held a number of positions in the ESA, including Secretary (1986–88) and Vice President (1988-90). He was also responsible for establishing the Clinical Weekend meetings and was actively involved in refining the format over a number of years. He has a major interest in Endocrine training and has been involved for many years with the RACP and its training committees. Although retired from hospital practice in 2004, Stephen remains chief examiner for the RACP and an editor of Clinical Endocrinology. In 2003, he was awarded a Medal in the Order of Australia (OAM) for his service to medicine, particularly in the field of endocrinology.

Richard G. Larkins AO

ESA member since 1970; awarded Life membership in 2003.

Richard Larkins graduated from the University of Melbourne with a MBBS in 1966. His research and clinical work were in the pathogenesis and complications of diabetes and in vitamin D and bone disease. He was ESA Secretary from 1978-1980, Vice-President from 1982-84 and President from 1984-86. Appointments held by Richard have included Chair of the National Health and Medical Research Council of Australia (1997-2000), President of the Royal Australasian College of Physicians (2000-02) and Dean of Medicine, Dentistry and Health Sciences at the University of Melbourne (1998-2003). He was made an Officer of the Order of Australia (AO) in 2002. He took up the appointment of Vice-Chancellor and President of Monash University in September 2003 and is also current Chair of Universities Australia and a member of the Prime Minister's Science, Engineering and Innovation Council.

Leslie Lazarus AO



ESA foundation member (1958); awarded Life membership in 1982.

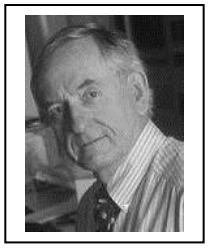
Leslie Lazarus is one of the foundation members of the Endocrine Society of Australia, was Vice President in 1972-74 and was appointed an Honorary Life Member in 1982. Born in Sydney in 1929, he was educated at Sydney Boys High School and the University of Sydney Medical School, from which he graduated in 1953. After general medical training and admission to the Royal Australasian College of Physicians, he was appointed a research fellow in endocrinology at the Middlesex Hospital Medical School, London, where he was mentored by Sir John Nabarro. In 1962, Les was appointed Staff Endocrinologist at St Vincent's Hospital, Sydney, the first full-time staff endocrinologist appointment in Australia. In 1968, he was appointed Director of the Garvan Institute of Medical Research at St Vincent's Hospital, Sydney, where he undertook research in diabetes and pituitary function. He was appointed an Officer in the Order of Australia in 1988.

Thomas B. Lynch OAM

ESA member pre-1971; awarded Life membership in post-1998.

Tom Lynch is a pathologist who is based in Rockhampton. He was awarded a Medal in the Order of Australia for service to Medicine in 1994.

T. John Martin AO



ESA member pre-1971; awarded Life membership in 2003; elected to Australian Academy of Science in 1998.

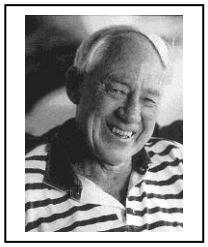
T.J. Martin is Emeritus Professor of Medicine, University of Melbourne and John Holt Fellow, St Vincent's Institute of Medical Research. He was Professor of Chemical Pathology at the University of Sheffield (1974-77), then Professor and Chairman of the University of Melbourne Department of Medicine until 1999. He was Director of St Vincent's Institute of Medical Research from 1988–2002. His research has been in bone cell biology, the mechanisms of action of hormones that influence bone and calcium metabolism, intercellular communication in bone and the differentiation of bone cells, and the effects of cancers upon the skeleton. He is a Fellow of the Royal Society and of the Australian Academy of Science, has been President of the International Bone and Mineral Society and Vice President of the International Cancer and Bone Society. He was ESA Honorary Secretary from 1970-72. He has received the Dale Medal in 1992 (UK), the Chemofux Research Prize in 1988 (Vienna), the William F Neuman Award in 1994 (USA), The Pieter Gaillard Award in 2003, the Ramaciotti Award in 2004, and the Gideon Rodan Award for Excellence in Mentorship, 2007. He has published more than 600 scientific articles and reviews and six books.

Len Martin

ESA foundation member (1958); awarded Life membership in 1982.

Len Martin graduated in zoology (ecology and entomology). He planned to become an insect physiologist but ended up pursuing a PhD in 1955 in Cliff Emmens' department on the mode of action of female sex hormones and their antagonists. He was a 24 year-old student who was one of the Foundation members when ESA was formed. In 1965 he joined the UK Imperial Cancer Research Fund researching the endocrine regulation of reproductive tract cell proliferation, embryo implantation, and the (anomalous) biological activity of anti-oestrogens, such as Tamoxifen. On his return to Australia in 1981, he joined the Department of Physiology and Pharmacology at the University of Queensland. Research on female sex-hormones and anti-hormones continued, with additional interest in how oestrogen and progesterone interact to regulate motility of the rodent myometrium. He retired as Reader in Physiology in 1996. He was member of the organising committees for the 1986 and 1994 Brisbane meetings. Len is also well known for his expertise in the biology and population dynamics of Australian flying-foxes, which have very unconventional reproductive cycles and anomalous sex-hormone levels. In this way, he has brought a unique undertanding that bridges classic zoology and endocrinology.

Frank I.R. 'Skip' Martin AM



ESA foundation member (1958); awarded Life membership in 1982.

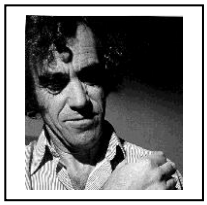
After studying Medicine, in 1957 Skip Martin became a Registrar at the Alfred Hospital under Pincus Taft and Bryan Hudson, who remained close friends and mentors. He attended the first meeting of ESA in May 1958, remembering some tension as Cliff Emmens, the Professor of Veterinary Physiology in Sydney, had little time for medicos. After time at Case Western Reserve University in Cleveland and Middlesex Hospital, UK, he was appointed Assistant Honorary Endocrinologist at the Royal Melbourne Hospital in 1961 and remained there until 1989. He was Physician to the ante-natal Diabetic Clinic at the Royal Women's Hospital from 1971-89. Skip's research interests were clinical diabetes, thyroid and pituitary disorders and he is an author on over 150 relevant publications. He believes he has been very fortunate to be involved in Endocrinology at a time when the whole field exploded with knowledge and techniques and having worked with many outstanding individuals who have made many significant contributions to the area. He was made a Member of the Order of Australia in 1995 for his service to medicine, particularly in the field of endocrinology and diabetes.

Ian C.A. Martin

ESA foundation member (1958); awarded Life membership in 1982.

Ian Martin joined ESA at its foundation as a PhD working under Cliff Emmens at the Department of Veterinary Physiology at the University of Sydney. Though not directly involved in endocrine research, most of the department staff were 'endocrinologists'. His research involved facets of endocrinology as part of reproduction in domestic and laboratory mammals, including spermatogenesis, oestrous cycle, fertilization, implantation, and lactation. Ian continued links with endocrinology from 1986 when his research became more genetics focussed. He was responsible for the care of the outbred colony of highly prolific mice (Quackenbush Swiss - 'QS'), the start of defining, over many years, the phenotypic characteristics of prolificacy, growth pre- and post-weaning, mammary development and lactation, relating these traits to quantitative trait loci within the mouse genome. He was also responsible for various inbred and congenic strains, including the development of some highly fecund lines. He is currently Honorary Research Associate in the Faculty of Veterinary Science, University of Sydney - a position he hopes to occupy, and enjoy, for a long time to come.

Ian R. McDonald



ESA foundation member (1958); awarded Life membership in 1982.

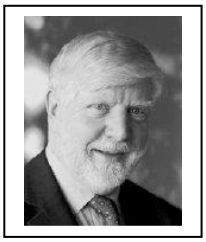
Ian McDonald completed his medical training at the University of Melbourne and following this, practised as a general practitioner in Heathcote, Victoria. He also spent some time in northern Tasmania in general practise, but was interested in moving into research. This he accomplished by working at the Florey Institute where he used his surgical skills to develop an *in situ* perfusion model of adrenal/renal function in sheep with Scoggins and Oddie. This was used to examine electrolyte control and hormonal influences in the renin-angiotensin system. When Monash University opened in the late 1960s, he moved to the Physiology Department, which is where he was very happy being able to choose his own research directions, focusing on marsupial and monotreme endocrinology, particularly water balance, stress physiology and, later, reproduction. The scope of Ian's work was very broad and his medical training seems to have given him a very good capacity for applying physiological and endocrine techniques to wildlife studies at a time when ecophysiology was quite a novel approach. Ian spent two sabbaticals with Don Bradshaw in WA, examining adrenal function in marsupials, with publications reporting, for instance, adrenalectomy in the quokka. Unfortunately, Alzheimer's overtook him, but he is remembered by many of his colleagues and former students as a very gifted experimental scientist and his knowledge of adrenal physiology profound.

Roger A. Melick

ESA foundation member (1958); awarded Life membership in 1982.

Roger Melick completed a MBBS at the University of Sydney in 1947, followed by a MD in 1972. He trained in Endocrinology with Fuller Albright in Boston and thereafter joined The Royal Melbourne Hospital as the third member of the foundation Department of Medicine. He was appointed Dean of the Clinical School in April 1979 but was forced to retire in 1986 because of cancer, dying in November of that year. Roger was particularly known for his kindness, consideration and empathy for both patients and students.

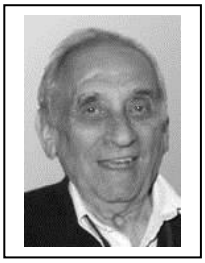
Frederick A.O. Mendelsohn AO



ESA member since 19xx; elected to Australian Academy of Science in 2003.

Fred Mendelsohn is Director of the Howard Florey Institute and R Douglas Wright Professor of Experimental Physiology and Medicine at the University of Melbourne. He held a Personal Chair in Medicine at the University of Melbourne until 1996 and was Senior Physician at the Austin and Repatriation Medical Centre. His research focuses on neuropeptides and their receptors. He initiated studies on the localisation of angiotensin receptor subtypes in the brain that triggered a large body of work in his own laboratory, and by groups around the world, on the local actions of these peptides in the brain. More recently his group discovered that the AT4 receptor is a transmembrane spanning enzyme that has dramatic effects in memory and learning. He was a Chairman of the Angiotensin Gordon Conference USA (1998), member of the Wills Committee on Health and Medical Research Strategic Review (1998-2000) and the Eccles Lecturer to the Australian Neuroscience Society (2001). He is immediate Past-President of the Australian Neuroscience Society and was made an Officer in the Order of Australia in 2004.

Solomon Posen



ESA member since 1961; awarded Life membership in 1992.

Solomon Posen, a past Secretary (1974-76) and President (1976-78) of ESA, retired from the Department of Medicine at Sydney University in 1990 and from clinical practice and teaching in 2000. However, he continues to attend scientific meetings, Grand Rounds and the weekly Endocrine Journal Club at RNSH and reviews contributions to scientific journals in the field of bone and mineral metabolism. Since his retirement, Sol has been writing his four-volume 'opus', an annotated anthology titled *The Doctor in Literature* (details on Amazon, Google and the publishers' websites). The first volume, *Satisfaction or Resentment*, appeared in 2005 (Radcliffe Publishing, Oxford, UK). The second volume, subtitled *Private Life*, came out in 2006. The third volume (*Career Choices*) is in the final stages of preparation. Sol and Jean have been married for 53 years. Both spend a good deal of time helping to look after their seven grandchildren.

Marilyn B. Renfree

ESA member since 1968; awarded Life membership in 2004; elected to Australian Academy of Science in 1997.

Marilyn Renfree graduated from the Australian National University with a PhD in 1972, and a DSc in 1988. Her research has contributed to understanding marsupial fauna and their ingenious alternative solutions to reproduction. Her laboratory is known internationally for its innovative studies of these unique Australian animals, especially in the field of sexual differentiation. Marilyn is a Laureate Professor of the University of Melbourne, an ARC Federation Fellow, the Ian Potter Chair of Zoology and Deputy Director of the ARC Centre of

Excellence for Kangaroo Genomics. She was elected a Fellow of the Australian Academy of Science in 1997 and of the Australian Institute of Biology in 1999, awarded the Gottschalk Medal of the Australian Academy of Science in 1980, the Whitley Book award in 1987 with Hugh Tyndale-Biscoe for their textbook *Reproductive Physiology of Marsupials* and the Mueller Medal of ANZAAS in 1997. In 2000 she was awarded the Gold Conservation Medal of the San Diego Zoological Society (USA). Marilyn was Chairman of the Australian Society for Reproductive Biology from 1999-2002 and Chair of the Australian Antarctic Division's ethics committee from 1997-2003. She has written one book, edited two others and co-authored around 260 papers.

Terry J. Robinson AM
ESA foundation member (1958); awarded Life membership in 1982.

Terry Robinson was born in 1919 in the UK, but was raised in Western Australia. He studied Agricultural Science at The University of Western Australia (UWA). After graduating, he joined the Royal Australian Navy as an anti-submarine officer. Between 1945-47, he returned to UWA, where he worked on 'clover disease' that caused severe infertility in sheep. He won a prestigious Hackett Scholarship and completed a PhD at Cambridge. Thereafter, Terry went to the University of California at Davis where he defined how oestrogen affects breeding behaviour, before returning to the University of Melbourne in 1951 as a senior lecturer. In 1956, Terry took up the post of foundation professor of Animal Husbandry at The University of Sydney. He built up the fledgling Department of Animal Husbandry, such that on his retirement in 1984 he left a thriving entity. He was one of the founding fathers of the Australian Society for Reproductive Biology and its first Chairman from 1969-73. Amongst many international committees he served on, he was on the Standing Committee of the International Congress on Animal Reproduction (1966-82) and the FAO conference in Rome (1963). He made his most outstanding research contribution in the field of artificial reproductive technology, particularly in sheep. This was recognized by the award of a Doctor of Science from Cambridge University (1973) and him being made a Member of the Order of Australia. Terry died in 2004.

Vicki R. Sara
Elected to Australian Academy of Science in 2001.

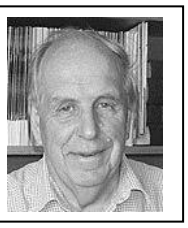
Vicki Sara returned to Australia in 1993 following a research career at the Karolinska Institute in Stockholm. She was appointed as a foreign Professor with the Karolinska in 1995. She was awarded the Rolf Luft medal in 1993 for excellence in endocrine research by the Karolinska and also received the Sir John Eccles Award from NHMRC in 1994. Vicki was awarded the Centenary Medal in 2003, was awarded an Honorary Doctor of Science by the University of Southern Queensland in 2004, the Victoria University in 2005 and Honorary Doctor of the University, Queensland University of Technology in 2006. She was elected Chancellor of the University of Technology Sydney in 2004, and appointed Chief Executive Officer of the Australian Research Council in July 2001. From September 1997 to June 2001 she was the Chair of the Council and a member of the Prime Minister's Science Engineering and Innovation Council (PMSEIC), and the CSIRO Board. She is a Fellow of the Australian Academy of Science, and the Australian Academy of Technological Sciences and Engineering. In 2006, Vicki was appointed Consul General for Sweden in Sydney.

Rodney P. Shearman AO
ESA member since pre-1971; awarded Life membership in 1992.

Rodney Shearman was Professor and Head of the Department of Obstetrics and Gynaecology at the University of Sydney for 25 years. He studied Medicine at the University of Sydney and became a HMO at the Royal Prince Alfred Hospital in 1951. Having experienced the challenge of treating adrenal insufficiency during pregnancy, he spent three years at the MRC Clinical Endocrinology Research Unit in Edinburgh. He built on this expertise on his return to Australia where he set up his own laboratory at the University of Sydney in the early 1960s, resulting in him completing a MD degree in 1965.The Obstetrics and Gynaecology Department he headed became one of the outstanding units in Australia, with research interests and at the forefront in infertility, contraception, prenatal diagnosis, gynaecological oncology and sociological determinants of maternal and child health. He became President of the Australian Society for Medical Research in 1963 and the Royal Australasian College of Obstetricians and Gynaecologists in 1979-81. He served on various NHMRC Committees and the Human Pituitary Advisory Committee (1972-84) and was advisor to various international organisations such as the WHO Human Reproduction Programme and the Ford Foundation. He was made an Officer of the Order of Australia in 1991 and died in November, 1993, aged 65.

Roger V. Short AM

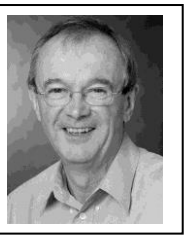
Elected to Australian Academy of Science in 1984.



Roger Short originally trained as a vet in Britain but switched to reproductive biology. After coming to Australia in 1982 as a Professor of Physiology at Monash University, holding a Personal Chair in Reproductive Biology from 1982-95. He is currently a Professorial Fellow in the Department of Obstetrics and Gynaecology at the University of Melbourne (appointed in 1996). Roger has published over 300 scientific papers in a wide variety of scientific journals. His major research interest has been the evolution of human reproduction, where he has shed new light on the causes of the current human population explosion. He has been actively involved in contraceptive research and development for the past two decades, currently focusing on developing new ways to stop HIV transmission in developing countries. He has also been keenly interested in the scientific and ethical debates surrounding therapeutic cloning and stem cells, and in 1999 he and Professor Malcolm Potts of the University of California, Berkeley published *Ever Since Adam and Eve: The Evolution of Human Sexuality* (Cambridge University Press), an illustrated account of the evolution of our ideas about human reproduction, from Aristotle to the present day. It has been translated into Italian, Spanish, Korean, and is due to appear in Chinese this month. He was elected a Fellow of the Australian Academy of Science in 1984 and is a Member of the Order of Australia.

Evan R. Simpson

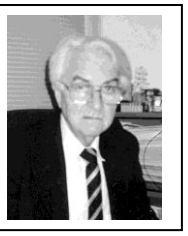
ESA member since 1998; ESA Council member since 2000; elected to Australian Academy of Science in 2006.



Evan Simpson is recognised as the world leader in the area of oestrogen biosynthesis. Over the last 25 years, his research has had a major impact in a variety of fields, including embryology, endocrinology, reproduction, tumour biology, and human physiology and pathophysiology. As Head of the Sex Hormone Biology Group and the Victorian Breast Cancer Research Consortium Laboratory at Prince Henry's Institute, his current work is directed toward understanding the relationship between disfunction of metabolism and carcinogenesis, discovering new and better therapies for breast cancer prevention and treatment, as well as understanding the complexities of oestrogen action in both males and females. Evan has received numerous awards, including the Trans-Atlantic Medal and the Asia and Oceania Medal from the UK Society for Endocrinology, the President's Scientific Achievement Award from the US Society for Gynaecological Investigation, the Roy O. Greep lectureship from the US Endocrine Society, and the Brinker Award from the Susan Komen Breast Cancer Foundation.

Alf W. Steinbeck

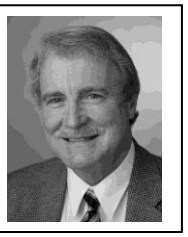
ESA foundation member (1958); awarded Life membership in 1982.



Alf Steinbeck was introduced to endocrinology after meeting Bryan Hudson on a visit from Brisbane. When the ESA was set up following inputs from Bryan, Hal Breidahl, Ian Thomas and Roger Mellick, Alf became a Foundation Member. His active introduction to Clinical Endocrinology was at Hammersmith Hospital in London with luminaries such as RIS Bayliss, CL Cope and Russell Fraser. They were the days when cortisone was being used initially in Clinical Medicine and its promising effects in treating Addison's Disease. He also worked on a new method of measuring 17-hydroxycorticosterone in plasma that allowed Addison's disease to be safely diagnosed. Back in Australia, he was appointed the second full-time academic in the Faculty of Medicine, University of Queensland, as Reader in Medicine. When the Faculty of Medicine was established at the University of NSW, he was asked to apply for the Associate Professor of Medicine. He began a laboratory in the original hospital for essentially adrenal hormones and began double isotope dilution derivative assays of steroid hormones. Alf took up a Fulbright Scholarship (Senior Research Scholar) and this enabled him to work with Dr Ralph E Peterson at Cornell Medical School on aspects of adrenal hormones and their assays. At the same time a clinical service in endocrinology was undertaken, with the attendant difficulties of two strong endocrine services already offering service in that area of Sydney.

Jim R. Stockigt

ESA member since 1968; awarded Life membership in 2003.



Jim Stockigt came to Australia at age seven and, after education at Trinity Grammar and Scotch College, graduated from the University of Melbourne in 1961, with the prize in clinical surgery. Training in Melbourne at the Alfred hospital and the nascent Monash Department of Medicine at Prince Henry's hospital was followed by five years at the University of California, San Francisco and St Mary's hospital, London. Mentors included Pincus Taft, Fran Ganong and Edward Biglieri. He was director of Endocrinology at the Alfred for 18 years and was president of ESA in 1990-92, after being Secretary in 1988-90. He has served on the editorial boards of JCEM and Endocrinology and is the author of over 150 reviewed papers and book chapters in the thyroid and renin fields. He is currently in Endocrine Practice at Epworth Hospital, with special interest in Thyroid Disorders, is Professor of Medicine at Monash University and Emeritus Consultant Endocrinologist at the Alfred Hospital, Melbourne. Recent effort has been directed towards improvement of Australian pharmaceutical product and consumer medicine information, so far with limited success. Hobbies include bassoon, baroque and modern,

and he has recently published the definitive collection of arias with obligato bassoon from baroque and classical opera and oratorio.

Roderick F.A. Strang
ESA foundation member (1958); awarded Life membership in 1982.
Rod Strang graduated in medicine from the University of Melbourne in 1939, where apart from academic excellence he was a gifted sportsman, destined for an Olympic career in skiing if World War II had not intervened. After graduation, Rod became a Resident Medical Officer at Prince Henry's Hospital before joining the Royal Australian Army Medical Corps in 1941, rising to the rank of Major. After the war, he pursued postgraduate study at Leeds and Manchester before returning to Australia, completing his RACP membership in 1947. He returned to Manchester Royal Infirmary to study rheumatic diseases, leading to him setting up a rheumatology practice in Melbourne. He was also Honorary Physician at Prince Henry's Hospital until 1962 and Honorary Rheumatologist at Royal Melbourne Hospital until 1973. As well as being a foundation member of ESA, Rod helped found the Australian Rheumatology Association and was very active in the Arthritis Foundation. He passed away in 2002 aged 87 years.

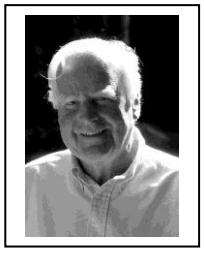
E. Pincus Taft
ESA foundation member (1958); awarded Life membership in 1979.

Pincus Taft immigrated to Australia with his family in about 1914. He completed a shortened wartime medical course in 1942 and then served as a captain in Army Medical Corps from 1944-47. Upon returning to the Royal Melbourne Hospital, he focused in endocrinology and diabetes and was the appointed a Cleveland Exchange Fellow at Western Reserve University in 1950-51. After time at King's College Hospital in London, he took up the appointment of Honorary Physician to the diabetes clinic at the Royal Melbourne in 1951, establishing a diabetic clinic at the Royal Women's' Hospital the year after. In 1957, with Roger Melick, he established an endocrine clinic at the Royal Women's. In 1963 (head from 1965-74), he was appointed Director of the Diabetic and Metabolic Unit at the Alfred Hospital and became an associate professor in Biochemistry at Monash University, holding both positions until 1978, but continuing as a consultant for some years. At the Women's' Hospital, from 1965-74 he was in charge of the endocrine clinic in which the early use of gonadotrophin-stimulated ovulation for infertility was conducted. Along with Bryan Hudson and Basil Hetzel, he was one of the prime movers resulting in the foundation of ESA, was its first Secretary-Treasurer (1958-60) and later President (1968-70). He was a founding member of the Australian Diabetes Society, President (1978-80) and foundation chairman of the RACP specialist advisory committee in Endocrinology (1976-78). He was a superb clinician and teacher but had a continuing scientific curiosity about clinical problems particularly in diabetes. He died of lung cancer in 1993.

Ian D. Thomas
ESA foundation member (1958); awarded Life membership in 1982.

Ian Thomas studied medicine at the University of Sydney, where he graduated with a MBBS in 1946. Despite his initial resident training being affected and delayed by illness, he then had registrar appointments at Sydney Hospital and Royal North Shore Hospital (RNSH), passing his MRACP exam in 1952. In 1954, he passed the MRCP exam and subsequently went to Boston and worked with Astwood and Raven. In 1957, he returned to RNSH to work with Rundle and Oddie, where he made contributions to the rational use of radioiodine in thyroid disease and medical management of thyroid eye disease. He subsequently was appointed as an HMO at RNSH where he continued his clinical activities with emphasis on Endocrinology. During his tenure at RNSH, he was involved in teaching both undergraduates as well as post graduate trainees in endocrinology. He retired from the active staff in 1985. Ian was a foundation member of ESA and was Secretary/Treasurer of the Society from 1962-64. He died in 2005.

Geoffrey Tregear AO
ESA member since 1968; elected to Australian Academy of Science in 2008.



Geoff Tregear is the Deputy Director of the Howard Florey Institute at The University of Melbourne. He is a graduate of The University of Melbourne (BSc, 1962) and Monash University (PhD, 1969). Geoff is an NHMRC Senior Principal Research Fellow and has professorial appointments in the Department of Biochemistry and Molecular Biology at The University of Melbourne and the Department of Pharmacology at Monash University. He was awarded a Member of the Order of Australia in 2007 and elected a Fellow of the Australian Academy of Science in 2008. Geoff is a peptide and nucleic acid chemist with a particular interest in peptide synthesis. His early work was with the development of solid-phase radioimmunoassay and the chemistry of parathyroid hormone and calcitonin. Geoff's current research interest is with the relaxin family of peptide hormones. He is the leader of the Neuropeptide team at the Florey Institute. Geoff was elected to the Council of the Endocrine Society of Australia in 1986 and was Secretary of the Society from 1990-92.

Victor M. Trikojus OBE

ESA foundation member (1958); awarded Life membership in 1968; elected to Australian Academy of Science in 1954.

Known as 'Trik' to many of his friends and colleagues, Victor Trikojus studied chemistry at Sydney University and then did a DPhil at Oxford University. After returning to his *alma mater*, in 1943 he became Chair of the Biochemistry Department at the University of Melbourne. Trik's lasting area of research was thyroid hormones, with his department involved in the isolation, separation, identification and quantitative analysis of thyroxine, its precursors and products. A consequence of this basic research was the improvement of diagnostic procedures involved in thyroid function and monitoring patient status once conventional treatments had commenced. In addition to being the long-serving department head, he fulfilled several senior roles within the University. He also spent several years as a member of the Medical Research Advisory Committee for NHMRC. Trik was elected a Fellow of the Australian Academy of Science in the year of its establishment (1954). He died in 1985.

John R. Turtle AO

ESA member since 1967; awarded Life membership in 2003.

John did his medical training at University of Sydney, with MBBS in 1960 and MD in 1969. He spent several years at Royal Prince Alfred Hospital (1960-64), before pursuing overseas Fellowships at the Washington University School of Medicine in St. Louis and then at Hammersmith Hospital in London. On his return to Australia, he has held a number of clinical appointments at the University of Sydney, various hospitals in Sydney and was the head of the Department of Endocrinology at Royal Prince Alfred, commencing in 1971. He has also been on central Committees of the Australian Drug Evaluation Committee, International Diabetes Federation, RACP and founded the Australian Diabetes Society with Hal Breidahl. He was on ESA Council from 1972-78 and Vice-President from 1975-76. His research has centred on diabetes mellitus at all levels from patho-physiology, insulin action, intermediary metabolism, pathogenesis of complications, epidemiology, psychopathology, education and record systems, with over 300 publications. He was made an Officer in the Order of Australia (AO) in 1992 and an Officer in the Order of Fiji (OF) in 1999.

Robert Vines

ESA foundation member (1958); awarded Life membership in 1982.

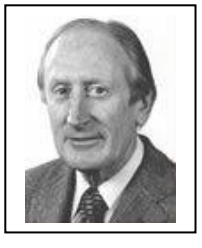
Bob Vines graduated with Honours from the University of Sydney in 1943 and enlisted in the Royal Australian Army Medical Corps (1944-47), serving in Bougainville. After training at Great Ormond Hospital for Children, London, he practised as a Consultant Physician at Royal Alexandra Hospital for Children, Sydney from 1952-86. In 1965 he worked in Baltimore with Dr Lawson Wilkins. Bob was one of the fathers of Paediatric Endocrinology in Australia, being instrumental in establishing the Australian Human Pituitary Program with the first child being treated with extracted growth hormone in 1963. He was Chairman of the Human Pituitary Advisory Committee for 7 years. He was co-author of a very successful manual for diabetes management. He was the first President of APEG. A literary man of impeccable integrity, he is best remembered as a quiet achiever who never sought the limelight, but who had an enormous influence on paediatric endocrinology in Australia. He died in 1986.

Alan L. Wallace

ESA foundation member (1958); awarded Life membership in 1982.

Alan joined CSIRO as a research scientist in the 1950s, working in what was later known as the Division of Animal Production. His initial research was with Ken Ferguson on the endocrinology of wool growth. He prepared sheep hormones, including sheep growth hormone (GH) for injection into sheep and went on to prepare human GH. Later, he studied sheep metabolism, principally using immunoassays of sheep GH and insulin, which he helped develop. Alan made a detailed investigation of the effect of sheep GH preparations on sheep and studied thyroxin levels in sheep across a wide area of Australia. He also performed research in other fields, including endocrine studies of cattle. In his final years at CSIRO, Alan concentrated on researching fetal mortality in sheep with the aim of developing an immunoassay to detect early pregnancy in sheep.

H. Norman Wettenhall



ESA foundation member (1958); awarded Life membership in 1982.

Norman Wettenhall studied medicine at the University of Melbourne and graduated in 1940. He worked as a HMO at the Royal Melbourne Hospital and then as a Surgeon Lieutenant with the Royal Australian Navy for two years before being discharged due to ill health. He returned to the Royal Children's Hospital, from which his long-standing interest in paediatric endocrinology arose. Apart from a two year period working at The Hospital for Sick Children in London, he spent the remainder of his career at the Royal Children's Hospital, until he retired in 1980. Norman was noted for his pioneering achievements in paediatric endocrinology. He was the first of these specialists in Australia and established the Endocrine Clinic at the Children's in 1962. He was a

foundation member of ESA and established the Australasian Paediatric Endocrine Group (APEG). In 1964 he was the second physician in Australia to prescribe growth hormone and instigated many clinical trials of hormone use to control short or tall stature in children. Norman passed away in November, 2000, age 85.

F.H. Hales Wilson
ESA foundation member (1958); awarded Life membership in 1982.
After growing up in Mudgee, NSW, Hales Wilson studied at the University of Sydney, graduating with a BSc in 1921. He became interested in Medicine, working as a Chemistry and Physics demonstrator and then tutor at St. Paul's College while he completed a MB in 1928. He subsequently became a member of RACP in 1946 and a Fellow in 1953. After his MB, he spent a year at Sydney Hospital and then almost five years at the Coast Hospital in Sydney. Following four years in general practice, Hales joined the Australian Army Medical Corps in 1942 and saw service in Australia, New Guinea and Borneo. After the War, he held a number of honorary staff appointments at several Sydney hospitals from 1946-64 and thereafter was Emeritus consultant at these institutions. He was heavily involved at Royal North Shore Hospital, where he was Chairman of Medical Staff for a period as well as on the Council of the Medical Association of the hospital. Among other appointments, he was on the Council of the Royal Flying Doctor Service of Australia. In addition to his physician duties and associated teaching, he also lectured in pharmacology and therapeutics in 1947-48 at the University of Sydney, pending the appointment of a full-time professor, and also taught therapeutics there until 1960. His clinical interests were infectious diseases and the medical complications of diabetes and pregnancy. At the age of 65, he moved to South Australia and joined a group practice in Port Pirie. He was involved in a major car accident in 1975 where his wife was killed and which he suffered major injuries. Nevertheless, he was able to eventually resume independent living and working until he was 85, passing away four years later in 1989.

Marelyn Wintour-Coghlan
ESA member since 1960; awarded Life membership in 2003; Elected to Australian Academy of Science in 2004.

Marelyn Wintour studied Science at the University of Queensland, on a State Open Scholarship (top 25 matriculants), majoring in physiology and biochemistry. She moved to Melbourne (1960) to take up a demonstrator's position, in the Department of Physiology, University of Melbourne. During the next 12 years of full-time teaching, she married (John Coghlan), had four children, as well as earning an MSc (1964), and a PhD (1972). By 1980 she had been promoted to Reader; she was awarded a DSc in 1988. In 1990 she became a Senior Principal Research Fellow, NHMRC, at the Howard Florey Institute. In 2003 she was recruited to Monash University, Department of Physiology, and became Honorary Professor there for 2005-07. Currently she is Honorary Professor in the Department of Anatomy and Developmental Biology at Monash. In her career to date, she has over 230 scientific publications (publishing as EM Wintour), largely on the endocrinology of the pregnant mother and developing fetus, and the effects of short periods of stress in early pregnancy causing hypertension in the adult offspring. She has served on the Council of the International Union of Physiological Sciences, and helped promote physiological sciences in Africa and South America. She was an early member of ESA, and elected to Life Membership in 2002. In 2004 she was elected as a Fellow of the Australian Academy of Science, one of only 20 females to be so honoured in the first 50 years of this Academy.

Ken N. Wynne
ESA foundation member (1958); awarded Life membership in 1982.

Ken Wynne graduated with a BSc from the University of Sydney in 1948. He initially worked on steroid metabolism in relation to sheep reproduction for the CSIRO at a facility then located in Prospect just outside Sydney. Using his new-found skills as a steroid biochemist, he moved to the Cancer Institute, NSW, attached to the Prince of Wales Hospital at Randwick and for the next 20 years studied steroid metabolism in humans, particularly in relation to breast cancer. In 1970, with the help of a windfall from the Opera House Lottery Commission, he moved to Cambridge, UK, and completed a PhD on steroid metabolism. On returning to Australia in 1974, he worked at the Peter MacCallum Cancer Institute in Melbourne, continuing his research on breast cancer. In 1977 he moved to the Ewen Downie Metabolic Unit at the Alfred Hospital in a co-joint appointment between the Alfred and Prince Henry's Hospital with Jim Stockigt and John Funder as chief investigators. He continued to work on steroids and steroid metabolites particularly in relation to novel hypertensinogenic compounds, but expanded his interests to opiate activity of caffeic acids, metabolites of thyroxine as potential thyroid hormone antagonists and the role of free fatty acids in regulating hormone levels in serum. He retired from active laboratory work in 1989.

INFORMATION FOR DELEGATES & PRESENTERS

Venue layout - session locations

The registration desk is on the You Yangs level, as is the main John Batman plenary theatre and the trade display. The trade display will not open until Tuesday. Breaks will be taken in the trade area from Tuesday. This level is known as **LEVEL 2.**

The level above this is called the Bellarine level. A number of breakout rooms are on this level and the posters, breaks on Monday only, and the dinner will all be on this level. This level is known as **LEVEL 4.**

The level below the registration level is in two parts. All of the Corryong Breakout Rooms are accessed by the escalators at the far end of the trade display. The Latrobe Theatre is at the bottom of the escalators directly across from the registration desk – turn hard left at the bottom of the escalators. This is also the level used to access the front door on Spencer Street and has a number of small session rooms – the Otways and Howqua rooms – on it. This level is known as **LEVEL 1.**

The Speaker Preparation Room

The speaker preparation room is adjacent to the main John Batman theatre and is opposite the registration desk. All rooms are connected by a computer network to this room and that is where speakers should load their talks. There are both PCs and Macintosh computers in the speaker preparation room. You should report with your presentation on a USB or CD at least 2 hours before your session. Technicians will be in attendance in the room to assist the loading of talks.

Registration

The Full Delegate Registration fee includes:

* all delegate materials (name tag, satchel, abstract book)
* lunches, Monday, Tuesday and Wednesday
* morning teas from Tuesday until Thursdday
* afternoon teas from Monday until Wednesday

The Day Registration fee includes:

* all delegate materials (name tag, satchel, abstract book)
* lunch for the specified day
* morning tea for the specified day
* afternoon tea for the specified day

Name Tags

Delegates are required to wear their name tags to all scientific and catered sessions. Uniformed security is in attendance on the doors of the exhibition area and name tags are required to gain access.
Delegates should note that within their name tag pouch are any specific function tickets they have ordered as well as a second smaller name tag which should be placed in the holder on your satchel.

Poster Viewing

Delegates with posters can find the correct position for their poster by finding the appropriate abstract number on the display panels. The panels are set up on the Bellarine level. The program provides your abstract number which is how you find you placement position. **Posters can remain on display all of Monday and Tuesday and must be removed by lunchtime on Wednesday.** During formal poster discussions (on Tuesday evening), the presenters should attend their poster to answer questions and meet colleagues with similar research interests. The posters are grouped in categories and refreshments will be served.

Social Functions

- The **Welcome Function** is in the Melbourne Convention and Exhibition Centre on the Monday evening from 4:30pm. Light refreshments and drinks will be served and the function is complimentary for all registration types. The function will take place amongst the posters on the Bellarine Level.

- The **ESA Government House Reception** is at Government House from 6:30-8:30pm on Monday night. **This is a ticketed function – access can only be gained by those with a pass sent by the Governor.** Buses have been organized and will commence leaving from the elevated driveway entrance on the level 1 of the convention centre (the same level as the LaTrobe Theatre). Please note it will not be permissible to take your

satchel into Government House. Please use the small name tag provided to identify your own satchel and leave it in the bus.

- The **Women in Endocrinology Function** will be on the Tuesday starting at 6pm in **Otway 2**. Canapes and drinks will be served. **This is a ticketed function** and they must be purchased in advance.

- The Tuesday night **Student Function** is being held at Star Bar, The Star Hotel, 160 Clarendon St, South Melbourne. Delegates who have already purchased a ticket should find their ticket with their registration papers on arrival. The ticket cost includes your meal, entertainment and limited drinks. The function begins at 7:30pm and dress is neat casual. To get to the Star Bar, exit from the convention centre onto Spencer St, turn right. As you walk over the Yarra River, you are now on Clarendon Street. You need to walk for 5-10 minutes to get to the Star Bar. It is on the same side of the road you are already on and about a block after you have walked under the freeway bridge. **This is a ticketed function** and they must be purchased in advance.

- The **Conference Dinner** will be held on **Wednesday evening** onsite in the Bellarine Room. Pre-dinner drinks will be served from 7:00pm for a 7:30pm start. Dress is neat casual. **This is a ticketed function** and they must be purchased in advance.

The Trade Passbook Competition - Amongst delegate's registration papers is a "Trade Pass Book" entry form. The form has spaces for the stamp or signature of each of the trade exhibitors. Once you have collected 20 stamps or signatures, place your completed form in the entry box at the registration desk by the end of afternoon tea on the Wednesday. The prize for the first completed entry form drawn from the box is a Western Digital 320GB Essential Passport Pocket Hard Drive donated by ASN Events. *Trade representatives are not eligible to enter the competition.

Insurance - The hosts and organisers are not responsible for personal accidents, any travel costs, or the loss of private property and will not be liable for any claims. Delegates requiring insurance should make their own arrangements.

Smoking - is not permitted in the venue.

Mobile Phones - Please ensure they are turned off during any session you attend.

Message Board - will be available at the registration desk.

Occasional Meetings - A number of special meetings and functions have been called by various interested parties throughout the conference. Those involved and uncertain of which room they should be in will be able to obtain guidance from the registration desk.

Disclaimer - The hosts, organisers and participating societies are not responsible for, or represented by, the opinions expressed by participants in either the sessions or their written abstracts.

Monday, 25 August 2008

11:00am

Opening Mark Hedger, Convenor 2008 11-11:10am; John Batman Theatre

Governor Professor David de Kretser

Leon Bach (President ESA)

11:15am

ESA Pincus Taft Lecture

11:15-12:15pm; John Batman Theatre

Chair: David Healy

William F Young Jnr

Adrenal Conundrums: The Adrenal Incidentaloma *abs#001*

SRB/ANZPRA Orals - Placental function

11:15-12:30pm; Bellarine 2

Chairs: Jeff Keelan, Kirsty Pringle

11:15am **Amy Chui**
Homeobox gene *DLX3* Regulates Forskolin Induced Trophoblast Differentiation *abs#201*

11:30am **Hassendrini Peiris**
Differential dietary regulation of placental and muscle myostatin in a transgenerational rat model of maternal under-nutrition *abs#202*

11:45am **Peter Mark**
Partial progesterone withdrawal during late gestation increases placental expression of 11ß-HSD1 in the rat *abs#203*

12:00pm **Kimberley Crawford**
Proteomic analysis of the effluent from perfused placental cotyledons identifies proteins associated with Pre-eclampsia *abs#204*

12:15pm **Padma Murthi**
Homeobox gene *TGIF* is increased in human idiopathic fetal growth restriction. *abs#205*

SRB Orals - Growth factors and signalling

11:15-12:30pm; Bellarine 3

Chairs: Sarah Robertson, Craig Harrison

11:15am **Vanessa Eede**
Differential regulation of activin and inhibin production by interleukin 1 (IL1), transforming growth factor ß1 (TGFß1) and protein kinase C (PKC) in the Sertoli cell and granulosa cell *abs#206*

11:30am **Wendy Ingman**
Effect of TGF ß1 on mammary gland development is dependent on cellular source of gene expression *abs#207*

11:45am **Brandon Menzies**
Absence of GH-R exon 3 in marsupials and monotremes argues for a eutherian specific origin and fetal specific purpose of this domain *abs#208*

12:00pm **Mai Sarraj**
The absence of betaglycan affects Sox9 m RNA expression at the time of sex determination in a mouse model *abs#209*

12:15pm **Jinwei Chung**
Fibroblast growth factor 9 (FGF9) in the developing marsupial *abs#210*

12:15pm

ESA Lunch 12:30-1:30pm; Bellarine 6-7

12:30pm

SRB Founders Lecture 12:30-1:30pm; John Batman Theatre

Chair: Michael Holland

Jeffrey Robinson

Fetal autonomy to health across generations *abs#002*

ESA Meet the Expert 12:30-1:30pm, Bellarine 4-5, Collect lunch first

Chair: Ken Ho **Session sponsored by Ipsen**

David Cook - Combination Medical Therapy For Acromegaly *abs#003*

1:30pm

SRB Lunch Bellarine 6-7, finish 2:30PM

ESA Orals – Novartis Junior Scientist Award Finalists 1:30-3:00pm; John Batman Theatre

Chairs: Leon Bach, Marianne Elston **Session sponsored by Novartis Oncology**

1:30pm **Kathryn Backholer**
Melanocortin stimulation of reproductive neuroendocrine function *abs#101*

1:45pm **Caroline Jung**
Cortisol response to intravenous dexamethasone in patients with Cushing's syndrome compared to normal and overweight subjects, with and without type 2 diabetes *abs#102*

2:00pm **Sue Lau**
Dysregulation of hypothalamic neuropeptide expression and metabolic rate in offspring of diabetic pregnancy. *abs#103*

2:15pm **Prue Cowin**
Differential Patterns of DNA Methylation in the Prostate and Testis Following *In Utero* Endocrine Disruptor Exposure *abs#104*

2:30pm **Peter Simm**
Molecular mechanisms of steroid and growth factor regulation of growth plate chondrogenesis *abs#105*

2:45pm **Kavitha Iyer**
Role of SLIRP in androgen receptor signalling in prostate cancer *abs#106*

2:30pm

SRB Symposium - Lifestyle and environmental influences on oocytes and offspring

Chairs: Robert Norman, Marie Pantaleon 2:30-4:30pm; Bellarine 2

2:30pm **Michael Davies**
Lifestyle, Environment and Reproductive Function *abs#004*

3:00pm **Rebecca Robker**
Effects of obesity on oocytes and embryos *abs#005*

3:30pm **David Gardner**
Regulation of embryonic and fetal development through maternal protein intake and by amino acid exposure in vitro *abs#006*

4:00pm **Gayle Jones**
Oocyte gene expression profiling and the relationship to developmental competence *abs#007*

SRB Orals - Implantation placentation gestation

2:30-4:30pm; Bellarine 3

Chairs: Larry Chamley, Peter Mark

2:30pm **Belinda Hardman**
Proteomic Identification of Caldesmon as one of the Physiological Substrates of Proprotein Convertase 6 during Decidualization *abs#211*

2:45pm **Neil Borg**
Specific targeting of uterine proprotein convertase 6 (PC6) facilitates the development of dual function contraception *abs#212*

3:00pm **Natalie Hannan**
Chemokines: Key players at the maternal-fetal interface *abs#213*

3:15pm **Alicia Filby**
Altered placental gene expression following disruption of mitochondrial metabolism in mouse embryos *abs#214*

3:30pm **Brendan Waddell**
Placental expression of uncoupling protein-2 is reduced by glucocorticoid treatment in late pregnancy: implications for placental oxidative stress *abs#215*

3:45pm **Chelsea Stoikos**
Activin A regulates trophoblast cell adhesion: implications for uterine receptivity and embryo implantation *abs#216*

4:00pm **Jeffrey Keelan**
Inflammatory stimulation of human decidual cells by periodontopathic bacteria *abs#217*

4:15pm **Sharon Qin**
Homeobox gene *HLX* is expressed in choriodecidua mesenchymal stem cells and regulates their ability to migrate. *abs#218*

3:00pm

ESA Orals - Clinical Case Reports

3:00-4:30pm; John Batman Theatre

Chairs: Mathis Grossmann, Cathy Choong

3:00pm **Caroline Badam**
Hyperthyroid related pulmonary hypertension *abs#107*

3:15pm **Ashley Fong**
Relapsing Remitting Hypophysitis *abs#108*

3:30pm **Sybil McAuley**
A case of adult hypophosphatasia: induction of osteoblast response by teriparatide *abs#109*

3:45pm **Paul Lee**
Transplant recipients on the edge of the hypocalcaemia abyss *abs#110*

4:00pm **Izabella Czajka-Oraniec**
The severe skeletal and metabolic effects of the long-term estrogen deprivation in an aromatase deficient woman. *abs#111*

4:15pm **Malgorzata Brzozowska**
Hypercalcemia caused by a carcinoid tumour -case presentation *abs#112*

ESA Orals - Pregnancy/Parturition/Lactation

3:00-4:30pm; Bellarine 4

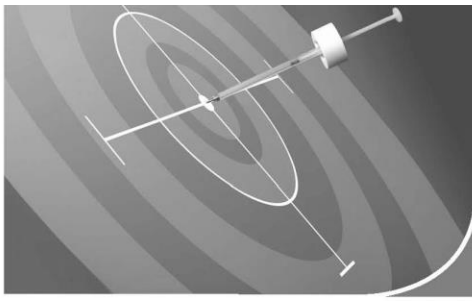
Chairs: Kathy Gatford, Vicki Clifton

3:00pm **Ursula Alexandra Ciller**
Variations in the isoform composition of equine chorionic gonadotrophin across early gestation in the horse. *abs#113*

3:15pm **Carolyn Mitchell**
Chronic suppression of Prostaglandin Endoperoxide H Synthase(PGHS-2) expression in the human amnion by glucocorticoids in vivo *abs#114*

3:30pm **Elizabeth Rivalland**
The influence of predator stress on the activity of the hypothalamic-pituitary-adrenal (HPA) axis of lactating animals *abs#115*

3:45pm **Annika Sjoeholm**
Reproductive experience increases the responsiveness of the hypothalamus to prolactin in female rats *abs#116*



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Somatuline Autogel can now be administered at home by patients or their carers.*[1]

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Reference

1. Somatuline Autogel Product Information, 30 July 2007.

PBS Information: Authority required (Section 100). Acromegaly; Symptoms of carcinoid syndrome. Refer to PBS schedule for full information.

Before prescribing please refer to full Product Information, which is available from Ipsen Pty Ltd.

Somatuline® Autogel®: lanreotide as acetate in a pre-filled syringe (60, 90 & 120 mg). **Indications**: the treatment of acromegaly when circulating growth hormone and IGF-1 levels remain abnormal after surgery and/or radiotherapy or in patients who have failed dopamine agonist therapy; the treatment of symptoms of carcinoid syndrome associated with carcinoid tumours. **Contraindications**: lactation; hypersensitivity to lanreotide or related peptides. **Precautions**: may experience hypoglycaemia or hyperglycaemia (monitor blood glucose levels); may reduce gall bladder motility (recommend gall bladder echography); exclude presence of obstructive intestinal tumour; monitor kidney and liver function; may reduce heart rate in patients with an underlying cardiac problem (monitor heart rate). Not recommended for use in children. See full PI for further information. **Adverse Events**: common to very common: fatigue, headache, dizziness, sinus bradycardia, hypoglycaemia or hyperglycaemia, anorexia, diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, flatulence, cholelithiasis, bilirubin increase, injection site reaction. See full PI for further information. **Dose**: Acromegaly: for first time treatment the starting dose is 60 mg every 28 days; for patients previously treated with Somatuline LA every 14, 10 or 7 days, the starting dose is 60 mg, 90 mg or 120 mg respectively every 28 days. Dosage should be adjusted according to GH and/or IGF-1 response. Patients well controlled on lanreotide can be treated with 120 mg every 42–56 days. Carcinoid syndrome: 60 to 120 mg every 28 days, adjusted according to symptomatic relief. **Administration**: deep subcutaneous injection in the superior external quadrant of the buttock (healthcare professional or carer); or the upper, outer thigh (self-administration). **Storage**: 2°C–8°C. **Date of TGA approval**: 30 July 2007.

For further information about Somatuline Autogel, contact Ipsen Pty Ltd:
T (03) 8544 8100 **F** (03) 9562 5152 **E** info@ipsen.com.au Suite 6, 40 Montclair Avenue, Glen Waverley, VIC 3150 Australia All correspondence to: PO Box 820, Glen Waverley, VIC 3150 Australia

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lanreotide

4:00pm **Sarah Holdsworth-Carson**
The effect of labour status on human gestational tissue mRNA and protein expression of PPAR isoforms *abs#117*

4:15pm **Mary Wlodek**
Growth restriction is transmitted to the next generation fetus with compensation in early postnatal life *abs#118*

ESA Orals - Breast/Prostate/Cancer

3:00-4:30pm; Bellarine 5

Chairs: Wayne Tilley, Renea Taylor

3:00pm **Judith Clements**
Direct progesterone receptor and indirect androgen receptor interactions with the kallikrein-related peptidase 4 gene promoter in breast and prostate cancer. *abs#119*

3:15pm **Emily Payne**
A new profile for the Thr^{201}Met isoform of human aromatase: effects on functional responses to inhibitors and substrate and product concentrations *abs#120*

3:30pm **Goswin Meyer-Rochow**
Denaturing high performance liquid chromatography (DHPLC) detection of SDHB, SDHD and VHL germline mutations in phaeochromocytoma *abs#121*

3:45pm **Preetika Balanathan**
Tumor suppressive activity of inhibin-α subunit is altered during prostate cancer progression *abs#122*

4:00pm **Renea Taylor**
Altered Differentiation Of Mammary Stem Cells By Prostatic Mesenchyme; Cross-Talk Between Ectoderm- And Endoderm-Derived Tissues *abs#123*

4:15pm **Kara Britt**
Parity induced breast cancer protection against breast cancer – an estrogen sensitive issue? *abs#124*

4:30pm

ESA - SRB Reception/Poster Viewing

4:30-5:30pm; Bellarine 6-7

Function sponsored by Novartis Oncology

6:30pm

ESA Government House Reception (by invitation)

6:30-8:30pm; Government House

Buses will depart from level 2 of the conference centre from 6pm.

8:00am

ESA Breakfast Career Workshop for Junior Scientists

8:00-9:30am; Bellarine 4

Chair: Helen MacLean

Light Breakfast provided

8:00am **Adrian Herington**
Tips for Developing Your CV for the Fellowship Systems *abs#008*

8:25am **Gail Risbridger**
How to write a paper that will get published *abs#009*

8:50am **Leon Bach**
The basics of grantsmanship *abs#010*

ESA Breakfast Career Workshop for Junior Clinicians

8:00-9:30am; Bellarine 5

Chair: Elke Hendrich

Light Breakfast provided

8:00am **Bu Yeap**
Academic medicine and clinical endocrinology for junior clinicians. *abs#011*

8:25am **Murray Gerstman**
Private Practice *abs#012*

8:50am **Jane Holmes-Walker**
Work life balance *abs#013*

8:30am

RCRH SRB Midcareer Researcher Award

8:30-9:00am; Bellarine 1-2

Chair: Robert Norman

Session sponsored by Research Centre for Reproductive Health (Adelaide)

Sarah Robertson
Seminal Plasma and Male Factor Signalling for Female Tolerance of Pregnancy *abs#014*

9:00am

SRB Merck Serono Young Investigator Award

9:00-10:30am; Bellarine 1-2

Chair: Michael Holland

Session sponsored by Merck Serono

9:00am **Gabrielle Wilson**
Parkin co-regulated gene (Pacrg) is an axonemal protein involved in sperm tail and ependymal cell function and is a candidate primary ciliary dyskinesia gene *abs#219*

9:15am **Gayathri Rajaraman**
Homeobox Gene *HLX* is a regulator of HGF/c-met Mediated Trophoblast Migration. *abs#220*

9:30am **Lenka Vodstrcil**
Localisation of relaxin receptors (Rxfp1) in the uterine artery and the effects of blocking circulating relaxin on passive mechanical wall properties in the uterine artery of late pregnant rats *abs#221*

9:45am **Tu'uhevaha Kaitu'u-Lino**
A new role for activin in endometrial restoration after menses *abs#222*

10:00am **Premila Paiva**
Interleukin-11 inhibits human trophoblast invasion via STAT-3 and not MAPK, indicating a likely role in the decidual restraint of trophoblast invasion during placentation *abs#223*

10:15am **Christine Yeo**
Disruption of Bi-directional Oocyte-Cumulus Paracrine Signalling During Oocyte In Vitro Maturation Reduces Subsequent Mouse Fetal Survival *abs#224*

9:30am

ESA Clinical/Basic Symposium - Endocrine Cancer

9:30-11:30am; John Batman Theatre

Chairs: Diana Learoyd, Christine Clarke

Session sponsored by Sanofi-Aventis

9:30am **William Young**
Malignant Pheochromocytoma and Paraganglioma *abs#015*

10:00am **Geoffrey Lindeman**
BRCA1 and 2 in hereditary breast cancer - molecular genetics going mainstream *abs#016*

10:30am **John Burgess**
Multiple Endocrine Neoplasia Type 1: Cancer Syndrome or Chronic Disease ? *abs#017*

11:00am **Duncan Topliss**
Thyroid carcinoma *abs#018*

ESA/AACB Joint Clinical Symposium - Immunoassays: tackling the next 50 years

Chairs: Jim Stockigt, Ee Mun Lim

9:30-11:30am; Bellarine 4

Session sponsored by Dorevitch

9:30am **Andrew Wootton**
Vitamin D measurement: A for effort but B or C for performance. *abs#019*

10:00am **Greg Ward**
Lighting up the Laboratory. *abs#020*

10:30am **Jennifer Wong**
Limitations and future developments in assayng thyroglobulin *abs#021*

11:00am **Howard Morris**
International Standardisation of Immunoassays *abs#022*

ESA / Neuroendocrinology Australasia Joint Basic Symposium - Energy Expenditure: the other side of the obesity equation

9:30-11:30am; Bellarine 5

Chairs: Brian Oldfield, Greg Anderson

Session sponsored by Novo Nordisk and DSL Australia

9:30am **Sheila Collins**
Kinases and transcription targets in adipocyte cell fate and thermogenesis *abs#023*

10:00am **Andrew Butler**
Investigation of the coupling of nutrient intake with energy metabolism by melanocortins. *abs#024*

10:30am **Belinda Henry**
Identifying novel sites of thermogenesis: profiling post-prandial responses in sheep *abs#025*

11:00am **William Blessing**
Ultradian Rhythms In Basal Metabolic Rate *abs#026*

10:30am

SRB Morning Tea

10:30-11:00am; Youyangs - Atrium (exhibition)

Function sponsored by Sanofi-Aventis

11:00am

SRB Orals - Fertilization and Embryo

11:00-12:00pm; Bellarine 1-2

Chairs: Megan Mitchel, Darryl Russell

11:00am **Chris O'Neill**
Characterization of a diverse secretome generated by the mouse preimplantation embryo. *abs#225*

11:15am **Matthew Dun**
Characterisation of a putative mouse sperm-zona pellucida receptor complex *abs#226*

11:30am **Larry Chamley**
Eggs with a surprise: the “sperm-specific” protein SPRASA is also expressed in the oocyte. *abs#227*

11:45am **Peter Kaye**
Proteasomal activity during mouse preimplantation development *abs#228*

SRB Orals - Male Reproductive Tract

11:00-12:00pm; Bellarine 3

Chair: Mark Hedger

11:00am **Helen Martyn**
Identification of Transforming Growth Factor beta2 (TGF-ß2) and its receptors TGF-ßRI and TGF-ßRII in the possum (Trichosurus vulpecula) prostate: evidence of seasonal changes. *abs#229*

11:15am **Melissa Gamat**
Megalin, RAP and Nkx3.1 expression in the developing reproductive tract of a marsupial, the tammar wallaby *abs#230*

11:30am **Gerard Tarulli**
Sertoli cells de-differentiate in men after chronic gonadotrophin suppression *abs#231*

11:45am **Catherine Itman**
Developmentally regulated activin A signal transduction by Sertoli cells is required for normal mouse testis development *abs#232*

11:30am

ESA Morning Tea

11:30-12:00pm; Youyangs - Atrium (exhibition)

Function sponsored by Sanofi-Aventis

12:00pm

ESA Harrison Plenary Lecture

12:00-1:00pm; John Batman Theatre

Chair: Leon Bach

Colin Ward
Structural insights into ligand-induced activation of the insulin receptor. *abs#027*

SRB Lunch

12:00-1:00pm; Youyangs - Atrium (exhibition)

Function sponsored by Novo Nordisk

SRB Meet the Professor

12:10-1:00pm; (collect lunch first) Bellarine 5

1:00pm

ESA Lunch

1:00-2:00pm; Youyangs - Atrium (exhibition)

Function sponsored by Novo Nordisk

ESA Meet the Expert

1:10-2:00pm; Bellarine 1-2, collect lunch first

Chair: Warrick Inder

David Hurley - Hypopituitarism *abs#028*

2:00pm

ESA Orals - CSL Biotherapies Bryan Hudson Clinical Award Finalists & Clinical Orals

Chairs: Donald Cameron, Morton Burt

2:00-4:00pm; John Batman Theatre

The first three session presenters are Award Finalists

Session sponsored by CSL Biotherapies

2:00pm **Ann McCormack**
Low MGMT Expression is Associated with Response to Temozolomide in Aggressive Pituitary Tumours *abs#125*

2:15pm **Emma Hamilton**
Structural decay of bone in males treated with androgen deprivation therapy for prostate cancer *abs#126*

2:30pm **Bu Yeap**

Lower testosterone levels predict incident stroke and TIA in older men. The Health In Men Study. *abs#127*

2:45pm **Lucia Gagliardi**
ACTH-Independent Macronodular Adrenal Hyperplasia: A Familial Disease? Detection of Early Manifestations. *abs#128*

3:00pm **Carolyn Allan**
Testosterone Therapy Increases Sexual Desire in Aging Men with Low-Normal Testosterone Levels and Symptoms of Androgen Deficiency *abs#129*

3:15pm **Debra Renouf**
STOP Fracture study: Southern Health Osteoporotic Fracture Screening Project *abs#130*

3:30pm **Carolyn Fennell**
Pharmacokinetics and Pharmacodynamics of Depot Testosterone: Randomized Cross-over Clinical Trial of Injectable vs Implantable Testosterone in Androgen Deficient Men *abs#131*

3:45pm **Flora Ip**
Trough serum testosterone levels predict the development of polycythemia in men with organic androgen deficiency receiving testosterone replacement therapy *abs#132*

ESA Orals - Metabolism/Obesity/GH

2:00-4:00pm; Bellarine 5

Chairs: Evan Simpson, David Kennaway

2:00pm **Kristy Brown**
LKB1 - the link between obesity and breast cancer in postmenopausal women *abs#133*

2:15pm **Qiang Sun**
The Effect of GHS on the Transient Outward K^+ Current in Rat Ventricular Myocytes *abs#134*

2:30pm **David Kennaway**
Genetic disruption of rhythmicity in peripheral tissues of mice alters adipocyte function *abs#135*

2:45pm **Chen Chen**
In vitro regulation of membrane ion channels by adiponectin in GFP-GH transgenic mouse pituitary somatotropes *abs#136*

3:00pm **Kesha Rana**
Increased adiposity in androgen receptor knockout (ARKO) mice due in part to decreased physical activity with no change in food consumption *abs#137*

3:15pm **Jenny Chow**
The generation of a doxycycline-inducible, tissue-specific aromatase-expressing mouse *abs#138*

3:30pm **Andy Chang**
Stanniocalcin 2 knock-out mice are larger and leaner *abs#139*

3:45pm **Michelle Van Sinderen**
Sex hormones: A role in adiposity and insulin resistance. *abs#140*

ESA/SRB Orals - Male Reproduction

2:00-4:00pm; Bellarine 4

Chairs: Paul Farnworth, Liza O'Donnell

2:00pm **Laura Tubino**
A role for activin/inhibin in mouse gonocyte relocation and proliferation *abs#233*

2:15pm **Peter Liu**
Genetic and hormonal control of gender preference and sociability of XXY mice *abs#141*

2:30pm **Zeliha Sahin**
Hedgehog signalling components in adult rat testis spermatogonial cells *abs#234*

2:45pm **Keely McNamara**
Increased response to exogenous estradiol in mice with prostate epithelial androgen receptor inactivation *abs#142*

3:00pm **Elspeth Gold**
Activin C antagonizes activin A *in vitro* and over-expression leads to prostate pathologies *in vivo* *abs#235*

3:15pm **Alicia Mulligan**
Direct leptin actions on GnRH neurons effect fertility in male but not female mice *abs#143*

3:30pm **Sarah Meachem**
Effects of Long Term Recombinant Rat Follicle-Stimulating Hormone Replacement on the Restoration of Spermatogenesis after Chronic Suppression of Gonadotrophins in Adult Rats *abs#236*

3:45pm **Peter Stanton**
Proteomic expression analysis reveals androgen-regulated functions in rat pachytene spermatocytes. *abs#244*

SRB Symposium - Reproductive Strategies 'viva la difference' 2:00-3:30pm; Bellarine 1-2

Chairs: Theresa Hickey, Kirsty Walters

2:00pm **David Abbott**
Developmental Origins of Adult Female Hyperandrogenic Reproductive Function *abs#029*

2:30pm **Frank Grutzner**
Higher-order genome organisation in platypus and chicken sperm and repositioning of sex chromosomes during mammalian evolution *abs#030*

3:00pm **Erik Wapstra**
Too hot too handle? environmental effects, climate change, reproduction and offspring phenotypes in lizards *abs#031*

4:00pm

Afternoon refreshments 4:00-6:00pm; Bellarine 6-7
Function sponsored by Sanofi-Aventis

ESA Poster Session, See listing at end of Program 4:00-6:00pm; Bellarine 6-7

SRB Poster Session, 4:00-6:00pm; Bellarine 6-7

5:00pm

ESA AGM 5:00-6:00pm; Bellarine 4

6:00pm

SRB Post Doc Function 6:00-6:30pm; Bellarine 1-2

ESA Women in Endocrinology Function 6:00-7:00pm; Otway 2
Function sponsored by DSL Australia

7:30pm

ESA-SRB Student Function 7:30-11:00pm; Star Bar, The Star Hotel
Function sponsored by Dorevitch Pathology

Wednesday, 27 August 2008

8:30am

ESA Japan-Australia Plenary Lecture
8:30-9:30am; LaTrobe Theatre

Chair: Jeffrey Zajac

Shigeaki Kato
Function of nuclear sex hormone receptors in target tissues *abs#032*

SRB RFD Award Lecture
8:30-9:30am; Bellarine 4-5

Chair: Jeremy Thompson, Sharon Mortimer **Session sponsored by CSIRO/RFD**

Hamish Fraser
Regulation and manipulation of angiogenesis in the ovary and endometrium *abs#033*

9:30am

ESA-SRB Morning Tea
9:30-10:00am; Youyangs - Atrium (exhibition)

10:00am

ESA Clinical/Basic Symposium - Androgens in women
10:00-12:00pm; Bellarine 4-5

Chairs: Carolyn Allan, Theresa Hickey

10:00am **Helen MacLean**
Physiological actions of androgens in females: lessons from knockout mouse models *abs#034*

10:30am **Anne Corbould**
Sex and fat: androgens and adipose tissue metabolism in women *abs#035*

11:00am **Susan Davis**
A role for androgen therapy in women? *abs#036*

11:30am **Bronwyn Stuckey**
Androgens in PCOS *abs#037*

SRB Orals - Female reproductive tract
10:00-12:00pm; Corryong 3

Chairs: Guiying Nie, Caroline Gargett

10:00am **Jacqueline Donoghue**
Endometrial vessel morphology is altered following progestin treatment in a mouse xenograft model. *abs#238*

10:15am **Jane Fenelon**
Expression of PAF-R and p53 in the endometrium during entry into and reactivation from diapause in the tammar wallaby. *abs#239*

10:30am **Kirsty Walters**
AR-mediated androgen actions are essential for normal mouse uterine growth and development but not implantation and embryo development *abs#237*

10:45am **Jane Girling**
Reduced Endometrial Angiogenesis during Early Pregnancy in Relaxin-Deficient Mice *abs#240*

11:00am **Kee Heng**
Relaxin and INSL3 receptors and their signaling in primary human myometrial cells. *abs#241*

11:15am **Mashitah Shikh Maidin**
Reproductive performance of Australia Cashmere goats supplemented with lupin grain. *abs#242*

11:30am **Sarah Robertson**
Interleukin-6 is an essential regulator of parturition and perinatal viability in mice *abs#243*

11:45am **Yu Soh**
Effects of Relaxin Treatment on Hyaluronic Synthase Expression in the Cervix of Pregnant Relaxin-Deficient ($Rln^{-/-}$) Mice *abs#244*

SRB-ESA Joint Basic Symposium - Germ cell development

10:00-12:00pm; Bellarine 3

Chairs: Marilyn Renfree, Eileen McLaughlin

10:00am **Keith Jones**
The First Meiotic Division in Oocytes is the Nemesis of Fertility for Women in the 21st Century *abs#038*

10:30am **Josephine Bowles**
Regulation of the mitosis to meiosis switch and germ cell fate in the mouse embryo *abs#039*

11:00am **Patrick Tam**
Allocation and navigation of primordial germ cells during early mouse embryonic development *abs#040*

11:30am **Vincent Harley**
Animal models of germ cell sex reversal *abs#041*

ESA Basic Symposium - Renin-angiotensin system, function & dysfunction

Chairs: Marelyn Wintour-Coghlan, David Torpy

10:00-12:00pm; Corryong 1-2

10:00am **Michael McKinley**
Thirst in angiotensin-deficient mice *abs#042*

10:30am **Siew Yeen Chai**
Insulin-regulated aminopeptidase is the specific binding site for angiotensin IV – role in the brain *abs#043*

11:00am **Richard Weisinger**
The role of angiotensin II in obesity and insulin resistance *abs#044*

11:30am **Mark Cooper**
The role of the renin-angiotensin system in diabetic vascular complications. *abs#045*

12:00pm

ESA - SRB Lunch

12:00-1:00pm; Youyangs - Atrium (exhibition)

ESA Meet the Expert

12:10-1:00pm; Bellarine 4-5m, collect lunch first

Chair: Cherie Chiang

Session sponsored by Eli Lilly

John Bilezikian – Primary Hyperparathyroidism: A lesson in how a disease can change by just observing it! *abs#072*

1:00pm

ESA Orals - Clinical

1:00-3:00pm; Bellarine 4-5

Chairs: Creswell Eastman, Gerry Fegan

1:00pm **Huy Tran**
Detailing the Evolution of Interferon-α2ß Induced Thyroiditis in Patients with Hepatitis C Infection *abs#145*

1:15pm **Nicolette Hodyl**
Relationship between placental glucocorticoid receptor expression and fetal growth in pregnancies complicated by asthma *abs#146*

1:30pm **Roger Smith**
The Onset of Human Labor is Associated with a Fall in the Ratio of Progesterone to Estrogens and an Increase in the Estriol to Estradiol Ratio *abs#147*

1:45pm **Nigel Stepto**
Aberrant skeletal muscle mitochondrial responses to exercise in overweight women with PCOS *abs#148*

2:00pm **Thuy Vu**
Evaluating patients presenting with severe hypotonic hyponatraemia *abs#149*

2:15pm **Sue Lynn Lau**
25-hydroxyvitamin D levels inversely correlate with HbA1c in a gestational diabetes clinic

population *abs#150*

2:30pm **Mathis Grossmann**
Lack of association between early spontaneous preterm delivery and thyroid autoantibodies *abs#151*

2:45pm **Paul Lee**
Relationship between obesity and vitamin D: is vitamin D supplementation a sliding scale based on body size? *abs#152*

ESA Orals - Nuclear Hormone Receptors

1:00-3:00pm; Corryong 3

Chairs: George Muscat, Ulle Simanainen

1:00pm **Emily Lam**
Ligand- and Salt- Specific Induction of Mineralocorticoid Receptor-Mediated Cardiovascular Injury *abs#153*

1:15pm **Tammy PS Pang**
Investigating non-classical signalling pathways of the androgen receptor *abs#154*

1:30pm **Morag Young**
Purification and Characterization of the Human Mineralocorticoid Receptor. *abs#155*

1:45pm **Omar Akram**
Androgenic biopotencies of nutraceutical-derived steroids in a yeast-based androgen bioassay *abs#156*

2:00pm **Michael Pearen**
Regulatory Crosstalk Between beta-Adrenergic and Nuclear Hormone Receptor Signalling in Skeletal Muscle *abs#157*

2:15pm **Stephen Wong**
Novel mechanism of catecholamine metabolism by glucocorticoids via activation of a sulfotransferase in mice *abs#158*

2:30pm **Nicole Lee**
The roles of *Odc1* and *Tceal7* in skeletal muscle hypertrophy *abs#159*

2:45pm **Timothy Cole**
Overlapping progenitor cell differentiation defects in the developing lung of GR and CREB-deficient mice *abs#160*

SRB Orals - Spermatogenesis and sperm

1:00-3:00pm; Corryong 1-2

Chairs: Moira O'Bryan, David Sharkey

1:00pm **Hongshi Yu**
Aristaless-related homeobox gene is involved in early development and spermatogenesis in mammals *abs#245*

1:15pm **David Jans**
Developmental switches in male sex determination and spermiogenesis; importin-chromatin remodeling factor interaction *abs#246*

1:30pm **Vinali Dias**
BMP signalling in the induction of germline precursors from mouse embryonic stem cells *in vitro* *abs#247*

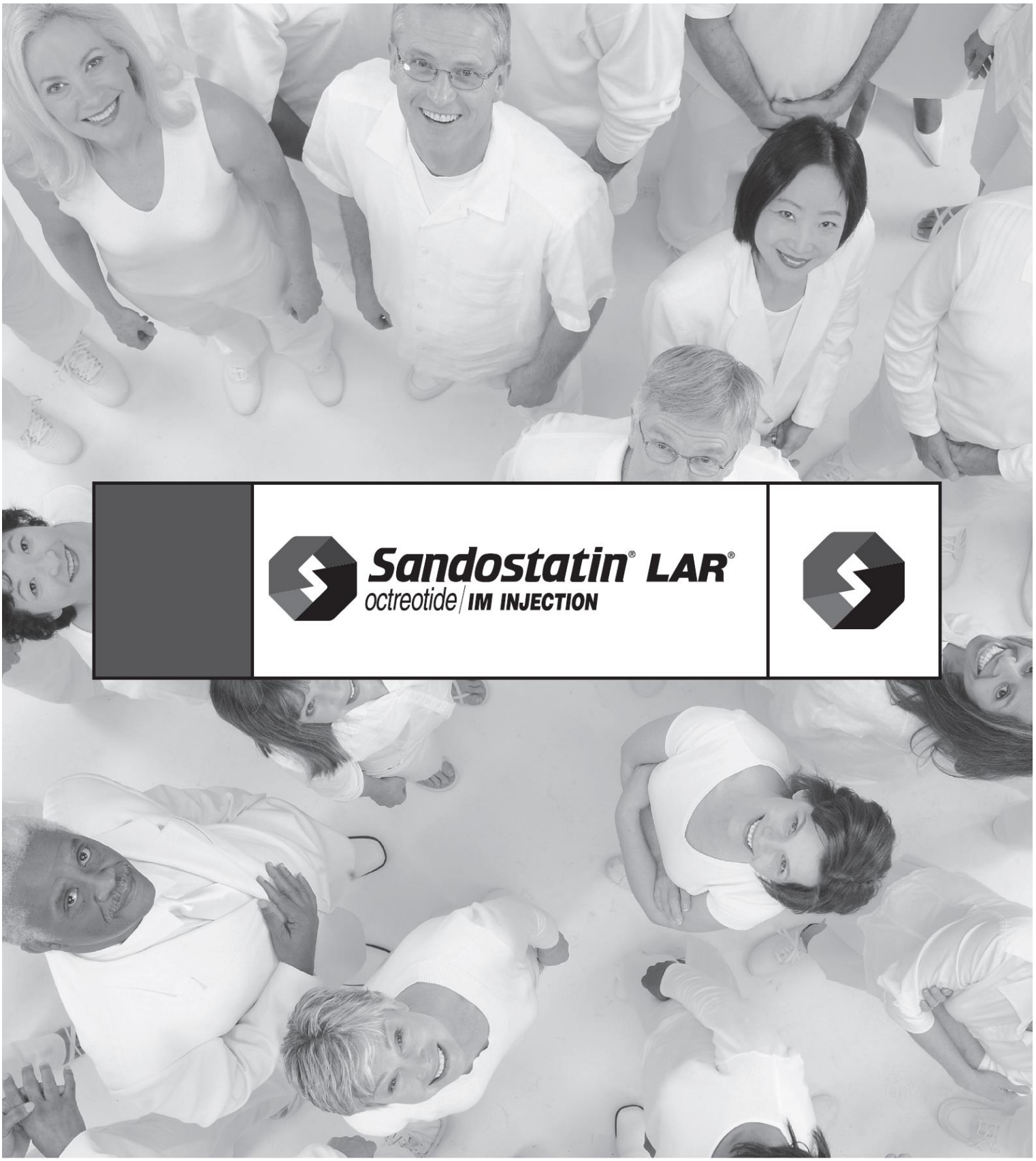
1:45pm **Geoffry De Iuliis**
Oxidative stress and DNA damage in human spermatozoa *abs#248*

2:00pm **Sridurga Mithraprabhu**
Regulated expression of KIT protein in juvenile and adult germ cells of the rodent testis *abs#249*

2:15pm **Jennifer Ly-Huynh**
Importin α2-recognised testis cargoes; relevance to spermatogenesis. *abs#250*

2:30pm **Muren Herrid**
Production of donor-derived live lambs following testis germ cell transplantation *abs#251*

2:45pm **Shiva Prakash**
Regulated Nuclear Import of TATA Binding Protein Associated Factor 9 (TAF9) in Spermatogenesis *abs#252*



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ESA/SRB Orals - Female Reproduction

1:00-3:00pm; Corryong 4-5

Chairs: Ann Drummond, Chris Grupen

1:00pm **Kelly Walton**
Regulation of inhibin heterodimer assembly and secretion by residues within the pro-domain *abs#161*

1:15pm **Marie Pantaleon**
Toxic effects of hyperglycaemia arise from induced O-linked glycosylation in early mouse embryos *abs#253*

1:30pm **Yao Wang**
Extra-ovarian expression and actions of Growth Differentiation Factor (GDF)-9 *abs#162*

1:45pm **Maxime Sasseville**
Evidences for a novel cAMP-phosphodiesterase expressed in the bovine ovarian follicle. *abs#254*

2:00pm **Yogeshwar Makanji**
In vivo and *in vitro* bioactivities of human recombinant inhibin A and inhibin B *abs#163*

2:15pm **Seng Liew**
Hormonal manipulation on the phenotype of ArKO female mice *abs#255*

2:30pm **Jeremy Smith**
Evidence that kisspeptin neurons in the arcuate nucleus are central processors for generating the preovulatory luteinizing hormone surge in ewes *abs#164*

2:45pm **Hannah Brown**
Ovarian lymphatic vascular development is hormonally regulated and Adamts1-dependent *abs#256*

3:00pm

SRB Afternoon Tea

3:00-3:30pm; Youyangs - Atrium (exhibition)

ESA/Australian Academy of Science Cinical/Basic Symposium - Rising Stars

Chairs: Mark McLean

3:00-5:00pm; Bellarine 4-5

3:00pm **Jenny Gunton**
HIF-1α (Hypoxia Inducible Factor 1 α) is required for normal ß-cell function *abs#046*

3:30pm **Craig Harrison**
Redefining the Biological Roles of Inhibin A and B *abs#047*

4:00pm **Peter Liu**
Translating testicular axis physiology to clinical practice *abs#048*

4:30pm **Louise Hutley**
New Fat Cell Generation in Adult Humans – Regulation and Intervention *abs#049*

ESA Clinical/Basic Symposium - Obesity: causes, effects and management

Chairs: Ian Martin, Brian Oldfield

3:00-5:00pm; Corryong 1-2

Session sponsored by GSK

3:00pm **Joseph Proietto**
The genetics of obesity: lessons from mouse models *abs#050*

3:30pm **Matthew Sabin**
Management of Childhood Obesity *abs#051*

4:00pm **Michael Cowley**
Leptin Resistance in Melanocortin Circuits *abs#052*

4:30pm **Paul O'Brien**
Obesity, Type 2 Diabetes and weight loss surgery *abs#053*

3:30pm

SRB Orals - Oocytes and embryos / ART

3:30-5:30pm; Corryong 3

Chairs: Kylie Dunning, Peter Kaye

3:30pm **Yan Li**
Activation of a calcium-activated chloride channel by paf is required for normal preimplantation mouse embryo development in vitro *abs#257*

3:45pm **Georgia Kafer**
Differential expression of H2A and H3 variant histones in mouse preimplantation embryos and R1 ES cells *abs#258*

4:00pm **Stephen Frankenberg**
Pluripotency genes in a marsupial, the tammar wallaby. *abs#259*

4:15pm **Firas Albuz**
Synergistic effects of cAMP modulating agents in pre-IVM and in IVM on bovine cumulus and oocyte functions. *abs#260*

4:30pm **Sarah Wakefield**
Disruption of mitochondrial function in the blastocyst alters expression of the chromatin remodeler ATRX *abs#261*

4:45pm **Kathryn Gebhardt**
Human cumulus cell gene expression as a marker of clinical embryo grade *abs#262*

5:00pm **Zamira Gibb**
Substitution of skim milk with bovine serum albumin in a stallion semen diluent *abs#263*

5:15pm **Danielle Hickford**
Primordial germ cell specification in a marsupial, the tammar wallaby. *abs#264*

SRB Symposium - New concepts in contraceptive development

Chairs: Eva Dimitriardis, Sarah Meachem 3:30-5:30pm; Corryong 4-5

3:30pm **Robert Aitken**
Dual purpose contraceptives: targeting fertility and sexually transmitted disease *abs#054*

4:00pm **Brett Nixon**
Molecular basis for sperm-egg interaction; prospects and problems for contraceptive development *abs#055*

4:30pm **Catherine Herbert**
Development of a contraceptive approach for the management of highly-valued marsupial populations in Australia: Science, efficacy and ethics *abs#056*

5:00pm **Eva Dimitriadis**
Targeting endometrial cytokines as a non-hormonal contraceptive strategy *abs#057*

5:15pm

ESA Plenary Lecture

5:15-6:15pm; LaTrobe Theatre

Chair: Peter Ebeling

John Bilezikian
Primary Hyperparathyroidism *abs#058*

5:30pm

SRB AGM

5:30-6:30pm; Corryong 4-5

7:00pm

ESA-SRB Conference Dinner

7 for 7:30pm; Bellarine 7

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Thursday, 28 August 2008

7:00am

Trade Breakfast Session - An Update in the Management of Thyroid Cancer

Light breakfast provided — 7:20-8:20am: Corryong 1-2

Session sponsored by Genzyme

8:30am

ESA Plenary Lecture

8:30-9:30am; Bellarine 1-2

Chair: Mark McLean

Lynnette Nieman

Is hypercortisolism pathologic in the absence of Cushing's syndrome? *abs#059*

SRB Symposium - Molecular control of reproductive tissue function

Chairs: Kate Loveland, Darryl Russell — 9:00-10:30am; Bellarine 3

9:00am **Richard Ivell**
The biology of the testis hormone INSL3 *abs#060*

9:30am **Moira O'Bryan**

10:00am **Charles Allan**
FSH and female reproductive ageing: ovarian function and premature infertility in transgenic FSH mice *abs#062*

9:30am

ESA Morning Tea

9:30-10:00am; Youyangs - Atrium (exhibition)

10:00am

ESA/ANZBMS Joint Clinical/Basic Symposium - Osteoporosis: mechanisms and therapies

10:00-12:00pm; LaTrobe Theatre

Chairs: Richard Prince, John Eisman — **Session sponsored by Servier**

10:00am **Matthew Brown**
Progress (at last) in osteoporosis genetics *abs#063*

10:30am **Peter Ebeling**
Bisphosphonate use in osteoporosis, benefits and risks *abs#064*

11:00am **Shigeaki Kato**
Estrogens mediate osteoprotective effects by controlling osteoclast life cycle *abs#065*

11:30am **John Bilezikian**
Osteoporosis: Therapeutic concepts for the present and the future *abs#066*

ESA Basic Symposium - Approaches to investigating endocrine gene function in the post-genome era

Chairs: Tim Cole, Peter Fuller — 10:00-12:00pm; Bellarine 1-2

10:00am **Douglas Hilton**
New approaches to study gene function in vivo *abs#067*

10:30am **Emma Whitelaw**
The Role of Epigenetics in the Determination of Phenotype *abs#068*

11:00am **Bridget Mabbutt**
Structural genomics: generating new approaches for structure definition *abs#069*

11:30am **Klaus Matthaei**
Genetic manipulation of mice: Providing all the answers or just more problems? *abs#070*

10:30am

SRB Morning Tea

10:30-11:00am; Youyangs - Atrium (exhibition),

11:00am

SRB Orals - Ovarian folliculogenesis

11:00-1:00pm; Bellarine 3

Chairs: Ann Drummond, Ray Rodgers

11:00am **Kirsten McTavish**
Increased FSH activity increases primordial follicle reserve and enhances preovulatory follicle survival in transgenic FSH female mice. *abs#265*

11:15am **Maree Bilandzic**
Loss of betaglycan expression contributes to malignant properties of human granulosa tumour cells. *abs#266*

11:30am **Ileana Kuyznierewicz**
A role for transforming growth factor-ß1 (TGF-ß1) during the establishment of folliculogenesis *abs#267*

11:45am **Eileen McLaughlin**
Suppressors of Cytokine Signalling (SOCS): Roles in Ovarian Follicle Activation *abs#268*

12:00pm **Emily Alvino**
CD44 Signaling in Mouse Ovulatory Cumulus Oocyte Complexes. *abs#269*

12:15pm **Davina Rosairo**
TGF-ß and ovarian follicle development *abs#270*

12:30pm **Michael Bertoldo**
Effect of season on sow ovarian morphology *abs#271*

12:45pm **Karen Reader**
Signalling pathways involved in mouse GDF9 and BMP15 stimulated thymidine uptake by rat granulosa cells. *abs#272*

SRB Orals - Endocrine regulation of reproductive function

11:00-1:00pm; Corryong 3

Chairs: Wendy Ingman, Kaye Stenvers

11:00am **Phillip Matson**
The development of an immunoassay to measure progestogen using printed biosensors, and its application to the assessment of ovarian function in the Numbat (*Myrmecobius fasciatus*) *abs#273*

11:15am **Traute Flatscher-Bader**
Brain gene expression changes in MHC Class II genes and Neuropilin 2 associated with the transition from acyclic to cyclic ovarian function in postpartum beef cows *abs#274*

11:30am **Chris Scott**
The endocrine disruptor, bisphenol A, alters gene expression in the hypothalamus of the ram lamb but does not alter LH secretion. *abs#275*

11:45am **Phillip Matson**
The technical and biological validation of an LH assay for use with the Western Grey Kangaroo (*Macropus fuliginosis*) and Black-flanked Rock Wallaby (*Petrogale lateralis lateralis*). *abs#276*

12:00pm **Ursula Alexandra Ciller**
Equine chorionic gonadotrophin isoform composition in commercial products compared to isoform composition in pregnant mare plasma. *abs#277*

12:15pm **Steven Thompson**
IGF2 polymorphisms predict pregnancy outcome *abs#278*

12:30pm **Ainu Suhaimi**
Expression of oestrogen receptor-α and modulators of steroid receptor signalling, proline-rich nuclear receptor-2 and peptidylprolyl isomerade-D, in the hypothalamus of suckled and weaned postpartum beef cows *abs#279*

12:45pm **Ravinder Anand-Ivell**
INSL3 is a measure of human Leydig cell functionality both during fetal and adult life. *abs#280*

12:00pm

ESA Meet the Expert

12:00-1:00pm; Bellarine 4-5

Chair: Helena Teede

Henry Burger - Menopausal endocrinology and management *abs#071*

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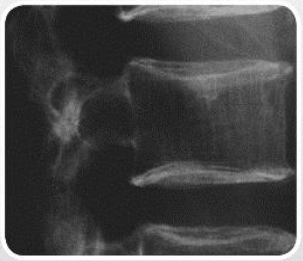
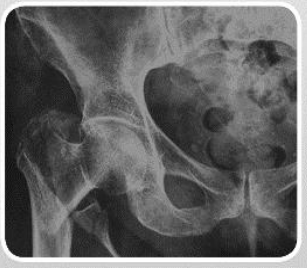
*age ≥70, T-score ≤-3.0

A first-line treatment for postmenopausal osteoporosis[1-5]

References

- *Australian and New Zealand Bone Mineral Society*
- *Osteoporosis Australia*
- *MIMS, disease management guidelines*
- *PBS listings*
- *Department of Health and Ageing, Therapeutic Goods Administration*





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1. www.nps.org.au/site.php?page=1&content=/npsradar/content/strontium_correspondence.html Accessed 18th Feb 2008 2. www.osteoporosis.org.au Accessed 10th May 2008
3. MIMS Issue No.2 2008 4. Pharmaceutical Benefits Schedule May 2008 5. Department of Health and Ageing, Therapeutic Goods Administration

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BONE

Warwick Howe: Pamidronate Improves Bone density, Fracture Rate, Pain & Wellbeing In 14 Children and Adolescents With Chronic Neurological Conditions. *abs#301*

Soelaiman Ima-Nirwana: Distribution of Alpha-Tocopherol in Bone and its Relationship to Bone Structure and Biomechanical Strength. *abs#302*

Emma Hamilton: Simple is not always best: Failure of simple guidelines for the management of osteoporosis in patients with a recent hip fracture *abs#303*

THYROID

Helen Barrett: Lithium-associated Hyperthyroidism *abs#304*

Katherine Tonks: Primary papillary thyroid cancer in a thyroglossal duct cyst: case report and review of the literature. *abs#305*

Veronique Gibbons: Are GP's using TSH indiscriminately? *abs#306*

Alexia Pape: Thyroid Disease during Pregnancy – A Review of Dose Requirements and Thyroid Function Test Changes in the Liverpool Hospital Antenatal Clinic. *abs#307*

Constance Yap: The pattern of pregnancy nutritional supplement intake in Sydney West Area Health Service. *abs#308*

CLINICAL

Kirsten Campbell: The Half Life of Plasma Free Metanephrines Following Resection of Pheochromocytoma *abs#309*

Casey Smith: Identification of Endothelin Converting Enzyme 2 as an Autoantigen in Autoimmune Polyendocrine Syndrome Type 1 *abs#310*

Sue Lynn Lau: The Vanishing Testis (*testiculus evanidus)* - Y men are disappearing from endocrinology *abs#311*

Katherine Tonks: Time to take notice of the hospital inpatient with hyperglycaemia *abs#312*

Amy Herlihy: Should we be screening for Klinefelter Syndrome? A research proposal *abs#313*

Sandie Staermose: Familial, bilateral macronodular adrenocortical hyperplasia with autonomous secretion of both cortisol and aldosterone. *abs#314*

Richard Gordon: Hypothesis: With increasing age, less flexible hormone secretion in genetically-predisposed individuals may contribute to conditions such as aldosterone-dependent hypertension or vasopressin-dependent hyponatremia. *abs#315*

Lisa Moran: Inflammatory adipokines in overweight women with and without polycystic ovary syndrome *abs#316*

Helen Barrett: Epidural Lipomatosis – A complication of Ectopic ACTH Syndrome *abs#317*

Jeremy Hoang: "Of Jugulare and Zuckerkandl", uncommon presentations of Paragangliomas and the role of Nuclear Medicine in diagnosis and management *abs#318*

Venessa Tsang: Clinical Case Report: Acute Pancreatitis due to Hypertriglyceridaemia *abs#319*

A N Pham: Hyperandrogenism due to Hyperthecosis and a Steroid-Cell Ovarian tumour – Diagnostic challenges of localising the source of hyperandrogenism *abs#320*

Y K Ku: A case of Bilateral Phaeochromocytoma in Neurofibromatosis Type 1 *abs#321*

K Y Thong: Case report: ^{123}I-MIBG negative malignant paraganglioma *abs#322*

CANCER

Peter Gleeson: Trends in Radioiodine Remnant Ablation for Differentiated Thyroid Cancer *abs#323*

Gail Risbridger: The Australian Prostate Cancer BioResource: An Update on its Role in Translational Research into Prostate Cancer in Australia *abs#324*

Kevin Knower: Epigenetic regulation of estrogen synthesis in human breast adipose fibroblast cells *abs#325*

Theresa Hickey: Androgen Receptor Signalling Inhibits Breast Epithelial Cell Survival in an Explant Model of Normal Human Breast Tissue *abs#326*

METABOLISM & OBESITY

Paul Lee: Do ß—blockers increase the risk of obesity? *abs#327*

George Muscat: Understanding the link between RORalpha and the control of adiposity *abs#328*

Malgorzata Brzozowska: An association between non-alcoholic fatty liver disease and polycystic ovarian syndrome *abs#329*

Hui Chen: Long term maternal cigarette smoke exposure contributes to glucose intolerance in offspring independent of maternal diet *abs#330*

Johanna Barclay: The role of STAT5 in obesity. *abs#331*

Scott Clarke: Differential effects of acute versus chronic estrogen treatment on energy expenditure in the

ovariectomised ewe *abs#332*

Yue Qi: RFRP-3 neurons project to hypothalamic nuclei and provide synaptic input to gonadotropin releasing hormone (GnRH) cells in the ovine brain *abs#333*

Priya Sumithran: An investigation of the threshold for the development of ketosis with a low carbohydrate diet *abs#334*

Deborah Sloboda: Maternal high fat feeding leads to obesity in offspring independent of post-weaning diet *abs#335*

Larissa Prior: Altered nutrition during suckling in mice: impact on plasma hormones and genes involved in thermogenesis. *abs#336*

Frederik Steyn: Pituitary and hypothalamic expression of receptors for metabolic factors regulating growth hormone secretion. *abs#337*

Bruce Wong: Modulation of macrophage fatty acid content and composition by varying triglyceride concentration in vitro *abs#338*

Margaret Morris: Programming adverse metabolic profile in male progeny by different levels of maternal overnutrition *abs#339*

Judy Luu: Dietary Fat Intake and Sleep Durationi n Chinese Adults *abs#340*

Chantacha Anukulkitch: Expression of gene for melanin concentrating hormone, but not the gene for orexin is increased with intrauterine growth restriction (IUGR) of sheep fetuses. *abs#341*

Reece Kyle: Serum from a hyperlipidemic patient results in altered macrophage lipid content, fatty acid composition and gene expression *abs#342*

GH/IGF

Ken Ho: The Power of the Mind: an evaluation of the placebo effect in a study of GH on physical performance *abs#343*

NUCLEAR HORMONE RECEPTORS

Fredrik Olsson: Analysis of Glucocorticoid-Antagonised Retinoic Acid-Responsive Genes during Pre-Term Lung Development *abs#344*

Sathiya Ramakrishnan: Rev-erbbeta (NR1D2) Regulates SREBP-1c mRNA Expression in Skeletal Muscle Cells *abs#345*

Julie McManus: The classical signalling pathway of the androgen receptor is required for androgen mediated erythropoiesis *abs#346*

Maria Alexiadis: Nuclear Receptor Gene Expression in Granulosa Cell Tumours of the Ovary *abs#347*

Francine Brennan: Aldosterone-Regulated Genes in the Duodenum *abs#348*

Amanda Rickard: Deletion of mineralocorticoid receptors from macrophages protects against mineralocorticoid-induced hypertension and cardiac fibrosis *abs#349*

Yizhou Yao: Identification of Ligand-Specific Coactivators of the Mineralocorticoid Receptor *abs#350*

Kirstyn Carey: Analysis of Different Glucocorticoid Receptor Gene Promoter Activities in the Mouse Brain *abs#351*

Adriane Lechtken: ROR alpha 4 is phosphorylated by GSK 3 beta in vitro *abs#352*

Isabelle Hoong: Glucocorticoids regulation of adipocyte-specific genes *abs#353*

Suryaprakash Raichur: The orphan nuclear receptor, RORalpha, regulates the insulin signalling cascade *abs#354*

Stephen Myers: Beta-adrenergic signalling induces nuclear receptor (NR) 4A1-3 in metabolic, cardiovascular, endocrine and gastrointestinal tissues *abs#355*

NEUROENDOCRINOLOGY

Mohammed Rizwan: RFRP-1 and -3 neurons are not hypophysiotropic gonadotrophin inhibitory neurons in the rat. *abs#356*

HPA

Marianne Elston: Loss of cytoplasmic membrane E-Cadherin is associated with nuclear accumulation of E-Cadherin in pituitary tumours *abs#357*

Anne Turner: Cortisol responses to exercise, endotoxin and wetting stress in sheep: Importance of sex and type of stressor *abs#358*

Ika Sari: Effect of RFRP-3 on gonadotropin synthesis and secretion in ovine pituitary gonadotropes *abs#359*

Julie Hetherington: A picture tells a thousand words The Insulin Tolerance Test – Getting the most from the data collected *abs#360*

Lyndal Tacon: The syndrome of generalised glucocorticoid resistance. *abs#361*

REPRODUCTIVE HORMONES

Hui Wu: Blockade of gene expression modifies the acute inflammatory release of activin A in response to lipopolysaccharide *abs#362*

David Phillips: Generation of normal ranges in serum for activin A, activin B and follistatin *abs#363*

REPRODUCTION - FEMALE

Daniel Inglis: A comparative assessment of three cell lines for use in the E-screen. *abs#364*

Fiona Young: Development of an *in vitro* assay to detect endocrine disrupting compounds (EDCs) using cryopreserved ovine luteal cells *abs#365*

Vicki Edwards: The effects of a reproductive homeopathic remedy & novel anti-cancer agents on female human reproductive cells *abs#366*

Javed Iqbal: *In vitro* characterisation of the rapid effects of estradiol-17ß in ovine pituitary gonadotropes *abs#367*

Helena Teede: Women with polycystic ovary syndrome (PCOS): Experiences with diagnosis and treatment options. *abs#368*

Huy Tran: The spectrum of thyroid disease following Interferon-α2ß therapy for chronic hepatitis C infection *abs#369*

REPRODUCTION - MALE

Liza O'Donnell: Transcriptional profiling of the mid-spermatogenic stages in the rat reveals mechanisms of hormone action *abs#370*

Debora Romero: Effects of human chorionic gonadotrophin on the mouse leydig cell proteome *abs#371*

PREGNANCY

Kirsty Pringle: The intrauterine (Pro)Renin/(Pro)Renin receptor system and its role in prostaglandin synthesis during pregnancy *abs#372*

Annette Osei-Kumah: A model of pregnancy induced changes in asthma *abs#373*

Kathryn Gatford: Maternal parity and growth hormone administration differentially affect fetal growth and muscle development in pigs *abs#374*

Penelope McLernon: Maternal Circulating Antioxidant Levels In Pregnancies Complicated By Asthma *abs#375*

Kaushik Maiti: Presence of the novel membrane estrogen receptor G-Protein coupled receptor 30 (GPR30) a membrane estrogen receptor in human pregnant myometrium and its biochemical characterization *abs#376*

Warwick Howe: High prevalence of suboptimal Vitamin D in first-trimester pregnancy *abs#377*

PARTUITION

Martha Lappas: Resveratrol, an activator of FoxO, inhibits LPS-induced cytokine and prostaglandin release from human gestational tissues. *abs#378*

Claire Abou-Seif: Tissue specific epigenetic regulation of CRH gene expression *abs#379*

Jonathan Paul: Phospho-Proteomic Determination of Contraction Associated Proteins in the Human Uterus *abs#380*

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Email: wormald1@optusnet.com.au
Web: www.pituitary.asn.au

BD Medical – Diabetes Care **Booths 13 & 14**
4 Research Park Drive
North Ryde NSW 2113
Ph: 02 8875 7136, Fax: 02 887 5711
Contact: Ben Hohmann
Email: benjamin_hohmann@bd.com
Web: www.bddiabetes.co.uk
BD is a medical technology company that manufactures and sells a broad range of supplies, devices and systems for use by healthcare professionals, medical research institutions, industry and the general public. BD Medical - Diabetes Care is investing in product development activities that can yield more convenient, high quality devices that improve the comfort of Insulin injection.

Bioclone Australia **Booth 26**
71-73 Railway Parade
Marrickville NSW 2204
Ph: 02 9517 1966, Fax: 02 9517 2990
Contact: Graham Davison
Email: sales@bioclone.com.au
Web: www.bioclone.com.au
Bioclone Australia Pty Limited is an ISO9001, ISO13485, GMP and CE Mark accredited company, with a business spanning 27 years, which specialises in the design, manufacture (including contract services, R&D and manufacturing), sales and distribution of high quality immunodiagnostic kits, reagents and antibodies for medical and laboratory markets globally.

Biometrica **Booth 28**
Level 1, 459 Toorak Rd
Toorak VIC 3142
Ph: 03 9296 2020, Fax: 03 9826 1436
Contact: Christie Freeman
Email: christiefreeman@biometrica.com.au
Web: www.biometrica.com
Biometrica is a Melbourne company focusing on innovative products for the treatment and diagnosis of cardiovascular disease and diabetes. We are proud to be exclusive distributor for the Diagnoptics® AGE Reader. The role of Advanced Glycation End-products in many chronic diseases, especially diabetes and its complications, is well established and the AGE Reader provides the only simple, accurate and non-invasive measurement method with powerful prognostic value. Our products also include the Accumetrics® VerifyNow® platelet function analyser, a point-of-care device that measures platelet dysfunction after antiplatelet agents, providing valuable information on both platelet inhibition levels and bleeding risk. Biometrica also proudly support AGGRASTAT® (tirofiban hydrochloride), a GPIIbIIIa antagonist for use in Acute Coronary Syndromes.

CSL Biotherapies **Sponsor, Booth 17**
45 Poplar Road
Parkville VIC 3052
Ph: 03 9389 1925, Fax: 03 9389 2721
Contact: Charmaine Caple
Email: charmaine.caple@csl.com.au
Web: www.csl.com.au
CSL Biotherapies (Australia) is a subsidiary of CSL Limited which provides innovative vaccines and pharmaceuticals to Australia and global markets. CSL Biotherapies in-license a number of pharmaceutical products from our partner companies to ensure a comprehensive range of products are available to meet the needs of all Australians at home and abroad. We are delighted to add Vaniqa (a topical treatment for the management of hirsutism in women) to our portfolio. CSL Biotherapies is proud to continue its commitment to Australian health care.

Diabete-ezy **Booth 16**
PO Box 227
Samford QLD 4520
Ph: 0439 892 617, Fax: 07 3289 5448
Contact: Elissa Renouf
Email: elissa@diabete-ezy.com
Web: www.diabete-ezy.com
Diabete-ezy is focused on developing convenient, practical, user friendly products. Company founder Elissa Renouf has 3 sons and a husband who all have Type 1 diabetes. With her experience, she has developed a company that produces convenient products for managing diabetes. Visit Elissa and Steve at the Diabete-ezy stand and see their innovative product range.

Diabetes Australia **Booth 52**
GPO Box 3156
Canberra ACT 2601
Ph: 02 6232 3800, Fax: 02 6230 1535
Contact: Jane Outteridge
Email: joutteridge@diabetesaustralia.com.au
Web: www.diabetesaustralia.com.au
Diabetes Australia is the national peak body working in partnership with diabetes health professionals and educators, researchers and health care providers to minimize the impact of diabetes on the Australian community. Diabetes Australia is committed to turning diabetes around through awareness, prevention, detection, management and a cure.

Diabetes Australia – NSW **Booths 42 & 43**
26 Arundel St
Glebe NSW 2037
Ph: 02 9552 9903, Fax: 02 9566 4235
Contact: Donna Beeching
Email: donnab@diabetesnsw.com.au
Web: www.diabetesnsw.com.au
Diabetes Australia-NSW is a non-profit, non-government, consumer based organisation. Our mission is to provide support for people living with Diabetes and those at risk of Diabetes. We achieve this through members' financial support, donations and fund raising. Funds are spent on supporting research, education programs, public awareness campaigns and advocacy.

Diabetes Australia – Victoria **Booth 41**
570 Elizabeth Street
Melbourne VIC 3000
Ph: 03 9667 1719, Fax: 03 9667 1778
Contact: Anigtha Vasudevan
Email: avasudevan@diabetesvic.org.au
Web: www.dav.org.au
Diabetes Australia - Vic is the peak consumer body and leading charity representing all people affected by diabetes and those at risk. Our purpose is to help all people affected by diabetes and to contribute to the search for a cure. Our work covers type 1, type 2 and gestational diabetes, as well as programs for people at risk.

Diabetes Centre – The Queen Elizabeth Hospital **Booth 22**
3 Woodville Road
Woodville South Australia 5011
Ph: 08 8222 6770, Fax: 08 8222 6044
Contact: Lesley Roberts
Email: Lesley.roberts@nwahs.sa.gov.au
Web: www.diabetes.org.au
The display will feature various diabetes education booklets, manuals, a series of diabetes information leaflets, and PowerPoint teaching packages for both consumers and health professional development. Orders can be taken, with some stock available to purchase on the day.

Diabetes Vaccine Development Centre **Booth 27**

384 Victoria Street
Darlinghurst NSW 2010
Fax: 03 8610 0323
Contact: Robyn Johnston
Email: rjohnston@intuitiveinnovations.au.com
Web: www.dvdc.org.au
The Type 1 Diabetes Prevention Study (INIT II) is a multicentre, placebo-controlled trial to determine if intranasal insulin will:

- Reduce the rate of development of diabetes,
- Prevent expected loss of pancreatic β-cell function,
- Improve insulin action, and
- Stimulate immune responses consistent with the induction of immune tolerance to insulin

Any relatives (aged 4-30 years) of people with Type 1 diabetes are urgently sought to have a blood test to determine potential eligibility-only 2 percent have the antibodies that qualify them to participate in the one-year study. For further information contact the DVDC on 029295-8357 or email: dvdc@dvdc.org.au

Dorevitch Pathology **Sponsor, Booth 23**

18 Banksia St
Heidelberg VIC 3084
Ph: 03 9244 0444, Fax: 03 9244 0222
Contact: Helen Firfilionis
Email: helen.firfilionis@symbionhealth.com
Web: www.dorevitch.com.au
Dorevitch Pathology provides a comprehensive range of professional, high quality services throughout metropolitan and regional areas in Victoria. Established for over 35 years our tradition of service to General Practitioners, Specialists, Hospitals and the general medical community remains. Our goal is to provide superior quality, speed and convenience to doctors and their patients. Dorevitch Pathology has over 45 pathologists, covering all sub-specialties, ensuring thorough, accurate result interpretation, comment and diagnostic advice. Enquiries to our pathologists are welcome at any time. In addition to our reputation for high ethical standards and pathologist expertise, Dorevitch Pathology has become recognised for the professional partnership with the medical community due to their continued support of in-house registrar training.

Eli Lilly **Sponsor, Booth 48**

112 Wharf Road
West Ryde NSW 2114
Ph: 02 9325 4444, Fax: 02 9325 4410
Contact: Krishna Sai
Email: gsw@lilly.com
Web: www.lilly.com.au
Diabetes is the foundation on which Lilly was built. During its 130 year history, Lilly has developed numerous diabetes treatments and devices that have helped health care professionals improve the lives of millions of people around the world. With one of the most comprehensive diabetes portfolios available to you and your patients, Lilly will continue to lead the way in understanding diabetes and its impact on everyday life. Lilly shares your passion and commitment to improving the outcomes for people affected by diabetes & growth hormone related disorders in Australia.

Endocrine Society of Australia **Booth 25**

Contact: Ivone Johnson
Email: esa@racp.edu.au
Web: www.endocrinesociety.org.au

Genzyme **Sponsor, Booth 15**

PO Box 282
North Ryde B/C NSW 1670
Ph: 02 9978 3900, Fax: 02 9889 3900
Contact: Eilis Quinn
Email: eilis.quinn@genzyme.com
Web: www.genzyme.com.au
One of the World's foremost biotechnology companies, Genzyme has a diverse portfolio of medical products that treat a variety of disorders including rare genetic, renal, transplant and immune diseases to name just a few. The oncology and endocrinology range includes the product Thyrogen, thyrotropin alfa-rch, an adjunctive agent used in the diagnostic and therapeutic management of well differentialted thyroid cancer.

GlaxoSmithKline **Sponsor, Booth 55**

1061 Mountain Highway
Boronia VIC 3155
Ph: 03 9721 6000, Fax: 03 9729 5319
Contact: Daniel Henry
Email: daniel.x.henry@gsk.com
Web: www.gsk.com.au
GlaxoSmithKline (GSK) Australia is one of Australia's largest pharmaceutical and healthcare companies and is committed to improving the quality of human life by enabling people to do more, feel better and live longer. GSK has four main sites in

Australia, employing more than 1500 people. It is Australia's largest supplier of vaccines and a leading supplier of medicines for asthma, bacterial and viral infections, depression, migraine, gastroenterological disease, epilepsy, smoking cessation and pain relief. The company invests up to $30 million in research and development each year, making it one of Australia's top 10 R&D companies. We are the only pharmaceutical company to tackle the three "priority" diseases identified by the World Health Organization: HIV/AIDS, tuberculosis.

HemoCue Australia **Booth 12**
35 Longview Close
Wamberal NSW 2260
Ph: 02 4384 6855, Fax: 02 4384 7919
Contact: Lyn Hatherly
Email: lyn@hemocue.com.au
HemoCue, world renowned for point of care analysers providing lab accurate results, are now proud to release their new WBC analyser. Safe, efficient and well proven, HemoCue technology is widely used in hospitals and primary care throughout the world.

iNova Pharmaceuticals (Aust) **Booth 4**
9-15 Chilvers Road
Thornleigh NSW 2120
Ph: 02 9875 6305, Fax: 02 9875 6412
Contact: Julieann Tyson
Email: j.tyson@inovapharma.com
Web: www.inovapharma.com
iNova Pharmaceuticals develops and markets a range of over-the-counter and prescription medicines to Australasia, Asia-Pacific, South Africa, the Americas and other international markets directly and also through other pharmaceutical companies and agents. These include prescription medicines in the areas of weight management, dermatology, heart conditions, asthma and pain management.

IPSEN **Sponsor, Booth 40**
Suite 6, 40 Montclair Avenue
Glen Waverly VIC 3150
Ph: 03 8544 8100, Fax: 03 9562 5152
Contact: Briana Rowson
Email: briana.rowson@ipsen.com
Web: www.ipsen.com.au
Ipsen Pty Ltd is the Australian affiliate of a European pharmaceutical group.
Globally Ipsen focuses on developing highly specialised products to meet specific needs in therapeutic areas such as oncology, endocrinology and neuromuscular disorders. Ipsen has research and development facilities in Paris, London, Boston and Barcelona. Since establishing in Australia in 2001, Ipsen has successfully launched Somatuline® Autogel® (lanreotide) for the treatment of acromegaly and the symptoms of carcinoid syndrome, Dysport® (botulinum toxin type A) for the treatment of various neuromuscular disorders, and most recently, NutropinAq® (recombinant human growth hormone), a growth hormone therapy for adults and children. Ipsen delivers customised solutions to healthcare professional and their patients according to their needs.

Juvenile Diabetes Research Foundation **Booth 10**
PO Box 183
St Leonards NSW 1590
Ph: 02 9966 0400, Fax: 02 9966 0172
Contact: Michael Sluis
Email: msluis@jdrf.org.au
Web: www.jdrf.org.au
The Juvenile Diabetes Research Foundation (JDRF) is the world's largest not-for-profit supporter of diabetes research, investing more than $130 million per year into the search to find a cure for type 1 diabetes. JDRF supports Australian diabetes research via the strategic provision of funding and, through the establishment of successful long-term partnerships with business and leading government agencies, has ensured the translation of research outcomes into real clinical options for people with type 1 diabetes. JDRF Australia also plays a key role in advising and influencing health policy direction across all levels of government and building community awareness of type 1 diabetes.

Life Bioscience **Booths 31 & 32**
10 Atherton Road
Oakleigh VIC 3166
Ph: 03 9568 4140, Fax: 03 8660 2785
Contact: Mark Thacker
Email: info@lifebioscience.com.au
Web: www.lifebioscience.com.au

Medical Specialist Recruitment/Calvary Health Care Riverina **Booth 20**

PO Box 618, Wagga Wagga NSW 2650
Ph: 02 69 232264, Fax: 02 69 232320
Contact Joy Ross
Email: joy.ross@calvary-wagga.com.au
With a catchment population in excess of 250,000 Wagga Wagga provides a great opportunity to establish an exciting practice and for you and your family to enjoy all the benefits of a regional city lifestyle and be only 1 hour away from Sydney and Melbourne. Opportunities exist to apply for VMO rights at both Wagga Wagga Base Hospital (220 beds) and Calvary Health Care Riverina (104 beds), to be involved in teaching and/or research, and support is available to establish practice, relocate your family and promote yourself to the GPs in the area.

Medical Specialties Australia **Booths 8 & 9**

PO Box 764
Willoughby NSW 2068
Ph: 02 9417 7955, Email: 02 9417 7955
Contact: Jonathon Peters
Email: jpeters@msa.com.au
Web: www.msa.com.au
The Cozmo Insulin Pump combines insulin pump therapy and personalised programming and data management. Only the Deltec Cozmo insulin pump offers these features: Deltec Cozmo Insulin Pump is Watertight!; Small and lightweight; similar in size to a mobile phone; Personalisation of screens to fit your lifestyle; Custom bolusing by grams of carbohydrates or units of insulin; Correction bolus to accurately adjust for high blood glucose; Disconnection feature; Site change reminder alerts you when you should change your infusion set; Blood glucose test alert reminds you to test your blood glucose; "Basal testing" food data base; Hypo Manager. CoZmanager PC Communications Software makes it easy to personalise programs that will help keep your diabetes on track. While you can program your pump directly, using the CoZmanager software lets you personalise it to fit your lifestyle. For more information, please call, Medical Specialties Australia on 02 9417 7955

Medtronic Diabetes **Booth 49**

97 Waterloo Road
North Ryde NSW 2113
Ph: 02 9857 9000, Fax: 02 9887 1829
Contact: Amy Trikha
Email: australia.diabetes@medtronic.com
Web: www.medtronic-diabetes.com.au
Medtronic Diabetes is the world leader in insulin pump therapy and continuous glucose monitoring and is firmly committed to helping people living with Type 1 diabetes live healthier lives by providing superior technology and responsive customer support. Our products include external insulin pumps, related disposable products and continuous glucose monitoring systems. With our Clinical/Sales Specialist team, 24 hour pump Helpline, large research and development resources in insulin pump therapy and continuous glucose monitoring, Medtronic Diabetes sets the standard in diabetes care. Visit the Medtronic Diabetes Stand (no. 49) to learn about the latest technologies in Diabetes Management.

Merck Sharp and Dohme **Booth 44**

PO Box 79
Granville NSW 2142
Ph: 02 97959002, Fax: 02 97959602
Contact: Libby Bailiss
Email: elizabeth_bailiss@merck.com
Web: www.msd-australia.com.au
Merck Sharp & Dohme is the Australian subsidiary of the global research-based pharmaceutical company Merck & Co., Inc. Since 1995 the company has brought 17 innovative new therapies to Australians – from osteoporosis and high cholesterol to antibiotics and HIV medicines. Our late stage pipeline includes vaccines for shingles, human papillomavirus and rotavirus-induced infant diarrhoea; and a DP-IV inhibitor for the treatment of Type II diabetes. Merck Sharp & Dohme is actively partnering with Australian researchers to bring their discoveries to the world. Our significant investment in Australian medical research ranks us among Australia's top 40 firms.

Merck Sharp and Dohme / Schering-Plough **Booth 53**

Merck Sharp & Dohme
PO Box 79
Granville NSW 2142
Phone: 02 9795 9500
Fax: 02 9795 9595
Samantha Gregson
Email: samantha_gregson@merck.com
Web: www.msd-australia.com.au

Schering-Plough
Locked Bag No. 2234
North Ryde NSW 1670
Phone: 02 8988 8000
Fax: 02 8988 8801
Sharon Brouillard
Email: sharon.brouillard@spcorp.com
Web: www.schering-plough.com.au

Merck Sharp & Dohme (MSD) Australia is a research based pharmaceutical company that was established in Australia in 1952. In partnership with Schering-Plough Australia, also a research based pharmaceutical company established in 1958, the two organisations have undertaken a joint marketing agreement to market and develop new cardiovascular medicines in the Australian market. Both organisations have a proud history in Australian pharmaceutical research and development and the joint marketing agreement represents their commitment to best practice.

Novartis Oncology **Sponsor, Booths 5 & 6**
54 Waterloo Rd
North Ryde NSW 2113
Ph: 02 9805 3755, Fax: 02 9888 3708
Contact: Nicki Sidwell
Email: nicki.sidwell@novartis.com
Web: www.novartisoncology.com
Novartis Oncology provide a broad range of innovative therapies and practical solutions that improve and extend the lives of cancer patients. Every day, around the world we are exploring and pioneering new treatments that are likely to transform the way cancer is treated. Our current portfolio includes: **Glivec**, which has set a new standard in the treatment of CML and GIST; **Femara**, a first-line treatment for postmenopausal women with hormone dependant early and advanced breast cancer; **Zometa**, for multiple myeloma and for malignancies involving bone, including breast, prostate and lung cancers, as well as the treatment of hypercalcaemia of malignancy; **Sandostatin LAR** for the symptomatic control and reduction of GH and IGF-1 in patients with active acromegaly and to control symptoms in patients with functional carcinoid tumours and VIPomas; and **Exjade**, a once-daily, oral, iron chelator for the treatment of iron overload in patients receiving frequent blood transfusions.

Novo Nordisk **Sponsor, Booth 47**
Level 3, 21 Solent Circuit
Baulkham Hills NSW 2153
Ph: 02 8858 3757, Fax: 02 8858 3799
Contact: Kate Alger
Email: kalg@novonordisk.com
Web: www.novonordisk.com.au
Novo Nordisk is leading the fight against diabetes. Defeating diabetes is our passion and our business. One of the first companies to introduce insulin, Novo Nordisk is now the world's largest insulin manufacturer, the leading supplier of insulin in Australia, and has the broadest insulin product portfolio in the industry. Our strong commitment to changing diabetes is reflected in our focus on research and development in Australasia. Working together with Diabetes Australia, Juvenile Diabetes Research Foundation and supporting Pacific Island communities through our World Diabetes Foundation. A world leader in diabetes care, Novo Nordisk is committed to fighting this growing epidemic with the ultimate aim of finding a cure.

Pfizer Australia **Booths 18 & 19**
38-42 Wharf Rd
West Ryde NSW 2114
Ph: 02 9850 3996
Contact: Margaret Foster
Email: margaret.foster@pfizer.com
Web: www.pfizeraustralia.com.au
With a history dating back to 1886, Pfizer Australia has grown to become the nation’s leading provider of prescription medicines. Today, employing more than 1500 staff, and export $A100 million worth of product around the region annually from three manufacturing plants across the nation. We take our individual leadership and our commitment to the healthy future of all Australians seriously. Aside from the direct benefits our medicines make to the nation’s health, Pfizer Australia works hard in the community to help make our nation a happier, healthier place to live. With many prescription medicines leading their therapeutic areas, it’s easy to see why millions of Australians trust Pfizer Australia everyday.

Point of Care Diagnostics **Booth 39**
PO Box 780
Artarmon NSW 1570
Ph: 02 9437 1355, Fax: 02 9437 1399
Contact: Georgina Kyprianou
Email: gkyprianou@pocd.com.au
Web: www.pocd.com.au
Point of Care Diagnostics (POCD) is a specialist in patient-side medical diagnostics. Our core businesses are diabetes testing, INR and cholesterol testing. POCD is making point of care testing easy and more affordable.
POCD offers a range of products including the SENSOCARD PLUS - TALKING BLOOD GLUCOSE MONITOR for vision impaired patients and the AFINION HbA1c / ACR and CRP analyser. Our LDX cholesterol testing machine is considered gold standard within the diagnostic industry. The LDX is able to perform a range of tests such as full lipid profile, glucose, liver function and high sensitivity C - reactive protein. Visit stand #39 to view our range.

ResMed **Booth 11**
1 Elizabeth MacAuthur Dr
Bella Vista NSW 2153
Ph: 02 8884 1000
Contact: Ben Mar
Email: benm@resmed.com.au
Web: www.resmed.com.au
ResMed is committed to raising public awareness about the potentially serious health consequences of untreated sleep-disordered breathing and associated commorbitieis including Diabetes. We constantly strive to develop innovative technologies to improve the lives of people suffering from this condition. In doing so, we continue to lead the industry in both clinical education and product development. We continue to invest in research and product development demonstrating our commitment to developing innovative therapies that increase patient comfort, convenience and compliance

while improving health. ResMed promotes industry growth by investing in programs to educate the medical community and the public about sleep-disordered breathing. ResMed disburses grants through the ResMed Foundations in the US and Australia.

Roche Australia **Booth 45**
31 Victoria Avenue
Castle Hill NSW 2154
Ph: 02 9860 2257, Fax: 02 9860 2388
Contact: Sophia Aquino
Email: sophia.aquino@roche.com
Web: www.roche.com
Roche Diagnostics is a world leader and innovator in medical diagnostics. The Accu-Chek® brand is recognized for 30 years of quality and innovation in diabetes care worldwide. We offer the Accu-Chek® range of: blood glucose monitors, insulin pumps, lancing devices and diabetes information management systems. Come to the Roche stand and see how Accu-Chek® products can help you manage your patients with diabetes.

S4S Software 4 Specialists **Booth 7**
PO Box 810
Faifield NSW 1860
Ph: 1300 133 308
Contact: Dana Segelov
Email: dana.segelov@s4s.com.au
Web: www.s4s.com.au
Software 4 Specialists, an Australian company, have designed and developed an innovative clinical software program called Audit4, for Endocrinology/Diabetes. Audit4 is both a complete paperless solution and an audit tool enabling a powerful and instant audit of all aspects of endocrine/diabetes practice. An invaluable tool for MOPS. Clinical practice efficiency is enhanced through electronic tools including automatic express letter to the GP, electronic scripts including streamline authority, investigation requests and downloading results, media manager for organising scanned images/photos and imported documents, instant graphing of pathology results with ability to mark interventions. Links to the front-desk windows-based billing system for patient demographics.

Safety Medical Products **Booth 34**
25 Fenden Road
Salisbury Plain SA 5109
Ph: 08 8285 3228, Fax: 08 8285 3228
Contact: Chris Harnett
Email: chris@safetymed.com.au
Web: www.safetymed.com.au
Safety Medical Products is an Australian company supporting Australians with diabetes. Utilizing Australian design and manufacturing capabilities, it has developed a simple and low-cost unique range of retractable safety syringes; it also markets a specific range of products to assist people with diabetes. It aims to be a global medical and health products manufacturer, distributor and developer.

Sanofi – Aventis Australia **Sponsor, Booth 54**
Building D, 12 - 24 Talavera Road
Macquarie Park NSW 1670
Ph: 02 8666 2477, Fax: 02 8666 3345
Contact: Richard Gerke
Email: richard.gerke@sanofi-aventis.com
Web: www.sanofi-aventis.com.au
Sanofi-aventis is committed to helping manage and reduce the burden of diabetes by providing support for research, education and patient resources. This is demonstrated by Lantus Navigator, a patient support program that has been developed to guide and support Lantus patients in partnership with healthcare professionals. Sanofi-aventis' diabetes product portfolio includes Lantus SoloSTAR, Apidra SoloSTAR and an exciting new pipeline of new diabetes and metabolism products.

Sapphire Bioscience **Booth 30**
Suite 1, 134 Redfern St
Redfern NSW 2016
Ph: 02 9698 2022, Fax: 02 9698 1022
Contact: Sue Goodman
Email: sales@sapphirebioscience.com
Web: www.sapphirebioscience.com
Sapphire Bioscience provides an extensive line of assay kits for measuring adipokines, steroids, neuropeptides, and gut peptides as markers and mediators of endocrine function. Assay kits for free radical biomarkers, lipid mediators, and environmental stress indicators are also available. Other products include an extensive range of antibodies, inhibitors, receptor agonists/antagonists, and transcription factor assays for metabolic and nuclear receptor research. Custom antibody, peptide & biochemical synthesis services are also available.

Servier Laboratories **Booth 46**

3 Cato Street
Hawthorn VIC 3122
Ph: 03 8823 7333, Fax: 03 9822 8688
Contact: Karen Clinton
Email: karen.clinton@au.netgrs.com
Web: www.servier.com.au

Servier is a privately owned pharmaceutical company with a long-standing commitment to research and development. In 2005, company founder Dr Jacques Servier revealed that all profit from Servier worldwide operations is now channelled into research and development projects through the recently formed Servier Foundation. Servier Australia's commercial interests are presently in cardiovascular disease (Coversyl - perindopril arginine, Coversyl Plus – perindopril arginine/indapamide and Coralan - ivabradine), diabetes (Diamicron MR - gliclazide), disseminated malignant melanoma (Muphoran - fotemustine), and most recently, postmenopausal osteoporosis (Protos - strontium ranelate).

Solvay Pharmaceuticals **Booth 50**

Level 1, BLDG 2, 20 Bridge Street
Plymble NSW 2073
Fax: 02 9440 0910
Contact: Ben Lingam
Email: ben.lingam@solvay.com.au
Web: www.solvay.com.au

Solvay Pharmaceuticals is a healthcare company active in more than 50 countries world wide with interests in 5 therapeutic areas Cardio-metabolic, Neuroscience, Women's & Men's Health, Vaccines and Gastroenterology. Founded in 1863 it is headquartered in Brussels, Belgium employs over 9,000 people worldwide and in 2007 had sales of over 2.59 Billion Euros.Over the past 20 years Solvay Pharmaceuticals has built a reputation in cardiovascular research making a substantial contribution to the current treatment of hypertension, dyslipidaemia and related disorders. Solvay Pharmaceuticals was established in Australia in 1996, and currently focuses on the following therapeutic areas: Cardio-metabolic, Neuroscience (especially Parkinson's disease), Vaccines and Gastroenterology.

Society for Reproductive Biology **Booth 24**

Contact: Christopher Grupen
Email: c.grupen@usyd.edu.au
Web : www.srb.org.au

LANTUS® SoloSTAR®
insulin glargine

Achieve A1C* ≤ 7%

with a significantly lower risk of hypoglycaemia[1-3]†

Apidra® SoloSTAR®
insulin glulisine

EFFECTIVE. FAST. FLEXIBLE.[4]

*** A1C=HbA_{1c}**

† Fewer hypoglycaemic events vs. NPH and Premix (reg/NPH 30/70 and BIAsp 30/70)

Lantus (insulin glargine). Indications: Once-daily subcutaneous administration for type 1 diabetes mellitus patients (adults and children) and type 2 diabetes mellitus patients (adults) who require insulin for control of hyperglycaemia. **Contraindications:** Hypersensitivity to insulin glargine or any excipient. **Precautions:** Hypoglycaemia, hepatic, renal and visual impairment; lipodystrophy and other injection site; antibody production; intercurrent conditions, not studied in children < 6 years, pregnancy category B3, lactation; not intended for i.v. use; not recommended for treatment of diabetic ketoacidosis; LANTUS MUST NOT BE DILUTED OR MIXED WITH ANY OTHER INSULIN OR SOLUTION. **Interactions:** Oral antidiabetic agents; cardiovascular, analgaesic, anti-inflammatory, neurological, antipsychotic agents (see full PI); antibiotics; corticosteroids, other hormonal therapies (see full PI); diuretics; protease inhibitors; sympathomimetic agents; lithium; alcohol; sympatholytics including beta-blockers; others, see full PI. Side effects: Hypoglycaemia; injection site reactions; visual disturbances; others, see full PI. **Dosage and Administration:** Subcutaneous, once daily. Lantus is equipotent to human insulin. Initial dose should be determined depending on desired blood glucose levels and doses and timing of any antidiabetic medication. For changeover from once-daily NPH or ultralente, initial dose usually not changed; for changeover from twice-daily NPH to once-daily Lantus, initial dose usually reduced by approximately 20% compared to total daily NPH dose; for initiation of type 2 patients, initial dose is usually approximately 10IU. PBS dispensed price: Lantus SoloSTAR 5x5x3mL ($431.45) and Lantus cartridges 5x5x3mL ($431.45). **Please review full Product Information before prescribing Lantus.** Full Product Information is available on request from sanofi aventis australia pty ltd, 12-24 Talavera Road, Macquarie Park NSW 2113. ABN 31 008 558 807. Date created: Jan 2008.

PBS Information: Lantus SoloSTAR and Lantus cartridges are listed on the PBS as a long acting insulin analogue for the treatment of type 1 and type 2 diabetes.

Apidra (insulin glulisine). Indications: For type 1 and type 2 diabetes mellitus patients (adults and children older than 12 years) who require insulin for control of hyperglycaemia. **Contraindications:** Hypersensitivity to insulin glulisine or any excipient. **Precautions:** Hypoglycaemia; hepatic, renal and visual impairment; lipodystrophy and other injection site reactions; antibody production; intercurrent conditions; not studied in children <12 years, pregnancy category B3, lactation. Apidra may be mixed with NPH insulin; mixtures should not be administered intravenously. **Interactions:** Oral antidiabetic agents; cardiovascular, analgaesic, anti-inflammatory, neurological, antipsychotic agents (see full PI); antibiotics; corticosteroids, other hormonal therapies (see full PI); diuretics; protease inhibitors; sympathomimetic agents; lithium; alcohol; sympatholytics including b-blockers; others, see full PI. **Side effects:** Hypoglycaemia; injection site reactions; others, see full PI. **Dosage and Administration:** Apidra is equipotent to human insulin, with more rapid onset and shorter duration of action. Apidra should be injected within 15 minutes before or immediately after a meal. **Please review Product Information before prescribing.** Full Product Information is available on request from sanofi-aventis australia pty ltd, 12-24 Talavera Road, Macquarie Park NSW 2113. ABN 31 008 558 807. Date created: 30 May 2007. Reference Document: PI, approved August 2007. Apidra® SoloSTAR® is a registered trademark of sanofi-aventis. AVENA5293. AU.LAN.08.07.07. PBS dispensed price: Apidra SoloSTAR 5 x 5 x 3mL ($263.12).

References: 1. Janka H, et al. Diabetes Care 2005;28: 254-259. **2.** Riddle M, et al. Diabetes Care 2003;26(11): 3080-3086. **3.** Raskin P, et al. Diabetes Care 2005;28(2): 260-265. **4.** Apidra Product Information, Approved 15 November, 2006.

PBS Information: Apidra SoloSTAR is listed on the PBS as a rapid acting insulin analogue for the treatment of type 1 and type 2 diabetes.

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AUTHOR INDEX

INVITED ORALS

001

Adrenal Conundrums: The Adrenal Incidentaloma

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Introduction: A conundrum is defined as: 1) a riddle whose answer is or involves a pun; 2) a question or problem having only a conjectural answer; 3) an intricate and difficult problem. Despite its small size (4 gm), the adrenal gland has given the endocrinologist many conundrums! This presentation will focus on the patient with an incidentally discovered adrenal mass—"adrenal incidentaloma". Two byproducts of the revolution in diagnostic imaging techniques over the past 3 decades are unintended discoveries and uncertainty for the patient and clinician. To address the uncertainty associated with adrenal incidentalomas, clinicians need a clear understanding of the definition, differential diagnoses, and options for assessment with respect to functional status and malignant potential.

Methods: Data will be presented based on extensive clinical experience, published studies from Mayo C linic, and literature review.

Results: Adrenal incidentaloma is defined as a mass lesion > 1-cm in diameter serendipitously discovered by radiologic examination, in the absence of symptoms or clinical findings suggestive of adrenal disease. The differential diagnosis includes 3 broad categories of possibilities: non-functioning mass, a subclinical hyper-functioning mass, and pseudo-adrenal mass. The adrenal incidentaloma should be characterized with respect to: a) functional status – history and physical examination and hormonal assessment; and, b) malignant potential – " imaging phenotype " and size. All patients should be assessed for: a) subclinical Cushing syndrome with a 1- or 3-mg overnight dexamethasone suppression test; b) pheochromocytoma with 24-hr urinary excretion of fractionated catecholamines and metanephrines; and, c) primary aldosteronism (if hypertensive) with plasma aldosterone concentration to plasma renin activity ratio. CT-guided adrenal fine needle aspiration biopsy is rarely needed and is only helpful in diagnosing metastatic disease or infection. The type of and frequency of imaging follow-up is guided by clinical circumstances (eg, patient age) and imaging phenotype.

Conclusion: Although a member of the adrenal conundrum family—and it may be intricate and difficult—the uncertainty surrounding the management of the adrenal incidentaloma can be resolved in part by a thoughtful step-by-step approach.

002

Fetal autonomy to health across generations

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By 1969 when a group of clinicians and physiologists reviewed a new concept, fetal autonomy, it was already clear that events occurring in the perinatal period could set function for life. Levine and Harrison demonstrated that handling pups or exposure to androgens led to changes in function in adults. However, it was not until the early 1980s that David Barker and his colleagues began to relate growth before birth to the early onset of common adult diseases including coronary heart disease, diabetes and components of the metabolic syndrome. Many epidemiologists were reluctant to accept this hypothesis; some setting out to disprove it. In contrast, perinatal clinicians and physiologists were able to integrate this readily into their concepts of development and critical periods. Lucas defined this new association, programming as the "Physiological setting by an early stimulus or insult at a sensitive period, resulting in long term consequences for function; the effects could be immediate or deferred".

Barker and his colleagues proposed that poor maternal nutrition led to the association between poor fetal growth and early onset of adult disease; setting a new agenda for fetal physiologists. Several groups rapidly developed new experimental paradigms in which it was remarkably easy to show that poor maternal nutrition or restriction of fetal growth caused pathophysiological changes that resulted in high blood pressure, obesity and abnormal glucose tolerance. In time, these were also shown to alter longevity, especially when combined with a "cafeteria style" diet after weaning. Deficiency of a single nutrient was sufficient to induce these associations and in contrast, supplementation of a single amino acid or folate could prevent induction of the associations. Evolutionary biologists relate these mechanisms to reproductive fitness and to transgenerational signalling of the likely future environment to offspring – predictive adaptive responses. Human disease occurs early when there is a mismatch between such predictions and conditions prevailing in childhood and adult life.

More recently, the mechanisms underpinning these associations have begun to be defined and strategies for prevention or reversal tested in experimental animals. These may involve hormones and growth factors that indicate organ size, such as leptin. Furthermore these mechanisms may be initiated to re-set the individual on a previously determined trajectory analogous to the phenomena of catch-up or catch-down growth that occurs in the first few months after birth. Parallel studies in human cohorts have included long term follow up of randomised clinical trials that may provide insights to the similarity of mechanisms across species.

Translating these findings into public health policy and into interventions that will improve long-term health outcomes remains a significant challenge. Amongst the obvious are recommendations changing life-style, nutrition and even the age in the life cycle when pregnancy would be preferable.

003

Combination Medical Therapy For Acromegaly

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Patients with Acromegaly have an average delay in diagnosis of 10 years dating from the onset of symptoms. Because of this delay, 75% of these tumors at the time of diagnosis are macroadenomas. Factors, which assure incomplete removal from an anatomic basis of these large tumors, include either extension of the tumor lateral to the internal carotid on either side or arachnoid invasion. Because inexperienced pituitary surgeons often operate on many of these macroadenomas, or they are not respectable to begin with, many acromegalic patients are not cured by surgery, and require long-term medical therapy. In the last 20 years there has emerged a number of medications for control of excess growth hormone (GH) and IGF-1. These include somatostatin analogues, GH antagonists and dopamine agonists. In addition to these newer drugs, epidemiologic studies have emerged which clearly define safe control of GH and IGF-1 at defined levels, above which, there is an increase in mortality. If control of GH and IGF-1 is achieved by medical therapy, mortality is equal to the reference. Conversely, if GH and IGF-1 are not achieved within these defined parameters mortality is increased. After extensive experience with the above named agents somatostatin analogues have clearly emerged to remain the backbone of therapy for uncontrolled GH and IGF-1. There are two somatostatin analogues currently on the US market including octreotide and lanreotide. Both have virtually strong affinities to somatostatin receptors 2 and 5 and have virtually identical safety and efficacy profiles. Because either agent will only control about 50-60% (GH and IGF-1) of patients, other measures must be taken. These include doubling of the dose of somatostatin therapy, a very expensive tactic, or adding a second agent or removal of remaining tumor which is referred to as "debulking" the tumor. This latter option is especially attractive if the patient is partially responsive to somatostatin analogue and an inexperienced surgeon performed the first surgery. One strategy, which has emerged, is to wait a period of time on a long acting somatostatin analogue before prematurely adding a second therapeutic option. It appears that a longer of time with the highest dose of a somatostatin analogue can eventually result in successful control of GH and IGF-1. Doubling the dose of somatostatin therapy can also be successful, but is very expensive and should probably be placed after the option of either adding a dopamine agonist or the addition of pegvisomant a GH antagonist. The author currently prefers one dose of somatostatin and, if not successful, adding the GH antagonist. Lastly, the option of irradiating the remaining tumor can be selected, however, radiation has four drawbacks, including the gradual development of hypopituitarism, the very long time radiation takes to control GH or IGF1 which is numbered in the 10 to 20 year range, the instigation of a new tumor such as a fibrosarcoma, in the radiated bed and lastly the acceleration of cerebrovascular disease by the irradiation creating a new early mortality risk.

In the era of medical therapy for acromegaly over the past 20 years it is apparent that the increased mortality associated with this disease can be reduced to that of the normal population if judicious use of drugs, especially somatostatin analogues, is carefully employed.

004

Lifestyle, Environment and Reproductive Function

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This review focuses on the impact of potentially modifiable, non-communicable lifestyle factors on reproductive function. Factors including; age, weight, smoking, diet, exercise, psychological stress, caffeine consumption, and alcohol consumption are considered. Instances are drawn both from a review of available evidence internationally and results of work undertaken in Australia in the general population and the infertile population undergoing assisted reproductive technology (ART) treatment.

There is strong evidence that age, weight and smoking impact on general health and adversely on reproductive performance. However there is a need for further research focusing specifically on the relationship between specific aspects of diet and levels of exercise on reproductive performance. Evidence related to modest levels of exposure to psychological stress, caffeine consumption is equivocal. It is concluded that lifestyle modification can assist couples to conceive spontaneously or optimize their chances of conception with ART treatment, and that these exposures can, under certain circumstances, also have important implications for the long term health of offspring..

005

Effects of obesity on oocytes and embryos

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Obese women are affected by longer times to conception than moderate weight women and once pregnant experience higher rates of early pregnancy loss. It is hypothesized that critical events within the ovary, including ovulation, steroid production and oocyte quality are affected by obesity. In women undergoing ART, follicular fluid (FF) insulin and glucose levels positively correlated with increasing Body Mass Index (BMI). Additionally, FF testosterone was elevated and SHBG decreased, leading to an increased Free Androgen Index. Gene expression in granulosa and cumulus showed cell type-specific differences in insulin signalling genes IRS-2 and Glut4, but no effect of BMI. In contrast lipoprotein receptors CD36 and SRBI tended to be increased in granulosa cells with increasing BMI. To mechanistically examine how obesity affects ovarian biology, female mice were fed control or high fat diet to induce hyperinsulinemia, and fertilized zygotes were isolated. Although progesterone levels were not different, females fed high fat were more likely to experience anovulation, yet those that ovulated released more oocytes. Fertilization rates were unaffected by diet but on-time development to blastocyst was impaired and cell fate partitioning in embryos was altered. Thus obesity-induced hyperinsulinemia caused ovarian defects, most strikingly impaired oocyte developmental competence. Importantly, acute peri-conception treatment with the insulin sensitizer rosiglitazone (a PPARg transcription factor agonist), but not AICAR or sodium salicylate, reversed the developmental defects observed in zygotes from obese mice. PPARg-regulated genes were upregulated in ovaries of obese rosiglitazone-treated mice further indicating that PPARg

signalling in follicular cells mediates oocyte quality determination. To more directly examine how follicular metabolism impacts oocyte quality mouse follicles were cultured in vitro. In this context high insulin altered differentiation of the cumulus oocyte complex. Cumulatively these studies indicate that maternal diet, namely overnutrition, alters the ovarian follicular environment and has detrimental consequences on oocyte developmental competence.

006

Regulation of embryonic and fetal development through maternal protein intake and by amino acid exposure in vitro

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Oocytes and embryos collected from cows on a high nitrogen intake are typically atretic. This has been related to increased levels of urea and ammonium in the fluids of the female reproductive tract. In the mouse an increase in protein level in the diet from 14% to 25%, resulted in an increase of ammonium in oviduct fluid from 68µM to 356µM. Embryos collected from females on the higher protein diet had a higher incidence of apoptosis and a decrease in total and inner cell mass numbers. Transfer of such embryos to females on a 14% protein diet, resulted in a significant decrease in implantation, fetal development and weight.

Significantly, the pathologies induced by diet are similar to those when human and mouse embryos are cultured in the presence of amino acids in a static system in vitro. This is due to the lability and metabolism of amino acids during embryo culture, which results in the generation of ammonium. After 96h incubation at 37^{o}C, medium containing amino acids can generate 300 µM ammonium. Exposure of embryos to an increasing gradient of ammonium in vitro, not only impairs development, but also affects embryo physiology, metabolism and gene expression. Notably, embryos appear most vulnerable to such stress prior to compaction. Amino acids are amongst the most important regulators of embryonic development, being involved in the regulation of metabolism and pHi, signalling and differentiation. However, accumulation of ammonium, due to the non-renewal of media containing amino acids, not only compromises embryo integrity during the preimplanation period, but may also induce birth defects.

The observed effects of changing maternal diet and/or culture conditions highlights the sensitivity of the preimplantation embryo, especially prior to the generation of a transporting epithelium at compaction, and how such stress can be manifest downstream during fetal development.

007

Oocyte gene expression profiling and the relationship to developmental competence

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Mammalian oocytes progressively acquire meiotic and developmental competence during the growth phase within the ovary. Most of the mRNA and proteins required for nuclear maturation and subsequent embryonic development, at least until activation of the embryonic genome, are accumulated during this time. In fact, transcription in mammalian oocytes virtually ceases at the time of meiotic resumption. During the final stages of meiosis the polyadenylated mRNA undergoes deadenylation. Approximately 50% of these transcripts are degraded and the rest remain stable with short Poly(A) tails and are readenylated when required later in development. Oocytes that fail to complete the growth phase or fail to accumulate and regulate genes and proteins resulting in an incorrect temporal utilization would be expected to exhibit delays or failure in progression through preimplantation development following fertilization.

The advent of commercial microarrays and high fidelity RNA amplification techniques makes it possible to profile the mRNA transcripts in the rarely available human oocyte. Global gene expression profiling and data mining has provided evidence for the relatively poor developmental competence of immature human oocytes recovered from gonadotrophin stimulated cycles and matured in vitro compared to cohorts matured in vivo. In vitro matured human oocytes have a large number of genes expressed at significantly higher expression levels at the Metaphase II stage of development than oocytes matured in vivo. Similarly the oocytes of women of advanced maternal age express a large number of genes at significantly higher levels than the oocytes of younger women. The higher expression levels associated with oocytes of poorer developmental competence indicates a failure of the normal post-transcriptional regulatory mechanisms. G-tailing experiments indicate that the Poly(A) tail length of transcripts expressed by oocytes matured in vitro is longer than for oocytes matured in vivo

Understanding of the molecular events that result in a developmentally competent human oocyte and the extent to which gene expression profiles can be altered by pathologies that underlie infertility, such as oocyte ageing, or the cellular manipulations that are used for assisted reproductive procedures, are critical for understanding and addressing improvements in fertility.

This research was supported by a grant from the NIH (U01 HD044778-01) as part of the NICHD Cooperative Program on Female Health and Egg Quality.

008

Tips for Developing Your CV for the Fellowship Systems

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Postdoctoral and early career researcher fellowships for further training here in Australia and overseas can be a key stepping stone for seriously aspiring researchers in establishing a research career. They are, however, increasingly highly competitive and success can hinge on a well-constructed CV. Fellowship assessors generally look for four things:- 1) an indication of your potential for independence and future leadership in research, 2) a strategic basis for your choice of institution, 3) a strong and well-thought through project and, most importantly, 4) track record - evidence of strong research outcomes in relation to your career stage and opportunities. It is the latter where your CV particularly comes into play. In addition to the usual personal details, current position/role and qualifications (including dates and institutions) you should consider adding a brief description of your research background, career strategy/goals and research philosophy/approach. These need to be carefully thought-through and planned – it is important to sell yourself but don't overdo it. The core part of the CV is a listing of your research outcomes – awards, publications, patent filings (and current status, even if lapsed), conference presentations, invited talks and reviews. Your publications are critical and should indicate the journal Impact Factor, journal rank within the discipline area, citations (if any – less likely for recent publications) and your role in the publication, particularly if you are not first or last author and in the middle of a team. Publishing as your PhD progresses, and highlighting these in your CV, is a good strategy. Track record is no longer just about publication numbers but now rests on a strong balance with quality and impact. Presenting your work at significant national and international meetings/institutions can help offset the disadvantage of "opportunity" for those at the earliest stages of their careers. Keeping these key elements in mind from the beginning will allow you to build a CV strategy that optimises and provides evidence for your research outcomes and potential.

009

How to write a paper that will get published

G. Risbridger

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Publication outputs are one of the metrics used to evaluate researchers at all stages of their career development. Beginning with a PhD program, publications make all the difference as many Australian Universities allow students to submit their thesis as a collection of published papers. As an early career researcher or postdoctoral fellow, publications are used for ranking and merit awards. So how doe you write a paper to get it published.

Assuming you are the first author, decide what level of publication you aim to generate, is it a high impact paper, or aimed for a specialist journal? This will determine how you pitch your results. Read some of the recent articles from that journal and decide if your own work is appropriate and would be of interest to the journal readership.

Then write the paper – discuss the data with your co-authors and decide on the message you want to get across. Assemble the figures and results, asking yourself if these data prove the point you wish to transmit. If not, then identify what else needs to be done, or adjust your message and re-evaluate if what you have, is sufficient for publication. Next, write the abstract – many people use the technique of abstract writing as promoted by Nature (see their web site). Go back and write the introduction giving the reader the background information they need to understand what you are presenting to them. Finally construct a discussion of your data; this might include highlighting why these data are important in the context of what is already known, how your results change or provide new insight or mechanisms. If possible, link this forward to how you see future developments in the field, almost telling them what to expect in you next publication. Publications are like chapters in a book; it is your job to write many chapters and books during a productive career, so enjoy the challenge.

010

The basics of grantsmanship

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Although there is no 'magic formula' to ensure funding success, paying attention to a number of key points will increase your chances. • Read the instructions; am I and my project eligible? • Should I be the first-named Chief Investigator? Do I have sufficient publications in the area? Have I successfully managed grants in the past? Have I established my independence? • There should be a logical flow to your application; What is the issue? Why is it important? What needs to be done? Why should I be given funds to do it (what is my competitive advantage)? • Be realistic about what you can do within your expertise and the time frame. • Write with enthusiasm but without hyperbole. Don't assume that all of your assessors are experts in your field, so provide sufficient background information to ensure that the significance is obvious. • What are the weaknesses of my application? Do I need coinvestigators to help me deal with them? • Layout is important. Use figures and headings, and emphasise key points. Don't fill every square centimetre of the application with writing. Highlight your own preliminary data. Relate your experimental protocol to your aims. • You don't need to fill the entire space allocation. Do not add a gratuitous extra aim because you have space. • Suggest a referee if permitted. • Show your application to senior colleagues in time for them to make comments. • If you are unsuccessful, don't take it personally. Apply to all possible granting bodies.

011

Academic medicine and clinical endocrinology for junior clinicians.

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A career in clinical endocrinology is the culmination of years of endeavour starting with MBBS and progressing through FRACP. Once the stresses of the Fellowship examinations are safely past and you are securely placed in the training program, or are just past this stage with a freshly minted College diploma, a new menu of career choices is open to you. What are the benefits of a career in academic medicine inter-relating with and running alongside your continued practice of clinical endocrinology?

Many endocrinology trainees already engage in research and overlapping Advanced Training in the third elective year with enrolment in a higher research degree is not uncommon. This can be developed into an academic career within a university-affiliated teaching hospital. The principal attractions of academic medicine are protected research time, close involvement with undergraduate medical teaching and to some extent support from university infrastructure to further research and teaching interests. University employment generally includes salary supplementation from health services so that clinical academics are remunerated to a level approximating their hospital consultant colleagues. Continued practice of clinical endocrinology and involvement in hospital life as part of the consultant staff are integral to an academic appointment. Other benefits include provision for conference and sabbatical leave. However, there is pressure to perform, to attract research grants and to demonstrate productivity by regular research publications in journals with reputable impact factors. Academic advancement relies on demonstrating high level achievement in teaching, research and service to the community and the University. Another option is to hold a hospital appointment with an adjunct or clinical title from the University. This workshop aims to relate some useful experiences and provide advice to younger clinicians contemplating a career in academic medicine and clinical endocrinology.

013

Work life balance

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Is it possible to be a hospital specialist, obtain a Ph D, pursue a university academic career, write papers, present at National and International meetings and still feel like you have a work life balance? This session will reassure you all this and more can be achieved with a career in Endocrinology. Setting realistic and healthy goals in work and private life and being prepared to revise these with time is necessary in any profession. A review of the literature on work life balance revealed that having family and outside leisure pursuits did not influence prospects of career advancement in many settings. Physicians married to physicians in general also managed to achieve a reasonable career balance without either party feeling career advancement was compromised. The presentation will look at the role of mentoring, the gender balance in endocrinology, pursuits outside of work and how they influence work performance and what this means for the next generation of endocrinology trainees.

014

Seminal Plasma and Male Factor Signalling for Female Tolerance of Pregnancy

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Provision of sperm for conception is generally assumed to be the beginning and end of the male contribution to pregnancy. But this view is now outdated – as well as sperm, semen contains potent signalling molecules that influence the female's reproductive physiology and immune system to improve the chances of pregnancy success. Male-female tract signalling occurs in all mammals so far studied including humans, and can even be found in the insect kingdom wherever egg fertilisation involves intromission and deposition of male fluids into the female. Our studies in mice, pigs and human show that cytokines and prostaglandins secreted by male accessory glands target epithelial cells in the female reproductive tract, activating changes in gene expression leading to modifications in the cellular composition, structure and function of the cervix and uterus. Seminal signalling agents also exert effects in distal tissues including the ovary, spleen and peripheral lymphoid organs. The result is 'conditioning' of the female immune response to activate tolerance of paternal antigens expressed by the conceptus, and molecular and cellular changes in the endometrium that promote embryo development and implantation, as well as effects on spermatozoa to facilitate conception. We have defined active signalling components in human seminal fluid including members of the transforming growth factor-□ family, 19-OH prostaglandin-E, and interferon-□. In women, endometrial disturbances underpinning unexplained infertility and recurrent miscarriage might occur after insufficient or dysregulated seminal factor signalling, perhaps due to seminal plasma cytokine deficiency or female incapacity to respond to seminal factors. There are implications for assisted reproductive technologies, where pregnancies are routinely initiated without intercourse, and animal breeding programs where seminal constituents are diluted for artificial insemination. A better understanding of the physiological significance of seminal fluid in human reproduction may eventually yield new diagnostics and novel therapies for infertility and pathologies of pregnancy.

015

Malignant Pheochromocytoma and Paraganglioma

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Background: Distinguishing between benign and malignant catecholamine-secreting tumors is difficult on the basis of clinical, biochemical, or histopathologic characteristics. Malignancy is rare in patients with an adrenal familial syndrome, but is common in those with familial paraganglioma caused by mutations in *SDHB*. Although the 5-year survival rate for patients with malignant pheochromocytoma is 50%, the prognosis is variable: approximately 50% of patients have an indolent form of the disease, with a life expectancy of more than 20 years, and the other 50% of patients have rapidly progressive disease, with death occurring within 1 to 3 years after diagnosis. The clinician should first assess the pace of the malignant disease and target the level of therapy to the aggressiveness of the tumor behavior. A multimodality multidisciplinary individualized approach is indicated to control catecholamine-dependent symptoms, local mass effect symptoms from the tumor, and overall tumor burden.

Treatment Options: Metastatic sites include local tissue invasion, liver, bone, lung, omemtum, and lymph nodes. Metastatic lesions should be resected if possible to decrease tumor burden. Skeletal metastatic lesions that are painful or threaten structural function can be treated with external radiotherapy or cyroablation. Thrombotic therapy for large unresectable liver metastases and radiofrequency ablation for small liver metastases are options to be considered. Because of the risk of massive catecholamine release, ablative therapy should be performed with great caution and only at centers with experience with these techniques; in addition to alpha- and beta-adrenergic blockade, these patients are usually treated with alpha-methyl-paratyrosine pre-procedure. External radiotherapy can also be used to treat unresectable soft tissue lesions. Local tumor irradiation with therapeutic doses of ^{131}I-MIBG has produced partial and temporary responses in approximately one-third of patients. If the tumor is considered aggressive and the patient's quality of life is affected, combination chemotherapy may be considered with the CVD protocol (cyclophosphamide, vincristine, and dacarbazine every 21 days).

Conclusion: Management of a patient who has malignant pheochromocytoma can be frustrating because curative options are limited. Clearly, innovative prospective protocols are needed to seek new treatment options for this neoplasm.

016

BRCA1 and 2 in hereditary breast cancer - molecular genetics going mainstream

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Breast cancer is the most common cancer to affect Australian women, with approximately 1 in 11 women diagnosed before age 75. Although there has been a longstanding appreciation that breast (and ovarian) cancer may have a familial or hereditary component, the identification of the BRCA1 and BRCA2 genes in 1994 and 1995 has enabled profound advances in our understanding of the molecular framework underpinning the pathogenesis of hereditary breast cancer. These discoveries have been rapidly applied to clinical research and practice for individuals with a strong family history, or where pathologic features of the tumour raise the possibility of a heritable mutation.

Using a multidisciplinary approach, it is now possible to provide genetic counselling and testing to women affected by breast and/or ovarian cancer, where appropriate. Once a mutation is identified, it is possible to perform predictive testing to family members to ascertain their risk. This information is now informing routine clinical practice, both in terms of how patients are monitored to assist early detection and cure (including new strategies that include MRI screening), and on the potential suitability of prophylactic measures to prevent cancer.

Important aspects of endocrine manipulation are also forming the basis for cancer prevention in some patients. Bilateral salpingo-oophorectomy carried out at age 40 halves breast cancer risk and has a profound affect on reducing ovarian cancer risk. Tamoxifen has been shown to halve the risk of ER-positive breast cancer, although its relevance for BRCA1 and BRCA2 carriers is less certain.

Finally, since BRCA1 and BRCA2 are critical for high-fidelity repair of double stranded DNA breaks, clinical trials are now in place to evaluate the role for novel agents, such as Parp inhibitors and platinum-based chemotherapy, in treating cancers that occur in BRCA carriers, as well as sporadic cancers that ‘phenocopy' BRCA tumours.

017

Multiple Endocrine Neoplasia Type 1: Cancer Syndrome or Chronic Disease ?

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MEN 1 is an autosomal dominant disorder associated with the classic triad of parathyroid, pituitary and pancreatic neoplasia. However, a broad range of both, benign and malignant, endocrine and non-endocrine diseases can develop in gene carriers.

· Primary hyperparathyroidism (>95% of patients)

· Benign and malignant enteropancreatic tumours (25-70%)

· Benign (and rarely malignant) pituitary tumours (10-50%)

· Benign adrenal macronodular hyperplasia in (10-30%).

· Bronchial carcinoid tumour and malignant thymoma (3-10%)

· Multiple lipoma (~30%)

· Cutaneous lesions (40-90%)

· Diabetes Mellitus and cardiovascular disease

Primary hyperparathyroidism typically develops during the second decade of life and is treated by near-total parathyroidectomy. Promptly establishing and maintaining normocalcaemia is an important management goal in all patients with MEN 1. Pituitary tumours, typically prolactinoma and non-functioning adenoma, may also develop as an early manifestation of MEN 1. As is the case for sporadic disease, prolactinoma typically respond to dopamine agonists and small non-functioning microadenoma often do not progress in size or require specific therapy. However, pituitary lesions in the setting of MEN 1 are recognised to follow a more aggressive course than comparable

sporadic tumours, with locally invasive disease, and rarely malignancy, reported. Non-functioning enteropancreatic tumours (pancreatic adenomas) and insulinoma typically develop in the second and third decade, with surgery usually reserved for insulinoma or large / rapidly growing non-functioning pancreatic lesions. Malignant transformation of enteropancreatic tumours remains an important cause of mortality in later adulthood, but is rare prior to 30 years of age. Hypergastrinaemia is a useful risk factor/marker of patients at risk of enteropancreatic malignancy. Adrenal lesions are typically benign, asymptomatic and non-secretory, usually occurring in adults with coexistent enteropancreatic neoplasia. Bronchial and thymic carcinoid are typically non-secretory. Whilst bronchial carcinoid is usually indolent and often benign, malignancy is typical for the thymic tumours. With appropriate management, many patients now live beyond 65 years of age. MEN 1 should be managed as a chronic disease, with regular biochemical and medical imaging undertaken to facilitate early identification, treatment and/or prevention of emergent benign and malignant complications.

018

Thyroid carcinoma

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Thyroid carcinoma is the commonest endocrine malignancy and comprises 1-2% of all malignancies. The incidence is 20-100/million/year [1] . Differentiated epithelial carcinomas are the commonest: papillary (PTC) and follicular (FTC), then medullary thyroid carcinoma (MTC), from the calcitonin-secreting parafollicular cells. There is a rising incidence of small PTCs, the biological importance of which is uncertain [2] which relates to increasing ultrasonographic diagnosis [3] . Radiation is the only known initiator of thyroid cancer and raised TSH the only known promoter. Activating mutations of c-myc and h-ras are seen in thyroid adenomas and cancers. The BRAF V600E mutation is common in PTC. Tyrosine kinase domain rearrangement of ret linked to different promotors (ret-PTC 1, 2, and 3) is associated with PTC. A PAX8-PPARγ fusion oncogene is associated with FTC, and mutation/deletion of p53 tumour suppressor gene with anaplastic thyroid carcinoma. In familial and MEN 2-associated MTC activating germ-line ret mutations occur, e.g. at codon 618. In sporadic MTC ret codon 918 somatic mutation is associated with a poor prognosis. The presentation of thyroid carcinoma is usually a thyroid nodule but can be cervical lymphadenopathy or distant metastases. Cytology of fine needle biopsy material remains the standard diagnostic technique but the predictive value of genetic markers in cytological specimens is being investigated. Thyroglobulin found by assay of needle-wash from a non-thyroidal mass is a useful cancer marker. Thyroid carcinoma management remains total thyroidectomy, [131]I ablation of the thyroid remnant, and suppression of TSH by thyroxine. Surveillance is by serum thyroglobulin, whole body [131] scanning, and high quality neck ultrasonography. FDG-PET can identify dedifferentiated disease [4] . Therapy of recurrent or metastatic disease is neck re-operation and high dose [131] ablation if iodine-avid. Treatment of dedifferentiated non-iodine avid progressive disease is unsatisfactory. Experimental therapy includes 13-cis-retinoic acid redifferentiation [5] , and VEGF/multikinase receptor antagonists [6].

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019

Vitamin D measurement: A for effort but B or C for performance.

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Accurate assessment of 25-hydroxy vitamin D (25OHD) is essential, both to identify deficiency and to monitor safe and effective treatment. Manual immunoassay has been the most popular method of analysis for many years with recently, automated versions becoming available. These routine assays perform poorly due to issues such as variable antibody specificity and difficulties with the release of 25OHD from its binding proteins. Furthermore, analysis may be complicated by the requirement to detect both 25-hydroxycholecalciferol (endogenous) and 25-hydroxyergocalciferol (exogenous).

Isotope Dilution Liquid Chromatography-Tandem Mass Spectroscopy (LC-MS/MS) has the potential to be used as a reference method for 25OHD analysis and there is limited availability of this assay in Australia.

We compared patient samples by various commercial immunoassays with the MS method (1). All assays demonstrated a similar, slight negative bias compared with LC/MSMS when samples contained 25OHD3 only. Agreement was more variable in samples containing 25OHD2. Recent European data also supports our conclusions (2).

There is poor agreement between 25OHD immunoassays reported in external quality assurance programs with high coefficients of variation, suggesting there is variability in their response to biological samples. The improved CV of the MS method reflects its better specificity.

The concerns about the ability of the current immunoassays accurately to assess vitamin D status are well founded. Although the vitamin D supplements available in Australia have now been changed to D3, small numbers of D2 containing samples are still seen. Continuing caution is required for the interpretation of routine 25OHD results.

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020

Lighting up the Laboratory.

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It is almost 50 years since immunoassay was first described. Insulin was measured using polyclonal antibodies and radioactive tracer. Since then immunoassays have been developed for a wide variety of analytes with varying chemical structure. Until the mid 1980's immunoassays used isotopic labels, polyclonal antibodies and were manual procedures. The introduction of non-isotopic labels and development of monoclonal antibody techniques have allowed immunoassay to become a highly automated process. Luminescent labels are predominantly used. These techniques provide a fast turnaround time for clinical results and have functional sensitivity up to a million fold greater compared to conventional isotopic procedures (e.g TSH) which has improved clinical utility. Despite this early assay problems remain albeit in a different form with modern assays and include: specificity, standardisation and interferences. Current literature highlights problems for many analytes including insulin, testosterone and vitamin D. Insulin assays are now highly specific and do not cross react with pro-insulin or split forms of insulin. These assays are designed for use in insulin resistance studies and sometimes can be misleading when used in the differential diagnosis of hypoglycaemia. Further there is a wide variance in observed results which mass spectrometry studies have demonstrated to be a standardisation problem. Assays for steroid hormones suffer from standardisation, interference and an inability to measure low concentrations (e.g testosterone in women and pre-pubertal children). These problems have challenged the utility of immunoassay and mass spectrometry procedures have now been developed which can be used in routine laboratories. Similarly mass spectrometry procedures are now being developed for free thyroid hormones and aldosterone. Immunoassay, as a tool has provided much information on the nature of circulating hormones. Despite problems encountered immunoassays will continue to be developed and enhanced for clinical application.

021

Limitations and future developments in assayng thyroglobulin.

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Thyroglobulin (Tg) is a large glycoprotein (MW 660,00kDa) that is synthesized by normal thyroid tissue as well as most well differentiated epithelial thyroid carcinomas (DTC). It is in the context of DTC that Tg assessment is useful as it acts as a specific and sensitive tumour marker. The long term surveillance of patients including clinical decision making of patients with DTC is based predominantly on measuring serum Tg.

However there are significant clinical and laboratory issues with respect to the use of Tg measurements. Clinical factors include the timing of Tg measurement and the context in which it is measured, i.e. TSH status. There are also a number of technical issues including analytical problems with the assays which include standardization of the analytical procedure and assay comparability, long term stability of the assay, sensitivity and precision of the assay at the low range, effect of anti-thyroglobulin antibodies and different isoforms of the Tg that may be released by cancer cells.

In the course of establishing local guidelines for the management of DTC we found there was no comparability of Tg assays in Australia. Most assays are part of an external quality assurance program (EQA's), which ensures standardization of assays in Australia which is run by The Royal College of Pathologists of Australia (RCPA) and the Australian Association of Clinical Biochemists (AACB). When made aware that Tg was not part of the EQA program, The RCPA and AACB have recently included it.

This talk will discuss the current status of

022

International Standardisation of Immunoassays

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The comparability of clinical laboratory results between laboratories and clinical centres is necessary for the use of internationally agreed clinical protocols including common reference intervals and decision limits. The reliability of these results is dependent on precision and trueness or accuracy of the assay. Results from external quality assurance programs clearly indicate that current endocrine assays demonstrate major variations limiting the usefulness of clinical guidelines and common decision limits. A number of factors contribute to variation between assays including the recent adoption of a wide range of immunoassays onto a single assay platform to accommodate ever increasing work loads and to reduce assay turn-around-times. Such platforms have variable effects on the quality of individual assays with a deterioration of quality for many. International efforts towards standardisation of immunoassays have made considerable progress particularly with regard to developing a theoretical foundation or body of knowledge for this work. The principles for standardisation of immunoassays of relatively small molecular weight analytes such as steroid hormones have been clearly enunciated and are now being implemented albeit slowly. Standardisation of assays for large molecular weight polypeptides that often exist as a family of structurally similar proteins such a human chorionic gonadotropin has proven more difficult although two strategies have been used with various analytes with different levels of success. A major factor limiting progress is the lack of resources devoted to this activity. Currently professional organisations such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) in collaboration with other specialist societies are dependent on volunteers with the provision of small amounts of funding donated from the in vitro diagnostic corporate sector. If we are to make significant achievements within the foreseeable future we will require dedicated laboratory efforts requiring major resource allocation.

023

Kinases and transcription targets in adipocyte cell fate and thermogenesis

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Adrenergic receptor signaling in adipocytes controls not only the hydrolysis of triglycerides as fuel for other organs, but is also a driver of brown adipocyte recruitment in response to cold temperature or other challenges. Since the appearance of these mitochondria-rich, thermogenically active cells in 'white' adipocyte depots is correlated with resistance to over-nutrition and glucose intolerance, the molecular basis needs to be understood. Several important transcription factors such as the PGC-1s have already been discovered as elements that respond to adrenergic signals to increase mitochondrial biogenesis and Ucp1 expression. We have described a role for p38 a MAP kinase as the downstream mediators of adrenergically-driven cAMP signaling. In this presentation we show the consequences of adipose-specific "knock-out" of p38 a MAP kinase on white and brown adipocyte function, as well as the role of other nuclear receptors such as LXRα and associated co-modulators that function as lipid-regulated repressors of these pathways.

024

Investigation of the coupling of nutrient intake with energy metabolism by melanocortins.

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Most view the obesity epidemic from a viewpoint based on thermodynamics, with energy homeostasis involving maintaining equilibrium between energy intake and expenditure. While there is still debate over whether excess calorie intake or reduced energy expenditure are causing weight gain, there remains an interest in developing pharmaceutical interventions that target one or both components of the equation. Caloric intake can vary considerably due to environmental variables (i.e., feast or famine) and the caloric density of the available nutrients. Daily total energy expenditure (TEE) is comprised of several variables including physical activity, basal metabolic rate (i.e., energy required for maintaining homeostasis of body temperature and biomechanical processes), and the thermogenic response to food intake. Maintaining overall energy homeostasis involves a continuously variable response to variations in both energy availability and energy requirements. Essential for this process is an axis involving melanocortin neurons in the hypothalamus and brainstem that couple signals of calorie intake and energy balance with satiety and the autonomic and neuroendocrine systems regulating metabolism. Results from the analysis of conditional knockout mice and humans carrying spontaneous mutations have led to the Melanocortin-4 receptor (Mc4r) as the primary focus for the development of an anti-obesity medication. Studies in mice have demonstrated that the bi-directional regulation of Mc4r activity reciprocally regulates food intake and thermogenesis. Loss of Mc4r is associated with marked hyperphagia, reduced fat oxidation, and in some cases a reduction in TEE. A second melanocortin receptor expressed in the brain, the Mc3r, is also important for energy homeostasis. Loss of Mc3r in mice leads to an exacerbation of diet-induced obesity, however the homeostatic outputs affected by the Mc3r have remained enigmatic. Moreover, results from the analysis of knockout mice suggest that Mc3r are not coupled to homeostatic outputs classically associated with the obese phenotype. Early data from our and other laboratories suggested that the Mc3r regulates energy expenditure, as the obese phenotype of these mice is independent of the marked hyperphagia observed with loss of Mc4r function. Here I will present recent data from our laboratory for how Mc3r may couple nutrient intake with thermogenesis.

025

Identifying novel sites of thermogenesis: profiling post-prandial responses in sheep

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In rodents, it is well known that thermogenesis is an important component of energy expenditure; innate differences in thermogenic rate can alter predisposition to weight gain and obesity. In contrast, the overall contribution of thermogenesis to total energy expenditure in non-rodent species has been a somewhat controversial subject. Adult humans and sheep exhibit relatively low levels of brown adipose tissue and thus the relevance of thermogenesis was deemed questionable. Recently, we have demonstrated that in the sheep tissues such as adipose and muscle display thermogenic capabilities. Exposing sheep to a feeding window, where food is made available at set daily meal times, entrains a post-prandial increase in heat production in retroperitoneal and gluteal fat, as well as in skeletal muscle. This excursion in temperature represents diet-induced or post-prandial thermogenesis. We are particularly interested in identifying novel means of manipulating post-prandial thermogenesis in fat and muscle tissues of the sheep. We are investigating homeostatic (leptin and cortisol responsiveness) and non-homeostatic (innate differences in temperament) control of post-prandial thermogenesis in the sheep. This work reveals that muscle tissue is a novel candidate target for the development of anti-obesity therapeutics. Our results indicate that muscle tissue thermogenesis is driven by uncoupling proteins 2 and 3. These data indicate that muscle tissue is indeed capable of thermogenesis, independent of that of brown adipose tissue. Given, the high proportion of muscle mass within the body, changes in thermogenic output of this tissue are particularly pertinent to total energy expenditure and the regulation of body weight. Thus muscle represents a novel site whereby thermogenesis may be manipulated.

026

Ultradian Rhythms In Basal Metabolic Rate

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Drs Ootsuka, Menezes, Alimoradian and I have discovered in Sprague-Dawley rats that brown adipose tissue (BAT) metabolic thermogenesis occurs in a striking ultradian fashion, with a periodicity of approximately 90-100 minutes, thoughout the light-dark 24 hour cycle. Each increase in BAT thermogenesis is followed by a period of heat loss via a dilated tail artery vascular bed. I will argue that the falls in BAT thermogenesis, occurring between the peaks, constitutes "mini-torpor", with close physiological ties to daily torpor and hibernation, biological processes that function to preserve energy stores. The ultradian variability in BAT thermogenesis is a fundamental part of the Basic Rest Activity Cycle (BRAC) proposed by Kleitman. Since ultradian rhythms are controlled by the brain, it must be that brain control of basal metabolic rate (BMR) is much tighter, and more physiologically relevant, than has previously been recognized.

027

Structural insights into ligand-induced activation of the insulin receptor.

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The insulin receptor and the IGF-1 receptor are homologous multidomain glycoproteins that bind insulin and IGF with differing specificity. The structure of the IR kinase domain was solved in 1994[1] but the structure of the extracellular ligand-binding domain has proved elusive until recently[2]. Our structure reveals a folded-over conformation which places the known ligand-binding regions, [L1 domain, cys rich domain (CR), the last 16 residues of the a -chain (CT)] predominantly from one monomer, in juxtaposition with the loops at the junction of the first and second fibronectin type III domains from the other receptor monomer. The L1, CR and CT regions constitute site 1, the initial low affinity binding site that contacts the classical binding surface of insulin comprised predominantly of residues from the dimer face of insulin. When this classical site of insulin is modeled onto site 1 of IR it places the recently described second binding surface of insulin, the hexamer face in contact with residues in the loops at the junction of the first and second fibronectin-III domains of IR implicating these loops as site 2, the second binding site involved in high-affinity binding[2]. This arrangement is very different from previous models which implicated the L1 domains of both monomers in high affinity binding. Our structure shows the two L1 domains to be on opposite sides of the IR dimer, too far apart to allow insulin to bind both L1 domains simultaneously. The IR is heavily glycosylated and contains a total of 19 predicted N-linked glycosylation sites in each monomer. To provide a more complete description of the receptor structure we have characterized the composition of the O-linked[3] and most of the N-linked glycans[4] and modeled the most prevalent glycoform at each site onto the IR crystal structure. We have also determined the structure of the first three domains of the IR at 2.2 Å resolution and compared it with the corresponding fragment of IGF-1R[5]. There are major differences at two of the regions governing ligand specificity. One difference is at the corner of the ligand-binding surface of the L1 domain where the orientation of the side chain of Phe39 is very different to that of its counter-part Ser35 in the IGF-1R. The second occurs in the 6th module of the cysteine-rich region, where IR contains a larger loop, negligible sequence identity, more a -helix, an additional disulphide bond and opposite electrostatic potential compared to IGF-1R[5].

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028

Hypopituitarism

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Aetiology: |Multiple pituitary hormone deficiency is most often caused by a large pituitary adenoma via compression of normal pituitary tissue, portal vessels, the median eminence and hypothalamus. Other causes include craniopharyngioma, other sellar and suprasellar cystic lesions and tumours, several forms of hypophysitis, inflammatory hypothalamic lesions including Langerhans cell histiocytosis, head injury, surgery and irradiation. Modern obstetric care has greatly reduced the incidence of postpartum pituitary necrosis. Congenital hypopituitarism may be caused by mutations of pituitary transcription factor genes such as Prop-1.

Gonadotrophin deficiency may be caused by low body weight, chronic illness, opioids and hyperprolactinaemia as well as haemochromatosis and Kallmann's syndrome. Rare forms of isolated ACTH and TSH deficiency have been described. Central diabetes insipidus implies a hypothalamic lesion.

Diagnosis: Hypopituitarism is usually diagnosed late in those not known to have a pituitary lesion. TSH is frequently ‘'normal" in those with TSH deficiency, and hypopituitarism needs to be considered in all men with low plasma testosterone. Unstimulated early morning plasma cortisol is often diagnostic. Severe growth hormone deficiency is usually present in those with multiple pituitary hormone deficiency.

Management: Once daily hydrocortisone or cortisone acetate is often adequate in those with residual cortisol secretion. TSH should not be used to guide thyroxine dose adjustment. Transdermal oestrogen is preferable to oral therapy in patients with marginal GH secretion and in those receiving GH replacement. Three monthly testosterone undecanoate is highly effective and convenient. Growth hormone is needed for bone and muscle development beyond completion of growth, and should be continued at least until mid-20's in those with childhood

onset organic GH deficiency. GH treatment should be considered in most younger patients with adult onset hypopituitarism and in many older patients. Gonadotrophin therapy is able to restore fertility in the majority of men and women with gonadotrophin deficiency.

029

Developmental Origins of Adult Female Hyperandrogenic Reproductive Function

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In eutherian mammals, fetal exposure to elevated androgen levels normally contributes to male sexual differentiation. Depending upon the gestational age at exposure, however, fetal androgen excess in females can induce various masculinized somatic characteristics and behavioral features in the presence of ovarian dysfunction. Specifically, female mice, rats, sheep and rhesus monkeys exposed to exogenous androgen excess *in utero* develop at least one adult characteristic of the hyperandrogenic reproductive disorder known in women as polycystic ovary syndrome (PCOS). PCOS occurs in about 10% of reproductive-aged women, who often experience ovarian hyperandrogenism, infertility and metabolic dysfunction. Moreover, a hyperandrogenic antecedent of PCOS exists in premenarcheal life as precocious pubarche, suggesting that PCOS has its origin prior to puberty. Consistent with this hypothesis, newborn female rhesus monkeys, exposed to androgen excess during early to mid-gestation, show elevated circulating androstenedione levels, along with LH hypersecretion and altered ovarian morphology, implicating fetal programming of multiple organ systems as the underlying mechanism. Furthermore, such androgen exposed female monkeys experience a relatively hyperglycemic environment *in utero*, followed by exaggerated insulin sensitivity and secretion in early infancy, which predisposes to abdominal obesity, insulin resistance, beta cell impairment and type 2 diabetes mellitus in adulthood. Therefore reproductive and metabolic dysfunction coexist in our nonhuman primate model of prenatal androgen excess, as it does in PCOS, suggesting that the gestational onset of androgen excess during fetal development in females can alter reproductive and metabolic development and thereby eventually impair reproduction through distinctly altered adult phenotypes.

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030

Higher-order genome organisation in platypus and chicken sperm and repositioning of sex chromosomes during mammalian evolution

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In mammals chromosomes occupy defined positions in sperm, whereas previous work in chicken showed random chromosome distribution. Monotremes (platypus and echidnas) are the most basal group of living mammals. They have elongated sperm like chicken and a complex sex chromosome system with homology to chicken sex chromosomes. We used platypus and chicken genomic clones to investigate genome organization in sperm of both species. In chicken sperm about half of the chromosomes investigated are organized non-randomly, whereas in platypus chromosome organization in sperm is almost entirely non-random.

The use of genomic clones allowed us to determine chromosome orientation and chromatin compaction in sperm. We found that in both species chromosomes maintain orientation of chromosomes in sperm independent of random or non-random positioning along the sperm nucleus. The distance of loci correlated with the total length of sperm nuclei, suggesting that chromatin extension depends on sperm elongation.

In platypus most sex chromosomes cluster in the posterior region of the sperm nucleus, presumably the result of postmeiotic association of sex chromosomes. Chicken and platypus autosomes sharing homology with the human X chromosome located centrally in both species suggesting that this is the ancestral position. These results suggest that in some therian mammals a more anterior position of the X chromosome has evolved independently.

031

Too hot too handle? environmental effects, climate change, reproduction and offspring phenotypes in lizards

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Temperature has well known links to reproductive cycles in a range of animal taxa (both ecto- and endothermic), affecting processes such as frequency and timing of reproductive events, reproductive output and ultimately reproductive success. Clearly, if environmental temperatures change as predicted with current models of climate change, this may have significant effects on reproductive processes in a range of species. Thus, understanding individual and population responses to climate change is as an important challenge. For example, in species with environment-dependent sex determination, climate change may lead to skewed sex ratios at hatching or birth. Although such sex ratio fluctuations may impose selection on alternative sex determining systems, there are virtually no empirical data on the putative link between climatic parameters and sex ratios from natural populations. Here I will explore the temperature effects on timing of reproductive events and offspring traits in an integrated series of field and laboratory studies using a small live-bearing reptiles, *Niveoscincus ocellatus*. Reptiles, as ectotherms, are particularly sensitive to temperature fluctuations in the environment as it affects their thermoregulatory

opportunities, and thus their body temperatures, with concomitant effects on most body processes from foraging ability (and food intake), metabolism, vitellogenesis, spermatogenesis and embryogenesis. In *Niveoscincus ocellatus*, environmental temperatures affect the length of gestation, timing of birth, and offspring phenotypes, including sex (i.e., temperature-dependent sex determination (TSD)). There is an ongoing debate as to how TSD species are affected by fluctuating or directional changes in climate, but until now there has been no published data on the link between offspring sex ratio and climatic variables in this, or any other squamate reptile. Sex ratios at birth fluctuated significantly among years and closely tracked thermal conditions in the field, with the proportion of male offspring increasing in colder years. Given that our species of skink is relatively short-lived (as many small vertebrates are) the impact of population-wide fluctuations in sex ratios are likely to be more pronounced than in other species where sex ratio shifts have been reported. The results are discussed in terms of potential counter adaptations, both short and long term, that may (or may not) counter directional climate change.

032

Function of nuclear sex hormone receptors in target tissues

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Nuclear receptors (NRs) form a large gene superfamily, acting as two Zinc-finger type ligand-inducible transcription factors and require a number of co-regulators and complexes for their ligand-dependent and independent transactivation functions. Such co-regulatory complexes appear to be shared with the other classes of DNA-binding transcriptional factors. The heterodimer of dioxin receptor (AhR) and Arnt, basic helix-loop-helix (bHLH)/PAS family transcription factors, are known to mediate sex hormonal adverse effects. We have recently found a novel cross-talk mechanism whereby estrogen receptor (ER)-mediated estrogen signaling is modulated by a co-regulatory-like function of the activated AhR (Ohtake et al., Nature, 423, 545, 2003). Furthermore, biochemical identification of nuclear complexes compromising two receptors led to find a novel CUL E3 ubiquitin ligase complex containing AhR as a ligand-dependent component to accelerate protein degradation of ERs as well as androgen receptor (AR), reflecting anti-sex hormone actions of AhR ligands (Ohtake et al., Nature, 446, 562, 2007). Thus, these findings implicate that chemicals serving as AhR ligands modulate sex hormone actions through degradation of the AhR target proteins, constituting a non-genomic signaling pathway. The physiological impacts of ER and AR in the hormone target tissues have been studied by conventional gene disruption approach. However, systemic defects by receptor deficiency in brain often covered the expected function of receptors in the target tissues. Recently, by a cell-type specific gene disruption approach, we have succeeded to reveal the ERalpha function in bone to reflect the osteoprotective estrogen action in intact animals (Nakamura et al., Cell, 130, 811, 2007). Thus, the regulatory roles of sex hormone receptors in target tissues will be discussed at molecular and intact animal levels.

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033

Regulation and manipulation of angiogenesis in the ovary and endometrium

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The unique cyclical physiological angiogenesis in developing follicles, corpus luteum and endometrium suggests a critical role in health and disease. Our approach is to localize the temporal changes in putative angiogenic factors and their receptors in human and non-human primate tissue and use antagonists to dissect their role by specific inhibition at defined periods during the ovulatory cycle in vivo. The quantification of angiogenesis throughout the cycle and cellular and molecular effects of inhibitory treatments have been described in the marmoset ovary and uterus while consequences on pituitary-ovarian function have been monitored in macaque serum. Inhibition of vascular endothelial growth factor (VEGF) at the time of follicle recruitment or selection prevents endothelial cell proliferation and leads to inhibition of follicular development. When VEGF is inhibited during the early luteal phase, development of the luteal microvasculature is severely restricted. Inhibition of angiogenesis at all stages of the cycle leads to profound suppression of ovarian function. Even during the 'post angiogenic' period of the luteal phase, inhibition of VEGF precipitates a rapid suppression of progesterone secretion, suggesting a role for VEGF in addition to angiogenesis. In the endometrium, oestrogen drives endometrial angiogenesis through VEGF. Thus, oestrogen can restore angiogenesis after ovariectomy, but not during inhibition of VEGF. The regulation of vessel guidance, stabilization and permeability must also be elucidated, and novel compounds to explore the roles of factors such as delta-like ligand 4, the angiopoietins and thrombospondin are becoming available.

Such basic studies will enhance our understanding of the regulation of angiogenesis in the ovary and uterus and shed light on conditions with abnormalities in blood vessel growth such as polycystic ovarian syndrome, ovarian hyperstimulation syndrome, endometriosis, uterine fibroids and menstrual dysfunction. The challenge will be to develop therapeutic strategies to safely and effectively manipulate the vasculature in these complex conditions.

034

Physiological actions of androgens in females: lessons from knockout mouse models

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deThe physiological roles of androgens in females remain relatively poorly defined. Insights into hormonal function can be obtained from observations in humans with ligand or receptor dysfunction. However, the effects of hyperandrogenism in females identify pathological actions of androgens. Similarly, although exogenous androgen treatment in females can also elicit responses, these pharmacological actions indicate the ability of tissues to respond to androgens but not necessarily a normal physiological role of androgens. Loss of function mutations in the androgen receptor (AR) in males cause androgen insensitivity (AIS), with associated disorders in sexual differentiation; however, because the AR gene is on the X chromosome, females can only be heterozygous for AR gene mutations. The study of genetically modified mouse models is providing insight into physiological roles of androgens, as AR-null females can be generated using the cre/loxP approach.

To date, the major physiological actions of androgens in females identified using knockout mouse models are in the reproductive system. AR knockout (ARKO) females have reduced fertility, with a marked reduction in the number of corpora lutea and premature ovarian failure. In addition, mammary gland development is impaired, with a reduction in ductal branching and lobuloalveolar development. Total body mass is normal in ARKO females compared to control females. ARKO females also have normal muscle mass, indicating that although androgens are anabolic in female muscle when administered exogenously, they are not required to achieve normal peak muscle mass in females. ARKO females have decreased kidney mass and cardiac mass relative to total body weight. We are currently investigating the effect of AR deletion in adipose tissue and bone of ARKO females. These studies are continuing to shed light on the target tissues and physiological actions of androgens in females.

035

Sex and fat: androgens and adipose tissue metabolism in women

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Adipose tissue plays a central role in determining whole body insulin sensitivity. Many aspects of adipose cell function are known to be regulated by sex hormones. Testosterone treatment of cultured adipose cells from women caused impaired insulin-stimulated glucose uptake. This effect of testosterone was selective for glucose metabolic signalling: insulin signalling via the mitogenic pathway was unchanged by chronic testosterone treatment. These findings suggest that, consistent with epidemiological studies, androgen excess is metabolically adverse in women. Androgens could contribute to some of the defects in insulin signalling in PCOS, potentially setting up a vicious cycle whereby hyperinsulinemia causes increased androgen production which in turn contributes to insulin resistance in adipose tissue +/- skeletal muscle. Despite the potential importance of the metabolic effects of androgens for women's health, this area remains significantly under-researched.

036

A role for androgen therapy in women?

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The potential benefits of androgens in women include favourable effects on sexual function, bone density, muscle mass, vascular endothelial function and cognitive function. Potential adverse effects include acne, hirsutism, androgenic alopecia, fluid retention and weight gain. Effects on gynaecological cancer risk and cardiovascular disease (CVD) risk could potentially be positive or negative. There is no valid biochemical definition for “androgen deficiency” in women and this has presented a major obstacle for clinicians in this field [1] . Several large randomized placebo-controlled clinical trials involving naturally [2] and surgically [3] postmenopausal women presenting with low libido demonstrate that testosterone therapy, with and without concurrent estrogen therapy, improves the quality of the sexual experience, with preliminary data that this may also apply to premenopausal women [4, 5] . Our Cochrane review of the published literature up until the end of 2003 indicated that the addition of testosterone to postmenopausal hormone therapy is beneficial in terms of improved sexual function with an adverse effect of decreased serum HDL cholesterol, primarily with oral therapy [6] . Subsequent randomized controlled trials (RCTs) indicate that non oral testosterone therapy does not adversely effect plasma lipids or other CVD risk markers (lipoprotein (a) or high sensitivity CRP) [5, 7] . Virilisation is dose dependent with few women discontinuing therapy in RCTs due to acne or hirsutism. Improved mood has also been documented [4] . There is inadequate data pertaining to effects on cognition or cancer and long term safety data is lacking. A critical issue with respect to evaluating the sfatey of long term exogenous testosterone is that the women most likely to use testosterone therapy are relatively young and have a low incidence of disease, such that an adequately powered study to evaluate CVD risk, cancer risk or other potential risks is not feasible.

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037

Androgens in polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common form of endocrine disorder in premenopausal women. Reported prevalence of PCOS among women of reproductive age varies according to the mode of diagnosis and is estimated to be between 5 and 10%. The diagnostic hallmarks are hyperandrogenism and ovulatory dysfunction leading to hirsutism, acne, male pattern alopecia and oligo- or anovulation. The ultrasound appearance of "polycystic" ovaries is not necessary for the diagnosis. The diagnostic criteria for PCOS are broadly inclusive and there are undoubtedly subsets of PCOS with different pathophysiology. However, insulin resistance and subsequent hyperinsulinaemia are thought to be central to the pathophysiology in the majority of PCOS. High circulating insulin amplifies ovarian androgen production via insulin receptors on theca cells and increases androgen bioavailability by suppression of SHBG. The free androgen index, but not DHEAS, correlates with the high prevalence of metabolic syndrome in PCOS.

Traditionally, treatment for the hyperandrogenism of PCOS has been to reduce gonadotrophin-driven ovarian androgen production by the use of the combined oral contraceptive pill, with or without anti-androgen therapy. With recognition of the role of insulin resistance and hyperinsulinism in PCOS, attention has been given to dietary modifications, exercise, metformin and thiazolidinediones. Lifestyle modification, weight control and exercise and insulin sensitisers have all been demonstrated to ameliorate hyperandrogenism as well as menstrual irregularity.

038

The First Meiotic Division in Oocytes is the Nemesis of Fertility for Women in the 21st Century

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Oocyte quality is a major factor governing a woman's fertility. Quality is poor when chromosome segregation errors occur during the first meiotic division. Such errors, which include trisomy 21 (Down's Syndrome), affect between 20-40% of all human oocytes, and go on to produce mostly non-viable, aneuploid embryos; making chromosome segregation errors the leading cause of early embryo loss. The aetiology of aneuploidy in oocytes has been investigated by a number of groups but has remained frustratingly obscure, with female age being the only well-characterized correlate. Therefore, with increasing numbers of women wanting to delay having children until their late thirties /early forties, there remains an immediate need to understand why oocytes are so error-prone in segregating chromosomes, and why errors increase with female age. The Spindle Assembly Checkpoint (SAC) is a universal, error-detecting mechanism, employed by all dividing cells to stall cell division until chromosomes are ready to segregate. Although it was first thought that the SAC would be defective or absent in oocytes, our work and that of others has shown that this is not the case. Instead, we have recently found that the oocyte's susceptibility to chromosome mis-segregation is due to its peculiar and unique regulation of the SAC's target: the Anaphase-Promoting Complex (APC), and its two co-activator proteins CDC20 and CDH1. The oocyte uses a stalling mechanism to delay meiotic division based on APC-CDH1 activity, until chromosomes can be segregated equally, that is not observed in adult cells and is inherently error prone. We postulate that this activity provides a ready target for mis-regulation, and could account for the increasing rates of aneuploidy as women age.

039

Regulation of the mitosis to meiosis switch and germ cell fate in the mouse embryo

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In a mouse embryo, germ cells migrate into the developing gonads at about 10 – 11 days post coitum (dpc) where they continue to divide mitotically until about 13.5 dpc. At that time, germ cells cease division and, in a female gonad, begin meiosis or, in a male gonad, arrest in G0/G1 (mitotic quiescence). Recent studies have shown that germ cells in a female mouse embryonic gonad are induced to enter meiosis, rather than entering meiosis automatically. It seems that the inducing factor is retinoic acid (RA). RA probably enters the embryonic gonad at the anterior end, through open connections with the adjacent mesonephros, the site of RA production. RA induces germ cells to express Stra8, which encodes a protein essential for initiation of meiosis in both sexes. Germ cells in an embryonic mouse testis avoid entering meiosis because RA is actively degraded by a P450 enzyme, CYP26B1, which is produced in somatic cells shortly after male somatic sex is determined by SRY. In Cyp26b1 KO mice, XY germ cells enter meiosis prematurely, although they ultimately undergo apoptosis.

We are continuing to study the actions of RA in the mouse embryonic gonadal model and, in particular, are addressing the question of whether RA acts directly on germ cells and, if so, whether Stra8 is a direct transcriptional target of RA. We are also studying RA-induced Stra8 expression is specific to certain cell types only and whether germ cell fate is instructed also by a second male-specific factor.

040

Allocation and navigation of primordial germ cells during early mouse embryonic development

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The establishment of the germ cell lineage in the mouse begins with the formation of the precursors and the regionalization of primordial germ cells (PGCs). Analysis of genetic mutants reveals that the signalling activity of both bone morphogenetic proteins (BMP) and WNT factors are required for the specification of the precursors of the PGCs in the epiblast. During gastrulation, the PGCs congregate to the site of germ layer formation and are then relocated to the gut endoderm. The activity of two genes of the Interferon induced transmembrane (IFITM) protein family, Ifitm1 and -3, which are likely to be downstream of WNT and BMP signalling, are involved in the inter-cellular interaction of the PGCs with the surrounding tissues. IFITM1 mediates the repulsive activity between expressing and non-expressing cells while IFITM3 enables the cells to perceive some yet unknown guidance signals for homing to appropriate sites. Molecular dissection of these two IFITM proteins showed that the extracellular domain confers the functional specificity. The migration of PGCs within and between germ layers may be navigated by the differential expression of these cell surface proteins.

041

Animal models of germ cell sex reversal

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During mouse gonadal development, testis differentiation proceeds when Sry activates the transcription of Sox9 in pre-Sertoli cells, while in the absence of Sry, an ovary develops. In the fetal ovary mouse primordial germ cells proliferate until E13.5, and then enter meiosis under the influence of retinoic acid, leading to oogenesis. In the fetal testis, XY germ cells are prevented from entering meiosis by the action of the Sertoli cell retinoic acid degrading enzyme Cyp26b1, leading to spermatogenesis. We hypothesise that a male-specific factor must regulate Cyp26b1 expression in the XY gonad. Similar to Sox9 KO mice, we show that in XY mice lacking FgfR2, somatic cells fail to differentiate into Sertoli cells, and instead express markers of female gonadal development. In these mice at E13.5, Cyp26b1 is no longer expressed, and as a consequence, XY germ cells show sex-reversal - they enter meiosis, express Dmc1, Scp3, Stra8, and have condensed chromosomes typical of meiotic prophase. While FgfR2+/- and Sox9+/- singly heterozygous mice show no germ cell phenotype, FgfR2+/-; Sox9+/- mice phenocopy the germ cell sex reversal observed in the FgfR2 KO mice. Sox9 mice lack male-specific expression of FgfR2 and conversely, FgfR2 KO mice lack Sox9. We conclude that a feedforward loop of Sox9/FgfR2 regulation is required for expression Cyp26b1 and consequent inhibition of meiosis. Preliminary analysis of FgfR2 XX KO gonads reveal a drastic loss of XX germ cells entering meiosis, indicating that FgfR2 has a role in both male and female germ cell development.

042

Thirst in angiotensin-deficient mice

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Water drinking in response to hypertonicity, hypovolemia and dehydration were investigated in mice lacking angiotensin II because of experimentally-induced deletion of the angiotensinogen gene (Agt-/- mice), and in C57BL6 wild-type mice (WT-mice). Daily water intake in Agt-/- mice was threefold that of WT-mice because of a renal developmental disorder of urinary concentrating mechanisms in Agt-/- mice. Intraperitoneal (i.p.) injection of hypertonic saline (0.4 and 0.8 mol/l NaCl) caused a similar dose-dependent increase in water intake in both Agt-/- and WT-mice during the hour following injection. As well, Agt-/- mice drank appropriate volumes of water following water deprivation for 7 hours. By contrast, Agt-/- mice did not increase water drinking or 0.3 mol/l NaCl intake in the 8 hours following administration of a hypovolemic stimulus (subcutaneous 30% polyethylene glycol), but WT-mice increased intakes of both solutions during this time. Osmoregulatory regions of the brain, e.g. hypothalamic paraventricular and supraoptic nuclei, median preoptic nucleus, organum vasculosum of the lamina terminalis (OVLT) and subfornical organ, showed increased number of neurons exhibiting Fos-immunoreactivity (Fos-IR) in response to i.p. hypertonic NaCl in both Agt-/- mice and WT-mice. PEG treatment increased Fos-IR in the subfornical organ, OVLT, supraoptic and paraventricular nuclei in WT-mice, but only increased Fos-IR in the supraoptic nucleus in Agt-/- mice. Our results show that brain angiotensin is not essential for the adequate functioning of neural pathways mediating osmoregulatory thirst and the replacement of a water deficit following water deprivation. However, angiotensin II of either peripheral or central origin is necessary for thirst and salt appetite that results from hypovolemia.

043

Insulin-regulated aminopeptidase is the specific binding site for angiotensin IV – role in the brain

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Angiotensin IV (Ang IV) and LVV-hemorphin 7 (LVV-H7), elicit robust effects on accelerating spatial learning and facilitating memory consolidation. More importantly, they restore memory in animals with experimental amnesia induced by mechanical lesions of the perforant pathway, by scopolamine treatment and by ischemia. Following our identification of the specific binding site of these peptides as the enzyme insulin-regulated aminopeptidase (IRAP), we found that these peptides are potent competitive inhibitors of the enzyme. IRAP was initially cloned from a rat epididymal fat pad cDNA library as a marker protein for specialized vesicles (known as GSV-GLUT4 storage vesicles) containing the insulin-responsive glucose transporter, GLUT4. IRAP was thought to play a role in the tethering or trafficking of these vesicles. The same protein is also known as oxytocinase, an enzyme thought to play an important role in regulating circulating oxytocin levels during pregnancy.

Mapping the distribution of IRAP in the brain revealed an almost complete co-localisation of IRAP with GLUT4 in intracellular compartments resembling GSV in neurones in the hippocampus and cerebral cortex. We found that Ang IV and LVV-H7 enhanced activity-evoked glucose uptake in hippocampal slices. This effect was totally abolished in the absence of IRAP and is mediated by a GLUT4-dependent mechanism. Our findings confirm that there is an analogous GSV system in neurones that co-express IRAP-GLUT4 and is responsible for facilitating glucose uptake following neuronal activation.

044

The role of angiotensin II in obesity and insulin resistance

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Obesity, the excess accumulation of body fat due to an imbalance between energy intake and output, is reaching epidemic proportions and is a major health hazard worldwide. It is linked to the aetiology of a number of conditions such as cardiovascular disease, hypertension, stroke and diabetes. Adipose tissue not only acts as an energy store, but also behaves like an endocrine organ, synthesising and secreting numerous hormones and cytokines. Evidence exists suggesting that the cytokines secreted by small adipocytes enhance insulin sensitivity while the adipokines secreted by large, triglyceride loaded adipocytes interfere with the actions of insulin. Angiotensin II (ANG II) is the biologically active component of the renin-angiotensin system (RAS). The RAS is present in adipose tissue and is intimately linked to obesity. Indeed, ANG II inhibits lipolysis and interferes with adipocyte differentiation leading to expansion of existing adipocytes and secretion of adipokines that decrease insulin sensitivity. Evidence obtained using genetically modified animals has shown that the amount of body fat is directly related to the amount of ANG II, i.e., animals with low levels of ANG II (ACE knockout mice) have reduced fat stores while animals with excessive ANG II (Ren 2 rats) have increased fat stores. Furthermore, in animals maintained on high fat diets, evidence will be presented to show that blocking the production and/or actions of ANG II decreases body fat and improves glucose tolerance. The decrease in body fat caused by such treatments predominantly occurs in abdominal fat depots and appears to be independent of energy intake and digestibility. Clearly, ANG II has an important role in the accumulation of body fat and the possibility exists that treatment of obesity will be enhanced by the use of natural or synthetic substances that interfere with ANG II.

045

The role of the renin-angiotensin system in diabetic vascular complications.

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Over the last decade the evidence that blockade of the renin-angiotensin system (RAS) will play a pivotal role in the prevention and retardation of diabetic complications has been greatly strengthened by the results from large multi-centred multi-national trials. In particular, agents which interrupt the RAS appear to be particularly useful in diabetic renal disease. Although the retina has all the components of the RAS, the role of RAS blockade in diabetic retinopathy remains to be fully elucidated with positive reports such as the recent RASS study suggesting retinoprotection with enalapril and losartan. The imminent release of the DIRECT study using candesartan should further clarify the role of these agents for this disorder. Finally, diabetic macrovascular disease appears to be partly related to local activation of the RAS although the clinical evidence of a superior effect of drugs that interrupt the RAS when compared to other antihypertensive agents is not overwhelming. Over the last 5 years it is increasingly appreciated that the RAS is more complex than considered with various new receptors and enzymes identified such as the putative renin receptor and the enzyme ACE2. The role of these new components is not yet understood although interestingly the major sites of expression of these proteins are the kidney, heart and retina, major sites of diabetic complications. With increasing evidence that ACE2 generates vasodilatory angiotensins such as A1-7, it is now considered that disorders such as diabetes may be states of imbalance between the vasoconstrictor arm of the RAS with its major effector peptide, angiotensin II (A1-8) and the vasodilatory arm involving ACE2 and A1-7. It is predicted that over the next few years the relative imbalance of these 2 arms of the RAS in diabetes will be further evaluated leading to a more rational use of agents that interrupt the RAS in diabetes.

046

HIF-1α (Hypoxia Inducible Factor 1 α) is required for normal β-cell function

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We have previously reported that the transcription factor ARNT has markedly decreased expression in pancreatic islets isolated from people with type 2 diabetes. ARNT functions as a heterodimer. Our studies identify HIF-1α as the most important partner for ARNT in β-cells. HIF-1α expression is decreased in islets from people with type 2 diabetes, and HIF-1α protein is decreased in sections of pancreas from people with type 2 diabetes compared to controls.

HIF-1α knockdown causes impaired β-cell function. Mice with β-cell specific deletion of HIF-1α have glucose intolerance with impaired glucose stimulated ATP generation, accompanied by impaired glucose stimulated insulin secretion.

These studies demonstrate the HIF-1α is required for normal β-cell function and identify HIF-1α as a potential therapeutic target for the treatment of type 2 diabetes.

047

Redefining the Biological Roles of Inhibin A and B

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Inhibin A and inhibin B are dimeric glycoproteins that have primarily been studied for their ability to suppress follicle stimulating hormone (FSH) secretion from the anterior pituitary. The α- and β-subunits of the inhibin isoforms are synthesized as precursor proteins, which dimerise prior to proteolytic maturation. Our recent studies have shown that non-covalent interactions between the pro- and mature domains of the inhibin α- and β-subunits, respectively, are critical for the correct folding, dimerisation and secretion of the active ligand. Outside the cell, inhibin A activity is dependent upon interactions with its co-receptor, betaglycan. We have shown that betaglycan binds to key residues on the outer convex surface of the inhibin α-subunit and that this interaction promotes the formation of stable high affinity complexes involving activin type II receptors. The relatively ubiquitous expression of inhibin receptor components supports the concept that the inhibin isoforms may function in tissues (e.g. bone) outside the reproductive axis. Interestingly, the expression patterns of the inhibin isoforms are sexually, spatially and temporally dimorphic raising the possibility that inhibin A and B may be functionally/mechanistically distinct. In support, we have shown that an α-subunit mutation associated with premature ovarian failure preferentially affects inhibin B biological activity. Moreover, the ability of inhibin B to suppress activin-induced FSH release by rat pituitary cells in culture was not effected by disruption of the betaglycan binding site. These new studies support a distinct mechanism of action for inhibin B and provide evidence for inhibin activity in numerous organs throughout the body.

048

Translating testicular axis physiology to clinical practice

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Endocrine glands communicate continuously and through intermittent signal exchange. Pulsatile (intermittent) signals allow rapid large adjustments to maintain homeostasis in the face of environmental and other changes and orchestration of growth, development and reproduction in the case of pulses of growth hormone and luteinising hormone . Deconvolving pulsatile secretion and assessing the network male gonadal axis through validated mathematical models, experimental interventions (“clamp” studies) and entropic non-linear methods unveils impaired GnRH action, attenuated LH drive of testosterone secretion, and network dysynchrony as key changes of male reproductive aging. The application of these methods to other putative disorders of androgen regulation such as obesity, metabolic syndrome and obstructive sleep apnea is likely to generate further insights.

Testicular axis physiology can also be utilised in two reproductive paradigms of immediate clinical relevance. Harnessing negative feedback suppression of gonadotropin secretion through androgen-progestin administration is the basis for male hormonal contraceptive methods. More research into male directed contraceptive methods is needed because family planning is a shared responsibility and the currently available methods are either not sufficiently reliable, or not easily reversible. Hormonal methods remain the closest to clinical use, and recent landmark advances include documentation of the reversibility and predictors of response and the completion of a number of large-scale multicentre studies in Europe and Asia.

Feedforward stimulation of spermatogenesis is another function of the male gonadal axis, which is mimicked clinically to induce spermatogenesis during gonadotropin (or pulsatile GnRH) therapy in gonadotropin deficient men. Insights derived from treating gonadotropin deficient men with gonadotropin therapy will have implications for understanding physiology, pathophysiology and optimised clinical care. These advances will require multivariate analyses in sufficiently large clinical cohorts that are frequently and intensively assessed. Close collaboration, interdisciplinary approaches and national coordination will be increasingly needed for modern clinical research in reproductive endocrinology, and in other parts of health science.

049

New Fat Cell Generation in Adult Humans – Regulation and Intervention

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Obesity is a major contributor to death and disability due to its strong association with many chronic diseases. Even modest weight loss is associated with significant improvements in fat tissue endocrine function resulting in improved metabolic health yet the incidence of obesity continues to rise highlighting the inefficacy of current anti-obesity strategies. Recently new adipocyte generation in adult humans has been linked to obesity suggesting that inhibiting this cellular expansion may provide a basis for innovative approaches to obesity treatment[1]. To further develop this approach we need to understand the molecular processes which drive adipocyte formation. Adipocytes are derived from stem cells, termed preadipocytes (PA), through the process of adipogenesis and to study this process specifically in humans we have developed an efficient model using PA isolated from human fat. Using this model w e identified FGF-1 as a paracrine factor (produced by endothelial cells within fat tissue) which has potent stimulatory effects on human adipogenesis. We also identified components of the signalling pathway, including specific FGF receptors (FGFR), which mediate FGF-1 adipogenic actions. Importantly, we have now demonstrated that pharmacological inhibition of the FGF/FGFR signalling axis prevents *in vitro* development of new human adipocytes and also inhibits expansion of fat tissue mass in a murine model of diet-induced obesity. Further, the *in vivo* studies also demonstrate metabolic improvements in several parameters including insulin sensitivity and glucose handling in animals treated with FGF/FGFR inhibitors. These findings provide strong evidence that targeting this pathway may form the basis for development of novel anti-obesity strategies which directly target fat tissue mass. Such an approach, aimed at reducing fat cell number, has the potential to revolutionize the pharmaceutical treatment of obesity. This presentation will focus on our findings with regard the adipogenic role of FGF-1 both *in vitro* and *in vivo*.

1. Spalding et al., Nature, May 2008.

050

The genetics of obesity: lessons from mouse models

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A great frustration in the management of obesity is the very high rate with which weight is regained after weight loss. Given the strong desire for individuals to be lean this was perplexing until we began to understand body weight regulation.

Recent work has revealed a highly complex system involving the hypothalamus as the key central control unit. In turn the hypothalamus has inputs from a range of circulating hormones and nutrients and neuronal signals informing it of the nutritional and weight status of the body. Many proteins are involved in this complex system, which is known to have considerable redundancy. Experiments of nature producing individuals or mice with severe monogenic obesity (e.g leptin deficiency or leptin receptor) have been very informative. In addition, selective deletion of hormones or receptors have further clarified the roles of these pathways.

A large number of mouse models with body weight changes are available for study, in the time available only the most informative will be discussed. Not surprisingly many deal with hypothalamic function (NPY receptors, NPY, MCH-/- mice, leptin receptor, CB1 receptor, serotonin transporter, orexin, MC4R). Others investigate the role of adipose tissue proteins (leptin) and even the liver (Fructose 1.6 bisphosphatase, PEPCK).

Together these models have highlighted the genetic basis of obesity. Having identified the function of proteins a clearer understanding of their physiological role has brought us to a better understanding of why obesity is so difficult to treat with lifestyle methods alone.

051

Management of Childhood Obesity

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The problem: Prevention strategies remain a key focus in the battle against childhood obesity. However, in order to avoid an imminent pandemic of obesity-related disease we also urgently need to treat the increasing number of Australian children/adolescents who are already obese (currently approximately 250,000). Unfortunately, at present, an optimum management plan for these individuals does not exist.

Diagnosis: Initial detection and correct diagnosis are essential to any successful treatment program and yet these are often not straightforward procedures. We must therefore urgently improve our techniques in these key areas.

Assessment and investigation: While it is known that numerous co-morbidities, such as Type 2 diabetes and risk factors for heart disease, are more prevalent in obese vs. normal-weight children, we are only just realising that it is not necessarily the most severely obese who are at the highest degree of risk. Therefore, proper assessment must examine not only the multi-factorial causes of weight gain in youth, but also risk factors for co-morbidities, in all obese children. Unfortunately this is a time-consuming and difficult clinical challenge and, until we fully understand the processes that underlie disease development in obesity, we are not best placed to decide upon which obese children should be targeted for treatment.

Treatment strategies: ‘At-risk' obese individuals then need enrolment into effective treatment programs and, although numerous settings for childhood obesity management have been trialled (from community- to tertiary care-based services), to date virtually all community and primary-care initiatives have failed to produce tangible results. It is clear that more research is urgently required to identify the best setting in which to target and treat obese ‘at-risk' children.

Summary: We now need to think outside of the box if we are to develop effective management programs for all obese youth who are at risk of developing obesity-related complications.

052

Leptin Resistance in Melanocortin Circuits

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Leptin acts on several circuits in the brain, to regulate food intake and energy expenditure. In particular it has been shown that leptin can activate proopiomelanocortin (POMC) neurons, and that the melanocortin system is a necessary mediator of leptin action on energy balance. POMC neurons are activated by glucose, and this activation is necessary for normal glucose control. We have recently demonstrated that mice made obese by chronic consumption of a high fat diet have melanocortin systems that are unresponsive to leptin and glucose. Low fat diet reverses this leptin resistance, and reestablishes normal glycemic control. Here I will discuss leptin and glucose sensing in the melanocortin circuits of lean and obese mice.

053

Obesity, Type 2 Diabetes and weight loss surgery

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Intensive treatment of type-2 diabetes is associated with improved health outcomes and a better quality of life. For the obese patient, weight reduction should be a central part of that treatment and has been shown to improve the disease.

The laparoscopic placement of an adjustable gastric band (LAGB) offers a minimally invasive, controllable and reversible method for achieving substantial weight loss in a gentle manner and studies indicate its effectiveness in managing the "diabesity" patients

We compared LAGB with non-surgical methods for weight control in a randomised controlled trial of 80 mild to moderately obese patients (BMI 30-35). There was a highly significant differences in weight loss (85% of excess weight lost in the LAGB group versus 21% in the non-surgical group), resolution of the metabolic syndrome and improvement in quality of life. Adverse events were equal.

We then randomised 60 subjects with recently diagnosed type 2 diabetes to LAGB or optimal medical therapy. Remission of type-2 diabetes (fasting glucose <7mmol/l and HbA1c <6.2% while taking no glycaemic therapy). At 24 months surgical and conventional groups had lost mean (SD) of 20.7 (8.6) % and 1.7 (5.2) % of weight respectively at 2-years ($P < 0.001$). Remission was achieved by 22 (73%) in the surgical group, and 4 (13%) in the conventional group. Surgical group relative risk of remission was 5.5 (95% confidence interval 2.2 – 14.0). Remission was strongly related to weight loss ($R^2 = 0.46$, $p<0.001$); 10-14% weight loss provided 85% sensitivity and 88% specificity for remission. The surgical group had greater improvements in insulin, triglycerides and HDL-cholesterol. The metabolic syndrome was present in 29 (97%) in each group at baseline and was not present in 21 (70%) surgical and 4 (13%) conventional subjects at 2-years ($p<0.001$). There were no serious complications in either group.

Conclusion: There is a direct relationship between weight loss and remission of type 2 diabetes in obese subjects. Surgical therapy provided more reliable weight loss and should be considered when planning treatment for obese subjects with type-2 diabetes

054

Dual purpose contraceptives: targeting fertility and sexually transmitted disease

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There is an urgent need to develop novel, safe, effective, dual-purpose contraceptive agents that combine the prevention of pregnancy with protection against sexually transmitted diseases (STDs). In this context we have explored the chemical principles by which a topical contraceptive agent could be developed that selectively immobilizes spermatozoa, as opposed to the non-selective killing mechanism typical of commercially available spermicides. We have also successfully developed strategies by which spermatozoa could be used to activate a latent microbicide that would be active against pathogenic organisms (including viruses) while leaving the endogenous vaginal microflora unaffected. The compounds identified in this study are considerably more active and significantly less toxic than the reagent in current clinical use, nonoxynol 9. Moreover, analysis of microbicidal activity, using Chlamydia as the target, has revealed powerful inhibitory effects at the same low micromolar doses that suppress sperm movement. These findings open up new possibilities for the development of selective topical contraceptive agents that are women-centred and simultaneously prevent conception while reducing the risk of infection with an STD.

055

Molecular basis for sperm-egg interaction; prospects and problems for contraceptive development

B. Nixon

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At the moment of insemination millions of mammalian sperm cells are released into the female reproductive tract in order to find a single cell – the oocyte. The spermatozoa subsequently ignore the thousands of cells they make contact with during their journey to the site of fertilization, until they reach the surface of the oocyte. At this point, they bind tenaciously to the acellular coat, known as the zona pellucida, that surrounds the oocyte and initiate the chain of cellular interactions that will culminate in fertilization. This exquisitely cell- and species-specific recognition event is among the most strategically important cellular interactions in biology. Understanding the cellular and molecular mechanisms that underpin this interaction has obvious implications for the development of novel targets for contraception.

Elucidating the nature of sperm-zona pellucida interactions has therefore been the subject of intense investigation by many laboratories. Although this has led to extensive characterization of the respective gametes, such studies have failed to elucidate the molecular basis of this event. In our considered judgment this lack of success stems from the incorrect assumption that the sperm receptor is a single molecular entity that is constitutively expressed on the cell surface. In contrast, recent research from our laboratory has provided support for a novel hypothesis that sperm-egg interaction is mediated by a multimeric sperm receptor complex. Furthermore, we have compelling evidence that this complex is assembled on the sperm surface through the concerted action of a family of molecular chaperone proteins that reside within specialised membrane domains, known as lipid rafts. Our ongoing work is focusing on the composition of the sperm surface receptor complexes and delineating the role of molecular chaperones in their assembly.

056

Development of a contraceptive approach for the management of highly-valued marsupial populations in Australia: Science, efficacy and ethics

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In recent years, wildlife managers have been under increasing pressure to manage 'overabundant' marsupial populations using non-lethal methods. This has stimulated research and development of novel contraceptive techniques that can be efficaciously applied to free-ranging wildlife populations. We have been investigating the application of a long-acting GnRH agonist implant (Suprelorin®, Peptech Animal Health) to control fertility in kangaroos, wallabies and koalas. Evaluating the use of this commercial veterinary product in marsupials has involved studies on the physiological, endocrine and behavioural response to treatment, and measurement of the contraceptive duration. From these studies we have developed a model outlining the physiological processes resulting in successful GnRH agonist-induced contraception in macropodid marsupial species and we are in the process of developing efficient contraceptive delivery methods.

The benefits of this research extend beyond the potential applied outcomes, and include improved knowledge of pituitary-gonadal interactions in marsupials and of the process of GnRH agonist-induced pituitary desensitisation in general. For example, there appears to be a relationship between contraceptive dose and duration in tammar wallabies *(Macropus eugenii)*, as has been observed in other species. Tammars that received a higher dose of Suprelorin (9.4mg) were contracepted for longer than those receiving a lower dose (4.7mg). At the time of writing, all six low dose animals had resumed breeding 478±67 days (mean±sem) post-treatment, but only 5/10 high dose animals had resumed breeding 778days post-treatment. Subsequent investigations in tammars suggest that this dose-response relationship may be the result, at least in part, of a prolonged period of pituitary recovery post-treatment in animals that are exposed to higher doses. After six months of treatment, implants were removed from animals and the time to pituitary recovery (1st birth) was significantly greater in high dose animals (High=84±18days, Low=43±8days, Placebo=38±7days; n=6/group; anova $P<0.05$).

057

Targeting endometrial cytokines as a non-hormonal contraceptive strategy

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Despite huge increases in access to contraceptives globally, over 120 million couples have an unmet need for contraception. Eighty million women have unintended or unwanted pregnancies, and pregnancy related complications including unsafe abortions kill more than half a million women annually. There is an urgent need to develop contraceptive methods that are free from undesirable hormone – related side effects. As a novel approach for new non-hormonal contraceptives for women, we have used new antagonists to two endometrial cytokines, leukemia inhibitory factor (LIF) and interleukin 11 (IL-11). Both cytokines are produced maximally during the phase of uterine receptivity in women and their action is absolutely required for implantation in mice. Polyethylene glycol (PEG) was conjugated to LIF antagonist (LA) or IL-11 antagonist (IL-11A) to increase their serum half-life. Both antagonists have been tested for their effectiveness to block (i) their respective cytokine action in the endometrium and (ii) implantation following administration via intraperitoneal (IP) injection in mice. IP administration of PEGLA during early pregnancy resulted in total prevention of embryo implantation while having no embryo toxic effects[1]. Similarly, IP administration of PEGIL-11A blocked decidual cell IL-11 target proteins and uterine decidual transformation resulting in pregnancy failure. While each inhibitor was effective in completely blocking pregnancy in mice, the timing of administration was critical. If proven to be similarly effective at blocking implantation in primates, these inhibitors will offer new opportunities as pharmacological but non-hormonal contraceptives for women.

1. White CA, Zhang JG, Salamonsen LA, Baca M, Fairlie WD, Metcalf D, Nicola NA, Robb L, Dimitriadis E (2007) Proc Natl Acad Sci U S A. 104 : 19357-62

058

Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is a common endocrine disorder in which serum calcium and parathyroid hormone (PTH) levels are elevated. In most cases, the disorder is due to a single parathyroid adenoma that is generally amenable to removal by traditional and, now, more innovative and less invasive surgical approaches. Most patients with PHPT in the United States, and in many other parts of the world, are asymptomatic. They have neither signs nor symptoms that are commonly associated with elevated PTH or hypercalcemia. The guidelines for recommending surgery in asymptomatic patients have been in place since 2002, in connection with an NIH Workshop on PHPT that was held at that time. These guidelines include: a) serum calcium >1 mg/dl above the upper limits of normal; b) marked hypercalciuria, >400 mg/day; c) bone mineral density determination by dual energy X-ray densitometry (DXA) <-2.5 at lumbar spine, hip,

or distal radius (1/3 site); d) creatinine clearance reduced by >30% in comparison to age and sex-matched norms, e) age <50. Among asymptomatic patients with PHPT, about 40-50% of individuals will meet one or more of these guidelines. It should be emphasized that these guidelines are designed for asymptomatic PHPT; those with overt manifestations of disease such as kidney stones should have parathyroid surgery. Over the past 5 years, new information has become available and concepts developed giving new insight into this disorder and aiding the decision to recommend parathyroid surgery or not.

059

Is hypercortisolism pathologic in the absence of Cushing's syndrome?

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The association of hypercortisolism and a variety of physical and psychological signs and symptoms is codified and accepted as Cushing's syndrome, which may be lethal if not recognized and treated. Even subtle hypercortisolism, so called "subclinical Cushing's syndrome" may underlie diabetes, hypertension and weight gain. By extension, and as suggested by a variety of recent findings, one might speculate that increased cortisol action in the absence of frank Cushing's syndrome may be pathologic. This possibility is suggested by a number of associations linked to enhanced cortsiol activity in people and rodents, including 1) the association of fetal, neonatal and adult hypercortisolism with features of the metabolic syndrome in adulthood 2) the association of increasing cortisol exposure with decreased cognitive ability in the elderly and 3) the association of hypercortisolism with psychiatric disorders. Most of these studies are correlative, and thus cannot demonstrate causality. Possible pathogenetic mechanisms for these associations include fetal reprogramming of the HPA axis, possibly via changes in the mineralocorticoid-to-glucocorticoid receptor ratio in the brain or via decreased 11BHSD2 activity of the placenta; differences in glucocorticoid receptor haplotype and the presence of polymorphisms that enhance glucocorticoid sensitivity; decreased sensitivity to pituitary feedback in the elderly; repeated stressors; enhanced local regeneration of cortisol from inactive cortisone via 11BHSD1 in liver, adipose, brain, and endothelial cells; and central activation of AMP Kinase. These speculations allow for hypothesis generation and are testable by strategies to decrease cortisol levels and/or action.

060

The biology of the testis hormone INSL3

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Insulin-like factor 3 (INSL3) has evolved to address gender-specific functions in mammals, and is thus, like the closely related hormone relaxin, a member of the newly defined group of neohormones (1). In males INSL3 is secreted into the circulation by the mature Leydig cells of both the fetal and adult testes. In the fetus it is responsible for the initial transabdominal phase of testicular descent, being a major secreted male-specific fetal hormone acting on receptors in the gubernacular ligament. Our recent studies have also revealed an important interaction within the human maternal-fetal unit, with early second trimester amniotic INSL3 concentration being predictive of later preeclampsia and birth weight (2). In the adult male, INSL3 in rodents and humans is a major circulating hormone, though its primary target receptors appear to be on germ cells, where INSL3 appears to act as an anti-apoptotic or survival factor (3). INSL3 is also produced by the steroidogenic cells of the ovary, though circulating levels in the female mammal are lower than in males. It is made predominantly by follicular thecal cells, where it has been reported to be involved in follicle selection, and can also reflect the extent of PCOS in affected women. All results so far suggest that INSL3 is constitutively expressed, though as a function of the differentiation status of the producing cells. For example, we have recently shown that INSL3 is an excellent marker of the number and or functional capacity of the testicular Leydig cells in aging men (4). Unlike insulin and the IGFs, INSL3 signals with high affinity and specificity through a class C type G-protein coupled receptor, called LGR8 or RXFP2. Whilst transfected receptors demonstrate typical Gs-linked signalling through adenylate cyclase, naturally expressed receptors may may involve alternative pathways. *Research supported by ARC Discovery grant DP0773315.*

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(2) Anand-Ivell R et al. (2008) Hum Reprod. 23: 1180-1186
(3) Anand-Ivell R et al. (2006) Biol Reprod. 74: 945-953
(4) Anand-Ivell R et al. (2006) Int J Androl. 29: 618-626.

061

Gametogenetin (GGN) is a regulator of male fertility and embryo survival

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Gametogenetin (*Ggn*) is a relatively uncharacterized gene which produces three isoforms of protein (GGN1-3). The GGN1 and GGN2 forms are enriched within both the human and mouse testis. GGN1 was originally identified by us as a cysteine-rich secretory protein 2 (CRISP2) binding protein which was incorporated into the growing sperm tail. The carboxyl-most 158 amino acids of GGN1 binds to the ion channel regulatory region of CRISP2 within the principal piece of mature sperm (Jamsai et al, 2008 Reproduction 135:751-9). The GGN2 isoform is also produced within the mouse testis. GGN2 appears to be associated with the plasma membrane of the sperm principal piece. The presence of the GGN3 isoform in the mouse remains unclear. In order to further define the function of GGN, we knocked out the

entire *Ggn* locus using homologous recombination. GGN heterozygous and GGN wild type mice were produced in the expected ratio and were apparently healthy, however, knockout pups were never observed. An analysis of foetal, embryonic and zygotic survival using timed mating and *in vitro* fertilization (IVF) revealed that knockout zygotes arrested and then died at the one cell stage. Further, breeding experiments revealed a significant transmission ratio distortion in litter composition from both heterozygous sires and dams. Specifically, when heterozygous animals were mated with wild type partners, heterozygous pups were produced at ~70% of the expected frequency. The mechanisms of this unusual form of male and female sub-fertility and its relevance to human infertility are currently under investigation.

062

FSH and female reproductive ageing: ovarian function and premature infertility in transgenic FSH mice

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Female reproductive ageing features rising serum FSH levels, thought to reflect diminishing negative feedback due to declining ovarian follicle reserve, coinciding with an accelerated loss of fertility in women. Ovarian hyperstimulation by elevated FSH has wide-ranging implications for reproductive function and ageing, by increasing follicle recruitment, multiple ovulation, dizygotic twinning and advancing premature ovarian failure and post-menopausal diseases (eg. osteoporosis). Whether or not elevated FSH remains a passive reflection of a diminished follicle pool or actively contributes to age-related infertility has been difficult to study, due to a lack of models able to distinguish between effects of high FSH *vs* depleted follicle reserve. We produced transgenic (Tg) mice expressing rising serum human FSH independent of gonadal-pituitary-feedback or declining reserve. Progressively rising serum TgFSH (~2→10 IU/L, transgenic line-A) with unchanged LH had a biphasic effect on female fertility, first increasing littersizes (≤22 wo) then reducing littersizes (>23 wo) culminating in premature infertility (~34 wo). TgFSH increased ovulation and embryo-uterine implantation, but also increased embryo-fetal resorption and parturition failure. Serum anti-müllerian hormone levels, a proposed marker for ovarian reserve, were not a predictor of ovarian follicle reserve or fertility. Contrary to the view that elevated FSH may increase follicle recruitment and accelerate follicle depletion, ovaries from subfertile-infertile (26-40 wo) TgFSH females had more primordial follicles (60%, $P < 0.05$) and normal AMH *vs* age-matched controls. Females expressing higher TgFSH (10-45 IU/L, transgenic line-B) were mostly infertile and displayed age-related enlarged ovaries with pathogenic phenotypes including fluid-filled and hemorrhagic cysts (unlike line-A with lower TgFSH). Similar abnormal ovarian phenotypes were produced in gonadotrophin-deficient ($GnRH^{-/-}$) females expressing high TgFSH, indicating a threshold level for FSH-specific follicular dysfunction. Overall, higher FSH may enhance survival of both early (primordial) and late (preovulatory) follicle populations, but accelerate reproductive failure by disrupting embryo-fetal survival and follicle dynamics.

063

Progress (at last) in osteoporosis genetics

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The past 18 months has seen the emphatic demonstration that genomewide association studies (GWAS) are capable of identifying many genes involved in common diseases. Phenomenal advances have been made in the genetics and, as a result, our understanding of the aetiopathogenesis of many common diseases, providing basic researchers with solid foundations from which to pursue hypothesis-based research.

Two groups have recently published large GWAS studies in osteoporosis [1,2] , between them identifying at least eight genetic regions associated with bone mineral density (BMD). Key points from these studies are:

· Nearly all SNPs associated with BMD were associated with fracture risk.

· The level of association with fracture risk was much lower than with BMD.

· Whilst many of the SNPs lay close or within known ‘bone' genes, at least four had not previously been studied for their potential role in bone disease.

· The risk associated with each SNP was small, but as some SNPs were very common, on a population level they could have quite a large effect.

These findings suggest the previous belief that most genetic control of BMD did not also influence fracture appears to be incorrect. It is also clear that future studies with greater statistical power are likely to be quite fruitful in osteoporosis genetics. Translation of these findings to the Australian environment, and assessment of their role in fracture risk prediction, is clearly a critical next step.

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(2) Styrkarsdottir U, Halldorsson BV, Gretarsdottir S, et al. Multiple genetic loci for bone mineral density and fractures. N Engl J Med 2008;358(22):2355-65

064

Bisphosphonate use in osteoporosis, benefits and risks

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Bisphosphonates are the most commonly used first-line therapy for osteoporosis. Structurally similar to naturally occurring pyrophosphate, they have a high affinity for calcium hydroxyapatite crystals. Bisphosphonates are targeted drugs with a high specificity for osteoclasts. They potently inhibit bone resorption by interfering with osteoclast function and inducing osteoclast apoptosis. Bone formation is also

reduced. Once sequestered in bone, bisphosphonates are slowly released with a variable half-life. Clinically, they reduce vertebral, non-vertebral and hip fractures and improve quality of life. Administration of intravenous zoledronic acid following a hip fracture also reduced subsequent mortality.

Bisphosphonates are well tolerated and the rate of adverse events is very low. Upper gastrointestinal events, including gastric irritation, oesophageal erosions, and gastric ulcers are associated with oral administration, but are less likely with weekly dosing regimens. Such side effects can be related to pre-existing gastroesophageal reflux or failure to remain upright after dosing. Serious adverse events are more common with higher doses or when elimination is impaired and may differ in frequency depending on the route of bisphosphonate administration. Renal impairment, osteonecrosis of the jaw (ONJ), atrial fibrillation, musculoskeletal pain and unusual femoral diaphyseal fractures (related to low bone remodelling) have recently been uncommonly associated with bisphosphonate treatment. ONJ occurs rarely, but is a potentially serious event in patients treated for osteoporosis. It has an estimated frequency of 1:10,000-100,000, however, is seen more frequently in patients with multiple myeloma or bony metastases treated with higher total doses of intravenous bisphosphonates. Its aetiology is uncertain, but there is a strong association with periodontal disease and dental extraction, highlighting the need for collaboration with dental practitioners. The cause of atrial fibrillation associated with bisphosphonate use is unknown, but it may be more common with intravenous zoledronic acid.

The benefit-risk profile strongly favours the use of bisphosphonates in osteoporosis.

065

Estrogens mediate osteoprotective effects by controlling osteoclast life cycle

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Sex steroids, estrogens and androgens, display an osteoprotective effect and prevent bone loss associated with post-menopausal osteoporosis. However, the molecular mechanism of how this is accomplished remains to be elucidated. We have generated Cathepsin K-Cre recombinase knock-in mice (Ctsk-Cre) to generate osteoclast specific conditional knock-out mice. We then selectively ablated estrogen receptor (ERα) in differentiated osteoclasts using Ctsk-Cre mice mating with ERα floxed mice ($ER\alpha^{\Delta Oc/\Delta Oc}$). $ER\alpha^{\Delta Oc/\Delta Oc}$ females exhibited clear bone loss in plain X-ray and 3D-CT, similar to the osteoporotic bone phenotype. Also in DEXA, femurs of $ER\alpha^{\Delta Oc/\Delta Oc}$ a females showed low bone mineral density. Bone histomorphometric analysis revealed a significant increase in osteoclast surface, osteoclast number and eroded surface in with increased MAR and BFR. These results showed that $ER\alpha^{\Delta Oc/\Delta Oc}$ a females exhibit high turnover osteoporotic phenotypes.

Then, the genechip analysis was done in the femurs of $ER\alpha^{\Delta Oc/\Delta Oc}$ females to find the ER target genes, leading to the identification of Fas ligand (FasL) gene. In *in vitro* primary cultured osteoclasts from bone marrow cells, 17β-estradiol and tamoxifen, potentiated FasL gene expression with osteoclastic apoptosis only in osteoclasts from wild type, but not $ER\alpha^{\Delta Oc/\Delta Oc}$ mice. From these findings, we presume that the osteoprotective actions of estrogens are mediated at least in part through osteoclastic ERα in female.Abstract to be provided.

(1) Nakamura et al., Cell, 130, 811, 2007

066

Osteoporosis: Therapeutic concepts for the present and the future.

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Over the past 13 years, an increasingly large number of drugs have become available for the prevention and treatment of osteoporosis. The therapeutics that dominate the landscape at this time are the so-called antiresorptive agents. They are called antiresorptive because they have, as a common denominator, an action to impair the activity of the bone-resorbing cell, the osteoclast. By inhibiting the osteoclast, the bone remodeling unit is brought into better balance and bone loss is curtailed. Along with estrogens, raloxifene (a selective estrogen receptor modulator), calcitonin, and bisphosphonates, a menu of options is available for physicians and patients. Some of these agents provide global protection again vertebral, non-vertebral and hip fracture while for others the evidence, based upon prospective clinical trial data, is limited to effects at vertebral sites. Teraparatide [PTH (1-34)] is the first member of a class called anabolics in which the primary therapeutic effect is not to influence bone resorption primarily, but rather to stimulate processes associated with bone formation. Teriparatide reduces vertebral and non-vertebral fractures with evidence for its therapeutic action including improved microarchitecture of bone. Adverse events occur with each of these agents but generally they are well tolerated and safe. When used in a program of nutritional repletion (calcium and vitamin D), exercise, life style optimization, and measures to prevent falls, we can be confident of a good end result, namely reduced fracture incidence.

At this time, new concepts are being explored that might lead to use of the agents we already have to even greater advantage. One area, for example, is combination therapy with an antiresorptive and teriparatide. Although initial studies did not support the idea that combination therapy was better than monotherapy, subsequent work has given reason to expect that under certain circumstances and with specific combinations, there might be advantages over monotherapy. Another aspect of combination therapy involves using agents in sequence such as using teriparatide after bisphosphonate therapy. This is an important issue because many patients who receive teriparatide have previously been treated with a bisphosphonate and also because a few reports have suggested under certain conditions there might be a delay in responsiveness to teriparatide if bisphosphonate therapy precedes its use. The OPTAMISE has explored this issue with regard to previous treatment with risedronate or alendronate. The results (Miller et al. JCEM, 2008, in press) will be presented and discussed.

On the horizon are newer classes of agents that have different mechanisms of action. For example, strontium ranelate is said to harbor both antiresorptive and anabolic actions. While this is only one of several mechanisms, strontium ranelate does reduce both vertebral and non-vertebral fractures. Even newer therapeutic concepts are being explored due to our greater understanding of the pathways by which bone cells are regulated. The RANK L-OPG system that is critically important for intercellular bone cell signaling can be perturbed by the use

of a humanized antibody against RANK L. The antibody inhibits RANK L, a potent osteoclastic activator, leaving relatively unopposed the endogenous RANK L inhibitor, OPG to directly inhibit osteoclast action. The general mechanism utilized by the RANK L antibody therefore is ultimately an antiresorptive one but the means by which osteoclast action is impaired is uniquely different from any of the antiresorptives available at this time. The pivotal phase III clinical trial of Denosumab a humanized IgG anti-RANK L antibody, has just been completed and the results are expected soon.

Even newer therapeutic concepts, based upon anabolic pathways, are being developed at this time. The Wnt pathway, for example, is an essential means by which the osteoblast is regulated. Sclerostin, the SOST gene product, inhibits the Wnt pathway and is thought to serve as an endogenous control system. An antibody directed against sclerostin should release the Wnt pathway from that control and permit a greater anabolic effect. Animal data are consistent with this idea. The presentation will offer additional ideas by which the Wnt signaling pathway could be modified and thus lead to a therapeutic effect.

One can return to the osteoclast and identify molecules that are essential to osteoclast action, such as cathepsin K, and consider means by which the osteoclast could be inhibited by interfering with cathepsin K activity. Cathepsin K inhibitor therapy is in clinical trials.

In summary, newer molecules are being developed to improve on what we have, to creatively use new combinations of approved drugs, and to take advantage of bone cell pathways of activation and inhibition.

067

New approaches to study gene function in vivo

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Humans are mammals, not bacteria, or plants, yeast or nematodes, insects or fish. Mice are also mammals, but unlike sloth and stoat, fox and ferret, whale and walrus, gerbil and jackal, they are suited perfectly to the laboratory environment and genetic experimentation. Over the last 5 years we have performed a series of large-scale genetic screens, which have drawn on tricks and tools developed in lower organisms, to dissect the molecular control of blood cell production in the mouse. We have focused primarily on the platelet lineage and have isolated mutations that affect platelet number over three orders of magnitude. These mutations provide entrees into new pathways and our ongoing challenge is to understand these pathways in enough detail to exploit therapeutically.

068

The Role of Epigenetics in the Determination of Phenotype

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We have carried out a "sensitized" ENU mutagenesis screen in the mouse to identify genes that modify epigenetic state. We have screened 1000 F1 offspring for dominant mutations and have identified ten. In all cases they are homozygous lethal, indicating the obligate requirement for the genes that have been hit (Blewitt et al, 2005). So far, we have identified six of the underlying mutations. The remainder have been mapped to between 1 and 3 cM intervals. All tested so far affect expression at epigenetically sensitive loci such as the *agouti viable yellow* allele. Interestingly, in a number of cases the mutations show both paternal and maternal effects, i.e. wildtype offspring from heterozygous mutant parents are different from wildtype offspring from wildtype parents (Chong et al, 2007). One mutant shows signs of metabolic syndrome; including obesity, hepatic steatosis and diabetes.

This project has the potential to identify many more novel genes involved in epigenetic phenomena, and to produce hypomorphs and hypermorphs of known modifiers of epigenetic state. Furthermore, these mutant lines will be a valuable resource to study the role of epigenetics in gene / environment interactions. We are now extending the screen to saturation.

069

Structural genomics: generating new approaches for structure definition

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A major lesson learnt from the successes of whole genome sequencing is the value of high-throughput endeavours in providing rich resources for discovery-led research. Traditional structural biology developed as a paradigm in which biochemical evidence of a discrete protein function is confirmed through elucidation of high-resolution molecular structures (crystallography or NMR). An original and ambitious goal of structural genomics was instead to record all possible three-dimensional structures of protein folds, from which all functional forms must be derived.

I will overview the large-scale structural pipelines established internationally as part of these efforts, and contrast the different approaches taken. Even for small-scale projects focussed on a narrow range of molecular targets, there is much to be gained from the output of these well-funded “collaboratories”. A considerable cost benefit is derived for us all by adoption of the new repertoire of tools for target screening, batch-mode protein production and structure determination.

070

Genetic manipulation of mice: Providing all the answers or just more problems?

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The genetic manipulation of mice by Gene Targeting or conventional transgenesis is a powerful tool for investigating gene function in vivo. However, these methods can suffer from a number of deficiencies including embryonic lethality, genetic strain variation, transgenic "leakiness" etc (see reference 1). Improved techniques have therefore been devised to overcome these problems and modulate gene expression and function in a tissue and temporal-specific manner including CreLoxP and tetracycline response systems. Again however not all problems are solved. Indeed more recently it has become clear that there are previously unexpected epigenetic effects involving transfer of transgenic RNAs or proteins in oocytes or sperm to non transgenic offspring that produce changes in the complete absence of the transgene in the genome (see 2). Given these problems we reiterate the necessity for the use of completely reversible methods that will allow each experimental group of animals to act as their own control. We will review the current situation and present some recent results using tissue/temporal control of gene function in live animals using an innocuous compound given in the drinking water.

(1) Matthaei KI (2004) "Caveats of Gene Targeted and Transgenic Mice" in Handbook of Stem Cells, Volume 1: Embryonic Stem Cells, Elsevier Academic Press, (Lanza R et. al. ed) p589. (pdf available)

(2) Matthaei KI (2007) "Genetically manipulated mice: A powerful tool with unsuspected caveats" The Journal of Physiology 582, 481-488. (pdf available from author Klaus.Matthaei@anu.edu.au))

071

Menopausal endocrinology and Management

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In regularly cycling older women, the ovary contains about 1000 follicles. With the onset of cycle irregularity,there are about 100,and few if any remain after final menses. The Stages of Reproductive Aging Workshop (STRAW)proposed a classification, with final menses as reference point, in which Stage -4 described women approaching menopause with continuing regular cycles, without significant endocrine changes. Those who showed a rise in follicular phase FSH were at Stage -3. The onset of irregular cycles, persistently >6 days outside the range of previously regular cycles, marked Stage -2,the early menopause transition, and an episode of >60 days amenorrhoea defined Stage -1, the late transition. Follicular phase levels of inhibin B fall significantly in Stages -3 and -2. There are no specific endocrine cycle characteristics in Stages -2 and -1. Anovulatory cycles become relatively frequent in late transition. Mean circulating estradiol (E2) levels decrease in the late transition and following menopause, but fluctuate in cycle stages -2 and -1,with both increased and decreased levels compared with mid-reproductive age.As predicted by the endocrine changes, peri-menopausal women may have irregular cycles,abnormal bleeding patterns and symptoms indicating high and low E2. Perimenopausal mangement may therefore include cycle regulation with intermittent progestin, ovarian suppression with low dose OC's,and HRT, usually given sequentially. Postmenopausal management with E2(plus a progestin if the uterus is intact) is logical for symptom control. Many misconceptions regarding HRT were engendered by the original (misleading) reports of the US Women's Health Initiative randomised controlled trials, but more recent analyses of this and other data indicate that HRT, given both at standard and more recently lower doses, is safe and effective when initiated early after menopause to symptomatic women. It should be regarded as initial first-line prophylaxis for the risk of osteoporotic fracture in those few younger (<60 years) postmenopausal women at significantly increased risk.

072

Primary Hyperparathyroidism: A lesson in how a disease can change by just observing it!

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This workshop will focus on some of the issues that will not be presented in depth in the plenary lecture presentation on primary hyperparathyroidism (PHPT). One of the interesting observations that has been made since this disease was first recognized is how it seems to have changed over the course of the past 80 years. Initially, PHPT was a devastating disease of the skeleton, inevitably leading to bone loss, fractures, and kidney stones. The adage, "bones, stones, and groans" was apt. It was also considered to be a rather rare disorder. In fact, in the 1930s, cases of PHPT were often published as case reports. The first major change in this phenotype occurred in the context of the development of the multichannel screening test in which the calcium was inserted as one of the first twelve analytes to be offered in this panel. The decision to include calcium was an afterthought by those who made the decision (there was an empty position in the autoanalyzer slot), but it changed the entire clinical landscape of the disease. Rather than being a rare disorder characterized by marked hypercalcemia, PHPT became a common disorder marked by mild hypercalcemia. Rather than presenting with overt signs of bone and/or stone disease, those target organs, although still at risk, become less often involved. Hence, the term, Asymptomatic Primary Hyperparathyroidism became the designation for this more modern profile of the disease. Even throughout the past 35 years, however, when Asymptomatic PHPT has become the dominant form of the disease, the older, now uncommon variant of PHPT, is still seen. It appears to be more likely in countries where multichannel screening and general measures of preventative health are not routine. Moreover, the classic variant of PHPT is much more likely to occur in the setting of severe vitamin D deficiency. Why vitamin D deficiency fuels the processes associated with excess PTH production will be discussed in the MTP session. Now, we are embarking on yet another phenotype of this disease. Patients with PHPT are being discovered not because they have hypercalcemia, but because they are being evaluated for skeletal health and/or loss and, in this regard, we are routinely measuring the PTH. This rather new presentation of PHPT is called, Normocalcemic Primary Hyperparathyroidism. There is a further subset of subjects with normocalcemic PHPT that is likely to be

discovered. The first series of Normocalcemic Primary Hyperparathyroidism followed referrals to specialty clinics in metabolic bone diseases. Thus, these patients often have signs or symptoms related to the target organs of PTH, namely the bones and the kidneys. It is highly likely that there is another form of Normocalcemic Primary Hyperparathyroidism that will be discovered in the free living, asymptomatic community of patients who are not being referred for any skeletal issue but nevertheless demonstrate the earliest manifestations of primary hyperparathyroidism, namely an elevated PTH without any other cause. Finally, the MTP session will discuss the natural histories of normocalcemic PHPT. There are likely to be several different scenarios that could emerge with follow of these patients.

ESA ORALS

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Melanocortin stimulation of reproductive neuroendocrine function

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Intracerebroventricular (icv) infusion of the melanocortin receptor agonist MTII stimulated the gonadotropic axis in lean hypogonadotropic ovariectomised ewes (Backholer et al 2008. Proc. Endoc. Soc. # 851996). To further test the hypothesis that melanocortins stimulate the reproductive axis, we conducted two experiments 1) lateral ventricular (LV) infusion of MTII in anestrous ewes and 2) LV infusion of MTII during the luteal phase of the estrous cycle. In anestrous, the gonadotropin releasing hormone (GnRH)-gonadotropin axis is suppressed by increased negative feedback of estrogen and in luteal phase ewes, progesterone limits GnRH/gonadotropin secretion. Expt 1: Groups (n=6) of progesterone-primed seasonally anestrous ewes received lateral ventricular (LV) infusion of 10 µg/h of MTII or vehicle for 30h. Blood samples were taken 2 hourly from 4h before infusion until 6h afterwards for LH assay. Blood samples were then collected every second day for 14 days to monitor plasma progesterone levels. MTII infusion did not stimulate LH secretion or cause ovulation in anestrus. Expt 2: Groups (n=4) of ewes in the luteal phase of the estrous cycle received LV infusion of MTII (10µg/h) or vehicle for 3h and blood samples were taken every 10 min for 3h prior to infusion and during infusion. MTII infusion increased plasma LH pulse frequency (vehicle, 0.2 ± 0.09 pulses and MTII 0.9 ± 0.16 pulses/h : $P<0.01$) and average LH levels following infusion (vehicle, 0.05 ng/ml ± 0.03 and MTII, 0.44 ng/ml ± 0.09: $P<0.01$). A rise in pulse amplitude (0.22 ng/ml vs 0.64ng/ml) was not statistically significant ($P = 0.06$). We conclude that melanocortins stimulate the reproductive neuroendocrine system. During the luteal phase of the estrous cycle, melanocortin agonist treatment can over-ride systems that inhibit GnRH/gonadotropin secretion at this time. Seasonal changes in GnRH secretion may involve the melanocortin system, with reduced responsiveness in anestrous.

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Cortisol response to intravenous dexamethasone in patients with Cushing's syndrome compared to normal and overweight subjects, with and without type 2 diabetes

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Various forms of the intravenous dexamethasone suppression test (IVDST) have been used in the investigation of Cushing's syndrome (CS). Our institutions have employed a dexamethasone infusion protocol of 1mg/hour for 4 hours. There are limited published data on the cortisol response to the IVDST in normal subjects, and no level diagnostic of CS has been proposed. We evaluated the cortisol response to IVDST in normal (BMI 20-25) and overweight (BMI >25) subjects with and without type 2 diabetes (T2DM), compared to a large group of subjects with proven CS (n=83). The diagnosis and aetiology of CS was confirmed after review of medical records, histopathology and biochemical results. The series included 66 patients with Cushing's disease (CD), 14 with adrenal Cushing's (AC) and 3 with ectopic ACTH syndrome (EAS). Thirty control subjects (12 normal, 8 overweight and 10 with T2DM) were recruited. Dexamethasone was infused at 1mg/h for 4h. Plasma cortisol and ACTH were measured at -60min, -5min, +3h, +4h, +5h and on Day 2. Plasma cortisol (mean ± SEM) at -60min, +5h and on Day 2 is shown in the table. Measurement of ACTH did not provide any additional clinically useful information. Control subjects exhibited a marked suppression of cortisol in response to the IVDST which was maintained until Day 2. Patients with CD demonstrated partial suppression, with rebound hypercortisolism on Day 2. Patients with AC and EAS did not suppress, and could be distinguished by ACTH levels. A plasma cortisol of >130nmol/l on Day 2 diagnosed CS with 100% sensitivity and 98% specificity. CD could be differentiated from other causes of CS by suppression of +5h cortisol to <70% of baseline (sensitivity and specificity 94%). The IVDST is highly sensitive in distinguishing patients with CS from normal subjects and to differentiate the cause CS.

	Plasma cortisol mean ± SEM (nmol/l)		
	-60min	+5 hours	Day 2
Control group	414 ± 19	57 ± 4	20 ± 2
Pituitary (CD)	663 ± 28	215 ± 19	566 ± 38
Adrenal (AC)	614 ± 83	594 ± 83	638 ± 109
Ectopic (EAS)	2830 ± 588	3082 ± 507	2741 ± 686

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Dysregulation of hypothalamic neuropeptide expression and metabolic rate in offspring of diabetic pregnancy.

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Diabetes in pregnancy confers an increased obesity risk to offspring. We developed a model of diabetes in pregnancy, the ß-cell specific aryl-hydrocarbon receptor nuclear translocator knockout (ß-ARNT) mouse, which has mild gestational glucose intolerance due to ß-cell dysfunction. Male offspring have greater adiposity in adulthood. Aim: To examine the mechanisms for increased adiposity in male offspring of diabetic pregnancy (DP), through indirect calorimetry and the determination of hypothalamic gene expression. Methods: ß-ARNT-females were mated with floxed-control (FC) males, and FC-females with ß-ARNT-males to obtain DP and non-diabetic pregnancies (NDP) respectively. Litters were ~50% ß-ARNT and ~50% FC. Offspring were weighed weekly, DEXA was performed at 6,13 and 28 weeks, and indirect-calorimetry at 6 and 28 weeks. Food consumption was measured at 6 and 24 weeks. In situ hybridisation was performed for neuropeptide Y (NPY) and pro-opiomelanocortin (POMC) in arcuate nuclei of a separate cohort of 6wk-old offspring. Results: FC offspring from DP had increased body fat percentage at 6- and 13-weeks compared to FC from NDP, and decreased metabolic rate. ß-ARNT DP offspring had increased body fat percentage at 13- and 28-weeks and were 15% heavier from 8-weeks of age. Food consumption was not altered but the food: faecal weight ratio was increased. An increased respiratory exchange ratio (RER) was observed in 28-week old FC and ß-ARNT DP offspring. Consistent with increased adiposity, hypothalamic NPY expression was increased by 40% and POMC expression was decreased by 40%. Conclusions: Increased adiposity in DP offspring was associated with decreased metabolic rate in FC, and with dysregulation of hypothalamic appetite-regulatory neuropeptide expression in ß-ARNT males. RER was increased in both genotypes. Increased NPY expression and decreased POMC expression would contribute to increased weight and fat gain and provide a mechanism for the increased obesity which is seen following exposure to diabetes in utero.

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Differential Patterns of DNA Methylation in the Prostate and Testis Following *In Utero* Endocrine Disruptor Exposure

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Endocrine disrupting chemicals (EDCs) have the potential to induce disease through altering normal epigenetic mechanisms of gene regulation, including DNA methylation, histone modification and chromatin remodeling. Four mammalian DNA methyltransferases (DNMTs) are responsible for DNA methylation pattern acquisition during gametogenesis, embryogenesis and somatic tissue development. Therefore, this study aimed to examine effects of the anti-androgenic EDC Vinclozolin on DNA methylation in the prostate and testis, during a period of male reproductive tract (somatic tissue) development. Fetal rats were exposed to Vinclozolin (100mg/kg/body weight) or vehicle control (2.5ml/kg/body weight) *in utero* from gestational day 14 to 19 via oral administration to pregnant dams. DNA methyltransferase activity was examined in the prostate and testis of male off-spring aged 56 days. *In utero* Vinclozolin exposure resulted in adult-onset disease in the prostate and testis associated with differential and aberrant *Dnmt* expression. Specifically, male off-spring displayed increased *Dnmt3a* and *Dnmt3b* expression, but not *Dnmt1* or *Dnmt3L* expression in the prostate. The absence of a prostate phenotype in *Dnmt3L* knockout mice confirmed the absence of a role for *Dnmt3L* in the onset of prostate disease. In contrast, in the testis of male off-spring exposed *in utero* a significant reduction in *Dnmt1* and *Dnmt3L* expression and significant increase in *Dnmt3b* was accompanied by increased germ cell apoptosis and reduced daily sperm production. These data are the first to unequivocally demonstrate that *in utero* anti-androgenic EDC exposure during somatic tissue development results in prostate and testicular disease accompanied by differential patterns of DNA methylation and may provide further insight into toxicology and adult disease etiology.

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Molecular mechanisms of steroid and growth factor regulation of growth plate chondrogenesis

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The epiphyseal growth plate is the site of linear growth regulation and cessation, where local growth factors (including IGFs and FGF-2) and oestrogen (E) interact. They initially promote growth but E ultimately causes epiphyseal fusion, the mechanisms of which remain unclear.

The modified rat calvaria cell line RCJ3.IC5.18, which undergoes *in vitro* chondrogenesis and new bone formation when treated with specific medium, was used to determine the expression and functional role of oestrogen receptors (ER) and interactions of IGF-I and FGF-2 on chondrocyte differentiation.

ER α and β showed increasing expression during differentiation, with immunofluorescent ERα being predominantly nuclear and ERβ predominantly cytoplasmic. While E did not significantly affect cell proliferation (MTT assay) or differentiation (alkaline phosphatase (ALP) activity), treatment with ER antagonist ICI 182,780 caused an increase in proliferation, suggesting endogenous E support of differentiation or apoptosis. Ge ne expression profiling for regulation of chondrocyte differentiation and oestrogen signalling is underway.

FGF-2 and IGF-I had contrasting effects, with FGF-2 greatly enhancing proliferation but inhibiting differentiation as shown by inhibition of ALP activity and Col X mRNA expression. In contrast, IGF-I promoted differentiation, an effect attenuated by FGF-2. SOCS 2 expression, known to inhibit IGF-I expression, was increased with FGF treatment, a likely mechanism for this cross talk. There was no additive effect of IGF-I and oestrogen on differentiation, while FGF-oestrogen interaction is under examination.

In summary, an established model of epiphyseal maturation expresses both forms of ER during differentiation, demonstrating a role for locally synthesized E acting via both classical genomic (ERα) and non-genomic (ERβ) pathways. Local growth factors IGF-I and FGF-2 also appear to have contrasting key roles in these processes, with no evidence to date of cross-talk with the local oestrogen system.

We conclude that epiphyseal fusion via chondrocyte differentiation is dependent on (i) interactions between growth factor systems and (ii) local activation of oestrogen receptor mediated pathways.

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Role of SLIRP in androgen receptor signalling in prostate cancer

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There has been little progress in treatment of patients with high-grade prostate cancer (PCa) in the past decade. Few of the currently available standard therapies, such as hormone therapy, chemotherapy, radiation and surgical removal of the prostate have had long term success. The androgen receptor (AR) contributes to the development and progression of the disease, and throughout PCa progression, AR expression is typically maintained. Use of anti-androgens such as flutamide and casodex has been successful only in the treatment of hormone responsive PCa but not on the relapse into a much more severe hormone refractory PCa. Hence, it is important to find new ways and targets to suppress AR activity, to either inhibit or delay PCa progression. The activity of nuclear receptors (NRs) such as AR is modulated by the recruitment of coregulators that modulate transcription, either as coactivators or corepressors. The aim of this study was to characterise the functional role of SLIRP, a recently discovered NR coregulator, in PCa. In transfection reporter assays using androgen-responsive promoters, SLIRP functions as a potent repressor of AR-mediated signaling. Furthermore, in chromatin IP (ChIP) studies SLIRP is recruited to androgen-responsive promoters. Cell proliferation studies indicate that over expression of SLIRP modifies PCa cell growth. In summary, SLIRP acts as a potent AR corepressor in PCa with functional effects on cell growth. Further understanding the role of SLIRP as an AR corepressor and its interaction with other coregulators will provide insight into AR signalling in PCa.

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Hyperthyroid related pulmonary hypertension

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A previously well 46 y.o. woman was hospitalised with shortness of breath, ankle swelling and increasing abdominal girth. She had recent onset tremor, heat intolerance and alopecia. History was significant for obesity and 70kg intentional weight loss over the preceding 4 years. There was no anorectic use. She was tachycardic 120 beats/min with prominent JVP, bibasal dullness, a grossly distended abdomen and lower limb pitting to the level of the rib cage. She had a diffuse goitre with bilateral bruits but no evidence of ophthalmopathy. Thyroid function tests showed TSH <0.01 / FT4 = 98.0 and TSI 54. Thyroid ultrasound and uptake scan were consistent with Graves' disease and neomercazole was initiated. She was clinically in severe right heart failure and was managed with fluid restriction, diuresis and beta blockade. Echocardiogram revealed moderate tricuspid regurgitation with pulmonary hypertension PASP ~ 68mmHg. LV systolic function was normal with no segmental wall motion abnormality. Doppler examination of her lower limbs and V/Q were normal. HR CT chest showed normal results. ANA and HIV tests were negative. Right heart catheterisation and sleep study were deferred. Therapy was complicated by a downward trend in haematological parameters and treatment was changed to PTU without further complication. Three months later she was almost euthyroid and repeat echocardiogram was normal. A total thyroidectomy with Lugol's iodine preparation was arranged for the following month.

The patient presented with Graves' thyrotoxicosis and pulmonary hypertension at the same time. After treatment of her thyrotoxicosis there was no evidence of her pulmonary hypertension. An association between thyrotoxicosis and pulmonary hypertension has been suggested but this is not widely recognised. Several mechanisms have been proposed including an autoimmune mechanism, endothelial injury caused by increased cardiac output and increased metabolism of intrinsic pulmonary vasodilators. It is important to recognise this association as it is a treatable and reversible cause of pulmonary hypertension.

(1) Cohen et al., AJM 2003; 115: 76-77
(2) Chung et al., JCEM 2007; 92:1736-1742
(3) Yanai-Landau et al., Pathobiology. 1995; 63: 71-75
(4) Chu et al., Chest. 2002;122 (5): 1668-1673

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Relapsing Remitting Hypophysitis

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Case 1.

A 22 year old woman presented in December 2005 with headaches, peripheral visual loss and a mildly elevated serum prolactin. MRI demonstrated an asymmetrical non-homogenous enhancing pituitary mass with distortion of the optic chiasm. Surgery revealed granulomatous hypophysitis and lead to complete remission. Glucocorticoid was weaned off. Complicating surgery she had diabetes insipidus.

A year later, she had two clinical and radiological relapses, which responded promptly to reintroduction of corticosteroids. On 15mg of prednisolone she has good disease control but significant steroid induced complications.

Case 2.

In July 2005, a 57 year old gentleman was referred to a neurologist with headaches, right sixth and third cranial nerve palsy, mildly elevated prolactin and a CSF lymphocytosis. MRI demonstrated an inflammatory mass within the cavernous sinus extending to the pituitary fossa and right optic nerve. He was diagnosed with Tolosa Hunt syndrome and received 4 months of prednisolone with complete resolution of his headache and ophthalmoplegia. In March 2006, he relapsed. Attempts over the next 7 months to reduce prednisolone below 10mg were unsuccessful. Biopsy revealed Lymphocytic Hypophysitis and surgical debulking produced a clinical remission allowing gradual withdrawal of steroids. Currently he is back on 10mg of prednisolone following a relapse this year. Secondary hypogonadism and hypothyroidism was evident six months after biopsy.

These cases highlight the diagnostic and management problem of Hypophysitis, an uncommon disease of unclear pathophysiology that can mimic other suprasellar masses and have an unpredictable relapsing-remitting course.

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A case of adult hypophosphatasia: induction of osteoblast response by teriparatide

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A 53-year-old woman presented with an atraumatic, comminuted left femoral shaft fracture, on a background of soft teeth since childhood and a waddling gait. Family history was unremarkable, although both parents had "bad teeth". Fracture history included her left wrist while skiing and T10 vertebral body on minimal trauma. Previous X-rays and a nuclear bone scan to investigate lower back and hip pain revealed bilateral stress fractures of the lateral femoral cortices. Biochemical investigations showed very low serum ALP levels of 8IU/L (<120), high phosphate 1.68mmol/L (0.8-1.5), normal calcium 2.35mmol/L (2.1-2.6), and low iPTH 0.9pmol/L (1.2-6.5). The 25-hydroxyvitamin D level was low at 24nmol/L, and was corrected to 80nmol/L with supplementation. The urine phosphoethanolamine (PEA) level was elevated at 52µmol/mmol creatinine (5-18). These findings are consistent with hypophosphatasia[1].

Orthopaedic gamma nail surgery was performed, and a bone specimen demonstrated evidence of a severe bone mineralization defect (osteomalacia). Three months postoperatively the patient had ongoing hip pain and limited mobility, associated with absence of bony callus on X-Ray. She was commenced on teriparatide 20µg s/c daily. After four months of teriparatide therapy she discontinued analgesia, serum ALP levels increased from 8 to 19IU/L, and bone formation marker N-terminal propeptide of type 1 procollagen (P1NP) increased from 99 to 265µg/L (<76). The patient underwent a bone graft to assist her non-healing fracture, and a bone biopsy with tetracycline labelling was performed. Comparison with the biopsy pre-teriparatide revealed increases in osteoblast number and activity. However, osteoid formation was also increased because of the persistent defect in mineralization. TNSALP gene analysis is in progress[1].

We add to the few other reports of the potential benefit of teriparatide in hypophosphatasia[2,3], and document the first known biopsy-proven induction of osteoblasts with teriparatide in this condition.

(1) Whyte MP. Hypophosphatasia and the Role of Alkaline Phosphatase in Skeletal Mineralization. Endocr Rev. 1994;15(4):439-61.
(2) Whyte MP et al. Adult hypophosphatasia treated with teriparatide. J Clin Endocrinol Metab. 2007; 92(4): 1203-08.
(3) Camacho PM et al. Treatment of adult hypophosphatasia with teriparatide. Endocr Pract. 2008; 14(2): 204-8.

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Transplant recipients on the edge of the hypocalcaemia abyss

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We present a case series to highlight how the unique milieu of transplantation, created by the combination of specific immunosuppressive medications, anti-resorptive agents for transplant-related osteoporosis, on a background of chronic illness, exposes transplant recipients to significant risk of hypocalcaemia, which frequently escapes medical attention. While hypovitaminosis D is a recognised contributor to transplant-related disorders of bone mineralisation, its relationship to severe and life-threatening hypocalcaemia is under-appreciated. Case 1: A 59-year old man was admitted for bilateral sequential single lung transplantation (BSSLT) for pulmonary fibrosis. Post-operative biochemistry demonstrated acute hypocalcaemia (corrected serum calcium concentration=1.7 mmol/L, range:2.1-2.6 mmol/L), secondary to severe vitamin D deficiency. Initial attempted correction of hypocalcaemia with calcitriol and calcium supplement was unsuccessful. Serum calcium concentration eventually normalised after vitamin D was restored to sufficiency. Case 2: A 60-year old man with multiple myeloma was admitted for bone marrow transplantation, and developed decompensated cardiac failure post-transplantation. Biochemistry demonstrated acute hypocalcaemia (corrected serum calcium concentration=1.5 mmol/L, range:2.1-2.6 mmol/L) secondary to severe vitamin D deficiency. Trans-thoracic echocardiogram showed severe global hypokinesis. Cholecalciferol, calcitriol, and calcium supplement were commenced, with resolution of hypocalcaemia and cardiac function. Case 3: A 45-year old man who underwent BSSLT for cystic fibrosis 13 years ago presented with peri-oral numbness. Biochemistry confirmed severe hypocalcaemia (corrected serum calcium concentration=1.1 mmol/L, range:2.1-2.6 mmol/L) and severe vitamin D deficiency. Cholecalciferol, calcitriol, and calcium citrate were commenced. Normocalcaemia was achieved after one week, and calcitriol was ceased once serum calcium concentration began to rise. In conclusion, transplant recipients are at risk of severe hypocalcaemia because of unrecognized vitamin D deficiency, and side-effects from medications commonly used in the transplant setting. Vitamin D repletion with cholecalciferol allows safe restoration of calcium homeostasis. Vitamin D sufficiency not only reduces bone loss, but also reduces the risk of life threatening hypocalcaemia.

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The severe skeletal and metabolic effects of the long-term estrogen deprivation in an aromatase deficient woman.

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To date females with aromatase deficiency have been diagnosed at birth or puberty and have subsequently received replacement therapy.

A 54-year-old woman born with ambiguous genitalia and 46XX karyotype had no specific diagnosis made until now. Her parents were healthy with no consanguinity. In adolescence, adrenarche was normal, but she had primary amenorrhea and absent breast development. At age 25, she suffered a hip dislocation and fracture, and was found at surgery to have unfused epiphyseal growth plates. In her mid-late 30s, transdermal estrogen prompted breast development and menstrual bleeding, but treatment was discontinued a few years later. Her growth plates fused and she reached a final height of 200 cm. She is wheelchair bound because of extreme joint mobility, with spontaneous shoulder and hip dislocations, severe knee valgus and osteoarthritis. She developed a metabolic syndrome with obesity (BMI>45 kg/m2), hypertension, diet controlled type 2 diabetes (fasting glucose 7 mmol/L and HbA1c 7.1%) and severe acanthosis nigricans. Lipids and liver function tests were normal. Hormonal tests demonstrated hypergonadotropic hypogonadism with undetectable estradiol level (LH 22.3 U/L, FSH 55.3 U/L), increased testosterone and androstenedione levels (4.4 nmol/L and 7.8 nmol/L, respectively) and FAI in the hirsute female range (12.0).

Direct sequencing of the coding exons of the aromatase gene (*CYP19A1*) revealed a different mutation on each allele. The first is a T insertion at 1,058bp in exon IX leading to a frame shift and stop codon 9 codons later. The second is a C to T substitution at 1,369bp in exon X resulting in a stop codon (Arg457X). As a consequence truncated proteins are produced as shown by Western blot analysis. Transient expression in COS-7 cells showed that the mutant proteins had about 5% and <1% of the wild type activity, respectively.

This is the first case report of the long-term results of estrogen deprivation in an aromatase deficient woman. The severe skeletal and metabolic effects are similar to those described previously in men with this condition. The necessity of early introduction and continuation of estrogen replacement therapy to avoid these complications should be stressed.

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Hypercalcemia caused by a carcinoid tumour -case presentation

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Humoral hypercalcaemia produced by carcinoid tumours is uncommon. We would like to present the case of hypercalcemia due to excessive parathyroid hormone- related protein (PTHrP) secretion in a 77 year old woman with advanced carcinoid tumor. Clinical presentation was remarkable for the absence of hypersecretory syndrome in a patient with extensive hepatic metastatic disease, suggesting the diagnosis of a hindgut carcinoid.The diagnosis of humoral hypercalcaemia of malignancy (HHM) was confirmed by a biochemical pattern of hypercalcaemia, hypophosphataemia, suppressed PTH, elevated PTHrP and hypercalciuria, in the presence of a normal whole body technetium bone scan. The tumour cells were strongly positive for PTHrP and Fibroblast Growth Factor 23 (FGF 23) levels were elevated.

The hypothetical pathophysiological mechanisms responsible for significant elevations of FGF23 levels in patients with humoral hypercalemia of malignancy are: 1) production of excessive amounts of FGF23 by tumour itself or 2) direct effect of parathyroid hormone related protein or 3) effect of calcium on the synthesis or clearance of FGF23.

The hypercalcaemia responded to adjunctive therapy with Octreotide LAR, bisphosphonates and steroids. The role of PTHrP in HHM, its association with neuroendocrine tumours, the contribution of FGF 23 to HHM as well as therapeutic use of somatostatin analogues are reviewed.

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Variations in the isoform composition of equine chorionic gonadotrophin across early gestation in the horse.

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Equine chorionic gonadotrophin (eCG) is a heterodimeric glycoprotein hormone secreted by the placental endometrial cups during the first third of gestation in the horse. Previous research has shown that eCG is a highly heterogeneous molecule with significant differences in bioactivity between isoforms. The aim of this study was to investigate the eCG isoform composition across early gestation in the horse. Iso-electric focusing (liquid phase) was performed to fractionate plasma samples into 10 pH ranges between 3 and 10. Blood samples were collected from mares (n=33) weekly between 50 and 120 days of gestation and divided into 3 groups 50-60, 60-65 and greater than 75 days. A competitive ELISA was used to determine the immunoactivity in the plasma and fractionated samples. Data from the 10 fractions were grouped into acidic (pH 3.0-5.1), intermediate (pH 5.2-7.9), or basic (pH 8.0-10.0) isoform categories for analysis. In the period prior to and during the eCG peak around day 60 of gestation, there was no substantial change in acidic, intermediate, or basic isoform groups of eCG. However, after 75 days of gestation, the percentage of acidic isoforms of eCG decreased markedly with a concurrent increase in intermediate isoforms. Basic isoform composition did not differ to a significant degree in the specified timeframes. Isoform quantity in the relatively narrow pH range of 4.5-5.1 varied significantly between the three periods with the highest concentration in 60-75 gestation period which coincides with the eCG concentration. These results support previous work on hCG, the human analog of eCG that isoform composition changes across gestation. It has been shown that acidic isoforms of LH and FSH have slower clearance rates than the more basic isoforms which supports our finding that acid isoforms are dominant at the same time eCG concentrations peak in plasma.

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Chronic suppression of Prostaglandin Endoperoxide H Synthase(PGHS-2) expression in the human amnion by glucocorticoids in vivo

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PGHS-2 expression in the amnion is low during gestation and is increased at term, which is critical for generating prostaglandins that stimulate labour. The mechanisms that suppress PGHS-2 gene expression before term and increase it in preparation for labour are unknown. Glucocorticoids may be involved in both of these regulations, because they can stimulate or repress amnion cell prostaglandin production under various conditions in vitro. The aim of this study was to explore whether the stimulatory or the inhibitory glucocorticoid action predominates in vivo and may have physiological and pathophysiological relevance. Amnion tissue was collected after elective Caesarean section at term and was incubated for 24 hours in serum free medium. PGHS-2 and glucocorticoid receptor alpha (GR-alpha) mRNA abundance was determined by quantitative real-time RT-PCR. Chromatin immunoprecipitation was used to measure GR-alpha and NFkappaB factor binding to the PGHS-2 promoter. PGHS-2 mRNA level increased spontaneously several fold over the 24 hour incubation period indicating that PGHS-2 expression was suppressed in vivo. Dexamethasone (4-100 nM) dose dependently blocked the spontaneous increase of PGHS-2 mRNA expression. Chromatin immunoprecipitation showed that GR-alpha and the NF-kappaB transcription factors p65 and p50 were bound to the same PGHS-2 gene promoter region close to the transcriptional start site in amnion obtained before labour. No GR-alpha binding to the PGHS-2 promoter was detected after labour. GR-alpha mRNA abundance was significantly ($p<0.01$) reduced at term compared to late gestation. The data suggest that glucocorticoids suppress PGHS-2 expression in amnion by preventing the NFkappaB-dependent stimulation of the PGHS-2 gene. Withdrawal of the glucocorticoid inhibitory effect, perhaps through decreased GR-alpha expression and/or blockage of GR-alpha binding to the PGHS-2 promoter, may allow the up-regulation of PGHS-2 increasing prostaglandin synthesis sufficiently to initiate labour.

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The influence of predator stress on the activity of the hypothalamic-pituitary-adrenal (HPA) axis of lactating animals

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Activation of the HPA axis varies with sex, type of stressor and the physiological state of the animal. Lactating animals with their lambs present did not respond to a psychosocial stress with an increase in cortisol (Tilbrook *et al*., 2006). Lactating animals that had the lambs present but unable to suckle had a small increase in cortisol concentrations which was nevertheless smaller than non lactating animals. Thus lactating animals have a hypo-responsive HPA axis which was partly due to suckling. The mechanisms involved in lactating induced stress hypo-responsiveness are unknown but there is evidence to show that the HPA axis of lactating animals can be activated when the offspring are threatened. For example, lactating rats with pups present had higher corticosterone responses when exposed to a male intruder or predator odour than lactating rats without pups (Deschamps *et al.*, 2003). We tested the hypothesis that predator stress activates the HPA axis in lactating sheep. We used 3 groups of ewes (n=4/group): non-lactating, lactating with lambs suckling and lactating with lambs unable to suckle and exposed them to a predator stress. Barking dogs were introduced in the experimental shed after 4h of control sampling and barked continuously at the sheep for 5min. All groups responded to stress with a significant increase in cortisol concentrations ($P<0.01$). Non-lactating sheep had significantly higher peak cortisol (73.2±8.9ng/ml) than both groups of lactating sheep. Lactating sheep with lambs unable to suckle had higher ($P<0.05$) peak cortisol concentrations (45.2±5.3ng/ml) than lactating sheep with lambs able to suckle (25.3±5.1ng/ml). In conclusion we have shown that lactating sheep response to a predator stress with an increase in cortisol concentrations although it is still lower than non-lactating sheep.

(1) Deschamps S, Woodside B, & Walker CD (2003) Journal of Neuroendocrinology 15, 486-497.
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Reproductive experience increases the responsiveness of the hypothalamus to prolactin in female rats

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The experience of pregnancy and lactation produces long-term enhancements in maternal behaviour. Central actions of the hormone prolactin are vital for regulating the physiological and behavioural adaptations that enable the mother to nurture her offspring. We tested whether brain regions known to regulate maternal behavioural and neuroendocrine processes were more responsive to prolactin in reproductively experienced females. Activation of the primary signal transducer for the prolactin receptor, signal transducer and activator of transcription 5 (STAT5) was used in an immunohistochemistry study to test if reproductive experience increases prolactin responsiveness within the arcuate, paraventricular, supraoptic, periventricular and anteroventral periventricular nuclei, and in the organum vasculosum of the lamina terminalis. Female Sprague-Dawley rats were mated with breeder males and experienced a full pregnancy and lactation before the pups were weaned. Controls were age-matched virgin animals. At 20 weeks of age (4 weeks post-weaning) all rats had chronic intracerebroventricular cannulae surgically placed. One week later the rats received subcutaneous bromocriptine injections to suppress endogenous prolactin. Following this, half of the reproductively experienced and half of the virgin rats received a 4 µg injection of prolactin intracerebroventricularly, while the remaining rats received artificial cerebrospinal fluid vehicle only (n = 4-6 per group). The brains were perfused and sectioned and then underwent phosphorylated STAT5 (pSTAT5) immunohistochemistry. In all areas examined, there was a marked pSTAT5 response to prolactin regardless of reproductive history ($p<0.01$). However, in the medial preoptic and anterior hypothalamic (paraventricular, periventricular and supraoptic) regions the pSTAT5 response to prolactin was more than doubled in reproductively experienced animals compared to virgins ($p<0.001$). These results show that reproductive experience induces region-specific enhancements in prolactin-responsiveness. Considering that prolactin actions in these hypothalamic regions are implicated in maternal behaviour and stress responses, these data may have significant implications for understanding the mechanisms underlying disorders affecting maternal care.

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The effect of labour status on human gestational tissue mRNA and protein expression of PPAR isoforms

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Objective : Peroxisome proliferator-activated receptor (PPAR) is a candidate regulator of labour-associated mediators. The aim of this study was to examine if PPAR isoforms display labour-associated and tissue specific changes in human gestational tissues obtained before, during and after labour onset.

Methods: Placenta, amnion and choriodecidua were collected from women delivering at term (>37 weeks) from (i) Not-in-Labour (NIL; Caesarean section) n=7; (ii) In-Labour (IL; Caesarean section in labour) n=6; and (iii) Post-Labour (PL; normal vaginal delivery) n=7. QRT-PCR was used to analyse PPARα, PPARδ, PPARγ and transcription partner RXRα. Mean fold expression ratios were calculated using the $2^{\Delta\Delta CT}$ method. Immunoblotting was also performed on whole cell, nuclear or cytoplasmic lysates, to determine protein changes. The mean of the data was analysed by two-sample comparison. Statistical difference was indicated by $p<0.05$.

Results : For placenta, increased mRNA expression of PPARδ, PPARγ and RXRα was observed in the labour groups compared to the NIL. The mRNA expression of PPARδ from amnion obtained from the labour groups was significantly increased compared to the NIL group, whereas PPARγ mRNA in the amnion from the PL was significantly decreased compared to the NIL group. Compared to the NIL group,

choriodecidua PPARδ mRNA expression was increased in the labour groups and RXRα was increased in the PL samples. Increased protein expression was observed in the IL samples compared to NIL samples; PPARα and RXRα in placenta whole cell lysates and PPARγ in placenta nuclear lysates.

Conclusion: Labour at term is associated with tissue specific changes in the mRNA and protein expression levels of PPAR isoforms (α, δ and γ) and related transcription partner RXRα.

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Growth restriction is transmitted to the next generation fetus with compensation in early postnatal life

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In the rat, uteroplacental insufficiency restricts fetal growth and impairs mammary development further compromising postnatal growth. Offspring born small have a reduced nephron endowment but only males develop hypertension with glomerular hypertrophy which can be reversed by improving the lactational environment. Female offspring have uterine vascular dysfunction and increased vessel wall stiffness, which may restrict uterine blood flow during pregnancy, thereby altering fetal development, providing a mechanistic pathway for intergenerational programming. Our aim was to explore whether growth restriction and hypertension can be passed onto the next (F2) generation. Uteroplacental insufficiency and fetal growth restriction of F1 offspring was achieved by bilateral uterine vessel ligation (Restricted, R) or Sham (Control, C) surgery on WKY rats on pregnancy day 18. F1R and F1C females (F1 generation) were mated with normal males generating F2 offspring. Blood pressure (9 week) and body weight (day 20 pregnancy; postnatal days 6, 14, 35; 9 weeks) were measured in F1 (F1C, F1R) and F2 (F2C, F2R) offspring. F1R and F2R litter size was reduced after birth ($p<0.05$), but not during F2 pregnancy. F2 female blood pressure prior to or during pregnancy was not different between groups. F1R and F2R fetuses were smaller than controls ($p<0.05$). F1R, but not F2R, offspring were smaller and shorter from birth to 9 weeks ($p<0.05$). Male, but not female, F1R offspring were hypertensive by 9 weeks ($p<0.05$), with no blood pressure differences in F2 offspring by 9 weeks. Our study demonstrates that uteroplacental insufficiency reduces litter size after birth and that this is transmitted to the subsequent generation. Adverse pregnancy adaptations may have contributed to F2R fetal growth restriction. F2R fetal growth restriction is compensated for in early postnatal life possibly through effects on lactation. Intergenerational transmission of growth restriction suggests that programming of diseases may emerge later in life.

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Direct progesterone receptor and indirect androgen receptor interactions with the kallikrein-related peptidase 4 gene promoter in breast and prostate cancer.

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Kallikrein 4 (*KLK4*) is a member of the human *KLK* gene family of serine proteases, many of which are implicated in hormone-dependent cancers (HDCs). Like other *KLKs*, such as *KLK3*/*PSA* and *KLK2*, *KLK4* gene expression is also regulated by steroid hormones in HDCs, although the transcriptional mechanisms are ill-defined. Here, we have investigated the mechanisms mediating the hormonal regulation of *KLK4* in breast (T47D) and prostate (LNCaP and 22Rv1) cancer cells. We have demonstrated that *KLK4* is only expressed in breast and prostate cancers that express the progesterone receptor (PR) and androgen receptor (AR), respectively. Expression analysis in PR and AR positive cells showed that the two predominant *KLK4* variants that utilize either TIS1 or TIS2a/b are both up-regulated by progesterone in T47D cells, and androgens in LNCaP cells. Two putative hormone response elements (HREs), K4.pPRE and K4.pARE at -2419 bp and -1005 bp, respectively were identified *in silico*. Electrophoretic shift assays (EMSAs) and luciferase reporter experiments suggest that neither K4.pARE nor approximately 2.8 kb of the *KLK4* promoter interacts directly with the AR to mediate *KLK4* expression in LNCaP and 22Rv1 cells. In comparison, we have demonstrated that K4.pPRE interacts directly with the PR to up-regulate *KLK4* gene expression i n T47D cells. Further, chromatin immuno-precipitation experiments demonstrated a time-dependent recruitment of the PR to the *KLK4* promoter (-2496 to -2283) which harbours K4.pPRE. This is the first study to demonstrate that progesterone regulated *KLK4* expression in T47D cells is mediated partly by a HRE (K4.pPRE) at -2419 bp.

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A new profile for the Thr^{201}Met isoform of human aromatase: effects on functional responses to inhibitors and substrate and product concentrations

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The cytochrome P450 enzyme, aromatase (CYP19) plays a critical role in the estrogen pathway as the final step in its production. The T^{201}M variant of the human aromatase gene CYP19A1 (*rs28757184*) within exon 5 has been reported to alter prostate cancer risk. We hypothesised that this occurred by affecting the structure and therefore function of the enzyme. To test this hypothesis the aromatase activity of HEK293 cells transiently transfected with CYP19A1 gene transcripts modified by site directed mutagenesis was measured using tritiated androstenedione as the substrate. The study also analysed the effects of differing concentrations of substrate, product (E1 and E2) and four aromatase inhibitors to ascertain the functional profile of the enzyme isoform compared to wild type. The T^{201}M variant showed much greater maximal activity than wild type (V*max* pmol/hr/mg, wild type 189 ± 17, variant 738 ± 36; p=<0.0001) with a small effect on

Km (wild type nM, 46.6 ± 9.1, variant 64.4 ± 19.3; p=0.04). At a substrate concentration of 400nM the wild-type aromatase exhibits substrate inhibition, with enzyme activity decreasing by 20.6% (p=0.03) whereas the $T^{201}M$ variant increased by 411% (p=<0.0001) . Neither E1 nor E2 demonstrated product inhibition at concentrations up to 10mmol/L. Compared to wild type the variant showed no altered resistance to letrozole, chrysin or formestane however inhibition by aminoglutethimide was substantially reduced (IC50 wild type 1.3 ± 0.2nM; variant 45 ± 14.2nM; p=0.002, and Ki wild type 0.7 ± 0.2nM; variant 29.6 ± 9.7nM; p=<0.0001). These data demonstrate that common to other cytochrome P450 enzymes wild type CYP19 demonstrates substrate inhibition but not product inhibition. Second, the $T^{201}M$ variant has increased activity due to lack of substrate inhibition and demonstrates substantial resistance to aminoglutethimide. Individuals with this variant may occur in up to 7% of some populations and the altered enzyme function may have substantial effects on estrogen dependent disorders and treatment, including prostate cancer.

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Denaturing high performance liquid chromatography (DHPLC) detection of SDHB, SDHD and VHL germline mutations in phaeochromocytoma

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Background. Pheochromocytomas are neuroendocrine tumors of chromaffin cell origin which arise from the adrenal medulla and less commonly the extra-adrenal sympathetic paraganglia. Pheochromocytomas are component tumors of the familial syndromes Multiple Endocrine Neoplasia type 2, von Hippel Lindau disease, Neurofibromatosis type 1 and the Pheochromocytoma/Paraganglioma syndromes caused by mutations in the *RET, VHL, NF1* and succinate dehydrogenase subunit B (*SDHB*) / subunit D (*SDHD*) genes respectively. The aim of this study was to evaluate denaturing high performance liquid chromatography (dHPLC) as a screening tool for the detection of germline mutations within *VHL, SDHB* and *SDHD* in pheochromocytoma patients.

Methods . Polymerase chain reaction (PCR) of all exons of *VHL, SDHB,* and *SDHD* genes was performed on leukocyte DNA extracted from stored blood samples of 74 patients treated for pheochromocytoma. After dHPLC analysis all samples demonstrating variance were selected for sequencing.

Results. A total of five mutations and 15 polymorphisms were detected in the *SDHB* gene and seven mutations and one polymorphism were identified in the *VHL* gene. No *SDHD* mutations or polymorphisms were identified. With PCR and dHPLC followed by sequencing of variants only, the total amount of DNA sequencing required was reduced by approximately 88%. The variant dHPLC results correlated correctly for all patients who had undergone DNA sequencing analysis.

Conclusions. dHPLC is an effective screening tool for the detection of germline mutations in *SDHB, SDHD* and *VHL* and has application for diagnostic germline mutation analysis in pheochromocytoma patients.

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Tumor suppressive activity of inhibin-α subunit is altered during prostate cancer progression

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The inhibin field has been perplexed by the information that inhibin-α subunit (INHA), a member of the TGFβ superfamily is a tumor suppressor in mice yet is elevated in women with ovarian cancer. Similarly we have observed up- and down-regulation of INHA expression in prostate cancer (PCa) dependent on the stage of disease and proposed that INHA has tumor suppressive and pro-metastatic activity in different stages of PCa progression. Recently, loss of TGFβ receptor RIII (TGFβRIII), a receptor for inhibin has been proposed to be an explanation for the different activities of INHA in PCa. The present study was designed to elucidate the role of INHA in regulation of tumor cell growth, migration and the tumorigenic and metastatic potential of two metastatic PCa cell lines, LNCaP and PC3, which differ in androgen-responsiveness and growth characteristics. Tumor suppressive activity of INHA was observed in LNCaP cells which demonstrated reduced cell proliferation, migration and tumor growth. In contrast, loss of tumor suppressive activity/gain in metastatic properties of INHA was observed PC3 cells which demonstrated increased cell proliferation, migration and tumor growth. The shift in the tumor suppressive activity of INHA was further evident by increase in lymph node metastasis in the INHA over-expressing PC3 tumors which was accompanied by an elevation of lymphatic vessel density and tumor cell invasion into lymphatics. These effects were associated with up-regulation of VEGF-C. Consistent with other studies our work revealed that LNCaP cells expressed significantly more TGFβRIII than PC3 cells. The results suggest a correlation between loss of tumor suppressive activity of INHA to loss of TGFβRIII expression. INHA staining in clinical specimens suggested a potential paracrine role for INHA in promoting metastasis. Our results demonstrate the different roles of INHA in PCa and provide the first functional explanation for the paradoxical expression of INHA during PCa progression.

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Altered Differentiation Of Mammary Stem Cells By Prostatic Mesenchyme; Cross-Talk Between Ectoderm- And Endoderm-Derived Tissues

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Understanding the identity and biology of adult stem cells has wide implications for tissue regeneration and therapeutic medicine in hormone dependent tissues. Our focus has been on the role of the niche environment on dictating stem cell differentiation in vivo, particularly between tissues of different cell lineages. In this study, we sought to investigate if the inductive and instructive signals from the prostatic mesenchyme (normally associated with endoderm) could redirect ectoderm-derived mammary stem cell differentiation using tissue recombination. We isolated rat urogenital mesenchyme (UGM) and mammary gland epithelia (MGE) from balb/c-GFP mice at three different stages of development including fetal (E14.5), immature (2 weeks postnatal) and adult (20-40 weeks). In addition, we isolated a population of enriched mouse mammary stem cells (MaSCs) using the cell surface phenotype (Lin-CD29hiCD24+). Heterospecific tissue recombinants (UGM+MGE) were generated and grown under the kidney capsule of male host SCID mice for 4-8 weeks. As controls, UGM-UGE recombinants and mammary gland stroma (MGS)-MGE recombinants were sub-renally grafted alone into male hosts and compared to intact mammary gland epithelium from female mice. Upon harvest of UGM-MGE recombinants from the male hosts, we observed survival of mammary epithelia and extensive branching morphogenesis including ductal formation and elongation compared to MGS-MGE recombinants, which survived but showed limited branching. In addition, chimeric ducts were observed in UGM-MGE recombinants that possessed properties of both prostate and mammary gland epithelium based on morphological criteria and biomarker profiles, including expression of androgen receptors (prostate marker), estrogen receptor- (mammary gland marker) and Foxal (endoderm marker). We confirmed this finding using enriched MaSCs which when recombined with UGM resulted in significant branching morphogenesis and the formation of chimeric glands when grown in male hosts. These data provide evidence of directed differentiation of tissue-specific adult stem cells by local and systemic environmental cues. Our results demonstrated the importance of the appropriate selection of the stromal cell niche for stem cell differentiation and raise the possibility of cross-talk between different cell lineages that has implications for tissue regeneration.

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Parity induced breast cancer protection against breast cancer – an estrogen sensitive issue?

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Approximately 70% of human breast cancers express the estrogen receptor and are hormone dependent. Women who have undergone a full-term pregnancy/birth before 20 years of age have a 50% reduced lifetime risk of developing estrogen receptor positive / progesterone receptor positive (ER+ PR+) breast cancer compared to nulliparous women . The mechanisms underlying this protection are unclear. A similar protective effect of pregnancy is mirrored in mouse models of hormone responsive breast cancer, which allows us to use mouse models to address this. We hypothesize that the parity-induced protection is mediated via epithelial cells within the mammary gland and in particular by changes in the hormone responsive population of cells or their neighboring basal stem/progenitor cells. Previous studies in rodents have assessed the levels of ER, however it is difficult to draw general conclusions from these studies as they have used different experimental regimes, different analysis end points and/or analysis times. The effect of parity of stem cell number had not been definitively assessed. We used f low cytometric epithelial cell isolation to show that parity leads to a significant decrease in the proportion of basal/myoepithelial cells (which includes the stem cell population). Limiting dilution mammary fat pad tranplantations (assay for stem cell acitvity) confirmed that parous mammary glands have a reduction in the ability to repopulate a cleared fat pad. Immunofluorescence localisation of ERα and ERβ revealed decreased ERα expression and changes to the subcellular localization of ERβ . Together this suggests that the parous gland may have altered estrogen sensitivity compared to virgins as well as decreased stem cell acivity. Ongoing studies will determine whether the estrogenic effects of parity on the decreased stem cell activity are mediated directly on the ERα positive luminal epithelial cells or the ERβ positive basal cells.

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Low MGMT Expression is Associated with Response to Temozolomide in Aggressive Pituitary Tumours

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Context: Recent case reports detail the successful use of temozolomide in the management of aggressive pituitary tumours. 0^6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein that counteracts the effect of temozolomide.

Objective: To study MGMT expression in pituitary tumours and determine whether MGMT expression is associated with response to temozolomide therapy in aggressive pituitary tumours.

Patients: We report 2 patients with aggressive pituitary tumours treated with temozolomide, one who responded to temozolomide, and the other who did not. MGMT expression was assessed in these 2 cases and in a further 88 archived pituitary tumour samples.

Methods: MGMT expression was assessed by immunohistochemistry. *MGMT* promoter methylation was studied by methylation-specific PCR (MSP), sequencing of *MGMT* was performed and loss of heterozygosity analysis undertaken, in order to determine mechanisms of low MGMT expression.

Results: Low MGMT expression and *MGMT* promoter methylation was found in the pituitary tumour of the patient who responded to temozolomide. Conversely, high MGMT expression was seen in the patient demonstrating a poor response to temozolomide. Eleven out of 88 archived tumour samples (13%) had low MGMT expression. Prolactinomas were more likely to have low MGMT expression compared with other pituitary tumour subtypes ($p<0.001$). There was no significant difference in MGMT expression between invasive and non-invasive tumours, nor between recurrent and non-recurrent tumours. A significant inverse correlation was found between MGMT expression and promoter methylation ($p=0.012$).

Conclusion: MGMT expression as assessed by immunohistochemistry may predict response to temozolomide therapy in patients with aggressive pituitary tumours. *MGMT* promoter methylation is likely to explain low MGMT expression in some, but not all, pituitary tumours.

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Structural decay of bone in males treated with androgen deprivation therapy for prostate cancer

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Introduction: Sex steroids are important regulators of bone remodelling. In males, the use of androgen deprivation therapy (ADT) for treatment of prostate cancer reduces bone mineral density (BMD), but the structural basis of the deficit in BMD has not been determined prospectively.

Aim: We hypothesized that ADT will reduce cortical and trabecular thickness, increase cortical porosity and reduce serum testosterone levels in males treated for non-metastatic prostate cancer. Here we present preliminary data from an ongoing longitudinal study.

Methods: Prelimary data is presented for 11 males with baseline and 6 months data after commencing ADT. Assessment comprised medical history, physical examination and fasting blood analyses including sex-hormones. BMD was determined by dual energy x-ray absorptiometry (DEXA) and microarchitecture was assessed using high resolution peripheral quantitative CT (HR-pQCT).

Results: The mean age of subjects was 72 years at baseline. After 6 months, there was a decrease in total testosterone levels (12.26 to 0.73nmol/L, $p<0.001$), but no change in BMI or body weight. BMD was unchanged at the lumbar spine, but decreased at the femora1 neck (-2.2%, $p=0.004$). Microarchitecture changed at the distal tibia with a decrease in average bone density (-2.3%, $p=0.032$) due to a decrease in cortical density (a surrogate of porosity increase) (-1.3%, $p=0.04$), and cortical thickness (- 6.0%, $p=0.001$) not trabecular density. At the radius there was a decrease in average bone density (-2.6%, $p=0.014$) again due to a decline in cortical density (-1.3%, $p=0.037$) and thickness (-4.5%, $p=0.014$) and trabecular density (-1.9%, $p=0.036$).

Conclusions: Males with induced testosterone deficiency, as a result of treatment for prostate cancer, experience decay of both cortical and trabecular bone. Whether this is due to androgen or oestrogen deficiency remains to be determined.

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Lower testosterone levels predict incident stroke and TIA in older men. The Health In Men Study.

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Introduction: Low testosterone levels are associated with mortality and lower limb arterial disease in men, and inversely correlated with carotid intima-media thickness. However, data regarding the potential role of androgens as risk factor for cerebrovascular disease during male ageing are limited. We sought to determine whether lower serum testosterone predicted a higher incidence of stroke and transient ischemic attack (TIA) in older men.

Methods: Longitudinal analysis of 3,443 community-dwelling men aged ≥70 years. Serum total testosterone, sex hormone-binding globulin (SHBG) and luteinising hormone (LH) at baseline were assayed. Free testosterone was calculated using mass action equations.

Results: Incidence of stroke and TIA were determined over a median (interquartile range) follow-up period of 3.5 (2.8-4.2) years, or until death. Events occurred in 118 men (3.4%). Lower total and free testosterone concentrations (in the lowest quartile of values) were associated with reduced event-free survival (p=0.014 and p=0.019 respectively). After adjustment for age, waist-hip ratio, smoking, hypertension, dyslipidemia and medical co-morbidity, low total testosterone (defined as the lowest quartile of values) predicted increased incidence of stroke and/or TIA (hazard ratio [HR]=1.69, 95% CI 1.14-2.50). Low free testosterone was less strongly associated with incident stroke/TIA (HR=1.48, 95% CI 1.01-2.18). SHBG and LH were not independently associated with incident stroke/TIA.

Conclusions: In older men, lower total testosterone levels predict increased incidence of stroke and/or TIA independently of conventional risk factors for cardiovascular disease. Further studies are warranted to determine whether interventions which raise circulating testosterone levels might prevent cerebrovascular disease in men.

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ACTH-Independent Macronodular Adrenal Hyperplasia: A Familial Disease? Detection of Early Manifestations.

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Introduction: ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH) is a rare cause of late-onset sporadic Cushing's syndrome.[1] AIMAH has been extensively studied predominantly to detect aberrant cortisol responses to various secretagogues, including vasopressin (VPs-AIMAH).[2] We detected familial VPs-AIMAH in two kindreds (AIMAH-01 and AIMAH-03) after three siblings from each kindred presented with Cushing's. We also screened the family of an apparently sporadic case (AIMAH-02) for preclinical VPs-AIMAH. Aims: (1) To delineate the phenotype of familial VPs-AIMAH in three kindreds (AIMAH-01, -02 and -03) and (2) To investigate the aetiology of VP sensitivity in AIMAH-01. Hypotheses: (1) VPs-AIMAH is inherited and preclinical forms can be detected using biochemical testing, including VP stimulation, and adrenal imaging. (2) VP sensitivity is due to VP receptor overexpression on AIMAH cells. Methods: Forty-four individuals, from three kindreds, were screened for Cushing's and adrenal tumours. The genes for the VP receptors (VPR1a and VPR1b) from those with Cushing's (AIMAH-01) were sequenced. Candidate gene expression profiles (VPR1a, VPR1b, PRKAR1A, PDE11A) from normal adrenal and tumours (AIMAH-01) were compared using Affymetrix microarrays. Results: AIMAH-01 had three siblings with Cushing's, and four with biochemical and/or adrenal imaging abnormalities. In AIMAH-02 and -03, there are two and three individuals, respectively, with AIMAH. In AIMAH-01, there was no mutation of the VP receptor gene, nor differential candidate gene expression between tumour and normal adrenal. Conclusions: AIMAH is familial. The characteristic late-onset of Cushing's may have contributed to this previously being unrecognised. Adrenal imaging, biochemical evaluation for hypercortisolism and secretagogue testing may assist in early case detection in relatives of index cases. Early detection may prevent advanced disease and could be facilitated if familial AIMAH is found to be caused by a restricted number of heritable mutations. Heightened VP sensitivity may not be central to the pathogenesis of adrenal tumorigenesis in VPs-AIMAH.

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Testosterone Therapy Increases Sexual Desire in Aging Men with Low-Normal Testosterone Levels and Symptoms of Androgen Deficiency

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Background: Although decline in sexual function is a common reason for ageing men to seek advice regarding testosterone therapy, placebo-controlled trial data have been unable to show a consistent, beneficial role for testosterone.

Objective: To determine the effect of testosterone therapy on sexual function in non-obese ageing men with symptoms of androgen deficiency and low-normal serum testosterone levels.

Design, patients and measurements: 60 men aged 55 years or older in good general health with total testosterone (TT) levels <15nM, and with symptoms suggestive of androgen deficiency, were randomized in a double-blinded protocol to transdermal testosterone patches or placebo for 12 months. Sexual function was assessed using the International Index of Erectile Function (IIEF) at Weeks 0, 26 and 52.

Results: In men receiving testosterone TT levels increased by 30% (P=0.01) and LH decreased by 50% (P<0.001). Relative to placebo, testosterone therapy improved sexual desire (P=0.04) however other parameters of sexual function including erectile function were unaffected by treatment.

Conclusion: Ageing men in good general health and with symptoms of androgen deficiency and low-normal serum testosterone levels receiving 12 months of transdermal testosterone therapy experienced, relative to placebo, improved sexual desire but no effect on other parameters of sexual function.

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STOP Fracture study: Southern Health Osteoporotic Fracture Screening Project

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Background: Osteoporosis is a major healthcare issue with > 50% of postmenopausal women suffering an osteoporosis-related minimal trauma fracture over their lifetime. Vertebral fractures are the most common, are often asymptomatic and are unrecognised and untreated in ~80-90% of cases. Pharmacological intervention reduces fracture risk by 50-60%. Theoretically a simple screening lateral chest x-ray to detect vertebral fractures in a high risk population is a feasible and cost effective strategy to reduce the burden of osteoporosis through targeted recognition and treatment.

Methods: In this prospective study, 104 postmenopausal women (≥65 years), presenting to Southern Health for unrelated conditions and requiring an anterior–posterior CXR were recruited. After consent, a lateral CXR and a fracture risk questionnaire were completed. Patients and GPs were notified by letter recommending further assessment/treatment when fractures were detected and questionnaires were resent 12 months later.

Results: Of those consented, 96 women had a lateral CXR with 53 (55%) having one or more vertebral fractures. 73 completed the initial questionnaire (Table 1) and their 5 year fracture risk was calculated (Table 2).

Table 1: Results of the baseline questionnaire.

Personal history of minimal trauma fracture	28 / 73 (38%)
Previous assessment for osteoporosis	31 / 73 (42%)
Osteoporosis pharmacotherapy	37 / 73 (51%)
Bisphosphonates	13 / 37 (35%)
Calcium	30 / 37 (81%)
Vitamin D	11 / 37 (30%)
Hormone replacement therapy	1 / 37 (3%)
Raloxifene	2 / 37 (5%)

Table 2: The five year fracture risk calculated from accepted risk prediction tools.

5 year fracture risk	0%	10%	15%	20%	25%	40%
N = 73	1 (1%)	8 (11%)	21 (29%)	11 (15%)	21 (29%)	11 (15%)

On follow-up 1 year questionnaire (n=53, 8 participants died), 4 were already on bisphosphonates, 8 on calcium and 4 on vitamin D. After notification of fracture to GPs and Patients, 8 started bisphosphonates, 12 calcium and 6 vitamin D, whilst 8 sustained a symptomatic minimal trauma fracture, only 6 of whom received preventative therapy.

Conclusions: 55% of postmenopausal women aged ≥65 years presenting to Southern Health with unrelated medical conditions and capable of consent, had evidence of a previous vertebral minimal trauma fracture on routine lateral CXR and questionnaire to exclude significant

trauma. We propose that lateral CXR, a simple effective screening tool for osteoporotic fracture should be applied in this high risk population. However, despite patient and GP notification, only 30% of women commenced preventative therapy and only 15% had bisphosphonates, highlighting the need for education to encourage appropriate treatment.

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Pharmacokinetics and Pharmacodynamics of Depot Testosterone: Randomized Cross-over Clinical Trial of Injectable vs Implantable Testosterone in Androgen Deficient Men

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Testosterone (T) replacement for androgen deficient men requires life-long treatment so that depot products are attractive. Testosterone implants (TI) have a long (6 month) duration of action but the need for office surgical implantation as well as extrusions (5-10% per procedure) are limitations. Testosterone undecanoate (TU) providing 3 months duration of action with a 4 mL oily injection is a recent alternative. We studied these depot T products by enrolling 38 men using TI for organic androgen deficiency (excluding andropause) into a randomized-sequence, non-masked, cross-over study of TI (20-24 weeks) vs TU (30 weeks) that allows within-person comparisons. Study endpoints included T pharmacokinetics and pharmacodynamic effects on hormones (LH, FSH, SHBG), muscle (mass, strength), biochemistry (hemoglobin, lipids) and quality of life (QoL; SF-36, mood, energy and sexual activity) and preferences. Data were analyses by two-period, cross-over methods. There were no significant carry-over or sequence effects so data were pooled for each treatment. Both treatments produced similar 2 week peak T levels but blood T concentrations were more stable and SHBG decrease less sustained with TI whereas TU produced more sustained LH and FSH suppression in men with hypergonadotrophic hypogonadism. Both produced similar increased hemoglobin and decreased HDL cholesterol without other lipid changes. Both treatments produced no change in blood pressure, body composition or muscle strength apart from increased body weight (TU) and hand grip strength (TI). QoL measures were mostly unchanged except for improved energy levels and Social Functioning (both), improved Physical Functioning (TU) and improved irritability and cheerfulness (TI). Immediate post-study preference for further treatment was TU for most men. We conclude that, despite differences in pharmacokinetics and pharmacodynamics, TU and TI produce similar short-term outcomes so may be considered clinically comparable but most androgen deficient men with experience of both prefer TU.

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Trough serum testosterone levels predict the development of polycythemia in men with organic androgen deficiency receiving testosterone replacement therapy

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BACKGROUND: The association between testosterone (T) and pathologically increased hematocrit (or secondary polycythemia) is well recognised. However, polycythemia arising during long-term testosterone replacement is less well-defined, especially with testosterone preparations that exhibit more steady state pharmacokinetics which may stimulate excessive erythropoiesis less. METHOD: Trough blood testosterone levels were measured just before the next depot testosterone treatment at approximately 4-6 month intervals. Multiple logistic regression models were used to obtain odds ratios (OR) and 95% confidence intervals (CI). Polycythemia was defined in relation to our laboratory reference range, as a hematocrit of over 0.50. FINDINGS: 156 men aged from 17 to 84 years (mean age 46.8 years) were treated with testosterone implants for primary, secondary or mixed hypogonadism for 7.5 years on average (range 0 to 21 years). There was a strong univariate association between polycythemia and log (T) (OR 15.4 95% CI: 3.2 – 73.8, P<0.01) and a weak association with age (OR 1.1 95% CI: 1.0 – 1.1, P=0.02). There was no relationship with current smoking (OR 3.8 95% CI: 0.8 – 18.3, P=0.11). The independent odds ratio of developing polycythemia after adjusting for a priori confounders (smoking, age) for log (T) was 11.1 (95% CI: 2.0 – 61.0). Duration of testosterone therapy did not significantly alter the risk of polycythemia with or without adjustment for age and/or smoking status. A sensitivity analysis showed similar findings with more stringent definitions of polycythemia. INTERPRETATION: Higher serum testosterone trough levels but not duration of treatment predicts the development of polycythemia in men receiving depot testosterone treatment. These data suggest steady-state testosterone replacement should be titrated to the lowest efficacious dose but further regular surveillance of hematocrit is not required with longer term depot testosterone treatment. The mechanism by which testosterone causes polycythemia, particularly the long term role of erythropoietin remains to be elucidated.

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LKB1 - the link between obesity and breast cancer in postmenopausal women

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There is good epidemiological evidence that obesity is linked to an increased risk of cancers, including breast cancer (BC). Given the obesity problem worldwide, tens of millions more women may contract BC in their senior years than was previously thought. However, the cellular and molecular mechanisms underlying the increased risk of BC associated with obesity and aging are not well understood. We have recently demonstrated that altered sex hormone ratios, as are seen in women after menopause, regulate the expression and activity of LKB1, an upstream kinase for AMPK. The present work aims to examine the effect of adipokines, known to act on LKB1, on aromatase expression, as well as identify additional mechanisms by which PGE2, a known tumour-derived factor, causes increased aromatase expression in breast preadipocytes. In preadipocytes, adiponectin significantly and dose-dependently downregulated aromatase expression. Next, FSK and PMA were used to stimulate aromatase expression (simulating the effects of PGE2), and resulted in a significant decrease in LKB1 transcript expression and activity, as monitored by AMPK phosphorylation. AICAR, known to stimulate AMPK activity, significantly downregulated aromatase transcript expression. Moreover, FSK/PMA treatment of preadipocytes resulted in nuclear translocation of the CREB co-regulator TORC2, a downstream target of LKB1/AMPK. Aromatase promoter II (PII) activity assays were conducted in MCF-7 cells where co-transfection with TORC2 in addition to FSK/PMA treatment resulted in a significant increase in PII-induced activity compared to treatment alone. Finally, TORC2 binding to PII was examined by ChIP in preadipocytes and was shown to increase after FSK/PMA treatment. These results support the hypothesis that obesity is associated with increased local expression of aromatase and that this and the tumour-induced expression of aromatase are mediated, at least in part, by decreased LKB1 expression. Taken together with our previous results demonstrating that estrogens increase metabolic pathways in MCF-7 cells via LKB1, this study establishes LKB1/AMPK as a link between obesity, aging and BC in post-menopausal women.

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The Effect of GHS on the Transient Outward K^+ Current in Rat Ventricular Myocytes

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Ghrelin and hexarelin are endogenous and synthetic growth hormone secretagogues (GHS), which possess a variety of cardiovascular protective effects. Little information is available relating to the mechanism by which GHS modulate function of cardiac myocytes. Although it has been reported that synthetic GHS produced a positive inotropic effect on cardiomyocytes vias an increase in $[Ca^{2+}]_i$ through Ca^{2+} influx, modification of membrane ion channels by GHS has not been studied carefully [1]. This increase in Ca^{2+}-influx can be achieved by a direct increase in Ca^{2+} channel conductance and/or a decrease in K^+ channel conductance leading to a prolonged depolarization. In the present study, we examined effect of GHS regulated the transient outward potassium current (I_{to}) as well as the putative intracellular signaling responsible for the effects. I_{to} was recorded in fresh isolated adult Sprague-Dawley rat ventricular myocytes using the nystatin-perforated whole-cell patch-clamp recording technique. H exarelin and ghrelin (100 nM, 10 nM, 1 nM, 0.1 nM, and 0.01 nM) inhibited I_{to} in a dose-dependent manner. The inhibition appeared at doses above 0.01 nM, but less significant at doses above 10 nM resulting in a bell-shaped dose-response curve. The inhibition was abolished in the presence of the GHS-R1a specific antagonist BIM28163 (1 μM). G hrelin and hexarelin significantly prolonged action potential duration (APD). The GHS-induced I_{to} inhibition was totally abolished by the phospholipase C (PLC) inhibitor U73122 (5 μM), protein kinase C (PKC) inhibitors, Gö-6983 (1 μM) and calphostin C (0.1 μM), but not by cAMP antagonist Rp-cAMP (100 μM) or PKA inhibitor, H89 (1 μM). We therefore conclude that hexarelin and ghrelin activate PLC and PKC system through the activation of GHS-R1a on rat ventricular myocytes, resulting in a decrease in the I_{to} current, and prolongation of APD. Such change may lead to an increase in Ca^{2+} influx and myocyte contraction.

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Genetic disruption of rhythmicity in peripheral tissues of mice alters adipocyte function

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Shift work and disruption of circadian rhythms increase the prevalence of obesity, diabetes and the insulin resistance/metabolic syndrome in humans and shiftwork simulation in the rat impairs insulin action and glucose tolerance (1).

Clock $^{\Delta 19}$ +MEL mutant mice, which have normal central, but disrupted peripheral organ rhythmicity (as occurs in shiftwork), have impaired glucose tolerance and altered expression of key liver metabolic enzymes, due in part to poor insulin secretion as insulin sensitivity was enhanced (2). The latter may be due to elevated plasma adiponectin and reduced free fatty acids in mutant mice, suggesting altered adipocyte function.

We therefore measured adipokine and lipase mRNA expression in epigonadal adipose tissue across 24 hours in *Clock* $^{\Delta 19}$ +MEL and wild type (WT) mice fed control (7% fat) or high fat diets (22%) from 3-8 weeks of age.

On the control diet, adiponectin mRNA, but not that of leptin, resistin, visfatin, hormone sensitive lipase (HSL), adiponutrin or desnutrin, was increased in *Clock* $^{\Delta 19}$+MEL mice compared to WT. The high fat diet increased relative epigonadal fat depot weight similarly in both strains, but increased plasma glucose and free fatty acids to a lesser extent, in the mutant mice. High fat also increased plasma leptin, but

did not alter plasma adiponectin or adipokine mRNA in *Clock* $^{\Delta 19}$ +MEL mice compared to WT. High fat also increased HSL but not adiponutrin or desnutrin mRNA in mutant compared to WT mice.

These studies show that genetic disruption of peripheral cellular rhythmicity can alter adipocyte function and in a favourable manner even when challenged by excess caloric intake. Understanding the mechanistic basis whereby peripheral clock disruption promotes an 'insulin sensitising' phenotype in the adipocyte, may suggest novel interventions to prevent metabolic impairment in shift work.

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In vitro regulation of membrane ion channels by adiponectin in GFP-GH transgenic mouse pituitary somatotropes

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Adiponectin is a hormone produced by adipose tissue. Two receptors (AR1, AR2) have been identified as specific adiponectin receptors in muscle, heart, and liver. The main function of adiponectin is to increase insulin sensitivity and promote lipid oxidation in peripheral tissues. Obesity and diabetes are two conditions associated with reduced levels of adiponectin. Recently, it has been reported that secretion of GH was modified by adiponectin in vitro. Moreover, adiponectin mRNA has been found in the pituitary of a number of species. Although adiponectin has been reported to suppress or enhance GH secretion from rat pituitary cells, the cellular mechanisms are not known. In this experiment, adiponectin receptor expression has been demonstrated in mouse pituitary somatotropes. Electrophysiological properties of primary cultured mouse somatotropes, identified by GFP in GFP-GH transgenic mouse, were studied with perforated patch clamp recording. Voltage-gated K^+ currents were significantly reduced by 2 ug/mL of adiponectin. This reduction was not significant with concentrations below 1 ug/mL and not significantly enhanced with concentration of 4 ug/mL. Changes in K^+ currents were reversible within 10 minutes after adiponectin removal. By contrast, Na^+ and Ca^{2+} currents exhibited a significant increase respectively to adiponectin stimulation in a reversible manner. Intracellular signalling pathways employed by ARs have been studied. The PKA blocker, H89, abolished the K^+ current response to adiponectin whereas the Ca^{2+} current response was unaffected. The PKC inhibitor, Go6893, reduced the Ca^{2+} current response but not the K^+ current response to adiponectin. In conclusion, ARs exist in mouse somatotropes and adiponectin regulates three major membrane cation channels. PKC signalling regulates the Ca^{2+} channel response and PKA signalling regulates the K^+ channel response to adiponectin. The reduction of K^+ currents and increase in Ca^{2+} and Na^+ currents may lead to an increase in Ca^{2+}-influx and GH secretion.

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Increased adiposity in androgen receptor knockout (ARKO) mice due in part to decreased physical activity with no change in food consumption

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Our androgen receptor knockout (ARKO) mouse model has as in-frame deletion of the 2nd zinc finger of the DNA binding domain, which abolishes the genomic actions of the AR. At 12 weeks of age, ARKO males have increased adiposity compared to wildtype (WT) males, with subcutaneous fat mass increased by 75% ($p<0.001$, $n\geq17$/group) and infrarenal fat mass increased by 36% ($p<0.05$, $n\geq17$/group). However, total body mass of ARKO males is decreased by 13% versus WT males ($p<0.001$, $n\geq17$/group) at 12 and 30 weeks of age. Mean voluntary physical activity at 12 weeks, measured by wheel running, is 86% lower in ARKO mice ($p<0.05$, n=3-4/group). At 24 weeks of age, following 12 weeks of a high fat diet (containing 60% fat), total body mass is not different between WT and ARKO mice (n=11-12/group). Subcutaneous fat mass remains increased by 66% compared to WT males ($p<0.001$, n=11-12/group), however there is no difference in infrarenal fat mass. Average weekly food intake is not different, but mean voluntary physical activity is decreased by 49% in ARKO males compared to WT males ($p<0.001$, n=11-12/group). There is no difference in resting energy expenditure, fat oxidation or glucose oxidation rates between the two groups (n=11/group). This study suggests that increased adiposity in ARKO mice is in part due to decreased voluntary physical activity but not increased food consumption or decreased resting energy expenditure.

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The generation of a doxycycline-inducible, tissue-specific aromatase-expressing mouse

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Aromatase (estrogen-synthesizing enzyme) is expressed in other tissues (e.g. brain, adipose) besides gonads. Estrogen deficiency in male aromatase knockout (ArKO) mice causes unexpected phenotypes including male-specific fatty liver and neuronal apoptosis in the hypothalamus. As the circulating level in male animals is low, we hypothesize that the local production of estrogen in tissues is important for the regulation of physiological functions (e.g. energy homeostasis) or pathological development (e.g. breast cancer) by acting in a paracrine or intracrine manner. To test this hypothesis, we have generated a doxycycline-inducible, tissue-specific aromatase transgenic mouse.

The targeting construct consists of a full-length human aromatase cDNA (hArom) and a *luciferase* marker gene; both placed under the control of a bi-directional tetracycline-responsive promoter (pTetO) which is regulated by transactivators (rtTA or tTA) and doxycycline. This transgene was shown to increase hArom transcripts (16-fold, p=0.01), aromatase activity (3.4-folds, p=0.0008) and luciferase activity (16-fold, p=0.0006) in transiently transfected MBA-MD231tet cells that stably expresses rtTA, after induction with doxycycline.

Pronuclear microinjection of the transgene produced four pTetO-hArom founder mice. One female founder produced one positive male F1 (out of one live birth), and one male founder produced five positive F1 (out of 19 live births; two females and three males). Other female and male founders have no positive offspring to date.

We have successfully induced (by doxycycline administration in drinking water) the specific expression of the transgene in the mammary gland of the mammary gland-specific-rtTA/pTetO-hArom double transgene positive offspring, obtained by crossing a pTetO-hArom male founder with a female mammary gland specific-rtTA transgenic mouse.

The crossing of F1 offspring with heterozygous ArKO mice is in progress to generate ArKO mice carrying the transgene (pTetO-hArom/ArKO). In summary, we have generated a viable transgenic mouse that expresses human aromatase in a temporal- and spatial-specific manner.

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Stanniocalcin 2 knock-out mice are larger and leaner

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Stanniocalcin (STC) is a secreted glycoprotein involved in calcium and phosphate homeostasis that was first discovered in bony fish. Two homologues, STC1 and STC2, have been identified in mammals, and both are expressed in a wide variety of tissues including kidneys, bones, mammary glands, testes and ovaries. Many roles have been attributed to the mammalian STCs, including control of renal calcium and phosphate handling, bone development, wound healing, and protection against hypoxia (1).

No phenotype has been detected in *Stc1*-null mice, and to investigate whether *Stc2* could have compensated for the loss of *Stc1* we have now generated *Stc2*$^{-/-}$ and *Stc1*$^{-/-}$ *Stc2*$^{-/-}$ mice (2). Mice with *Stc2* deleted were 10-15% larger and grew at a faster rate than wild-type mice from 4 weeks onwards, and the *Stc1*$^{-/-}$ *Stc2*$^{-/-}$ mice had a similar growth phenotype. This growth phenotype was not mediated via the GH/IGF-1 axis. Although *Stc1* is expressed in the ovary and in lactating mouse mammary glands, like the *Stc1*$^{-/-}$ mice, the *Stc1*$^{-/-}$ *Stc2*$^{-/-}$ mice had no detected decrease in fertility or fecundity. Serum calcium and phosphate levels were normal in *Stc1*$^{-/-}$ *Stc2*$^{-/-}$ mice, indicating it is unlikely that the mammalian stanniocalcins have a major physiologic role in mineral homeostasis. The *Stc2*-null mice had less whole body fat than wild-type even though they were heavier. This suggests that STC2 may have a new role in adipocyte differentiation or fat metabolism.

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Sex hormones: A role in adiposity and insulin resistance.

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Sex hormones such as estrogens and androgens are known to play an influencing role in insulin resistance and adiposity, which contribute to many disease processes such as type 2 diabetes and metabolic syndromes. Estrogen (E2) and testosterone (T) are known to have bi-phasic effects on insulin resistance in a dose-dependent manner. To study the effects of sex hormones on insulin resistance we studied Aromatase knockout (ArKO) mice which are unable to convert androgens to estrogens.

Glucose tolerance and insulin sensitivity of 12 and 24 week-old animals were assessed by Glucose Tolerance Test (GTT; ip glucose injection, 1mg/g) and Insulin Tolerance Test (ITT; ip insulin injection, 0·05 or 0.025U/g) after a 6h fast. Blood glucose concentrations were measured at 0, 20, 40, 60, 90 and 120 min. Fed, fasted and GTT (20min) blood insulin concentrations were measured.

Twelve week-old ArKO mice showed a significant increase in omental adipose tissue in both males (1.8 fold, $p<0.05$) and females (2.3 fold, $p<0.01$) when compared to WT counterparts. At 12 and 24wks, ArKO mice also presented higher fasted basal glucose levels in both sexes as compared to WT. Female ArKO mice at 24wks also showed significantly higher fasted insulin levels (4fold, $p<0.05$). ArKO mice were less glucose tolerant at 12 and 24wks of age (males $p<0.05$ & $p<0.05$ respectively, females $p<0.05$, 12wk) and showed a trend for becoming less insulin sensitive by 24wks of age. Insulin resistance signaling pathway gene expression and protein phosphorylation changes in adipose tissue, skeletal muscle and liver are currently being assessed.

The ArKO with its inability to synthesize endogenous estrogens and its phenotype of increased adiposity provides a valuable model to study the multiple properties of sex hormones on the development and progression of insulin resistance.

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Genetic and hormonal control of gender preference and sociability of XXY mice

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Introduction: Klinefelter syndrome (KS, XXY males) is the most common sex chromosome aneuploidy, occurring in 1.2 per 1000 male live births. Population-based studies suggest impaired sociability and possibly increased homosexuality in KS men. We developed a XXY mouse model that exhibits a hormonal, testicular and cognitive phenotype analogous to human KS. We previously showed that XXY mice preferred to be in a chamber containing a male mouse using a video recorded three-chambered apparatus where the test mouse could choose to enter the left or right chamber from the middle chamber. The aims of the current studies were to determine whether differences in social investigative behaviours are karyotypically (androgen independent) or hormonally (androgen) driven.

Methods: Adult XXY (n=18) and XY (n=21) littermates were studied before, 2 weeks after castration and 2 weeks after standard testosterone replacement (1 cm subcutaneous implant). Approximately one third of these mice were studied in each of 3 separate experiments. After habituation to the 3 chamber apparatus, test mice could choose a: (a) male or female odor; (b) male or female mouse; or (c) aggressive male mouse or an inanimate object. Two blinded observers quantified time and entry to each chamber and sniffing behavior by digitized video. Data were analyzed by repeated measures two-way ANOVA using karyotype, hormone status and their interaction as factors.

Results: After statistically controlling for hormonal exposure, XXY (compared with XY) mice spent less time in the chamber containing a female mouse smell (73±7 vs 103±6 secs, P=0.006), or with a female mouse (82±9 vs 110±8 secs, P=0.040). XXY mice spent more time with the male mouse odor (173±7 vs 137±6 secs, P=0.002), but comparable times in chambers containing an aggressive (244±14 vs 212±15 secs) or normal (131±11 vs 116±10 secs) male mouse. Castration did not alter the time spent with the female mouse (90±7 vs 102±8 secs) or the female mouse odor (88±8 vs 88±8 secs). XXY mice exhibit less sniffing behavior, but this was explained by reduced time to explore.

Conclusion: XXY mice show reduced preference for female mice or their odors, and this is not explained by hormone status. Gender preference in KS men may also be androgen independent.

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Increased response to exogenous estradiol in mice with prostate epithelial androgen receptor inactivation

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Prostate is highly androgen-dependent, but is also known to respond to estrogen though the mechanism and interaction with androgen receptor (AR)-mediated mechanisms remain unclear. In order to characterize the estrogen responsiveness of the prostate in mice with inactivated AR, we used our prostate epithelial AR knockout (PEARKO) mouse model, a mouse line featuring exon 3 deleted, biologically inactive AR selectively in prostate epithelium. At 8 weeks of age PEARKO males had significantly reduced weight of dorsolateral (DLP) and anterior prostate (AP), but increased proliferation of epithelial cells compared with littermate controls. PEARKO epithelial cells showed increased estrogen receptor (ER)α immunostaining compared to controls. Three weeks after orchidectomy, AP weights were reduced to similar extent in control and PEARKO (3.5±0.1 vs 3.0±0.3 mg for DLP; 5.4±0.3 vs 5.0±1.0 mg for AP). Estradiol (E_2) treatment via subdermal silastic implant for 1 week starting 2 weeks after orchidectomy significantly increased AP and DLP weight in castrate PEARKO compared with non- E 2 treated castrate PEARKO (4.5±0.3 vs 3.0±0.3 mg, p=0.003 for DLP; 8.5±1.3 vs 5.0±1.0 mg, p=0.008 for AP; N=8) but had no significant effect in castrate controls (4.4±0.5 vs 3.5±0.1 mg for DLP; 6.4±0.8 vs 5.4±0.3 mg for AP). E2 treatment increased predominately basal epithelial cell proliferation (PCNA immunostaining) and induced abnormal epithelial thickening and keratinization (cytokeratin 10) that was more pronounced in PEARKO than in control. These results demonstrate that prostate epithelial AR inactivation influences estrogen sensitivity by increasing the expression of ERα. The findings show that estrogen responsiveness is enhanced in the AR inactivated AP and DLP epithelium of mouse and suggests that estrogen related mechanisms may be involved in hormone-dependent prostate pathologies such as benign prostate hyperplasia and prostate cancer.

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Direct leptin actions on GnRH neurons effect fertility in male but not female mice

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Leptin's actions in the hypothalamus are critical for fertility (1), but it is not known whether this effect of leptin occurs directly on the GnRH neurons or indirectly via interneurons such as pro-opiomelanocortin and kisspeptin. In order to examine whether leptin acts directly on GnRH neurons to control fertility, leptin receptors were conditionally knocked out of GnRH neurons via a cre-loxP transgenic system in mice. This was accomplished by crossing *Lepr-flox* mice (loxP markers inserted into the genome flanking the functional part of the leptin receptor) with mice transgenic for GnRH neuron-specific cre recombinase. In this model cre recombinase causes a GnRH neuron-specific deletion of *Lepr* coding for exon 17 in mice homozygous for *Lepr-flox*. Onset of puberty (date of vaginal opening and first estrous) and fertility (estrous cyclicity, number of litters born and litter size) were measured (5-8 mice per group). When paired with wild type females, control male mice all sired litters (date of puberty back-dated to 50.6 ± 2.6 days) whereas only two Lepr-knockout males sired litters. In contrast there was no difference in puberty onset between control (*Lepr-flox* only) and Lepr-knockouts females (vaginal opening 32.4 ± 1.05 & 32.7 ± 0.8 days; first estrous 36.0 ± 1.05 & 37.0 ± 1.13 days respectively) (P > 0.05). Estrous cyclicity (assessed over 10 days by

vaginal cytology) was normal in both control and Lepr-knockout females, and all control and Lepr-knockout females produced litters of normal size after 1 month of pairing with wild type males. Based on these findings we conclude that direct leptin actions on GnRH neurons are required for normal fertility in males but not females.

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(1) Quennell, Tups & Anderson (2007) Endocrine Journal 54 (suppl);pp105

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Proteomic expression analysis reveals androgen-regulated functions in rat pachytene spermatocytes.

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Genomic assessments of the androgen-regulation of spermatogenesis have been conducted in various models, but the effect of androgens on the testicular proteome is unknown. As meiotic progression of germ cells in the testis requires androgenic support, the aim of this study was to identify androgen-regulated proteins in rat pachytene spermatocytes using a proteomic approach. Pachytene spermatocytes were isolated by elutriation from controls rats, androgen-suppressed rats [testosterone (T) and estradiol (E) implants, 8 weeks], androgen-suppressed and antagonist-treated rats [TE 8wks, + flutamide 1 wk], and androgen-replaced rats [TE 8wks + high-dose T 4d] (all n=4/group). 2D-PAGE analysis with DIGE minimal dye labelling was conducted on 24cm pI 4-7gels, from which differentially expressed proteins were assessed by SameSpots software and identified by MALDI-Tof mass spectrometry. A total of 738 annotated separate spots were detected in the pI range 4-7, of which 263 were significantly different ($p<0.05$) between the 4 groups, with a false discovery rate <3% ($q<0.028$). Principle components analysis recognised 4 distinct spot groups, indicating unique protein expression profiles. These were i) positive regulation by androgens, ii) negative regulation by androgens, iii) no regulation by androgens, but positive regulation by other factors and iv) no regulation by androgens, but negative regulation by other factors. Of the 26 proteins identified thus far by MALDI-Tof, 8 were in group (i), 6 in group (ii), 9 in group (iii), and 3 in group (iv). Androgen-regulated functions included nuclear transport, RNA regulation and processing, organelle formation and function, and meiotic progression. This study demonstrates that androgens are able to regulate proteins within pachytene spermatocytes, either directly, or by influencing other testicular cell types. It is concluded that a diverse range of cellular processes are regulated by androgens in pachytene spermatocytes, and that proteomic expression analysis provides a means by which to examine these phenomena.

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Detailing the Evolution of Interferon-α2β Induced Thyroiditis in Patients with Hepatitis C Infection

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Background : Interferon-α2β is well known to cause both *hyper*- and *hypo*-thyroidism. In the former, the commonest aetiology is thyroiditis. As there are no previous data to fully document the characteristics of thyroiditis in interferon related therapy, the aim of this study to document in detail the evolution of the thyroiditis in a cohort of hepatitis C patients treated with pegylated interferon-α2β (IFN-α2β) and Ribavirin (RBV).

Methods : A prospective observational study was conducted in patients who developed thyroid dysfunction whilst receiving combination of pegylated IFN-α2β and RBV for hepatitis C. The patients were followed closely with monthly thyrotropin (TSH). Where TSH was undetectable, free tetra- (fT4) and tri-iodothyronine (fT3) were added. Anti-thyroperoxidase (TPO), anti-thyroblobulin (Tg) and Thyroid Stimulating Immunoglobulin (TSI) levels were also performed at diagnosis, during and at the end of IFN therapy. All patients were assessed and followed up closely with monthly TSH, fT4 and fT3 levels until the completion, after 6 and 12 months of treatment.

Results : There were 7 females and 4 males over a 30-month period. All patients were found to have thyroiditis. No other form of thyrotoxicosis was found. The time to the development of thyroid disease was on average 10 weeks. The duration of disease was on average 9 weeks. All patients eventually recovered normal biochemical thyroid function although two patients required short-term supplementation.

Conclusions : Thyroiditis was found exclusively in our cohort of patients. Both the hyper- and hypo-thyroid phase can be short lived, extreme and transient in nature which mandates monthly TSH monitoring. Careful follow-up of all patients is mandatory as complete recovery is expected.

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Relationship between placental glucocorticoid receptor expression and fetal growth in pregnancies complicated by asthma

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Asthma is the most common condition to complicate pregnancy, occurring in approximately 12% of the Australian population. Asthma results in an elevation of endogenous glucocorticoid levels in maternal circulation, which is commonly associated with fetal growth inhibition. The physiological response to glucocorticoids is mediated by the presence of the glucocorticoid receptor (GR). As we have previously observed sexually dimorphic differences in fetal growth in asthmatic pregnancies, the present study aimed to investigate whether differential regulation of placental GR occurs in response to asthma between the sexes. Following term delivery at the John Hunter Hospital NSW, placenta and cord blood were collected from control (n=51) and asthmatic women (n=123), and birth weight and infant sex were recorded. Placental RNA was extracted and RT-PCR was used to measure GR hnRNA, total GR mRNA and the predominant GR mRNA variant, GRα, while western blot was used to measure GRα protein levels. Cord blood cortisol was measured by RIA. Results demonstrated that cortisol levels in cord blood were higher in asthmatic pregnancies compared to controls, in both male and female pregnancies; however, only in females was cortisol inversely associated with birth weight (p=0.003). In placenta from females, total GR mRNA expression was significantly lower in asthmatics compared to controls (p=0.03), while no difference was observed in either placental GR gene activity or GRα protein levels between these groups. In placenta from males, no differences were observed in any GR transcripts or in protein levels between the asthmatic and control groups. These data suggest that there is differential regulation of GR transcription in asthmatic pregnancies between the sexes. Further, the equivalent levels of GRα protein in asthmatic and control pregnancies suggest that post-translational modifications occur. Further work will address functional differences in placental GR to elucidate contributing mechanisms of reduced fetal growth in asthmatic pregnancies.

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The Onset of Human Labor is Associated with a Fall in the Ratio of Progesterone to Estrogens and an Increase in the Estriol to Estradiol Ratio

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BACKGROUND: Estriol (E3) is an estradiol (E2) antagonist at low concentrations but becomes an estrogen agonist as the concentration increases. We hypothesized that changing ratios of E3 to E2 combined with a declining ratio of progesterone (P) to estrogens at the end of pregnancy are robust characteristics of human labor onset.

METHODS: 500 unselected pregnant women provided 2-9 plasma samples from 7 weeks of pregnancy to labor. Samples were assayed for P, E2 and E3. Results were used to form trajectories for each analyte.

RESULTS: Interpolated P, E2, E3 median concentrations at 26 weeks gestation in singleton pregnancies with preterm deliveries (PTD) were not significantly different from those with term deliveries (P, p=0.63; E2, p=0.96; E3, p=0.29). In multiple pregnancies P, E2 and E3 concentrations were higher than in singletons. As pregnancy progressed the ratio of P to E2 in term singletons fell from 18:1 at 12 weeks to 11:1 at labor. P to E3 ratios fell from 7:1 at 12 weeks to 1:1 at labor. In contrast E3 to E2 ratios rose from 2:1 at 12 weeks to 11:1 at labor.

CONCLUSIONS: Our data is consistent with the hypothesis that the onset of human labor is associated with a progressively declining ratio of progesterone to estrogen in maternal blood, and a critical increase in E3 to E2 ratios at the end of pregnancy, that turns the weak E3 into an effective estrogen agonist. The results provide a rationale for progesterone supplementation in women at risk for preterm delivery.

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Aberrant skeletal muscle mitochondrial responses to exercise in overweight women with PCOS

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Background: Skeletal muscle constitutes 45% of body mass, accounting for 80% of insulin stimulated glucose uptake and is implicated in the pathogenesis of insulin resistance (IR) and type II diabetes mellitus (DM2), although the mechanisms of IR remain unclear. Diminished mitochondrial oxidative capacity and mitochondrial damage have been shown in DM2. Exercise training has been shown to promote mitochondrial biogenesis and function in skeletal muscle, and is currently believed to be a key mechanism for enhancing insulin sensitivity after exercise training. The present study aimed to compare the effects of 12 weeks of exercise training (treadmill) on mitochondrial biogenesis in skeletal muscle of normoglycaemic, overweight women with polycystic ovary syndrome (PCOS; an IR, pre-diabetic condition) to age and weight matched controls.

Materials and Methods: Quadriceps femoris muscle biopsies from 8 overweight PCOS women and 8 overweight tightly defined controls, matched according to age and BMI. Quantitative gene expression analyses (real-time PCR) and muscle protein expression measurements were completed.

Results. Normalised gene expression for Tfam, NRF1, PGC1 a and UCP3 remained unchanged or increased to a similar extent in the PCOS and controls in response to training. COX4 gene expression increased to a greater extent in PCOS vs. Control trained muscle (Fold change; mean±SEM; 1.9±0.1 vs 1.4± 0.2; P<0.05). In response to training, protein expression of electron transport chain (ETC) protein complex 2 30kDa, trended towards an increase in Controls vs. PCOS muscle (1.8±0.3 fold vs 0.9±0.2 fold; P=0.06), with an apparent trend towards this differential effect of exercise seen across the ETC.

Discussion: Markers of mitochondrial biogenesis and function in normoglycaemic, overweight IR women with PCOS showed aberrant gene and protein expression in response to exercise training, compared to age and weight matched controls. Potentially, this is related to the IR state observed in PCOS, impairing mitochondrial response to exercise.

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Evaluating patients presenting with severe hypotonic hyponatraemia

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Aims: Previous studies have focused on hospital-acquired hyponatraemia, but information on patients presenting with severe hyponatraemia are lacking. Aims (1) to define the major causes of severe hypotonic hyponatraemia (SHH, defined as serum sodium < 120 mmol/L) presenting to hospital; (2) to assess the adequacy of diagnostic workup; (3) to determine treatment outcomes.

Methods: Patients were identified by biochemistry search from January 2000 to August 2007 and data obtained from medical records.

Results: 256 patients were studied with a female to male ratio of 2:1. Mean age was 71 ± 14 years. Main presenting complaints were confusion (26%), falls or lethargy (25%) and gastrointestinal symptoms (22%). SHH was due to thiazides in 24%, SIADH in 21%, hypovolaemia in 8% and other causes in 13%, including hypocortisolism in 1% of patients. In 34% of cases, multifactorial causes, including thiazides and hypovolaemia were commonly implicated. CT brain was diagnostic in 3 of the 102 patients. The most common cause of sodium /=14mmol/L/1st24hours. Mean length of hospital stay was 7 days (range 1-100). Overall mortality was 10% and not related to sodium level at presentation, but to co-morbidities.

Summary: The single most common cause of SHH were thiazides. Endocrine investigations and brain imaging had a low diagnostic yield. High urinary osmolality/sodium excretion may identify SIADH even in fluid-resuscitated patients. Mortality directly related to hyponatraemia and treatment-related complications were rare.

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25-hydroxyvitamin D levels inversely correlate with HbA1c in a gestational diabetes clinic population

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Maternal vitamin-D deficiency is prevalent in Australia and is a risk factor for neonatal hypocalcaemia and rickets. Animal models suggest that adequate vitamin-D is also required for normal β-cell function. The insulin-resistance of late pregnancy is a significant β-cell stressor. We therefore hypothesised that vitamin-D deficiency would contribute to the development of gestational diabetes (GDM) and that low levels in late pregnancy would be associated with worsened glycaemic control.

We conducted a retrospective study of 25hydroxyvitamin D (25OHD) levels in our GDM clinic, to determine the prevalence of insufficiency/deficiency, factors influencing 25OHD, and associations with measures of glycaemia. Over 1 year, 147 women with GDM (diagnosed by ADIPS criteria) had their HbA1c and 25OHD levels measured at an average of 35 ± 2 weeks gestation.

Using cutoffs of <25 nmol/L, 25-50 nmol/L, and >50 nmol/L, 9%, 32% and 59% of women were deficient, insufficient and sufficient respectively. Only 26% had levels >75nmol/L. Mean 25OHD differed significantly between ethnic groups (Caucasian 68±25nmol/L, Asian 67±26nmol/L, Middle-Eastern 52±33nmol/L, Indian subcontinental 50±24nmol/L, p=0.004) and between seasons (summer 71±31nmol/L, autumn 55±19nmol/L, winter 53±27nmol/L, spring 51±24nmol/L, p=0.002) . Women in paid employment had higher levels than those performing home duties (63±29nmol/L versus 50±21nmol/L, p=0.003) .

25OHD was inversely correlated with fasting and 2 hour glucose on diagnostic OGTT (r=-0.16, p=0.05 for both). A highly significant inverse correlation was found between 25OHD and HbA1c (r=-0.32, p<0.0001). HbA1c correlated with booking-in BMI (r=0.246, p=0.012) but not with ethnicity, season, occupational status or age. On a general linear model, after adjusting for BMI, 25OHD remained a highly significant negative predictor of HbA1c (p=0.001).

These results implicate vitamin-D in glycaemic regulation during pregnancy. Given the high prevalence of 25OHD insufficiency, and of GDM, there would be important public health and therapeutic implications if these results are confirmed in prospective trials.

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Lack of association between early spontaneous preterm delivery and thyroid autoantibodies

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Objective: Early (< 34 weeks gestation) preterm delivery is a leading cause of neonatal morbidity and mortality. A recent study in pregnant women with positive thyroid auto-antibodies (TAb), but normal thyroid function tests (TFT) found that thyroxine administration reduces the incidence of preterm delivery <37 weeks[1]. That study did not distinguish spontaneous from iatrogenic deliveries and included preterm deliveries > 34 weeks, which have an excellent prognosis. We investigated whether women with spontaneous premature delivery < 34 weeks are more likely to have positive TAb or abnormal TFT.

Design: Case-control study including 47 cases of delivery < 34 weeks and 127 controls (delivery at >38 weeks). Serum was collected at 10-13 weeks' gestation.

Methods: TSH, fT4, fT3, anti-TPO and anti-Tg antibodies were determined by chemiluminescent microparticle immunoassays (Architect, Abbot Laboratories). Reference ranges (for nonpregnant adults) were: TSH 0.3- 5.0 mIU/L, fT4 9.0-19.0 pmol/L, fT3 2.6-6.0 pmol/L, anti-TPO < 6 IU/l and anti-Tg < 6 IU/L.

Results: Cases and controls were of similar age and weight. There was no difference in TFT or TAb titre between cases and controls:

	Cases [N = 46]*	Controls [N = 124]*	p
Delivery (weeks)	33.1 (24.0-34.9)	40.4 (40-41)	<0.001
TSH (mIU/L)	0.70 (0.04-3.84)	0.88 (0.01-2.87)	0.07
fT3 (pmol/L)	15.3 (7.5-21.2)	15.3 (11.5-23.8)	0.93
fT4 (pmol/L)	4.8 (3.1-6.3)	4.8 (3.3-6.3)	0.63
Anti-Tg (IU/L)	3 (1-316)	3 (1-691)	0.51
Anti-TPO (IU/L)	8 (3-73)	9 (3-499)	0.89

*Median (range)

10.9% of cases and 9.7% for controls had anti-TPO or anti-Tg >30 U/L. A TSH <0.3 mIU/L was found in 17% of cases and 15% of controls, but none had biochemical thyrotoxicosis or a TSH above the normal range.

Conclusions: We found no evidence that thyroid autoimmunity increases the risk of spontaneous premature delivery <34 weeks gestation.

(1) Negro, R., et al. J Clin Endocrinol Metab 91, 2587-2591 (2006).

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Relationship between obesity and vitamin D: is vitamin D supplementation a sliding scale based on body size?

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Obesity is associated with hypovitaminosis D. Whether the degree of adiposity determines adequacy of vitamin D repletion has not been examined. AIMS: To determine the relationship between Body Mass Index (BMI) and serum 25-OH vitamin D (25-OH D) concentration, and the increments in serum 25-OH D concentration with vitamin D supplementation in relation to BMI. METHODS: Part 1: Body Mass Index (BMI) and serum 25-OH D concentrations were measured in 202 patients attending clinics at St Vincent's Hospital and Concord Hospital, Sydney. Part 2: Seventeen inpatients from St Vincent's Hospital, Sydney, with severe vitamin D deficiency (serum 25-OH D concentration <15 nmol/L) were supplemented with 10,000 units vitamin D3/day orally for 1-week. Biochemistry was compared before and after vitamin D replacement in relation to BMI. RESULTS: Part 1: Serum 25-OH D concentrations correlated negatively with BMI ($r^2=0.11$, $p<0.01$). Part 2: At baseline, serum intact parathyroid hormone (iPTH) concentrations correlated positively with BMI ($r^2=0.84$, $p<0.01$). Serum 25-OH D concentrations achieved following 1-week of vitamin D3 replacement correlated negatively with BMI ($r^2=0.63$, $p<0.01$). Baseline (57±9 vs 23±2 pmol/L) and final (35±11 vs 18±3 pmol/L) serum iPTH concentrations were significantly greater ($p<0.01$) in overweight/obese patients (n=9), compared to normal weight patients (n=8). Baseline serum 1,25-(OH)2 vitamin D concentrations were lower in overweight/obese patients (107±34 vs 146±34 pmol/L, $p=0.03$), but the final serum 1,25-(OH)2 vitamin D concentrations (171±18 vs 182±23 pmol/L, p=NS) were not different. SUMMARY: Obesity is associated with hypovitaminosis D. Efficacy of vitamin D supplementation is dependent on BMI. CONCLUSIONS: BMI should be accounted for in prescription of vitamin D supplements. While hyperparathyroidism may be explained by vitamin D deficiency, vitamin D/PTH resistance associated with obesity cannot be excluded.

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Ligand- and Salt- Specific Induction of Mineralocorticoid Receptor-Mediated Cardiovascular Injury

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Recent evidence indicates that elevated circulating levels of aldosterone together with a high salt diet, have deleterious effects on the cardiovascular system. We have shown that mineralocorticoid receptor (MR) activation, by either exogenous mineralocorticoid (MC) or endogenous glucocorticoid (GC) in the absence of 11βHSD2 protection, results in oxidative stress, vascular damage and cardiac fibrosis. While it is known that salt plays a critical role in the fibrotic response, the mechanisms involved are unclear. The aim of the current study is to investigate the gene expression profiles induced by deoxycorticosterone (DOC) and salt-mediated MR activation in the heart.

Eight groups (n=7) of Sprague-Dawley rats were treated as follows: Group 1 control; Group 2 high salt diet; Group 3 deoxycorticosterone (DOC) alone; Group 4 DOC plus salt (DOC/salt); Group 5 DOC plus salt plus the MR blocker potassium canrenoate (Kcan); Group 6 the 11βHSD2 antagonist, carbenoxolone (CBX) alone; Group 7 CBX plus salt (CBX/salt); Group 8 CBX plus salt plus Kcan. RNA was extracted from heart tissues and analyzed with an Endothelial Cell SuperArray and Affymetrix microarray and confirmed by real-time RT PCR.

The SuperArray analysis identified two genes that were specifically up-regulated by DOC/salt angiotensin I converting enzyme 2 and xanthine dehydrogenase whereas CBX/salt selectively upregulated the NADPH oxidase subunit, $gp91^{phox}$. 36 genes were identified by Affymetix microarray analysis to be selectively upregulated by DOC/salt, of which calcium binding protein and steroidogenic acute regulating protein were confirmed by real RT-PCR.

These findings indicate that high salt loading in combination with mineralocorticoids have distinct effect on cardiac gene expression that may contribute to MR-mediated cardiovascular disease. This is the first study to identify genes regulated by MC plus salt but not by either stimulus alone. The functional role of these salt-dependent genes in this model and other models of heart disease will ensure the determination of their potential for targeted pharmaceutical intervention.

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Investigating non-classical signalling pathways of the androgen receptor

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Classical androgen receptor (AR) actions involve DNA binding and regulation of gene transcription. *In vitro* studies suggest that non-classical AR signalling occurs in the absence of DNA binding, via either phosphorylation of second messenger cascades, including ERK and CREB, or via indirect repression of target genes. To investigate the physiological relevance of non-classical AR signalling, we designed an AR knockout (ARKO) mouse model [1], which expresses a mutant AR that cannot bind DNA or activate classical signalling, but theoretically retains non-classical actions. Our aim is to characterise non-classical pathways in this ARKO model.

Cultured genital skin fibroblasts were established from wildtype (WT) and ARKO males (n=3/genotype). Preliminary data of AR ligand binding assays shows that the mutant AR is able to bind androgen. The *AR* gene in ARKO males is expressed at normal levels in kidney, fat and bone, but is expressed 6.5-fold higher than WT male in testis ($p<0.001$) and 1.5-fold higher in muscle ($p<0.05$) (quantitative real-time PCR, n=6/genotype). Expression of the classical AR target gene, *ornithine decarboxylase 1* (*Odc1*) [2], is 5.6-fold lower ($p<0.001$) in ARKO male kidney compared to WT (n=6/genotype), demonstrating at the molecular level that classical AR action is abolished. The expression of the non-classical target gene, *Ngfr* [3], is 57-fold higher ($p<0.001$) in ARKO testis compared to WT (n=6/genotype), demonstrating that an intact DNA-binding domain is required to repress this non-classical target *in vivo*. Total and phosphorylated ERK-1/2 and CREB were detected by Western analysis in kidney, muscle and femur from WT and ARKO males (n=4/genotype). There is no difference in the degree of phosphorylation between WT and ARKO males, consistent with the hypothesis that the ARKO model retains non-classical pathways.

This study suggests our ARKO model is a powerful model to investigate non-classical AR signalling pathways *in vivo*.

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Purification and Characterization of the Human Mineralocorticoid Receptor.

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The mineralocorticoid receptor (MR, NR3C2) is the largest member of the steroid receptor family of transcription factors and plays a critical role in fluid and electrolyte homeostasis. The MR also has a well described role in the pathology of cardiovascular disease and is thus an attractive therapeutic target for heart failure but current therapies are limited by side effects. Of all the members of the steroid receptor family, the MR is the least well understood, due in part to difficulties in producing large quantities of pure, biologically active full-length protein for analysis. Here, we describe expression and purification of full-length human MR. The human MR with an N-terminal biotin acceptor peptide (BAP) tag was overexpressed in Sf9 insect cells in the presence of aldosterone. Site-specific biotinylation of BAP was achieved *in vivo* by co-expression of E. coli biotin holoenzyme synthetase. The BAP-tagged MR exhibited ligand binding specificity similar to that of the native protein in whole-cell binding assays. Single-step affinity purification using a modified avidin matrix was dependent on the presence of aldosterone (or other agonist ligands), and yielded 200 µg MR protein from 0.5lt Sf9 culture. The recombinant MR had an apparent molecular weight of 120-140kDa, possibly reflecting the presence of multiple glycosylated species. Recombinant MR was shown to bind a known GRE in vitro, and interacted with a known coregulator, PGC-1α, in a GST pull-down assay.

Similar transcriptional activities for biotinylated BAP-tagged and wild-type MR were found in both HepG2 (liver) and H2C9 (cardiac) cell lines. Given the ligand binding pocket conformation is dependant upon the context of the full-length receptor or the ligand-binding domain alone, analysis of MR structure and ligand interactions in the context of the full-length receptor is crucial for future development of ligand-selective MR antagonists for the treatment of cardiovascular disease.

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Androgenic biopotencies of nutraceutical-derived steroids in a yeast-based androgen bioassay

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Under the jurisdiction of the World Anti-Doping Agency (WADA), androgens are banned in sports as they may provide unfair competitive advantage to elite athletes. The increased stringency of doping control tests for known androgens has led to growth in development of designer androgens aimed at evading doping control test detection. Using a yeast-based androgen bioassay, we determined the bioactivities of a variety of non-marketed steroids isolated from nutraceuticals available illicitly over the internet. We used a yeast cell-based *in vitro* androgen bioassay[1] created by transforming yeast with plasmids containing human AR and a β-galactosidase reporter gene under the control of an androgen responsive element (ARE) to provide sensitive, specific and reproducible dose-response to androgenic activity in defined media. Androgenic potency was defined as EC_{50} relative to a standard androgen estimated from a 4 parametric sigmoidal curve fit. Most extracted nutraceutical steroids were androstenedione (A_4) analogues with similar (6-methyl-androsterone, EC_{50} 55 nM) or lower potency (Oxyguno, 4-chloro-17α-methyl-androsta-4-ene-17β-ol-3,11-dione, EC_{50} 650; Trena, androst-4,9-diene-3,17-dione, EC_{50} 92 nM) relative to A_4 (EC_{50} 45 nM). However one, Hemapolin (2α, 3α-epithioandrostane-17α-methyl-17β-ol, EC_{50} 7.4) was 6-fold more potent than A_4. A fifth steroid of unknown structure, Furazadrol was the most potent androgen isolated with an androgenic potency (EC_{50} 1.2 nM) greater than testosterone (EC_{50} 2.5 nM) and dihydrotestosterone (EC_{50} 1.9 nM). We conclude (1) that some nutraceuticals sold over the internet contain potent, non-marketed androgens, (2) that a high-throughput, yeast-based in vitro androgen bioassay can define the androgenic potency of steroids regardless of whether the steroid or other chemical structure is known and (3) an in vitro androgen bioassay is a useful, rapid first pass screen to identify designer androgens not yet specified on the WADA's Prohibited List.

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Regulatory Crosstalk Between beta-Adrenergic and Nuclear Hormone Receptor Signalling in Skeletal Muscle

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Previous studies from this laboratory demonstrated that β-adrenoceptor (β-AR) signalling selectively induced Nur77 and Nor-1 (1, 2) in an *in vitro* skeletal muscle cell culture model. These investigations were recently extended and showed that the NR4A (3) subgroup were induced by β-AR signaling *in vivo* in fast fibre dominant (type II) glycolytic and slow-fibre dominant (type I) oxidative muscles. Characterisation of the NR4A induction mechanism implicated the involvement of a phosphorylation cascade containing protein kinase A, MAPK and cAMP response element-binding protein. In the context of β-AR signalling and skeletal muscle, systemic administration of β-AR agonists have been shown to elicit hypertrophy and significant metabolic changes. Moreover, β_{1-3}-AR-deficient mice are unable to regulate energy expenditure and consequently develop obesity on a high-fat diet. To specifically examine the function of Nor-1 in skeletal muscle, we studied the effects of Nor-1 siRNA transfection in skeletal muscle cells. This analysis revealed decreased fatty acid oxidation and increased anaerobic utilisation of glucose. In concordance with these observations, ATP production in the Nor-1 siRNA (but not control) transfected cells was resistant to (azide-mediated) inhibition of oxidative metabolism. In concordance, candidate-based expression profiling in the *in vitro* muscle cell culutre model revealed aberrant expression of genes involved in fatty acid oxidation (eg. Pgc1α and lipin1α), carbohydrate oxidation (eg. Pdp1r/c), and hypoxia (Hif1α). ChIP analysis indicated several of the genes modulated by adrenergic treatment, and/or Nor-1 siRNA transfection were direct targets of Nor-1. Moreover, microarray mediated expression profiling of type II skeletal muscle following systemic administration of a β2-AR agonist revealed significant changes in genes associated with muscle hypertrophy, metabolism, circadian rhythm, transcription, histones, oxygen homeostasis, angiogenesis and oxidative stress. In conclusion, our data suggest Nor-1 expression is necessary for the control of oxidative metabolism and regulates genes involved in the control of skeletal muscle mass.

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Novel mechanism of catecholamine metabolism by glucocorticoids via activation of a sulfotransferase in mice

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Glucocorticoids are steroid hormones critical for maintaining metabolic homeostasis and in the response to stress. During times of stress such as starvation and intense exercise, the successive release of catecholamines and glucocorticoids has been shown to increase heart rate/blood pressure and increase gluconeogenesis respectively. Studies have shown that glucocorticoids enhance gluconeogenesis by increasing transcription of target genes (e.g. tyrosine aminotransferase) via the glucocorticoid receptor (GR). Other direct genetic targets of GR in the liver involved in metabolism and detoxification remain largely unknown. Using gene microarray analysis on glucocorticoid receptor null mice, we have identified novel GR regulated hepatic target genes following 3 hrs of treatment with dexamethasone. Significant induced genes included Ddit4, Fkbp5, Megf9 and SULT 1D1. We further investigated SULT1D1 because of its role in detoxifying endogenous compounds such as dopamine through sulfate conjugation. Treatment of primary mouse hepatocytes with dexamethasone for 6 hrs rapidly increased levels of SULT1D1 mRNA 8 fold. Stimulation of SULT1D1 mRNA levels by dexamethasone was blocked by co-treatment with the GR antagonist RU486, confirming that dexathamanesone induction was mediated directly via GR. Further investigation of mice treated with dexamethsone showed SULT 1D 1 mRNA was induced in whole kidney and studies using IMCD3 cells, showed that induction of SULT1D1 was present in the cortical collecting duct. To study the SULT1D1 gene promoter, CHIP assays have revealed a neighbouring estrogen sulfotransferase (SULT1E1) potentially sharing a glucocorticoid response element ~39kb away from the SULT1D1 transcription start site. This suggest a novel dual regulation of both genes by glucocorticoids in mouse liver. In summary, our findings have demonstrated an important GR regulated pathway that may act as a negative feedback mechamisn to reduce elevated catecholamine levels following the stress response.

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The roles of *Odc1* and *Tceal7* in skeletal muscle hypertrophy

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The aim of this study is to identify the androgen receptor (AR)-dependant mechanisms through which androgens increases skeletal muscle mass. We have previously characterized gene expression in our global AR knockout (ARKO) male mice, which have a 15-22% reduction ($n \geq 12$/group, $p<0.001$) in the mass of different muscles compared to WT males. Two potential AR target genes that showed altered expression by real-time PCR in ARKO muscle (n=12/group) are being examined in the current study:

(I) *Odc1* (2.6-fold decrease, $p<0.001$), which encodes the rate-limiting enzyme in polyamine biosynthesis and may promote myoblast proliferation

(II) *Tceal7* (2.4-fold increase, $p<0.001$), an ovarian tumor suppressor that we hypothesize suppress myoblast proliferation and induce myotube differentiation

To further characterize these genes, their expression in muscle from orchidectomized males treated with control (orx+C) or DHT-filled (orx+DHT) implants was measured. Expression in control (orx+C) versus treatment (orx+DHT) was similar to the global ARKO, with *Odc1* decreased 2.9-fold ($p<0.01$) and *Tceal7* increased 2.4-fold ($p<0.01$). We have generated myofibre-specific ARKO (mARKO) mice, and also showed these genes are differentially expressed in muscle from mARKO versus WT males (n=12/group) (*Odc1* 2.6-fold decrease, $p<0.05$; *Tceal7* 1.9-fold increase, $p<0.001$). These data demonstrate that these genes are regulated directly via androgen actions in skeletal muscle.

To investigate these genes in muscle further, we examined their expression in the C2C12 muscle cell line, in proliferating (myoblasts) and differentiated (myotubes) cells ($n \geq 6$/group). *Odc1* was decreased 2-fold in myotubes, compared to myoblasts ($p<0.001$) and *Tceal7* was increased 4710-fold in myotubes ($p<0.001$). Therefore, we propose that androgens may induce hypertrophy in part by prolonging muscle cell proliferation through upregulation of *Odc1* and down-regulation of *Tceal7*. We are currently generating C2C12 cell lines with either overexpression or shRNA knockdown of *Odc1* to further investigate this hypothesis.

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Overlapping progenitor cell differentiation defects in the developing lung of GR and CREB-deficient mice

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The glucocorticoid cortisol provides important developmental cues for the late maturation of the human fetal lung and antenatal synthetic glucocorticoids are used to treat respiratory distress syndrome suffered by preterm babies. The intracellular cAMP signaling pathway is important for promoting synthesis of lung surfactant yet little is known of its wider role in the differentiation and development of the respiratory system. To dissect the specific role of cortisol and cAMP signaling in fetal lung development, we have analyzed mice with targeted null mutations for either the glucocorticoid receptor (GR) or cAMP responsive element binding (CREB) protein gene. In the absence of functional GR, lung development is severely retarded; the lungs are hypercellular with reduced septal thinning. Histological and morphometric analysis reveal dramatically reduced proportions of differentiated type-1 alveolar epithelial cells (AECs). CREB null mice do not survive birth and have a more pronounced defect in the developing lung. The lung is very condensed with marked hypercellularity and hyperproliferation. There is no detection of differentiated distal type-1 AECs or proximal Clara cells and ablated expression of upper-airway respiratory markers. Whole genome expression microarray analysis has revealed both glucocorticoid and CREB-regulated gene targets that begin to map gene networks important for respiratory development and function. These results demonstrate that cortisol and

cAMP signaling pathways are essential for the embryonic development of the lung and have distinct yet overlapping roles in respiratory epithelial cell differentiation.

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Regulation of inhibin heterodimer assembly and secretion by residues within the pro-domain

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The α- and β-subunits of inhibin A are synthesized as precursor proteins, which dimerise prior to proprotein convertase-mediated proteolytic maturation. Analogous to other transforming growth factor β (TGF-β) superfamily members, non-covalent interactions between the pro- and mature domains of the inhibin α- and β-subunits, respectively, are critical for the correct folding, dimerisation and secretion of the active ligand. In this study, the binding interface between the pro- and mature domains of the inhibin α-subunit and β_A-subunit were characterized using inhibin A mutant proteins. We identified three hydrophobic residues near the N-terminus of the inhibin α-subunit pro-domain (Leu ^{30}, Phe ^{37}, Leu ^{41}) that, when mutated to alanine, disrupted heterodimer assembly and secretion. We next sought to identify the inhibin A residues in the mature region that interact with the pro-domain. A hydrophobic epitope required for dimer formation was detected on the outer convex surface of the mature α-subunit. Homology modelling indicated that Phe ^{271}, Ile ^{280}, Pro ^{283}, Leu ^{338} and Val ^{340} are located at the interface between two β-sheets of the α-subunit, and form a hydrophobic packing core. Mutation of these residues likely disturbs the conformation of this region, thereby disrupting non-covalent interactions with the pro-domain. In support, mutation of the corresponding hydrophobic residues in the activin β_A pro- (Ile ^{62}, Leu ^{66}), and mature domains (Phe ^{329}, Ile ^{338}, Pro ^{341}) disrupted the production and secretion of activin A and to a lesser extent inhibin A dimer formation. In addition, we generated wild-type and mutant β_A-subunit pro-domain constructs. Mutations in the β_A-subunit pro-domain reduced the binding affinity for inhibin A dimer. Conservation of the identified hydrophobic motifs in the pro- and mature domains of other TGF-β superfamily ligands, suggests we have identified a common biosynthetic pathway governing dimer assembly.

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Extra-ovarian expression and actions of Growth Differentiation Factor (GDF)-9

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GDF-9 produced within the ovary plays essential roles during follicle maturation, but GDF-9 expression has also been noted in the pituitary, adrenocortical cells, and testis. We previously found that mouse adrenocortical (AC), Leydig (TM3), Sertoli (TM4) and gonadotroph (LβT2) cell lines express mRNAs for the requisite GDF-9 binding and signalling molecules, BMPRII, ALK5 and Smad2/3. AC and LβT2 cells also strongly express GDF-9 mRNA. We have examined the ontogeny of GDF-9 expression in the adrenal gland, and characterized GDF-9 regulation of luciferase reporter gene constructs and endogenous genes in the above cell lines as initial steps towards identifying extra-ovarian actions of locally produced GDF-9.

Ontogeny studies using RT-PCR revealed that GDF-9 expression in the fetal (day 14.5 post coitum) and neonatal mouse adrenal was not maintained in adulthood. Partially purified recombinant mouse GDF-9 (50 ng/ml) stimulated expression of transiently transfected activin/TGF-β-responsive reporters, pGRAS-luc or pAR3-lux, in two granulosa cell lines, KGN and COV434, increased activity 2.5±0.2 –fold (mean±SEM, n=4) in TM4 cells and 16±2 –fold in AC cells, and but lacked specific effects on TM3 cells and LβT2 gonadotrophs. A matching GDF-9 control preparation (293H) lacked specific actions. GDF-9 also potently (IC50=4.7 ng/ml) suppressed the expression of *Cyp17* mRNA, and stimulated expression of inhibin α and β_B, but not β_A, subunit mRNA. In each case, GDF-9 actions were antagonized by the ALK4/5/7 inhibitor, SB431542 (5 μM), but not activin-blocking levels of follistatin-288 (10 nM).

In summary, our findings are consistent with the proposed mediation of GDF-9 signals by ALK5 to regulate the expression of multiple genes and reporters in extra-ovarian (adrenocortical and Sertoli) as well as granulosa cells, reveal that locally produced GDF-9 may regulate adrenal steroidogenesis during fetal life, and show that follistatin-288 poorly antagonizes GDF-9.

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In vivo and *in vitro* bioactivities of human recombinant inhibin A and inhibin B

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Inhibin A and inhibin B negatively regulate the production and secretion of FSH from the anterior pituitary, control intragonadal events including follicle development and steroidogenesis, and act as tumor suppressors in the gonads. Interestingly, the expression patterns of the inhibin isoforms are sexually, spatially and temporally dimorphic raising the possibility that inhibin A and B may be functionally distinct. In the current study, the activities of highly purified preparations of recombinant human 31kDa inhibin A and B were determined in ovariectomised adult rats based on suppression of serum FSH. The *in vivo* specific bioactivity of 31kDa inhibin B was 1.5 (1.0-2.7)-fold more potent compared to 31kDa inhibin A. As *in vivo* activity is subject to the rate of protein clearance from serum, the relative potencies of the inhibin isoforms were determined in a rat pituitary cell culture system. Inhibin B was 4-fold more potent than inhibin A suppressing FSH release by rat pituitary cells *in vitro*. To explain the enhanced pituitary actions of inhibin B, the relative affinities of the inhibin

isoforms for betaglycan were determined. In contrast to the pattern of *in vivo* and *in vitro* bioactivity, 31kDa inhibin B (IC_{50}–30 pM) had a 4-fold lower affinity than inhibin A (IC_{50} – 7 pM) for binding to cells expressing betaglycan. Betaglycan binds to the outer convex surface of the inhibin α-subunit and disruption of the binding site resulted in the loss of inhibin A *in vitro* bioactivity. However, disruption of the betaglycan binding site of inhibin B only resulted in a partial loss of activity suggesting that inhibin B biological activity is not entirely dependant on binding to betaglycan. Together, these results imply that the expression of additional proteins in the pituitary may explain the enhanced potency observed for inhibin B in this tissue.

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Evidence that kisspeptin neurons in the arcuate nucleus are central processors for generating the preovulatory luteinizing hormone surge in ewes

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Kisspeptins are products of the Kiss1 gene that bind to the GPR54 receptor and regulate gonadotrophin-releasing hormone (GnRH) secretion. Administered kisspeptins stimulate gonadotrophin secretion, in a GnRH dependant manner. In sheep, Kiss1 mRNA expression is up-regulated in the arcuate nucleus (ARC) of the hypothalamus just prior to the preovulatory luteinising hormone (LH) surge (1) and kisspeptin treatment induces ovulation in anestrous ewes (2). We examined whether kisspeptin neurons in the ARC become transcriptionally activated prior to the LH surge. Ovariectomised Corriedale ewes received (i.m.) 50 µg estradiol benzoate (EB) to induce an LH surge (n = 4) or vehicle (n = 4) and brains were harvested 1 h later. Coronal sections of the rostral, middle and caudal ARC were processed for immunohistochemical detection of kisspeptin and Fos (a marker of transcriptional activation). In the caudal ARC, 83% of kisspeptin neurons also expressed Fos following EB treatment (2-fold increase compared to vehicle; $P < 0.05$). There was a 1.7-fold increase in the middle ARC ($P < 0.05$), where 88% of kisspeptin neurons co-expressed Fos after EB treatment. No treatment effect was seen with kisspeptin/Fos co-expression in the rostral ARC and there was no change in the number of kisspeptin neurons 1 h after EB treatment in any area of the ARC. These data suggest kisspeptin neurons located in the ARC are involved as central processors generating the preovulatory GnRH/LH surge in the ewe, as they become transcriptionally activated following an estrogen positive feedback stimulus. This is consistent with earlier observations that Kiss1 gene expression in the ARC increases in the late follicular phase (1) and that kisspeptin causes ovulation in anestrous ewes (2). Supported by NHMRC Australia. JTS is supported by a Peter Doherty Fellowship and is a recipient of an ESA Postdoctoral Award.

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A role for activin/inhibin in mouse gonocyte relocation and proliferation

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Gonocytes in the testis resume proliferation after birth and relocate to contact the basement membrane of the seminiferous cords where they become spermatogonia. A previous *in vitro* study indicated that activin can increase gonocyte numbers on day 3 post partum (dpp) rat testis, while the activin antagonist, follistatin, together with FSH , increased the number of spermatogonia (Meehan *et al.,* 2000). The aim of this study was to understand how FSH, activin and inhibin, a potent activin antagonist, interact to influence gonocyte proliferation and relocation in the newborn mouse testis using in vivo and in vitro approaches.

Two mouse models were analysed, the inhibin alpha knock out (*inh a -/-*) mouse and the *InhbaBK* mouse. The *Inh a -/-* mouse lacks inhibin, and thus activin acts unopposed by its most potent antagonist (Matzuk *et al.,* 1992). The *InhbaBK* mouse has the *Inhbb* allele inserted into the *Inhba* locus, thus directing the expression of the less bioactive activin βB, in the spatiotemporal pattern of activin βA (Brown *et al.,* 2000). In addition, an *in vitro* model was developed in which 1dpp wild type testis fragments were cultured in hanging drops for 24 hours with the addition of combinations of activin, inhibin and FSH. Gonocyte proliferation in *inh a -/-* was assessed using proliferating cell nuclear antigen (PCNA). A significant increase in germ cell proliferation and relocation to the basement membrane was measured in 0dpp *inh a -/-* , while no difference was observed at 4dpp. The opposite was observed in *InhbaBK* mice, with reduced gonocyte migration in mutant animals at 0dpp. In vitro, inhibin seemed to inhibit proliferation and reduce the percentage of relocated gonocytes while FSH showed a tendency for the opposite effect on gonocyte migration. These findings show that inhibin levels affect germ cell development during early postnatal development in mouse testis influencing both cell maturation and proliferation.

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Hedgehog signalling components in adult rat testis spermatogonial cells

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In normal tissues, Hedgehog-induced progenitor cell proliferation is transient and tightly regulated, preventing continuous regeneration. However, activation of constitutive Hedgehog signalling results in unregulated self-renewal of progenitor cells in association with several human cancers. Although the contribution of Hedgehog signalling to cancers is widely accepted, its impact on spermatogonial stem cells and impact on male fertility are unknown.

In this study, we aimed to clarify the possible role of Hh signalling on normal spermatogenesis in the adult rat and in adult testicular stem cells in the irradiated model {1}. Adult male rats were obtained from Monash University Central Animal Service and killed by cervical dislocation before tissue removal and fixation in Bouins for routine histochemical procedures. For studies on irradiated testes, adult LBNF1 male rats (hybrids between Lewis and Brown–Norway) were purchased from Harlan Sprague–Dawley, Inc. (Indianapolis, IN, USA). Testes were irradiated with 6 Gy to deplete all maturing germ cell types. At 15 weeks after irradiation the animals were injected simultaneously with 1.5mg each of Cetrorelix pamoate and Cetrorelix acetate. Testes were collected 1, 2 or 4 weeks after injection. *In situ* hybridization combined with immunohistochemistry was performed using DIG-labeled cRNA probes to identify the cells in which Hedgehog signalling components are made {2}.

Signals for mRNAs encoding t he transmembrane receptors Ptc2 and Smo are most intensely detected in spermatogonia and spermatocytes and are much less intense in the round spermatids. The mRNA for the cytoplamic regulator, Fused, is restricted to the earliest germ cell types, whereas expression of the negative cytoplasmic regulator, SuFu, only begins in the round spermatids and persists in elongating spermatids. Gli1 and Gli3 are expressed from spermatogonia through to round spermatids, whereas Gli2 is restricted to spermatogonia and spermatocytes. This pattern mimics what was reported for mouse {2}. Examination of the irradiated rat testis model revealed that Hedgehog signalling machinery is produced by resting spermatogonial stem cells but is turned off when they differentiate in response to hormones. This matches the emerging understanding of Hedgehog signals in cancer stem cells and provides the first demonstration that Hedgehog signaling may influence stem cells in the adult testis.

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Activin C antagonizes activin A *in vitro* and over-expression leads to prostate pathologies *in vivo*

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Activin A is a well characterised inhibitor of proliferation in most epithelial cells. The actions of activin A on cell growth are mediated through Smad-dependent pathways. Activin A is potent at low levels, therefore its synthesis and bioactivity must be tightly regulated. Follistatin binding or inhibin subunit heterodimerisation block access to the activin receptor and/or receptor activation. We postulate that another mechanism of regulating activin A bioactivity is through the activin-β_C subunit. In order to test our hypothesis produced recombinant activin C and mice over-expressing activin-β_C. Recombinant activin C abrogated activin A-induced growth inhibition *in vitro* and the mechanism of action was down-regulation of activin A-induced Smad signalling molecules. In the prostate over-expression of activin-β_C increased epithelial cell proliferation while there was no significant difference in apoptotic epithelial cells. This imbalance between proliferation and apoptosis led to a significant increase in ventral prostate weight, prostatic hypertrophy and epithelial cell hyperplasia. A significant decrease in nuclear localisation of Smad-2 was associated with activin-β_C over-expression in the prostate which implies antagonism of activin signaling also occurs *in vivo*. This is the first study to provide evidence that activin-β_C is an antagonist of activin A *in vitro and in vivo* and implicates a role for the activin-β_C subunit in maintenance of tissue homeostasis in the prostate.

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Effects of Long Term Recombinant Rat Follicle-Stimulating Hormone Replacement on the Restoration of Spermatogenesis after Chronic Suppression of Gonadotrophins in Adult Rats

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Follicle stimulating hormone (FSH) in short term rat studies supports spermatogenesis at multiple levels, notably spermatogonial development. The role of FSH in supporting full spermatogenesis in rats is still in question as long term studies have not been possible due the development of neutralising antibodies to heterologous FSH preparations. This study sought to assess the effects of a homologous recombinant rat FSH (rr-FSH) preparation on the long term restoration of spermatogenesis. Adult rats were GnRH-immunised (GnRH-im) for 12 weeks then, administered an anti-androgen; flutamide (flut), alone or together with rr-FSH (8µg/rat/daily) for 56 days (1 spermatogenic cycle). Germ and Sertoli cell numbers were quantified using an optical disector stereological method. Testis weight, serum FSH and inhibin B and Sertoli cell nuclear volume were significantly reduced to 15%, 13%, 25% and 57% of controls respectively, following GnRH-im+flut treatment. GnRH-im+flut treatment reduced A/I spermatogonial, type B spermatogonial+preleptotene, leptotene+zygotene and early pachytene spermatocyte numbers to 28%, 68%, 50% and 19 % ($P < 0.001$) of controls respectively, with later germ cells rarely observed. After FSH treatment, no significant affect on testis weight, serum FSH and inhibin B or Sertoli cell number

were observed. However, rr-FSH treatment significantly increased numbers of A/I spermatogonia, leptotene+zygotene and early pachytene spermatocytes from 28=> 42%, 50=>69% and 19=>27% of controls, respectively, while no differences were observed in later germ cell types. rr-FSH also increased ($p<0.05$) the volume of Sertoli cell nuclei from 57=> 66% of control. In conclusion, FSH is unable to support full rat spermatogenesis; however, FSH can partially support germ cells notably spermatogonia through to early pachytene spermatocytes, despite the absence of androgenic support.

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Toxic effects of hyperglycaemia arise from induced O-linked glycosylation in early mouse embryos

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Glucose flux through the hexosamine biosynthetic pathway (HBP) which is essential for preimplantation development (1) produces uridine 5'-diphospho-N-acetylglucosamine, a donor substrate for multiple glycosylation reactions including O-linked glycosylation. This novel signaling arm of the HBP, known as the hexosamine signaling pathway (HSP) operates via reversible addition of an O-linked β-N-acetylglucosamine (O-GlcNAc) unit to serine and threonine residues of proteins including transcription factors, cytoskeletal components, metabolic enzymes and cellular signaling components. O-linked glycosylation is functionally reciprocal to phosphorylation at the same residues, altering the activity and/or stability of targeted proteins, thus providing a mechanism for modulating cellular physiology in response to glucose availability. The enzymes regulating this O-GlcNAcylation are the β-linked-O-GlcNAc transferase (OGT) and an O-GlcNAc-selective β-N-acetylglucosaminidase (O-GlcNAcase).

We hypothesized that the toxicity of hyperglycemia on early embryos arises from increased flux through HBP and increased O-GlcNAcylation of key proteins. Mouse zygotes (18h post hCG) were cultured under conditions of modified flux through the HSP including hypoglycemia, hyperglycemia or supplemented with glucosamine which feeds exclusively into the HBP to increase downstream O-GlcNAcylation. BADGP was used to inhibit OGT and O-GlcNAcylation. Blastocyst formation, cell proliferation and apoptosis were assessed.

Treatments that perturb levels of intracellular protein O-GlcNAcylation inhibited embryo development. Whilst some flux through HBP is required to activate embryonic differentiation (1), excess flux arising from a hyperglycemic environment or glucosamine supplementation reduced cell proliferation and blastocyst formation, confirming the criticality of this novel post-translational signaling pathway. Inhibition of OGT using 2 mM BADGP blocked the negative impact of hyperglycemia on blastocyst formation, cell number and apoptosis supporting our hypothesis that O-GlcNAcylation is a key mechanism used by the embryo to sense and respond to perturbations of glucose in its environment.

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Evidences for a novel cAMP-phosphodiesterase expressed in the bovine ovarian follicle.

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3'5'-Cyclic adenosine monophosphate (cAMP) is an important second messenger in the mammalian ovarian follicle implicated in gonadotrophin signalling as well as oocyte meiotic arrest. Cyclic AMP-degrading phosphodiesterases (PDE) modulate cAMP levels in the ovarian follicle, but the specific PDE subtypes responsible for this degradation in the different cellular compartments within the bovine follicle remain unknown. The current dogma, established principally in rodent, presents PDE3A as the "oocyte PDE", while PDE4D is the "granulosa/cumulus PDE". Our PDE activity measurements suggested that a PDE3 (cilostamide-sensitive, 10µM) was representing 79% of the total cAMP-PDE activity in the bovine oocyte, in agreement with the dogma. However, our results suggested that PDE4 (rolipram-sensitive, 10µM) is representing only 19% of the cAMP-PDE activity in the cumulus cells, while 65% of the activity was due to PDE8 (IBMX-insensitive, 500µM), a result in direct opposition with the accepted PDE distribution in the ovarian follicle. Mural granulosa cells were displaying equal amounts of PDE4 (31%) and PDE8 (30%) cAMP-PDE activities. Interestingly, cAMP-PDE activities were not varying during the first 9 hours of IVM in the bovine cumulus-oocyte complexes (COC), as seen in rat. COCs treated with an adenylyl cyclase stimulator (forkolin 100µM) in combinaison with the only known inhibitor for the PDE8 family, dipyridamole, are showing a dose-dependant increase of cAMP levels and a significant delay nuclear maturation, whereas a potent PDE4 inhibitor, rolipram (up to 100µM), was ineffective. This study provides the first insight into subtype-specific PDE cAMP degrading activities in the bovine ovarian follicle, especially around oocyte nuclear maturation. It demonstrates dramatic differential PDE subtype compartmentalisation between ovarian somatic cells and the germ cell, including the important contribution of a new PDE family member in the ovarian follicle, PDE8. PDE8 could be a novel pharmacological target to improve bovine oocyte IVM conditions and to increase developmental competence.

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Hormonal manipulation on the phenotype of ArKO female mice

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Gonadotrophins and steroid hormones are vital in controlling the cyclical pattern of ovarian follicular development essential for fertility. Previous studies have shown that ArKO (aromatase knockout) female mice are infertile due to the absence of estrogen, elevated levels of circulating gonadotrophins and testosterone and folliculogenic disruption. Therefore, the aim of this study was to determine the effects of E_2 (estradiol-17β) replacement, Acyline (GnRH antagonist) and Flutamide (anti-androgen) treatment on ArKO female mice. WT and ArKO female mice (C57B6/J129; 16 weeks old; n = 6-8/grp) were assigned into three main groups: group 1 - received either E_2 (0.05 mg) pellet or placebo, group 2 - received either a single s.c. injection of acyline (1.5 mg/kg/week) or placebo and group 3 – received either flutamide (25 mg) pellet or placebo for 3 weeks. Mice were subjected to daily vaginal smears. The ovaries and uterine horns were collected and weighed. One ovary and the uterine horns were fixed in formalin for histological assessment, while the other ovary was snap frozen in Ultraspec solution for RNA isolation and gene expression studies. Serum was collected for hormone measurements. All female ArKO mice exhibited an abnormal cycle that alternated between diestrus and early estrus . E_2 replacement restored the estrus cycle in ArKO female mice but acyline and flutamide treatment did not. Histologically, hemorrhagic cystic follicles were present in all placebo, acyline and flutamide treated ArKO ovaries, however, E_2 replacement improved the ovarian and uterine phenotypes. E_2 replacement and acyline treatment also led to a decrease in serum gonadotropin levels in ArKO mice. In summary, E_2 replacement could reverse the abnormal reproductive phenotype of the ArKO female mice. This study suggests that the reproductive phenotype of the ArKO female mouse is due to the direct effect of estrogen and not due to the elevated circulating levels of gonadotrophins and testosterone.

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Ovarian lymphatic vascular development is hormonally regulated and Adamts1-dependent

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The lymphatic system is important for return of extra-vascular fluid to the blood circulation, conductance of hormones and immune cell trafficking. Delicate hormonal control of fluid conductance during reproductive cycles is exemplified by the ovarian hyperstimulation syndrome, a dangerous condition of hypovolemia caused by fluid accumulation in the abdomen and reproductive tissues, in response to hormonal hyperstimulation. This study is the first to investigate the relationship between ovarian lymphatic development and follicle growth. Quantitative morphometric analysis of vessel size and number in mouse ovary revealed, for the first time, that the ovarian lymphatic vasculature develops postnatally and in synchrony with the induction of ovarian *CYP19a1* (*Aromatase*); the time when secondary follicles become FSH-responsive and estrogenic. Mechanistically, we found that the FSH-analogue eCG mediates induction of lymphatic vascular endothelial growth factor *Vegfd* and the receptor *Vegfr3* (*Flt4*) in granulosa cells. Importantly, stimulation with eCG also enhanced ovarian lymphatic vessel number and size. However, formation of ovarian lymphatics also required the matrix-remodelling protease Adamts1, since ovaries from *Adamts1*$^{-/-}$ mice failed to undergo normal lymphatic vascular development. Treatment of *Adamts1* null mice with eCG significantly increased the number and size of ovarian lymphatic vessels, however, the vessels were still smaller and fewer in number than wildtypes. These combined results indicate that the ovarian lymphatic system develops in response to hormonal signals, which promote folliculogenesis, through induction of lymphangiogenic factors in granulosa cells; as well as involving Adamts1-dependent mechanisms. This study is the first demonstration of the novel principle of hormonal regulation of lymphangiogenesis in any tissue and suggests a requirement for functional lymphatics during normal folliculogenesis. In addition our results inform the elucidation of the tightly regulated processes that control fluid dynamics and immune cell surveillance within reproductive tissues.

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Pamidronate Improves Bone density, Fracture Rate, Pain & Wellbeing In 14 Children and Adolescents With Chronic Neurological Conditions.

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Intravenous pamidronate has been shown to improve bone density in children with chronic neurological conditions but their role in treatment of symptomatic osteopenia is unclear. At Princess Margaret Hospital, Perth, the sole tertiary referral paediatric hospital for Western Australia a cohort of patients with chronic neurological conditions and low bone density, in whom fractures and bone pain were impacting on their daily care were being referred for treatment. To address this fourteen participants (M:F = 7:7, average baseline age 12.37 years.) were enrolled in a prospective uncontrolled study of pamidronate over a 2 year period. Pamidronate was infused every 6-8 weeks at a dose of 1mg/kg though due to patient illnesses &/or hospital admissions the average dose received over the 2 year period was 6.25 ± 0.72mg/kg/year. Outcome measures include: bone mineral density (BMD) z score, fracture rate, the effect of pamidronate on patient pain and wellbeing as assessed by carer's completing a visual analogue scale. Bone mineral density z score improved at all sites measured over the two years: whole body -4.84 to -3.14 (p = 0.01), lumbar spine -2.92 to -1.1 (p = 0.02) and femoral neck -4.6 to -3.58 (p = 0.04). Eight out of 14 patients reported significant pain at baseline and pain improved in seven out of these 8 patients. Of the 11 patients who answered the general wellbeing part of the questionnaire, eight patients reported an improvement in general wellbeing and 3 reported no change. Average annualised fracture rate decreased from 0.42+/-0.49 to 0.14+/-0.36 fractures per year, p=0.09. In a patient group with chronic neurological conditions and fractures or bone pain pamidronate has a positive effect.

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Distribution of Alpha-Tocopherol in Bone and its Relationship to Bone Structure and Biomechanical Strength.

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Alpha-tocopherol is widely found in plant oils used for food, such as corn and soy oils. Alpha-tocopherol is also available in various forms as vitamin supplements. It is popularly used for its strong antioxidant properties. The absorption of alpha-tocopherol is well documented, however, its distribution to bone has not been well studied. Free radicals have been proven to increase osteoclastic bone resorption activity and at the same time damage osteoblasts, thus increasing the risk of developing osteoporosis. In this study we wish to investigate the relationship between alpha-tocopherol levels in bone and bone structural and biomechanical properties. This is to determine whether alpha-tocopherol play an important role in preserving skeletal integrity.

Male Sprague-Dawley rats were divided into 2 batches, the first batch to study the absorption and distribution of alpha-tocopherol, while the second batch is used to study bone structural and biomechanical properties. The first group was divided into the Control (C), alpha-tocopherol 30 mg/kg body weight (ATF30), alpha-tocopherol 60 mg/kg body weight (ATF60) and alpha-tocopherol 100 mg/kg body weight (ATF100) groups. The second group was divided into the Baseline Control (BC), Control (C) and alpha-tocopherol 60 mg/kg body weight (ATF60) groups. The alpha-tocopherol was given by forced oral gavage six days per week for 4 months for both batches.

Results showed that all doses of alpha-tocopherol were well absorbed. Distribution to bone was significant only in the highest dose used, i.e. 100 mg/kg. However, significant improvements were already seen in bone structure and biomechanical strength compared to the control group at the lower dose of 60 mg/kg.

In conclusion, alpha-tocopherol was significantly distributed to bone at 100 mg/kg dose, however, improvements in bone structure and biomechanical strength were already seen at 60 mg/kg dose.

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Simple is not always best: Failure of simple guidelines for the management of osteoporosis in patients with a recent hip fracture

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Background: Hip fractures are associated with significant morbidity and great cost to the health system. It is well documented that osteoporosis management is neglected amongst patients with a recent hip fracture, however there is less data demonstrating approaches to improve this problem. [1] The successful protocols that have been published have been relatively costly and labour intensive, requiring a dedicated fracture nurse or orthogeriatrics service to ensure compliance with recommendations. [2-4] It is possible that a simple, clear protocol, which is easy for junior doctors to institute, may improve osteoporosis management, but be more cost-effective.

Hypothesis: Simple osteoporosis guidelines will improve management of inpatients with recent hip fracture.

Methods: A baseline audit of the management of osteoporosis in patients with a hip fracture was conducted between 1st November 2006 and 31st January 2007. New guidelines were then introduced focusing on:

1) Measurement of calcium and vitamin D levels

2) Initiation of calcium and vitamin D supplementation

3) Osteoporosis clinic follow-up

A second audit was conducted between 1st July 2007 and 31st October 2007, to examine rates of compliance with the new guidelines.

Results: 68 patients were included in the audit- 32 before and 36 after new guidelines were introduced. Despite improvement in calcium (75 to 83%) and Vitamin D (69 to 83%) measurement, rates of prescription of calcium supplements (53 to 47%), Vitamin D supplements (66 to 61%) and bisphosphonates (36 to 22%) declined. Referral to Osteoporosis clinic improved (3 to 14%) but remained below desirable levels (see Table 1).

Conclusions: Simple guidelines for osteoporosis management of inpatients with recent hip fracture failed to achieve an improvement in levels of calcium and Vitamin D supplementation and use of anti-resorptive therapy. The introduction of an additional measure, such as an osteoporosis co-ordinator, may be necessary to achieve desired levels of compliance.

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Lithium-associated Hyperthyroidism

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Lithium exerts multiple thyroid effects; including inhibiting coupling of iodotyrosine residues to T4 and T3, and releasing thyroid hormones. While hypothyroidism is a common sequelae of lithium therapy, hyperthyroidism is rare and the underlying mechanism poorly understood. We present a case of lithium-induced hyperthyroidism in a patient with schizoaffective/bipolar disorder, highlighting issues surrounding the pathogenesis of this complication.

A 36 year old woman was admitted with an exacerbation of psychiatric illness, on a background of poor adherence with chronic lithium therapy over the preceding three months, confirmed by a low serum lithium level of < 0.1 mmol/L (0.4 – 0.8). While biochemically euthyroid at admission, hyperthyroidism developed concomitantly with supervised administration of lithium over two weeks with fT4 of 28.3 pmol/L (10 - 20), suppressed TSH of 0.04 mIU/L and lithium concentration of 0.6 mmol/L. The thyroid gland was non-tender and normal in size.

Thyroid scanning demonstrated reduced uptake (0.3%, normal = 0.5 - 4%). Circulating levels of thyroglobulin (4.5 mcg/L, range 0 - 30) and inflammatory markers were normal with negative TPO, thyroglobulin and TSH receptor antibodies. Core biopsy of the thyroid demonstrated a lymphocytic infiltrate within the interstitium surrounding predominately normal sized follicles. There was some follicular atrophy but no active follicular destruction and no evidence of Hurthle cell change. This was consistent with a low-grade chronic non-specific inflammatory process.

Lithium therapy was ceased, and the patient managed conservatively. Hyperthyroidism initially worsened (fT4=33.1 pmol/L, fT3=13.1 pmol/L,), then improved, normalising by 3 months.

Here, lithium-associated hyperthyroidism was self-limiting, characterised by absent biochemical evidence of hyperfunction, inflammation or autoimmunity; and absence of histological features of follicular destruction or hyperfunction. The pathogenesis of lithium-induced hyperthyroxinaemia is unknown and cannot be explained by current mechanistic models of thyroid dysfunction. The diagnosis is contextual and established by a process of exclusion of other causes.

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Primary papillary thyroid cancer in a thyroglossal duct cyst: case report and review of the literature.

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Background: Thyroglossal duct cysts (TDCs) are common midline neck masses which may contain papillary thyroid cancer in approximately 1% of cases [1,2]. Clinical diagnosis is difficult, and concensus on optimal treatment is lacking [3,4].

Methods: We present imaging and histology of one new clinical case, and structured review the English adult literature available on Medline since 2002.

Results: A 44 year old lady presented with an enlarging mass in the suprasternal notch. Investigation included fine needle biopsy (FNB, not diagnostic), thyroid uptake scan (no uptake in the mass), ultrasonography (complex cystic lesion beneath the thyroidal isthmus) and CT scan. Following surgical excision, a 30x10x10mm papillary thyroid cancer was found in, and infiltrating the wall of, a thyroglossal cyst. Further therapy included total thyroidectomy, removal of the tract to the level of the hyoid bone, ablative radioiodine, and suppressive thyroxine. Of 21 other new cases identified in the literature, 19 articles were located. Including our case, the F:M ratio was 3:1, with median age for females less than males (38 years vs 53 years). The false negative rate of FNB was 56%. The size of the papillary thyroid cancer ranged from 4-50mm diameter. Treatment included Sistrunk's procedure in 70%, and thyroidectomy in 70% cases. Three patients had regional recurrence, and only one patient died of his disease, with median follow-up of 6.4 years.

Conclusions: FNB allows patients to be stratified for surgery, particularly if negative [5]. Appropriate surgical resection is the treatment of choice although adjuvant therapy is not unreasonable. Despite uncertainties, prognosis is generally excellent.

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Are GP's using TSH indiscriminately?

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Background: Thyroid dysfunction (TD) is common and usually managed in general practice [1, 2]. Whilst the classical signs and symptoms of both hypo- and hyperthyroidism are well known, the presenting features of early thyroid disease can be subtle and reliance on signs and symptoms alone may result in many cases being missed [3]. Consequently, general practitioners (GPs) have a low threshold for ordering thyroid function tests (TFTs) in adult patients.

Aim: The aim of this study was to measure the use of TFTs by GPs, identify the incidence of TD and draw conclusions as to the appropriateness of testing undertaken by GPs in patients without known TD.

Methods: We analysed use of TFTs over a 12 month period from laboratory data from two urban general practices with a total registered population of 21,461 patients. These data were linked to patient records held in general practice and outcomes were analysed by age and gender.

Results: In a 1-year period, 1 in 5 adult general practice patients had a TSH test. 8.4% had an elevated TSH concentration, mostly with subclinical hypothyroidism and 1.2% had a low TSH concentration, mostly with subclinical hyperthyroidism. The incidence of hyperthyroidism was 4.7/1000 and hypothyroidism was 2.2/1000. Rate of testing was higher in females compared with males.

Conclusions: GPs are using opportunistic screening with TSH alone to find new cases of TD. This strategy shows a cost per case of $1320 ($1313 in women, $2129 in men). The incidence of pituitary dysfunction is around 50 per million [4] and the cost per test is $7.30 giving a cost per case of $146,000. The current approach by GPs appears to be relatively cost effective, whilst the addition of FT4 to screening for TD due to pituitary disorders would seem to be much less attractive.

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Thyroid Disease during Pregnancy – A Review of Dose Requirements and Thyroid Function Test Changes in the Liverpool Hospital Antenatal Clinic.

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It is well established that thyroxine dose requirements increase during pregnancy, but less well established by how much.

Methods: We decided to audit the notes of 42 pregnant women with hypothyroidism who attended the Liverpool Hospital Antenatal Clinic between January 2006 and June 2008 to see what average dose change was required and if this differed depending on the aetiology of hypothyroidism.

Results: The average age of the women was 31.5years (21-45years), the average number of pregnancies was 3.07 (1-7), the self-reported ethnic background was 40.5% white (n=17), 19% Indian (n=8), 14.3% Middle Eastern (n=6), 11.9% Vietnamese (n=5), 7.1% South American (n=3), 7.1% other (1 Chinese, 1 Philippine, 1 Pacific Islander). Aetiology of hypothyroidism was: 45.2% total thyroidectomy (n=19; of those 16.7% (n=7) due to cancer; 28.6% (n=12) for other reasons), 35.7% Hashimoto's (n=15), 7.1% partial thyroidectomy (n=3), 4.8% post radioactive iodine therapy for thyrotoxicosis (n=2), and 7.1% unknown (n=3). The 19 patients post total thyroidectomy required an average dose increase from 129.1mcg thyroxine to 178.1mcg thyroxine, or an increase of 39.0%. The remaining 23 patients required an average dose increase form 90.5mcg thyroxine to 120.8mcg, or an increase of 33.4%. The average TSH fell from 12.06mIU/l to 1.05mIU/l, and the average FT4 increased from14.08pmol/l to 16.34pmol/l. In summary good thyroid function test outcomes were achieved, and the total dose increase required ranged between 33.4% and 39.0%, and was 5.6% higher in the total thyroidectomy group compared to the combined other aetiology group.

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The pattern of pregnancy nutritional supplement intake in Sydney West Area Health Service.

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Iodine is the main element for production of thyroid hormone, which is essential for the development of the central nervous system, a dynamic process occurring throughout all stages of pregnancy and continuing until an individual is about 2 years of age. During pregnancy the requirement for iodine is increased and insufficient iodine can have detrimental effects on the offspring. Currently, there are recommendations for women to take iodine-containing nutritional supplements during pregnancy and lactation to achieve an intake of 250µg/L daily. The Department of Diabetes & Endocrinology at Westmead and Blacktown Hospital, Sydney conducted a survey to ascertain the pattern and frequency of pregnancy supplement intake. We surveyed 90 women postpartum. Most women (n=82 [91%]) took pregnancy supplements during pregnancy. The majority (n=70 [85%]) commenced their pregnancy supplements in early pregnancy (≤12 weeks gestation) or preconception. Twelve women (15%) commenced their supplements in the second or third trimester. Sixty-three women (77%) intend to continue with pregnancy supplements during lactation while 10 (12%) did not, and another 9 (11%) did not intend to breast-feed. More women were on non-iodine containing supplements (55.5%) than iodine containing supplements (35.5%). When comparing iodine vs non-iodine containing supplements, women on iodine containing supplements were more likely to have been advised by midwives or obstetricians in their choice of supplements (p=0.002) while those on non-iodine containing supplements were more likely to have been advised by their general practitioner (p=0.007). Although non-significant, there was a trend for those on iodine containing supplements to have commenced supplements preconception, to be born in Australia and to identify iodine as an important micronutrient required during pregnancy. This survey reveals that currently not all women are taking iodine-containing pregnancy supplements during pregnancy and lactation. A larger survey will be required to clearly identify potential barriers in pregnancy nutritional supplement use.

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The Half Life of Plasma Free Metanephrines Following Resection of Pheochromocytoma

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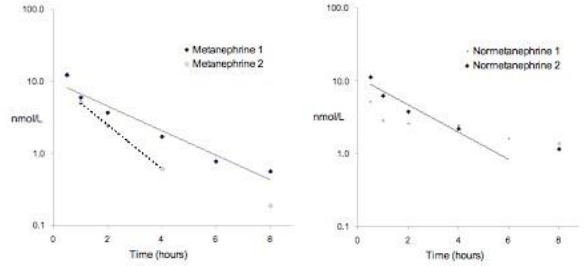
Aim: To evaluate the plasma half life of plasma free metanephrines. Background: Metanephrines have replaced catecholamines as the diagnostic test for phaeochromocytoma. The advantages are that metanephrines are the product of catechol-O-methyltransferase (COMT), which is predominantly adrenal, and secondly, metanephrines are said to have longer half lives than catecholamines in plasma. The plasma half lives of free metanephine and normetanephrine are unkown. Some authorities recommend collecting diagnostic samples from supine patients after 20 minutes, the importance of this is unknown. Methods: Serial blood samples were taken from two patients undergoing adrenalectomy for phaeochromocytoma over 48 hours from the clamping of the adrenal vein (T=0). Plasma free metanephrine and normetanephrine were measured by HPLC-tandem mass spectrometry. Patient one had a 10 cm left adrenal tumour predominanly secreting metanephrine and pateint two had a 3 cm right adrenal tumour predominanly secreting normetanephrine. Results: (insert charts) The half life of metanephrine was 105 minutes in patient 1 and 60 minutes in patient 2. The half life of normetanephrine was 95 minutes in pateint 2 and unable to be determined in patient 1. After 10 hours the results returned to baseline. The pharmacokinetics were non linear. Discussion: Metanephrines are metabolised to their sulphate metabolites by sulphotransferase (SULT) 1A3, the metabolites are cleared renally. A similar half life reported for R-salbutamol (145 min), cleared by the same pathway, supports the results of our study. The interindividual variability in half life of substrates of SULT1A3 is typically less than two fold. The reported intra-individual variability of plasma methanephrines is consistent with these findings. The half lives of metanephrine and normetanephrine observed in our two patients, argues against having patients lying supine for 20 minutes prior to collection of a plasma free metanephrine blood sample.



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Identification of Endothelin Converting Enzyme 2 as an Autoantigen in Autoimmune Polyendocrine Syndrome Type 1

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Background: Autoimmune polyendocrine syndrome type 1 (APS1) is a rare autosomal recessive disease caused by mutations in the autoimmune regulator (AIRE) gene. APS1 is characterised by the combined presence of at least two of the diagnoses Addisons disease, hypoparathyroidism or chronic mucocutaneous candidiasis. In addition, other organ-specific autoimmune diseases as well as ectodermal manifestations are found with variable penetrance. High titer autoantibodies are a hallmark of APS1 and serve as diagnostic markers and are sometimes predictive of disease manifestations.

Objective: To identify pituitary autoantigens in patients with APS1

Results: A pituitary cDNA expression library was screened with sera from two APS1 patients with growth hormone deficiency. Positive cDNA clones were isolated and partially sequenced revealing seven different clones in addition to tryptophan hydroxylase (TPH) isoform 1, a well known APS1 autoantigen. The cDNA clones were then used for *in vitro* transcription translation (ITT) followed by immunoprecipitation with the recombinant protein against a test panel of patients and controls. A protein encoding endothelin converting enzyme 2 (ECE2) showed encouraging results and was screened against a panel of 104 APS1 patients, 95 patients with other autoimmune diseases and 118 healthy blood donors. ECE2 autoantibodies were found in 46% (48/104) of APS1 patients but not in the sera from patients with Addison s disease, systemic lupus erythematosus, Sj gren s syndrome, type 1 diabetes mellitus, lymphocytic hypophysitis or healthy blood donors. Tissue expression profiling using quantitative PCR showed ECE2 to be highly expressed in the pancreas, pituitary and brain and with low expression in the small intestine, testis, ovary, prostate, colon, heart and thymus.

Conclusion: We have identified ECE2 as a major, highly specific APS1 autoantigen. ECE2 is a metalloprotease highly expressed in neuroendocrine tissue with 59% homology to ECE1. Our ongoing studies aim to elucidate the importance of ECE2 autoantibodies as markers for pituitary insufficiency or other disease manifestations in APS1.

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The Vanishing Testis (*testiculus evanidus)* - Y men are disappearing from endocrinology

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Within any endocrine system, maintenance of homeostasis is a central theme. In the gonadal system, minor perturbations in oestrogen and testosterone have widespread functional effects. Yet significant hormonal changes within the most central of endocrine systems, the endocrine workforce, have been largely unstudied. In 2006, females comprised 81% of Australian endocrine trainees.

Aims: 1. To identify the factors influencing endocrinology sub-specialisation in males vs females and older vs younger endocrinologists. 2. To determine factors influencing specialty choice and personal characteristics differentiating male endocrinologists from counterparts in male-dominated specialties.

We distributed anonymous paper/electronic surveys to physicians/advanced trainees from >7 NSW hospitals. Questionnaires assessed the influence of practical/intellectual/lifestyle motivations on specialty choice. Questions reflecting traditionally-perceived male vs female characteristics were included. Respondents were classified according to DOB (pre-1965=GenX and post-1965=non-GenX).

33 male (17 GenX, 16 non-GenX) and 29 female (all GenX) endocrinologists took part. Within GenX, the strongest influences regardless of gender, were (in order) intellectual stimulation, types of patients/diseases and work/life balance, however, flexible hours were more important for women. 33% of women rated gender as having strong or moderate influence vs 0% of men ($p=0.007$). All endocrinologists rated intellectual stimulation highly. More GenX vs non-GenX endocrinologists rated work/life balance, flexible hours, minimal on-call and public health/global significance as important. (94% vs 44%, 76% vs 38%, 80% vs 50%, 52% vs 19%, respectively, all $p<0.02$).

Male cardiologists/gastroenterologists ranked procedural opportunities and financial rewards as more influential compared to male endocrinologists (100% vs 9%, 82% vs 9% respectively, $p<0.001$). 100% of male cardiologists/gastroenterologists claimed to have good direction/orientation sense, whereas 27% of male endocrinologists reported difficulty locating their car in the carpark ($p<0.05$). Despite several respondents labelling endocrinology as a 'feminine/wussy' specialty, male endocrinologists did not demonstrate significantly more feminine characteristics, lower testicular volumes or preference for 'chick-flicks'.

Reasons for choosing endocrinology have changed, lifestyle factors becoming more influential. Gender-related reasons are attracting women towards endocrinology. Despite this, endocrinology's intellectual appeal remains significant for both sexes.

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Time to take notice of the hospital inpatient with hyperglycaemia

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Diabetes diagnosis is delayed four to seven years [1] and 50% are undiagnosed. Forty percent of hospitalised patients with a single blood glucose level (BGL) ≥ 10 mmol/L will have diabetes at three months post discharge [2], yet fewer than five percent are detected in hospital [3,4]. Patients with undiagnosed diabetes have higher hospital mortality [5]. Aims. We review current identification of, and responses to, hyperglycaemia in inpatients at an Australian teaching hospital. Methods. Retrospective review of medical records for inpatients with venous BGL ≥11.1 mmol/L over 12 months from 2005-2006 without known diabetes. Primary outcome was recognition of hyperglycaemia by annotation in medical records; secondary outcomes were documentation of follow-up and treatment. Logistic regression was performed with variables including BGL, admitting team, length of stay, and review by endocrine team. Results. Of 10,973 persons screened, 162 were eligible. Median age was 57 years and BGL 13.3 mmol/L. Hyperglycaemia was definitely noted in 42 (26%), and "probably" noted in a further 38 (24%). For 50% hyperglycaemia was not noted. Follow-up was documented for 24%. Forty percent of patients were treated in hospital and 19% on discharge. Higher BGL and review by endocrine team were strongly associated with clinical recognition on uni- and multivariate analyses. Conclusions. With evidence for improved inpatient outcomes when treated, and high short-term progression to frank diabetes, inpatient hyperglycaemia remains too frequently missed. Recognition does not require new expensive tests, allows initiation of treatment which can improve hospital outcome [6], and importantly provides the opportunity to prevent progression and complications. Systems to reduce errors in checking pathology results with improved education for medical officers are indicated.

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Should we be screening for Klinefelter Syndrome? A research proposal

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Klinefelter Syndrome (KS) is a genetic condition (47XXY) resulting in a spectrum of clinical features. The prevalence has been estimated at 1:650, yet 70% of males are never diagnosed. This indicates that there are 15,000 males with KS in Australia, yet over 10,000 remain undiagnosed, even though they may benefit from treatment.

Early identification of KS has long been advocated, but population-based genetic screening has never been explored. This study aims to:

i) Establish the prevalence and diagnosis rates of KS in Victoria

ii) Assess the potential risks and benefits that could arise from implementing genetic screening for KS at different ages and stages of development

iii) Develop a research proposal investigating the psychosocial impact of age at diagnosis in an adult cohort

KS diagnoses in Victoria since 1983 were obtained through multiple sources including the Birth Defects Register, the Prenatal Diagnosis Database and four cytogenetics laboratories. Over 400 diagnoses of 47XXY were made between 1983 and 2006, providing the first Australian estimation of prevalence and detection rates.

Evidence of potential risks and benefits of diagnosing KS at different ages was identified from the literature and analysed within a theoretical framework, developed using a biopsychosocial model of health. Results of this critical analysis indicate that while information is available on medical and educational interventions available for KS, little is known about the impact of age at diagnosis and the timing of interventions, on psychosocial and quality of life outcomes.

A research project has been developed and is currently being undertaken to fill these knowledge gaps and further inform decisions regarding genetic screening for KS. This will utilise quantitative and qualitative methods to follow-up Australian men diagnosed at different ages by questionnaire survey and semi-structured interview. This study design will be presented together with prevalence data and the critical analysis.

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Familial, bilateral macronodular adrenocortical hyperplasia with autonomous secretion of both cortisol and aldosterone.

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Familial "Adrenocorticotropin-Independent Cushing's Syndrome" (AICS) with bilateral adrenocortical nodules has long been recognised. In both Familial Hyperaldosteronism Types I (FH-I, glucocorticoid-suppressible) and II (FH-II), bilateral macronodules can occur (1). However, simultaneous, autonomous adrenal secretion of *both* cortisol and aldosterone by adrenocortical nodules has rarely been described. In a recent report from the Mayo Clinic (2) describing 10 patients with macronodular AICS treated surgically, only one had concurrent primary aldosteronism (PAL). We report two families with macronodular adrenal hyperplasia and simultaneous production of both cortisol and aldosterone. The propositus for family one was a 46 year old female who presented with hypokalemia, suppressed renin and bilateral adrenal masses. Neither cortisol (dexamethasone) nor aldosterone (saline infusion) suppressed normally, and right, laparoscopic adrenalectomy [after adrenal venous sampling (AVS) while on dexamethasone was consistent with bilateral disease] made cortisol suppressible with dexamethasone, but renin became unsuppressed only with amiloride. Her mother had bilateral removal of macronodular adrenals for PAL, an aunt has bilateral adrenal macronodules and subclinical Cushing's, and a sister has an adrenal macronodule. The propositus for family two was a 46 year old male with hypertension and bilateral adrenal masses. Neither aldosterone nor cortisol suppressed normally. After AVS indicated bilateral disease, both adrenals were removed, revealing exuberant, giant macronodular hyperplasia. A female cousin (their mothers both bled from Circle of Willis berry aneurysms) has PAL due to bilateral adrenal nodular hyperplasia. When bilateral macronodular adrenocortical hyperplasia causes Cushing's syndrome, or PAL, or both, AVS should guide management (2). The fact that AICS and PAL can occur not only in families, but in the same family, suggests that the responsible mutation(s) may predispose to adrenocortical nodule formation (and the hormone(s) autonomously produced depend on the particular cell type involved) rather than act by dysregulating a biosynthetic pathway, as in FH-1.

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Hypothesis: With increasing age, less flexible hormone secretion in genetically-predisposed individuals may contribute to conditions such as aldosterone-dependent hypertension or vasopressin-dependent hyponatremia.

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Ageing-associated deterioration in regulatory mechanisms is exemplified by unsuppressible, and therefore inappropriate, vasopressin (antidiuretic hormone) secretion (SIADH) despite hyponatremia, and is correctable by reduced fluid intake. Over the years, resistance of "normal" aldosterone levels to suppression by salt loading in some older, uncategorised and therefore apparently "essential" hypertensives has been recognised, but unexplained. If a generous salt intake is continued despite concurrent reduction in GFR due to "normal" glomerular fall-out causing reduced ability to excrete a sodium load, aldosterone action in the distal nephron not appropriately shut down would then represent a risk factor for salt overload hypertension. We should therefore perhaps not have been surprised by the recent findings (1) in the Framingham Offspring Study (mean age 59 years) of a positive relationship between progressive development of hypertension and serum aldosterone levels (throughout the normal range) measured three years earlier. Importantly, concurrent renin levels showed a negative relationship with rising blood pressure, identifying autonomous aldosterone (as in primary aldosteronism) as the problem. A most interesting further finding was heritability of the aldosterone-renin ratio (which also showed a strong positive relationship with rising blood pressure), with initial calculations suggesting linkage to chromosome 7p21-22, a locus currently under investigation by us for involvement in Familial Hyperaldosteronism Type II (2). By causing a failure of normal regulatory mechanisms, inappropriately normal, fixed levels of aldosterone could play a significant role in the development of apparently "essential" hypertension, so common after age 50, in a genetically-predisposed subgroup of the general population. If these patients could be identified by genetic testing, dietary salt restriction might be just as effective in preventing hypertension as water restriction is in preventing hyponatremia in SIADH. As previously hypothesised (3), when aldosterone excess plays a role in hypertension, it seems to be often genetically based.

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Inflammatory adipokines in overweight women with and without polycystic ovary syndrome

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Introduction: PCOS is associated with reproductive and metabolic abnormalities. Novel risk factors for cardiovascular disease include inflammatory adipocytokines such as leptin, adiponectin and the leptin-to-adiponectin ratio (L/A) as an atherogenic index. The aim of this study was to assess novel markers of inflammation in overweight women with and without PCOS and to examine alterations in these markers with pharmacological interventions modulating insulin resistance.

Methods: Overweight age and BMI-matched women with (n=80) or without PCOS (n=27) were assessed cross-sectionally. The subjects with PCOS were then randomised to 6 months metformin (1 g. b.d, n=26) or oral contraceptive pill (OCP) (35 µg ethinyl estradiol/2 mg cytoproterone acetate, n=30). Outcome measures were adipocytokines (leptin, adiponectin), inflammatory markers (highly sensitive C-reactive protein), lipid profile, homeostasis assessment of insulin resistance and androgen levels.

Results: Leptin levels were significantly lower (156.4±85.9 versus 208.5±105.2 ng/mL, P=0.015) while adiponectin (7022.1±5488.1 versus 7117.4±2807.2 ng/mL, P=0.225) and the L/A (0.034±0.003 versus 0.032±0.003, P=0.403) were not significantly different between women with and without PCOS. Leptin decreased equivalently for the OCP and metformin (P=0.010) with no effect of treatment (P=0.583). There was no change in adiponectin or the L/A ratio with the OCP or metformin. On multiple regression, the only significant predictor of leptin was BMI (r^2=0.485, p<0.001) and the strongest predictor of the change in leptin was change in weight (r^2=0.402, p<0.001).

Conclusions: In this insulin resistance group without diabetes, alterations in leptin between women with and without PCOS or with pharmacological interventions are primarily related to changes in adiposity and not insulin resistance.

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Epidural Lipomatosis – A complication of Ectopic ACTH Syndrome

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Ectopic ACTH syndrome (EAS) is a cause of Cushing's syndrome (CS). We report an unusual case of an ACTH-producing bronchial carcinoid tumour in a man with paraplegia caused by spinal cord compression from epidural lipomatosis.

A 34 year old man presented with hypertension and diabetes and clinical suspicion of CS was confirmed by a markedly elevated urinary free cortisol (UFC) excretion of >14000 nmol/24 h (normal < 300 nmol/24 h). He developed progressive lower limb weakness, cough and breathlessness and was admitted with paraplegia, pneumonia and multiple rib fractures. MRI demonstrated multiple vertebral crush fractures with extensive epidural lipoma compressing the thoracic region of the spinal cord. Thoracic laminectomy with resection of lipomatosis was undertaken, improving neurological status.

Endocrine investigations revealed elevated plasma cortisol and ACTH levels both of which failed to suppress with an 8 mg dose of dexamethasone, indicative of EAS. CT chest demonstrated a 2 cm nodule in the right upper lobe. Subsequent Octreotide/CT scan revealed avid uptake by this lesion and a hilar lymph node indicating metastatic disease. Hypercortisolism was controlled with ketoconazole 1800 mg/day, reducing cortisol excretion to 199 nmol/24h. A right lobectomy with lymph node clearance was performed two months later. Histology revealed a carcinoid tumour with lymph node metastasis. Postoperatively, the UFC excretion fell to 11 nmol/24h and he was replaced with dexamethasone. When reviewed 6 months later, there had been marked neurological recovery with the patient walking without assistance.

Epidural lipomatosis producing clinical spinal cord compression is a rare complication of EAS. Diagnosis can be difficult due to mimicry by steroid induced myopathy. While vertebral crushed fractures from Cushing's related osteoporosis can cause spinal cord compression, epidural lipomatosis should not be missed as prompt surgical decompression may be necessary. Understanding the pathogenesis of epidural lipomatosis in CS will require further study.

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"Of Jugulare and Zuckerkandl", uncommon presentations of Paragangliomas and the role of Nuclear Medicine in diagnosis and management

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We present 2 cases of metastatic paragangliomas.

The first case is that of a 25 year old female, who presented with several months' history of right ear deafness and postural dizziness. Initial head CT and MRI demonstrated a large mass at the right base of the skull invading the petrous temporal bone. Initial 24-hour urinary dopamine and noradrenaline levels were elevated, consistent with a glomus jugulare. Staging PET imaging demonstrated localized disease only. She subsequently underwent angiographically guided arterial embolization and then surgical resection with curative intent. However, significant residual disease remained with finding of 1 metastatic regional lymph node. Follow-up 24-hour urinary noradrenaline level remained at twice the upper limit. Subsequent treatment included radiotherapy for local control. She continued to attend follow-up reviews

The second case is that of a 26 year old male, who presented with an incidental finding of a 6cm mass below the aortic bifurcation on CT performed to assess for abdominal trauma following a vehicle accident. He was significantly hypertensive on presentation. Subsequent elevated 24 hour urinary catecholamines and avid I-123 MIBG uptake were consistent with a phaeochromocytoma of the Organ of Zuckerkandl. He underwent surgical resection with partial response. He was readmitted 2 years later with new abdominal pain and increase in urinary catecholamines. Restaging MIBG, Pentetreotide and PET imaging demonstrated widespread avid disease. He underwent therapeutic high dose I-131 MIBG ablation. Currently he continued to attend follow-up reviews.

The major issues which are presented for discussion are -

What is the diagnostic accuracy and role of various radionuclide imaging modalities in assessing metastatic paragangliomas?

What is the efficacy of various treatment modalities of metastatic paragangliomas, particularly I131-MIBG ?

What is the prognosis of metastatic paragangliomas?

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Clinical Case Report: Acute Pancreatitis due to Hypertriglyceridaemia

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A 44 year old woman presented with her fourth episode of severe acute pancreatitis, requiring intensive care management for ventilation and inotropic support. Initial serum triglyceride measurement was 91.4 mmol/L. Hypertriglyeridaemia had been previously diagnosed following an episode of gout at the age of 26 years of age, and she had been treated with a combination of diet, fibrates, and statins, with which she was not compliant. Her alcohol intake was minimal. She had no other signs of hypertriglyceridaemia, but has a strong family history of dyslipidaemia (particularly hypertriglyceridaemia) and pancreatitis. During this admission, serum triglycerides fell to a level of 11.2 mmol/L within 72 hours; she was re-commenced on fibrate therapy and an insulin infusion was required to control hyperglycaemia that developed with the use of fat-free parenteral nutrition. When oral intake was permitted, she began a very low fat diet together with supplemental medium-chain fatty acids. Serum triglycerides on discharge measured 5.77 mmol/L, and cholesterol measured 7.05 mmol/L with HDL 0.61 mmol/L. Fasting glucose and thyroid function was normal.

The presumptive diagnosis for the cause of hypertriglyceridaemia in this case is lipoprotein lipase deficiency. Lipoprotein lipase glycoprotein secreted by adipocytes and muscle cells, which in the presence of apolipoprotein C-II, hydrolyses both dietary and endogenous triglycrerides. It is thus the key enzyme regulating metabolism of triglyceride-rich chylomicrons and very low density lipoproteins. Familial LPL deficiency is a rare autosomal recessive disorder associated in most cases with mutations in the *LPL* gene. It causes familial chylomicronaemia syndrome, manifesting as severe hypertriglyceridaemia, chylomicronaemia, recurrent pancreatitis, eruptive xanthomas, and lipaemia retinalis. To date there have been over 200 *LPL* mutations described, which result in either reduced or abolished lipolytic activity.

Treatment involves extreme low fat diets of less than 10-15% total calories in combination with omega-3 polyunsaturated fatty acids and pharmacotherapy with fibrates orniacin.. Hypertriglyceridaemia is an independent risk factor of coronary artery disease, although its association with mortality is not clear.

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Hyperandrogenism due to Hyperthecosis and a Steroid-Cell Ovarian tumour – Diagnostic challenges of localising the source of hyperandrogenism.

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Hyperandrogenism can be due to tumourous and non-tumourous causes. We present two rare cases of hyperandrogenism, due to a steroid-cell ovarian tumour and ovarian hyperthecosis, respectively. Hyperthecosis, a benign cause of hyperandrogenism, may have clinical features and testosterone levels similar to that of androgen-secreting tumours. Virilising tumours arise from the ovary or adrenal cortex. The visualisation of ovarian tumours can be difficult as they can be small and embedded deep within the organ. Furthermore, the finding of an adrenal adenoma may not necessarily be the source of hyperandrogenism as there is a high prevalence of adrenal incidentalomas. When standard imaging is unsuccessful in detecting the source, other investigations may assist in the diagnosis including dexamethasone suppression testing, other imaging modalities and adrenal and ovarian venous sampling. We will explore the features of each case and examine the role and value of each investigation in the diagnostic challenge. An understanding of the above will allow early definitive management.

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A case of Bilateral Phaeochromocytoma in Neurofibromatosis Type 1

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Mr GP was a 59 year old Caucasian gentleman with known background of Type 1 neurofibromatosis and hypertension. He presented with progressive weakness of his lower limbs and abdominal pain. Magnetic resonance spinal imaging revealed multiple neurofibromas causing significant cord compression at C7/T1. Abdominal computed tomography scan revealed bilateral adrenal masses. Further investigation showed raised 24 hr urinary catecholamines on three occasions, and raised plasma free metanephrines. Levels of aldosterone renin ratio, twenty-four hour urinary free cortisol, DHEAS, corrected calcium and calcitonin were normal. MIBG scan was performed and this confirmed the presence of bilateral phaeochromocytomas.

He was started on phenoxybenzamine and subsequently propanolol. He proceeded to laparoscopic bilateral cortical sparing adrenalectomy with perioperative steroid cover. On the second post operative day, he had an abnormal short synacthen test after being off intravenous hydrocortisone for twenty-four hours. His blood pressure remained normal off anti-hypertensive medications. He was discharged on cortisone acetate.

Repeat twenty-four hour urinary catecholamines and plasma free metanephrine three weeks post operation were normal. He then went on to have laminectomy C5-T1 and removal of intradural, extramedullary neurofibroma one month after his adrenalectomy. He received perioperative corticosteroid cover and the operation was uneventful. Repeat short synacthen test on the fourth postoperative day was normal when performed off hydrocortisone. His cortisone acetate was thus ceased on discharge. At four months postsurgery he was found to have an adequate morning cortisol level and normal free plasma metanephrines

This case illustrates that cortical-sparing adrenalectomy can achieve clinical and biochemical cure for bilateral phaeochromocytoma. It can also preserve adrenocortical function avoiding the need for corticosteroid replacement. This may be the treatment of choice for familial bilateral phaeochromocytoma. Long term follow up should include monitoring of the remnant adrenal gland for recurrent phaeochromocytoma with at least yearly biochemical screening studies.

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Case report: ^{123}I-MIBG negative malignant paraganglioma

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A previously well 28 year old man presented with abdominal pain and a 12 month history of paroxysmal palpitations. He was hypertensive with a BP of 170/110mmHg.

CT abdomen and subsequent whole-body MRI, revealed a large, infra-renal retroperitoneal para-aortic mass measuring 6.3 x 4.0 x 7.2cm, and a 25mm para-aortic lesion at the level of T7/8 vertebra. He had a significantly raised 24-hour urine nor-adrenaline level of 12300nmol/D (<560) and plasma nor-metadrenaline of 14500pmol/L (<780). Chromogranin-A was elevated at 410 U/L (2-18). A functioning paraganglioma was suspected and he was started on phenoxybenzamine followed by propranolol.

A ^{123}I-MIBG scan showed intense uptake in the thoracic lesion but *no* significant uptake in the large abdominal lesion. He subsequently underwent a limited thoracotomy to remove the thoracic lesion, without complications. A [^{18}F]FDG-PET scan was only available after his thoracic surgery. It revealed intense uptake in the abdominal para-aortic mass, moderate uptake around his recent thoracotomy but no other areas to suggest metastatic disease. The patient then underwent a second operation to remove the remaining mass. Two enlarged lymph nodes superior to the mass were also removed. Due its close proximity to adjacent structures, a left nephrectomy and aortic graft had to be performed.

Post-operatively, the patient required no further antihypertensives. His urine adrenaline and plasma nor-metadrenaline normalized 4 days after surgery. Histology of the thoracic mass was consistent with a paraganglioma with no evidence of malignancy. However, the abdominal mass, again a paraganglioma, showed features of malignancy and lymph node invasion. Germline mutation analysis is awaited.

With positive biochemistry, a PET-postive but MIBG-negative tumour is suspicious of malignant pheochromocytoma. It is thought that tumour de-differentiation and loss of noradrenergic transporters account for the MIBG-negativity.

In patients with malignant disease[1,2],including metastatic SDHB–associated paraganglioma[3], [^{18}F]FDG-PET was able to show lesions not detected by ^{123}I-MIBG.

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Trends in Radioiodine Remnant Ablation for Differentiated Thyroid Cancer

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Background: Papillary (PTC) and Follicular (FTC) thyroid cancer are the most common endocrine malignancies. They generally have an excellent prognosis when treated appropriately with thyroidectomy followed by radioiodine remnant ablation (RIA) .

Aims: To determine the factors predicting use of RIA and trends in the use of RIA over the past decade.

Methods: Tasmanian Cancer Registry data for all diagnoses of follicular cell derived thyroid cancer (FCDTC) were correlated with RIA administered during the period 1994-2005.

Results: During the period 1994 – 2005 there were 273 new diagnoses of FCDTC in Tasmania, 158 (57.9%) of which were treated with RIA. Examination of the data for trends in RIA usage revealed a decline in treatment of small PTC and a rise in the likelihood of treatment for large PTC during the study period. However, inconsistent with guidelines, there was a decline in the likelihood for treatment of patients with multifocal primary tumours and those with PTC aged ≥45 years.

Conclusion: Whilst there is evidence for changing patterns of RIA utilization consistent with best practice treatment recommendations, a significant minority of eligible FCDTC patients continue not to receive appropriate RIA treatment. Centralised care for management of patients with thyroid cancer may improve patient treatment rates.

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The Australian Prostate Cancer BioResource: An Update on its Role in Translational Research into Prostate Cancer in Australia

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The Australian Prostate Cancer BioResource is a translational research tissue bank with associated database, initiated by the Australian Prostate Cancer Collaboration. Blood and fresh prostate tissue are collected from men treated by radical prostatectomy for early stage disease. Developmental funding came from Prostate Cancer Foundation of Australia and Commonwealth Bank of Australia. Currently, prospective tissue procurement is provided by an NHMRC Enabling (infrastructure) Grant (July 2004-June 2009, total $2.1 million). Four tissue procurement nodes, each with its network of affiliated public and private hospitals are situated in Adelaide, Brisbane, Melbourne, Sydney. Each node maintains a local tissue collection and clinico-pathological database, with the nodes to be linked via a web-platform database, to permit data mining and assembly of specific research cohorts. Procurement began October 2005. Total number of participants banked is 1300, current accrual rate is 575pa. Between 2-6x 5mm punch biopsies of fresh tissue per participant are stored at -80C and/or in liquid nitrogen vapour . Full blood is stored as Guthrie blots, and serum, plasma, buffy coats are stored at -80C. Also currently available are tissue microarrays of 150 contemporary early stage prostate cancer patients arrayed by Gleason score, prostate cancer cell lines, normal prostate, and transgenic mouse prostate cancer (TRAMP). An Access Policy is in place. Access is available to all Australian prostate cancer researchers with ethically approved, high quality research projects, after peer review. See www.apccbioresource.org.au . Over the last 12 months, tissue resources have been provided to 14 researchers from all mainland states. Although a partial cost recovery strategy is in place, to promote the BioResource, human tissue resources are currently being provided with no cost recovery component. There is no access for biotechnology and pharmaceutical companies until 2010, to permit building of the resource and acquisition of 5-year clinical follow up.

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Epigenetic regulation of estrogen synthesis in human breast adipose fibroblast cells

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Estrogen plays a significant role in the development and progression of breast cancer (BC). Cytochrome aromatase p450, encoded by the gene *CYP19*, is the key enzyme catalyzing the synthesis of estrogens from androgens. In post-menopausal women, adipose tissue becomes the major site for estrogen production coinciding with an increase in *CYP19* expression in breast adipose fibroblasts (BAFs). Therefore, understanding the mechanisms of *CYP19* regulation in BC is critical for the development of therapeutic measures. Previous studies of *CYP19* regulation in BC have focussed on hormone-induced regulation of transcription via upstream tissue- and promoter-specific regulatory regions. While this is clearly important, it is increasingly evident that epigenetic events, such as DNA methylation, are a common mechanism in the regulation of gene expression during the progression of cancers. The aim of this study was to investigate whether *CYP19* expression is under epigenetic regulation and to determine if such mechanisms contribute to the tissue- and promoter-specific expression of *CYP19* observed in BC.

CYP19 transcripts in cancer-free BAFs stimulated with cytokines and glucocorticoids (e.g. TNFα and dexamethasone) are derived from the distal promoter I.4, whereas breast tumour-derived paracrine signalling factors (e.g. prostaglandin E_2) induce a regulatory switch to the proximal promoters I.3 and II. DNA isolated from BAFs maintained under these two conditions was treated with sodium bisulfite allowing for methylation sequence analysis of CpG dinucleotides. Methylation mapping revealed a stochastic heterogeneous level of methylation among pI.4 (9 CpG sites) and pI.3/II (11 CpG sites). No correlation was observed between elevated pI.3/II transcription and promoter methylation. In contrast, hypomethylation at pI.4 was observed following induction, suggesting a potential inverse corelation. BAFs treated with 5-aza-2'-deoxycytidine – a DNA methylation inhibitor – increased total *CYP19* mRNA expression up to ~50-fold in a dose-dependent manner. This activation was deemed to be mediated via pI.4 through the up-regulation of trans-activating factors.

These studies uncover a new layer of complexity in the regulation of aromatase where *CYP19* is indirectly under tonic inhibition by methylation in BAFs, lending to the potential of epigenetic therapies. These findings will translate to BC by determining the methylation state of *CYP19* in clinical BC specimens, and will correlate with clinicopathological parameters.

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Androgen Receptor Signalling Inhibits Breast Epithelial Cell Survival in an Explant Model of Normal Human Breast Tissue

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Clinical evidence and studies of breast cancer cell lines suggest that androgen receptor (AR) signalling protects against development of breast cancer, in part by limiting epithelial cell proliferation. To test whether this occurs in normal human breast tissue, we employed a new culture method that retains stromal-epithelial cell interactions that are necessary for normal steroid receptor signalling. Human breast tissue was obtained from postmenopausal women following breast surgery and cultured as explants on gelatine sponges in medium containing 10% steroid-stripped fetal calf serum supplemented with experimental treatments. Following a 24-48 hour culture period, explants were embedded in paraffin, sectioned and stained with haematoxylin and eosin to assess morphology. Histologically normal tissues were analysed for expression of AR, human kallikrein 3 (hKLK3; an established AR-regulated gene), bcl-2 (a marker of cell

survival) and Ki 67 (a marker of cell proliferation) by immunohistochemistry. Video image analysis was used to measure intensity of immunostaining for AR, hKLK3 and bcl-2. The percentage of Ki67 positivity was assessed by an experienced pathologist by counting the number of positive cells per 200 epithelial cells. Treatment with the native androgen 5α-dihydrotestosterone (DHT; 1nM) increased expression of AR ($p<0.05$) and hKLK3 ($p<0.05$) in breast epithelial cells. The effects of DHT were abolished by inclusion of the specific AR antagonist bicalutamide, thereby confirming functional AR signalling in this model. DHT significantly decreased expression of bcl-2 ($p = 0.001$) and tended to reduce the percentage of Ki67 positive epithelial cells ($p=0.07$). In conclusion, we have demonstrated that functional AR signalling is evident in an in vitro human breast explant culture system and provide evidence that AR activity decreases expression of markers associated with epithelial cell survival. Future studies aim to determine whether inhibition of AR signalling perturbs the hormonal homeostasis of breast tissue and thereby promotes development of breast cancer.

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Do β—blockers increase the risk of obesity?

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The sympathetic nervous system (SNS) is a major regulator of energy balance and substrate utilisation. It stimulates energy expenditure and fat oxidation. Obesity has been associated with reduced sympathetic nervous activity, suggesting that SNS blockade may be a risk for developing obesity. The aim of our study is to determine whether chronic β-blocker users are more obese. Measurement of Body Mass Index (BMI) and/or waist circumference were undertaken in outpatients attending the diabetes clinic (n=219,F=87) and renal hypertension clinic (n=84,F=17), and in geriatric inpatients (n=47,F=27) from St Vincent's Hospital, Sydney. Amongst outpatients from diabetes clinic, a cross-sectional comparison revealed BMI to be higher in β-blocker users (n=64) (33.9 ± 6.3 vs 30.3 ± 6.4 kg/m2, p=0.0002). Amongst outpatients from renal hypertension clinic, BMI (32.7 ± 8.6 vs 26.1 ± 4.7 kg/m2, p=0.004) and waist circumference (109 ± 16 vs 89 ± 13 cm, p=0.0001) were higher in β-blocker users (n=42). According to waist circumference criteria used to define the Metabolic Syndrome (>102 cm in men and >88cm in women), 55% of β-blocker users compared to 21% of non-users were centrally obese ($p<0.001$). Amongst geriatric inpatients, no significant difference was present in BMI between β-blocker users (n=22) and non-users (n=25). However during the period of hospitalisation (6 ± 1.5 days), body weight fell significantly ($p<0.0001$) in non-users (-2.0 kg ± 1.2 kg), but not in β-blocker users (0.24 ± 1.3 kg). β-blocker use was the only independent predictor of weight changes in a multiple regression with age, gender and other medication use (adjusted $R2=0.43$, $p<0.001$). In summary, β-blocker use is associated with higher BMI and waist circumference. We conclude that β-blocker use may therefore increase the risk of obesity, but may have beneficial roles in weight preservation in elderly hospitalised patients. (Supported by the NHMRC of Australia)

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Understanding the link between RORalpha and the control of adiposity

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We have recently observed that homozygous staggerer mice (sg/sg) that display decreased and dysfunctional expression of the orphan nuclear receptor, RORalpha, are resistant to (high fat) diet induced obesity (J Biol Chem. 2008 Jun 27;283(26):18411-21), despite hyperphagia. The reduced adiposity in sg/sg mice is characterized by significantly increased expression of PGC-1alpha, PGC-1beta, lipin1 and beta(2)-adrenergic receptor mRNA in liver and white and brown adipose tissue from sg/sg mice. The dyslipidemia is associated with decreased hepatic expression of SREBP-1c, and the reverse cholesterol transporters, ABCA1 and ABCG1. This is consistent with the reduced serum lipids (J Biol Chem. 2008 Jun 27;283(26):18411-21). Further studies have revealed that sg/sg mice are also resistant to hepatic steatosis. Moreover, we demonstrate that these mice are characterised by changes in glucose tolerance, and in the kinase cascade that regulates insulin signalling. We will discuss the central role of this orphan nuclear receptor in the control of metabolism in the major mass metabolic tissues.

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An association between non-alcoholic fatty liver disease and polycystic ovarian syndrome

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BACKGROUND AND AIM: The aim of this study was to determine if there is an association between non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). NAFLD and PCOS are known to be associated with metabolic syndrome/insulin resistance.

METHODS: Fourteen consecutive female patients of reproductive age (20-45) either with liver biopsy proven NAFLD (50%) or abdominal ultrasound (US) consistent with steatosis together with elevated ALT levels (50%) were screened for PCOS using 2003 Rotterdam consensus meeting criteria. Other causes of hyperandrogenism were excluded. All subjects underwent relevant questionnaire and clinical exam together with hormonal assays, pelvic (1) or transvaginal US (13) and were screened for evidence of the metabolic syndrome.

RESULTS: Ten out of fourteen women with NAFLD matched 2003 Rotterdam consensus meeting diagnostic criteria for PCOS (71%). Eighth women suffered from oligo/ amenorrhoea, nine women manifested presence of hyperandrogenism and six had history of infertility. Three of ten patients with PCOS also had type 2 diabetes mellitus. Women with PCOS and NAFLD had higher triglyceride and cholesterol

and lower HDL level than group without PCOS. Five patients with NAFLD and PCOS had documented fibrosis on liver biopsy, indicative of more advanced liver disease.

CONCLUSIONS: We found evidence of PCOS in the majority of subjects with NAFLD. Women with NAFLD should be routinely screened for presence of PCOS, Diabetes mellitus and metabolic risk factors for cardiovascular disease. Equally, women with PCOS should be screened for NAFLD. Evaluation for liver disease should be considered at an earlier age in some women with PCOS particularly those with an evidence of metabolic syndrome

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Long term maternal cigarette smoke exposure contributes to glucose intolerance in offspring independent of maternal diet

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In humans, maternal smoking is associated with preterm delivery and low birth weight, and an increased risk of obesity in offspring. Evidence from animal and human studies suggests that intrauterine smoke exposure may alter neuroendocrine mediators involved in the regulation of energy homeostasis. Intrauterine undernutrition due to the anorectic effects of nicotine and hypoxia has been suggested to contribute. In humans, smoking per se leads to abdominal obesity and insulin resistance. We hypothesized that maternal smoking would lead to increased adiposity and glucose intolerance in offspring, which could be exaggerated by maternal dietary obesity. Female Balb/c mice (7wk) were either cigarette smoke exposed (SE, 2 cigarettes /day, 5 days/week) or sham exposed for 5 weeks before mating. Within each group, half were fed a high-fat diet (HFD, 33% fat) versus chow as control. The same treatment continued throughout gestation and lactation. Female offspring were fed chow after weaning and sacrificed at 12 weeks. Pups were born at similar weights across maternal groups, however at weaning pups from SE+chow, SE+HFD and sham+HFD mothers were 15%, 26%, and 36% heavier than those from sham+chow mothers, respectively. At 12 weeks, offspring from HFD-fed mothers were significantly heavier than those from chow-fed mothers (chow+sham 17.6 ± 0.3g; chow+SE 17.8 ± 0.2; HFD+sham 18.7 ± 0.3; 18.8 ± 0.4, $P < 0.05$ maternal diet effects), and fat mass was significantly greater in offspring from SE+chow, SE+HFD and sham+HFD mothers than those from sham+chow mothers, with significantly higher plasma leptin concentrations in pups from SE+chow mothers only. However, a similar level of glucose intolerance was observed in offspring from cigarette smoke exposed mothers, regardless of diet group. Thus maternal cigarette smoke exposure is an independent factor that disposes offspring to disorders of glucose metabolism. Therefore, smoking cessation during pregnancy is desirable to improve health outcomes in offspring.

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The role of STAT5 in obesity.

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Obesity is a prevalent health issue that is associated with other diseases such as type 2 diabetes, cardiovascular disease, liver and renal diseases and some cancers. Growth hormone (GH) is an important regulator of body composition and adiposity, although the mechanisms involved are unclear. Using a series of mice expressing targeted mutations of the GH receptor (GHR), which result in serially reduced STAT5 activation (1), we have examined the effect of STAT5 signalling on adiposity. The degree of late-onset obesity in these mice can be correlated with loss of STAT5 signalling, characterised by increased body weight, increased fat pad weight, hepatic lipid accumulation and adipocyte hypertrophy. Illumina micro-array analysis revealed differential regulation of a number of key metabolic regulatory genes. STAT5 regulation of these transcripts was confirmed by the expression of a STAT5 constitutively active construct in liver cells, followed by qPCR analysis for specific gene expression. These mice represent a unique model for the study of GH-induced STAT5 activation, and have allowed the identification of key metabolic regulatory genes expressed in a STAT5-dependant manner. This work was supported by the NHMRC.

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Differential effects of acute versus chronic estrogen treatment on energy expenditure in the ovariectomised ewe

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Sex steroids affect body weight, body conformation and food intake, but effects on energy expenditure are unclear. Using sheep, we aimed to determine the effects of acute and chronic estrogen treatment on 1) thermogenesis in muscle and fat tissues and 2) pathways involved in fuel repartitioning in muscle. The latter involved measurement of phosphorylation of AMP-activated protein kinase (AMPK) and Akt. For thermogenic measurements, temperature probes (set to record every15min) were implanted into retroperitoneal fat, gluteal fat, and skeletal muscle of the hind limb. Sheep ($n = 6$) were placed on a feeding regime (fed between 1100-1600h) to entrain a postprandial thermogenic response. For acute treatment, either vehicle (peanut oil) or estradiol benzoate (EB: 50µg) was injected (i.m.) at 0900h. The experiment was repeated and muscle biopsies were taken post-mortem (at 1400h). For chronic treatment, 3x3cm estradiol-17β implants were inserted (s.c.) for 1 week and controls received blank implants. Food intake was measured and blood samples were taken to measure follicle stimulating hormone (FSH) levels as an indication of the effectiveness of estrogen delivery. Chronic estrogen treatment reduced ($P<0.05$) food intake, but there was no effect of acute EB treatment. Acute EB treatment influenced thermogenic output in muscle and fat tissues, but there was no effect of chronic treatment. Injection of EB immediately increased ($P<0.05$) thermogenesis at all three sites and blocked the post-prandial response. Western blot analysis of muscle tissue showed that acute EB treatment increased the activity of p-Akt(Thr-308) ($p <0.05$) with a lesser effect on p-AMPK ($p = 0.06$), but had no effect on p-Akt(Ser473). Plasma FSH levels were reduced ($P<0.05$) with

chronic estrogen treatment. These data demonstrate that estrogen exerts acute effects on thermogenesis in fat and muscle tissues and affects pathways that are involved in glucose utilisation in muscle.

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RFRP-3 neurons project to hypothalamic nuclei and provide synaptic input to gonadotropin releasing hormone (GnRH) cells in the ovine brain

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We have identified a gene sequence in the ovine brain that encodes a peptide known as RFRP-3 (1). This is a mammalian equivalent of Gonadotropin Inhibitory Hormone (GnIH) discovered in birds. This peptide is produced in neurons within the paraventricular nucleus (PVN) and dorsomedial nucleus (DMH) of the ovine hypothalamus (1). The aims of the present work were to determine 1) whether RFRP-3 neurons project to other hypothalamic nuclei and 2) whether RFRP-3 neurons make contact with gonadotropin releasing hormone (GnRH) neurons in the preoptic area. Reterograde tracing was used for the first aim and double label immunohistochemistry for the second aim. A retrograde tracer (FluoroGold) was injected into the lateral hypothalamic area (LHA, n=5), the arcuate nucleus (ARC, n=3) or the ventromedial nucleus (VMN, n=4). The number of retrogradely labeled RFRP-3 neurons was counted. The majority of RFRP-3 neurons in either the PVN (54%) or the DMH (61%) projected to the LHA with lower percentages directed to the VMN (PVN =37% and DMH =36%) and the ARC (PVN=29 % and DMH =17%). In order to address the second aim, a double labeling procedure employing both RFRP-3 antibody (1) and a GnRH antibody were applied to sections through the preoptic area of 6 ewes. When examined at the light microscope level using z-stacks, 63% of GnRH cells in the medial preoptic area were seen to receive close appositions (presumptive synaptic contacts) from RFRP-3-positive fibres. We conclude that RFRP-3 neurons 1) project to hypothalamic regions involved in regulation of reproduction and appetite/energy balance and 2) provide direct synaptic input to GnRH providing a means for negative regulation of reproduction.

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An investigation of the threshold for the development of ketosis with a low carbohydrate diet

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Background: In recent years, low-carbohydrate "ketogenic" diets have received much attention as a means of rapid weight loss. However, the degree to which carbohydrates must be restricted in order for ketosis to occur remains unclear.

Aim: The aim of this study was to determine the threshold of carbohydrate intake below which ketosis will occur in overweight and obese subjects.

Design: Twelve healthy overweight or obese [mean (± SEM) body mass index 34.3 ± 1.1 kg/m^2] men (n=5) and women (n=7) aged 61.3 ± 1.4 years underwent 3 four-day periods of carbohydrate restriction to varying degrees (60, 110 or 150g) in random order, with minimal variation in dietary protein and fat content. Fasting plasma β-hydroxybutyrate and urinary ketones were measured on days 1, 3 and 5 of each diet period.

Results: The 4-day carbohydrate restriction periods resulted in an average weight loss of 2.1 ± 0.2 kg ($p<0.001$), with no significant difference between diets. Significant increases in β-hydroxybutyrate were seen between days 1 and 5 in all 3 diet groups. At day 3, β-hydroxybutyrate was significantly higher in the 60g/day carbohydrate group (0.39 ± 0.05 mmol/L) than the other 2 groups (110g 0.24 ± 0.03; 150g 0.23 ± 0.02 mmol/L; $p\leq0.022$). This trend persisted at day 5 although the difference no longer reached statistical significance ($p=0.091$ compared with 110g; $p=0.051$ compared with 150g). No significant differences in urinary ketones were found between the dietary groups.

Conclusion: In the short-term, modest restriction of daily dietary carbohydrate intake to 160g is sufficient to cause mild ketosis in overweight or obese subjects.

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Maternal high fat feeding leads to obesity in offspring independent of post-weaning diet

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An adverse prenatal environment may induce long-term metabolic consequences, in particular obesity and leptin and insulin resistance. Although the effects of developmental programming have been extensively characterized in models of maternal nutrient deprivation, there is a relative paucity of data on effects of maternal high fat (HF) feeding on subsequent health of offspring. The present study investigated the effects of maternal HF nutrition on growth and metabolism in offspring. Virgin Wistar rats were assigned to 1 of 3 experimental groups: 1) Controls (CONT): dams fed a standard chow diet pre-conceptionally and throughout pregnancy and lactation; 2) MHF: dams fed a HF diet from their weaning and throughout conception, pregnancy and lactation, and 3) PLHF: dams fed a chow diet until conception, then fed a HF diet throughout pregnancy and lactation. At birth, MHF and PLHF pups were lighter and were hypoleptinemic and hypoinsulinemic compared to CONT pups. At weaning, offspring were fed either standard chow or HF diet for the remainder of the study (160 days). MHF and PLHF offspring had significantly higher body fat compared to CONT even when fed a standard chow diet and these effects were exacerbated when offspring were fed a HF postnatal diet. The increased adiposity in MHF and PLHF offspring was paralleled by elevated fasting plasma insulin and leptin levels and altered hepatic mRNA expression of the insulin and leptin receptors and PPAR- alpha and -γ. Our data suggest that the obese phenotype that develops in offspring of mothers fed a HF diet is independent of maternal pre-conceptional diet, as MHF and PLHF offspring displayed similar postnatal phenotypes. These data further reinforce the importance of maternal nutrition

during critical windows of development and show that maternal HF feeding can induce a markedly obese phenotype in offspring of both genders completely independent of postnatal nutrition.

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Altered nutrition during suckling in mice: impact on plasma hormones and genes involved in thermogenesis.

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Background: Nutrition during critical periods in early life has been shown to increase the risk of obesity and metabolic disease in adulthood. Recent evidence from our lab suggests that in rats skeletal muscle metabolism can be programmed by altered nutrition during suckling. Here we examined the impact of early under- and over-nutrition during suckling on plasma hormones involved in regulating appetite and metabolism, and mRNA expression of genes important for thermogenesis in brown adipose tissue (BAT) in Swiss mice. *Methods:* Following normal gestation, on day 1 of life mouse litters were adjusted to 19 (under-nourished), 11 (control), or 3 (over-nourished) pups per litter. At weaning (21 days) and adulthood (14 weeks) mice were anaesthetised with ketamine/xylazine (15/30 mg/kg) and killed by decapitation. Trunk (21 day) or cardiac (14 week) blood was taken; organs, BAT and retroperitoneal white adipose tissue (RpWAT) were weighed and snap frozen for mRNA analysis. *Results:* Body weights of under- and over-nourished pups were significantly different to control by 7 and 10 days of age respectively ($P < 0.01$), and these changes persisted into adulthood. Plasma adiponectin and RpWAT mRNA expression were elevated at 14 weeks in under-nourished compared to control mice ($P < 0.05$). Plasma leptin and RpWAT mRNA expression was doubled in 14 week over-nourished mice compared to control ($P<0.01$). Early under-nutrition was associated with elevated uncoupling protein-1 (UCP-1) mRNA expression in BAT at both time points ($P < 0.05$). This trend was also observed in UCP-3 expression. Over-nutrition had no impact on UCP-1 or UCP-3 expression in BAT. *Conclusion:* This study demonstrates the important role of early nutrition on body weight, plasma hormones and thermogenesis where under-nourished offspring had elevated UCP-1 expression suggesting improved thermogenic capacity by altering the functional activity of BAT. This may explain why these animals remain smaller as adults.

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Pituitary and hypothalamic expression of receptors for metabolic factors regulating growth hormone secretion.

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Growth hormone, produced by somatotropes located in the anterior pituitary gland, is an important anabolic hormone. It stimulates tissue growth and maintains normal energy balance and healthy body composition. Growth hormone release is mainly stimulated by growth hormone releasing hormone (GHRH) from hypothalamic GHRH neurons. Multiple factors, however, regulate growth hormone synthesis and secretion. Growth hormone levels decline in overweigh individuals. Given that growth hormone is a lipolytic and anabolic hormone it is likely that reduced levels of growth hormone secretion may promote additional weight gain and obesity. Obese individuals do not respond to stimuli of growth hormone secretion, including GHRH, somatostatin, ghrelin or synthetic analogues of growth hormone secretion (GHS). As body fat increases, levels of circulating free fatty acids (FFAs) increase while ghrelin and adiponectin, both key metabolic regulatory hormones, decrease. The relationship between growth hormone and these metabolic regulatory factors is unclear. It is likely that these compounds drive the diminished level of growth hormone secretion in overweight and obese individuals.

Evidence regarding the expression of receptors for FFAs (G-protein coupled receptors (GPR)-40 and -120), adiponectin (Adipo-R1 and Adipo-R2) and ghrelin (growth hormone secretagogue (GHS) receptor) within the hypothalamus is inconsistent. Little evidence regarding the expression of these receptors in somatotropes and GHRH neurons exist. Our preliminary data suggests that receptor expression for these metabolic factors vary. For example, GPR-120 and not GPR-40 is expressed in rat the pituitary gland and the GH3 somatotrope cell line. Using rtPCR, the current study mapped the expression of receptors for growth hormone, GHRH, somatostatin (SSTR-1 to -5), FFAs (GPR-40 and -120), adiponectin (Adipo-R1 and –R2) and ghrelin (GHS receptor) in micropunch-dissected areas of the hypothalamus associated with the control of growth hormone secretion, and whole pituitary glands.

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Modulation of macrophage fatty acid content and composition by varying triglyceride concentration in vitro

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Background: Macrophages in arterial walls accumulate fatty acids (FA) leading to the development of atherosclerotic plaques which progress to cause heart attacks or strokes. However, mechanisms underlying macrophage lipid accumulation and foam cell formation are often studied without accounting for risk factors such as dyslipidemia.

Objective: We sought to investigate the effect varying concentrations of triglyceride (TG) on macrophage FA accumulation and expression of cholesterol efflux proteins.

Design: Monocytes obtained from the Australian Red Cross Blood Service (ARCBS) were cultured in media supplemented with 10% sera containing either low (0.7 mmol/L) or high (1.4 mmol/L) TG. The resulting monocyte-derived macrophages (MDMs) were harvested after 10 days for analysis of FA content and composition and protein levels.

Results: Using Nile red staining, two phenotypes were observed. High TG in media resulted in MDMs with greater intracellular lipid content compared with MDMs cultured with low TG. Analysis of macrophage FA content using gas chromatography confirmed that MDMs in high TG had increased total FA compared with those in low TG (876 μg/mg protein vs 652 μg/mg protein). Compositional analysis revealed that MDMs in high TG had more C16:0, C18:1 and C18:2 than those with low TG. A novel finding was that FAs were primarily stored as TG instead of CE independent of whether MDMs were grown in a TG poor or CE rich environment. The key cholesterol efflux proteins ABCA1 and ABCG1 appeared to be augmented when high TG concentrations were present in the media while the scavenger receptor CD36, involved in lipoprotein uptake, was downregulated.

Conclusions: Culturing MDMs in conditions of high versus low TG influences macrophage FA content and composition, and levels of regulatory proteins. Replicating *in vitro* the dyslipidemia characteristic of Type 2 diabetes *in vivo* may provide an informative model for investigation of atherogenesis.

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Programming adverse metabolic profile in male progeny by different levels of maternal overnutrition

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The maternal nutritional state exerts an important influence on the development of hypothalamic appetite regulators in offspring and this is modulated by leptin. To examine the relationship between the degree of maternal overfeeding and the risk of obesity in offspring, we generated three groups of F1 female rats with different levels of nutrition. F0 founders were fed chow (C) or high fat diet (HFD). F1 females of chow fed F0 dams were raised in small (CS) or normal (CN) litters and fed a chow diet; while F1 females of HFD fed F0 were raised in normal litters and fed HFD (HN). These three F1 groups were mated and at weaning (20 days), F2 offspring were fed either chow or HFD diet, yielding 6 groups: CN-chow, CN-HFD, CS-chow, CS-HFD, HN-chow and HN-HFD (n=12-17). At weaning, F2 HN offspring were significantly heavier than CN offspring with increased fat mass, plasma leptin, triglycerides ($P<0.001$), and insulin ($P<0.05$) . In adulthood (21 weeks), there were significant effects of maternal HFD and small litter size on body weight, fat mass and caloric intake (all $P<0.01$). Offspring of HN dams consuming chow or HFD were 16% and 19% heavier with 100% and 62% increases in total fat mass respectively, compared with CN offspring . CS offspring consuming chow or HFD had 11% and 3% increases in body weight, 50% and 10% increases in total fat mass respectively compared with CN offspring. Importantly, offspring of HN dams showed 3 and 1.6 times elevated leptin levels when they consumed chow and HFD respectively ($P<0.01$). Our data suggest that the degree of obesity in F1 can program adiposity to F2 offspring, with a greater impact of HFD induced maternal obesity than that induced by early overfeeding due to small litter size. Additive effects were observed when F2 animals consumed HFD.

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Dietary Fat Intake and Sleep Durationi n Chinese Adults

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Background: Many recent studies have highlighted the complex interaction between sleep duration, food intake and metabolic balance. Although a causal link is yet to be established, emerging evidence suggests that short sleep duration may alter the balance between energy intake and energy expenditure. Thus far, most research has focussed on the link between sleep duration and carbohydrate metabolism. The role of sleep duration on fat intake and vice versa remains relatively unknown.

Objective: The aim of this analysis was to determine whether there exists a significant association between sleep duration and fat intake.

Design: Data from 2828 adults living in Jiangsu province, China collected during a national survey of nutrition and health conducted in 2002.

Results: The analysis showed a statistically significant association between sleep duration and fat and carbohydrate intake but not protein or fasting blood glucose. Those who slept less than seven hours a day had significantly higher ($p=0.005$) percentage of energy from fat intake than those who slept 7 to 9 hours per day. Analysis of the influence of high fat intake upon sleep demonstrated a trend to reduced sleep duration between the highest and lowest quartile of fat intake ($p =0.056$).

Conclusions: To our knowledge, this is the first time data from a large cross-sectional study has shown an association between decreased sleep duration and increased fat intake in humans. Given the trend towards decreased sleep duration in modern societies and the parallel obesity epidemic, the significance of this association warrants more research.

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Expression of gene for melanin concentrating hormone, but not the gene for orexin is increased with intrauterine growth restriction (IUGR) of sheep fetuses.

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IUGR alters the allometry of tissue growth during fetal life and postnatal metabolic functions. The lowered body weight may have consequences in terms of the expression of genes in the hypothalamus that regulate homeostatic systems. These systems comprise a range of cells that regulate appetite and energy expenditure. In the lateral hypothalamus, cells that produce the orexigenic peptides ORX or MCH are important in this regard. Emerging data from our laboratory show that ORX and MCH gene expression changes with genotype (fat or lean) and with seasonal changes in metabolic function. We hypothesized that ORX and/or MCH gene expression is affected by IUGR. We used a physiological model in which multiple pregnancy (≥ 5 fetuses) leads to IUGR in some fetuses. Finn x Dorset ewes were mated to rams of the same breed to produce multiple pregnancies. Ultrasound measurement of metacarpal bone length determined the size of fetuses. The pregnant ewes were euthanased at day 131 gestation and the fetal brains were processed for *in situ* hybridization. Body weights of the s mall (IUGR) and large fetuses (n=9/group) were 2411.1±100.4 and 3891.1±54.4 g (P< 0.001) respectively and the placental weights were 205.3±15.1 and 378.1±34.2 g (P< 0.001), respectively. Plasma leptin, insulin and IGF-1 levels were lower (P<0.05) in small fetuses. ORX expression was similar in the two groups but the number of MCH expressing cells in the lateral hypothalamus was lower (P<0.05) in small fetuses. MCH expression was strongly correlated with body weight (R = + 0.84, P = 0.0001). This occur s in spite of lowered leptin, insulin and IGF-1 levels, which would be expected to cause an increase in the expression of genes for orexigenic systems. We conclude that IUGR reduces MCH expression but not ORX expression and further studies will determine whether this effect has consequences in later life.

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Serum from a hyperlipidemic patient results in altered macrophage lipid content, fatty acid composition and gene expression

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Background : To investigate mechanisms underlying foam cell formation, macrophages are cultured in high concentrations of chemically oxidised or altered lipoproteins. We aimed to develop a more physiological model of macrophage to foam cell transition using human sera with contrasting endogenous lipid profiles.

Methods : Human monocytes were cultured in media supplemented with 10% sera from a subject with severe hyperlipidemia (hyperlipidemic) or sera from subjects with normal lipids (control). After 12 days, the resultant human monocyte-derived macrophages (hMDMs) were stained with Nile Red to assess lipid content and harvested for analysis of fatty acid (FA) levels using gas chromatography (GC). Levels of proteins involved in macrophage lipid metabolism were measured with Western blotting, and mRNA levels with real-time PCR.

Results: Two distinct phenotypes were observed on staining with hMDMs cultured in hyperlipidaemic sera displaying noticeably greater intracellular lipid than control macrophages. FA quantitation with GC indicated that hMDMs cultured in hyperlipidaemic sera possessed 6-fold higher total FA content than control macrophages. Analysis of FA composition revealed higher ratios of C16:1/16:0, C18:1/18:0 and C18:2/18:0 in hMDMs cultured with hyperlipidaemic sera, indicating a greater proportion of unsaturated FA. Compared with control macrophages, hMDMs cultured in hyperlipidaemic sera had a three-fold increase in CD36 scavenger receptor (CD36) and a two-fold increase in Stearoyl-CoA Desaturase (SCD) proteins. CD36 and SCD mRNA expression were upregulated three- and five-fold respectively in hMDMs cultured in hyperlipidaemic sera compared to controls.

Conclusion: Culture of hMDMs under conditions which reflect hyperlipidaemia found in a patient resulted in increased accumulation of FA and a greater proportion of unsaturated FA. Increased CD36 and SCD mRNA and protein levels were noted which could have facilitated macrophage lipid uptake and conversion of saturated FA to monounsaturated FA respectively. Macrophages reflecting *in vitro* hyperlipidemia encountered *in vivo* are informative models for studying mechanisms of atherogenesis.

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The Power of the Mind: an evaluation of the placebo effect in a study of GH on physical performance

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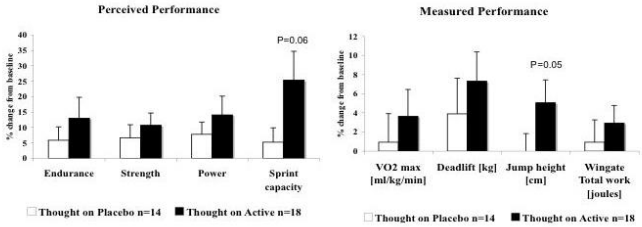
Doping with GH to improve sporting performance is prevalent despite a lack of evidence of any performance-enhancing effect. Perceived or real benefits of GH on performance may be due to a placebo effect. The aim was to evaluate the perceived and actual benefits in subjects allocated to placebo treatment in a double-blind controlled study assessing the effects of GH on physical performance.

64 recreational athletes, randomly allocated to placebo (n=32) or GH (2 mg/d, n=32) indicated at the end of treatment before testing performance whether they thought they received placebo (correct guess) or active GH treatment (incorrect guess). Physical performance measured (i) endurance: VO_2 max, (ii) strength: dead lift dynamometry, (iii) power: vertical jump height, and (iv) sprint capacity: Wingate test. Perceived benefit was assessed by a self-evaluation questionnaire for each performance type (analogue scale 1-10) without knowledge of physical performance measures. Statistical analysis of placebo-treated subjects was performed using a 2-sample Wilcoxon rank-sum (Mann-Whitney) test. Data are presented as change from baseline and expressed as mean ± SE.



Mean perceived performance scores were higher for incorrect guessers compared to correct guessers, however there was a trend to significance only for sprint capacity. Mean changes in measured performance were higher with a significant increase for jump height ($p=0.05$). More men than women believed they were on active treatment (81% vs 31%, $p<0.01$). Compared to baseline, men who guessed incorrectly had significantly improved self-assessed scores ($p<0.03$) for all categories and also increased measured performance for VO_2 max ($p=0.03$) and strength ($p=0.06$). For women, there were no significantly greater outcomes for those who guessed incorrectly compared to correctly.

In summary, athletes in the placebo group who believed they were on active treatment not only had a perceived improvement on performance, but also in measured physical performance. The effect was greater in men. In conclusion, a placebo effect may contribute to perceived and actual performance-enhancing effects of GH, particularly in men.

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Analysis of Glucocorticoid-Antagonised Retinoic Acid-Responsive Genes during Pre-Term Lung Development

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Glucocorticoid (GC)- and retinoic acid (RA) signaling are both involved in the processes of lung epithelium maturation and alveolarisation. More specifically, glucocorticoid treatment during late gestation induces differentiation of epithelial precursor cells into AEC (alveolar epithelial cell) type I and increases the expression of surfactant proteins A, B, C and D and CCSP. The result is an alveolar epithelium with a thinner air-blood barrier that is more suitable for aeration. Hence, the common practice of glucocorticoid administration to mothers undergoing premature labour. Most preterm infants born before 29 weeks of gestation would not survive without glucocorticoid treatment, due to respiratory insufficiency. However, glucocorticoids impair alveolarisation postnatally in rodents, a process that can be reversed by administration of all-*trans* RA, which activates transcription of retinoic acid response element (RARE) -containing genes through interactions with retinoic acid receptor (RAR) and retinoid X receptor (RXR) heterodimers. The cellular pathways inducing and regulating the process of alveolarisation are not well characterised, but it is clear that they involve both GC- and RA signalling.

In this study we have developed an *ex vivo* lung explant system, where lungs from E18.5 Glucocorticoid Receptor (GR) –null mice have been exposed to a-*t*-Retinoic Acid. Whole genome microarrays and quantitative Real-Time PCR have been utilized to identify GR-antagonised RA-responsive genes. These studies will provide a better understanding of the processes involved in alveolar development and the specific role GC- and RA-signalling play in alveolarisation in the lung and would have impacts on the procedures applied in the care of premature infants, and hence reducing the number and severity of the resulting patients suffering from respiratory distress syndrome.

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Rev-erbbeta (NR1D2) Regulates SREBP-1c mRNA Expression in Skeletal Muscle Cells

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The nuclear hormone receptor Rev-erbbeta, belongs to the NR1D subgroup of nuclear receptors [which also includes Rev-erbalpha] and operates as a transcriptional silencer. The NR1D subgroup is abundantly expressed in skeletal muscle and other peripheral tissues (including liver, kidney, white and brown adipose) that are actively involved in lipid metabolism. We previously demonstrated that exogenous expression of Rev-erbβΔE in murine skeletal muscle cells increased SREBP-1c mRNA expression. We validated these *in vitro* observations by injection and electrotransfer of an expression (and control) vector driving Rev-erbβΔE expression into mouse tibialis cranialis muscle and observed modulation of SREBP-1c mRNA expression. Interestingly, transfection of siRNA expression vectors targeting Rev-erbβ in skeletal muscle cells resulted in aberrant SREBP-1c and IL-6 expression in concordance with our previously published observation. Transient transfection and chromatin immuno-precipitation (ChIP) assays demonstrated that Rev-erbβ regulates the SREBP-1c promoter.

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The classical signalling pathway of the androgen receptor is required for androgen mediated erythropoiesis

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It is well documented that androgens stimulate erythropoiesis however the mechanisms are not clear. Among the proposed mechanisms are 1) that stimulation of erythropoiesis by androgens is mediated by the androgen receptor (AR) and 2) that this stimulation occurs by upregulation of erythropoietin (EPO). We are using an androgen receptor knockout (ARKO) mouse generated in our laboratory in which the genomic actions of the AR have been ablated, to study the effects of androgens on erythropoiesis. We treated ARKO male mice and their wt littermates with 5 α-dihydrotestosterone (5 α -DHT) for two weeks. Pre-treatment red blood cell parameters (red blood cell number, haemoglobin, haematocrit and reticulocytes) were determined in the blood of 6 week old ARKO male mice and wt male and female littermates. We observed a 22% decrease in the percentage of reticulocytes ($p<0.05$) in wt female mice compared with wt male mice. No other differences were noted between groups. Silastic implants, empty or containing 5 α -DHT, were inserted subcutaneously at the nape of the neck of 7 week old ARKO male mice and wt littermates. At the end of the two week treatment period red blood cell number, haemoglobin and haematocrit were increased by between 5 and 13% in response to 5 α -DHT ($p<0.05$, n=5-9 per group) in wt male and female mice but NOT ARKO male mice or wt mice treated with vehicle implants. Preliminary data shows that there is no difference in serum EPO levels between wt mice treated with vehicle or 5 α -DHT. These findings support the hypothesis that the classical signalling pathway of the AR is essential for androgen mediated erythropoiesis.

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Nuclear Receptor Gene Expression in Granulosa Cell Tumours of the Ovary

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The human nuclear receptor (NR) superfamily consists of 48 members that play roles in many processes including development, metabolism and homeostasis. In addition to their normal functions, NRs contribute to the pathogenesis of endocrine-related diseases such as breast and prostate cancer, diabetes and obesity. They are therefore ideal targets for drug discovery. Granulosa cell tumours (GCT) of the ovary are malignant sex-cord stromal tumours which synthesise and respond to both steroid and peptide hormones. We (1) and others have previously demonstrated abundant expression of NR superfamily members (ERα, ERβ, SF-1 and LRH-1) in GCT. In this study, we sought to characterise expression of all 48 NR superfamily members in 16 GCT and the GCT-derived cell lines, COV and KGN. RNA was extracted from samples of each and analysed using the TaqMan® Nuclear Receptor Gene Signature Array (Applied Biosystems) which contains all 48 human nuclear receptors. In the GCT samples the previous findings were confirmed, with relative levels of gene expression found to be SF-1>ERβ>LRH-1>ERα. Of the 48 NRs, expression of COUP-TFII was the highest. COUP-TFII is an orphan receptor that plays a role in steroidogenesis. Of the steroid receptors, expression levels of the MR and GR were the lowest, whilst those of the AR and PR were intermediate. Of the type 2 receptors, PPARγ showed prominent expression. PPARγ has been shown previously to be highly expressed in granulosa cells and to modulate estrogen synthesis. This may be of therapeutic relevance. Of the other receptors, expression of TRα, RARα, PPARδ, RXRα, EAR-2, COUP-TFI, TR4, LXRβ and REV-ERBα were comparable to, or higher than, ERα. The two cell lines which represent both pure cell populations and advanced disease stage are being analysed. This is the first systematic assessment of NR gene expression in human GCT.

(1) Chu S et al (2005) JCEM 85:1200-1205

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Aldosterone-Regulated Genes in the Duodenum

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The adrenal steroid hormone, aldosterone, acts through the mineralocorticoid receptor (MR) in epithelial tissues to regulate genes involved in sodium transport. We have found abundant expression of the MR in the duodenum, a tissue not usually considered to be involved in aldosterone-mediated sodium transport. Last century, peptic ulcer disease was treated with carbenoxolone (Duogastrone®). The beneficial effects were reversed by the MR antagonist, spironolactone; the mechanism of this MR-mediated effect in the upper gastrointestinal tract remains unexplained. This study aims to identify aldosterone-induced genes in the duodenum, in order to gain insights into the role of the MR in duodenal physiology and pathophysiology. Adrenalectomised rats were treated with a single dose of aldosterone or vehicle for 45 minutes. Duodenal RNA was extracted from rats showing a robust colonic *Sgk1* mRNA response to aldosterone, or low levels after vehicle treatment, and subjected to suppression subtractive hybridisation. Clones identified as being regulated by aldosterone were sequenced to determine their identity, and their responses to aldosterone were assessed using Northern blot analysis. *Sgk1* was found to be also upregulated in the duodenum. The most striking result was found for the intestinal alkaline phosphatase-II (IAP-II) gene, *Alpi2*. The mRNA levels were clearly increased relative to baseline at 45 minutes post-aldosterone, but returned to baseline by 4 hours. We have cloned fragments of the other three rat alkaline phosphatase genes in order to confirm the specificity of the response, and also to examine their responses to aldosterone. The identification of *Alpi2* as an aldosterone-regulated gene was unexpected. Despite many years of study, the functions of the APs remain remarkably poorly defined. We postulate that IAP-II is unlikely to play a role in sodium transport but may be involved in acid-base homeostasis, thereby contributing to the healing effects of carbenoxolone in peptic ulcer disease.

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Deletion of mineralocorticoid receptors from macrophages protects against mineralocorticoid-induced hypertension and cardiac fibrosis

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Activation of mineralocorticoid receptors (MR) in the cardiovascular system in the context of a high salt diet produces an early vascular inflammatory response followed by an extensive fibrotic response. Macrophages play a central role in orchestrating an inflammatory response; they are recruited to the myocardium as part of the inflammatory response in the mineralocorticoid/salt model. Macrophages express MR but not the MR-specificity conferring enzyme, 11βHSD2, thus under normal circumstances MR within macrophages are occupied by physiological glucocorticoids. In the present study we explored the role of macrophage MR in determining acute (8 days) and chronic (8 weeks) pathological responses in the mineralocorticoid/salt model. The Cre/LoxP-recombination system was used to specifically delete MR from monocytes/macrophages using the lysozyme M promoter to drive Cre expression. Eight-week-old mice from each genotype (wild-type (WT) and macrophage MR-null) were uninephrectomised, given 0.9 % NaCl solution to drink and treated for 8 days or 8 weeks with either vehicle or deoxycorticosterone (DOC, 7 mg/mouse/week). Deletion of MR from macrophages significantly reduced baseline mRNA expression of endothelial nitric oxide synthase (eNOS), transforming growth factor-β (TGF-β), collagen type-I (COL-1), connective tissue growth factor (CTGF), osteopontin, NADPH oxidase 2 (Nox2) and plasminogen activator inhibitor type-1 (PAI-1) at 8 days, compare to WT. DOC treatment for 8 days did not alter mRNA expression of these genes in either genotype. DOC-induced macrophage recruitment was not affected in macrophage MR-null mice at 8 days or 8 weeks. Interestingly, deletion of MR from macrophages protected against the characteristic DOC-induced increases in systolic blood pressure and cardiac fibrosis seen in WT mice at 8 weeks. In conclusion, we have demonstrated a novel and significant role for macrophage signalling in the regulation of hypertension and cardiac fibrosis. Furthermore, we have shown that MR signalling regulates basal monocyte/macrophage function, but not DOC-induced macrophage recruitment.

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Identification of Ligand-Specific Coactivators of the Mineralocorticoid Receptor

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The mineralocorticoid receptor (MR) responds to two physiological ligands, aldosterone and cortisol. In epithelial tissues, aldosterone selectivity is determined by the activity of 11 b -hydroxysteroid dehydrogenase type II. In other tissues, including the heart and regions of the CNS, cortisol is the primary ligand for the MR; in some tissues it may act as an antagonist. The structural determinants of tissue and ligand-specific MR activation have yet to be identified. So we sought to identify co-regulatory molecules that interact with the ligand-binding domain (LBD) of the MR. The human MR-LBD has been used to screen a yeast-2-hybrid kidney cDNA library in the presence of aldosterone and cortisol. 56 clones were identified that interact with the MR-LBD including the known coactivators, SRC-1 and PGC1 a ; most interact in the presence of both ligands. Clones which exhibited an interaction the presence of one but not both ligands were further examined in a mammalian-2-hybrid assay and as full length clones in a cotransfection assay using the MMTV-luciferase reporter. Eight independent clones were identified which interact only in the presence of aldosterone and one which responded with cortisol but not aldosterone. In the M-2-H assay, these clones exhibited a relative rather than absolute differential ligand-dependent interaction with the MR. This interaction is AF-2 dependent although not all proteins contain an LxxLL motif. Two clones, when expressed as full-length cDNA's exhibit this differential ligand sensitivity in a transactivation assay. Specificity has been assessed with the other steroid receptors. These differential interactions provide evidence of the adoption of ligand-dependent conformations by the MR LBD. The successful identification of ligand-specific interactions of the MR may provide the basis for the development of novel MR ligands with tissue- and or ligand-specificity.

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Analysis of Different Glucocorticoid Receptor Gene Promoter Activities in the Mouse Brain

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Glucocorticoids (GCs) are a class of steroid hormone that play an essential role in the regulation of biological processes such as growth, development, metabolism, behaviour and apoptosis. In the brain, glucocorticoid (GC) hormones modulate neuroendocrine activity, behavioural adaptation and memory formation. The actions of GCs are mediated via the widely expressed Glucocorticoid Receptor (GR), whose gene is composed of 9 exons. The GR is encoded by exons 2 - 9 and is expressed from multiple untranslated exon 1s to yield at least 11 alternatively spliced transcripts in humans and at least five in mice (1A-1H). Transcripts initiating from the GR1A promoter had previously only been localised to the cortex of the brain and to T-lymphocytes. We now report detection of transcripts initiating from the GR1A promoter in the anterior lobe of the pituitary. In T-lymphocytes the GR1A promoter is implicated in increasing sensitivity to Glucocorticoid Induced Cell Death (GICD). However, the role of the GR1A promoter activity in the brain is unknown. In the brain, particularly in the cortex, and also in the hypothalamus and pituitary (components of the Hypothalamic-Pituitary-Adrenal axis) GCs and their receptors have a key role in the response to stress. We observed a 2.5 fold increase in the level of GR1A promoter usage in the pituitary in response to treatment with the synthetic GC Dexamethasone. It is possible that a tissue/cell specific increase in activity of the GR1A promoter during periods of elevated levels of circulating GCs may help to make those cells more sensitive to these rising levels of GCs and serve as a fine tuning mechanism to aid in a rapid return to the normal state after stress. Deregulated levels of GCs or their receptors within the brain is associated with age related dementia and an abnormal response to stress.

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ROR alpha 4 is phosphorylated by GSK 3 beta in vitro

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Studies estimate that more than half of all Australian women (52%) and two-thirds of men (67%) are overweight or obese . Despite of changing diet and lifestyle, therapeutic options for the treatment of obesity are limited. The orphan nuclear receptor, Retinoic acid receptor-related Orphan Receptor alpha (ROR alpha), has been identified as a regulator of genes involved in lipid metabolism. Moreover, *staggerer* mice (*sg*/*sg*), that display decreased and dysfunctional ROR alpha expression, are dyslipidemic. In this context, it has been recently demonstrated that these animals are resistant to diet-induced obesity. Surprisingly, very little is known about the regulatory pathways modulating ROR alpha transcriptional activity. Most orphan nuclear receptors are regulated by posttranslational modifications, such as ubiquitination or phosphorylation, that influence their DNA binding affinity, and ability to recruit cofactors or protein stability. In this context, we have demonstrated that ROR alpha is phosphorylated by ERK 2 on a threonine residue at amino acid position 128. Pilot studies indicated ROR alpha is also phosphorylated by GSK 3 beta in vitro. This kinase is known to influence glucose uptake, glycogen synthesis and lipid homeostasis. We have identified 11 potential phosphorylation sites for GSK 3 beta , and have systematically mutated these sites by alanine mutation. Subsequently, we evaluated the effect of these mutations on ROR alpha mediated trans-activation of a synthetic reporter gene in fibroblast and muscle cells.

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Glucocorticoids regulation of adipocyte-specific genes

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Obesity is an increasingly important health problem in the Western world and is caused by a number of environmental and genetic factors. An important factor that plays a role in regulating adipose development in obesity the glucocorticoids. These steroid hormones are secreted in the body and are elevated in response to stress. Changes in adiposity in patients receiving glucocorticoid therapy and in Cushingoid patients indicate that glucocorticoids potentially play a role in regulating adipose tissue development and function. Previous studies have shown that glucocorticoids play a role in regulating appetite, adipocyte differentiation and in adipose tissue accumulation via alteration of the activity of specific genes such as leptin, UCP1 and adiponectin. This study examined the adipose phenotype and the role of glucocorticoids in regulating adipocyte function in glucocorticoid receptor (GR)-deficient mice, a mouse model of glucocorticoid resistance. Adult GR-deficient mice and wildtype (WT) controls were given food ad libitum and weights recorded weekly for a period of 6 months. Adipose tissue from various sites were obtained and analysed for histology. Adipose tissue mRNA levels for UCP1, leptin and adiponectin were determined by quantitative RT-PCR in GR-deficient and WT mice at baseline and three hours after dexamethasone (DEX) treatment. Preliminary results indicate that the GR-deficient mice were significantly lighter than WT mice, and there were morphological differences observed in brown adipose tissue of GR-deficient mice. Preliminary quantitative RT-PCR analysis showed significantly lower mRNA levels of leptin mRNA at baseline in gonadal adipose tissue from GR-deficient mice. No significant differences were observed in mRNA levels for UCP1, leptin and adiponectin in adipose tissues of GR-deficient and WT mice three hour after DEX treatment. These results indicate that glucocorticoid signalling via GR promotes adiposity and that basal transcription of the leptin gene in gonadal adipose is dependent on GR-mediated signalling.

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The orphan nuclear receptor, RORalpha, regulates the insulin signalling cascade

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Nuclear hormone receptors (NRs) are ligand activated DNA binding proteins which function as physiological sensors to regulate gene expression. Homozygous *staggerer* mice (*sg*/*sg*), with dysfunctional Retinoic acid receptor-related Orphan Receptor alpha (RORalpha) expression in all tissues, display a lean and dyslipidemic phenotype. Moreover, these mice are resistant to diet induced obesity (1). Pilot studies indicated that dysfunctional RORalpha expression was also associated with atypical insulin signalling. To explore this aspect of the phenotype in a more appropriate mouse model, we targeted expression of attenuated ‘dominant negative' RORalpha in skeletal muscle. This peripheral tissue accounts for the majority of glucose disposal, and energy expenditure. Consequently, this lean tissue plays an important role in insulin signalling, and energy balance. Interestingly, preliminary data suggests transgenic heterozygous animals exhibit changes in the expression of key regulators of glucose homeostasis, blood glucose, and serum adipokine levels. We will present data to 'test the hypothesis that the nuclear hormone receptor, RORalpha regulates the insulin signalling cascade and glucose metabolism in skeletal muscle'.

(1) Lau P et al, The orphan nuclear receptor, RORalpha , regulates gene expression that controls lipid metabolism: staggerer (sg/sg) mice are resistant to diet induced obesity.J Biol Chem. 2008 Apr 25.

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Beta-adrenergic signalling induces nuclear receptor (NR) 4A1-3 in metabolic, cardiovascular, endocrine and gastrointestinal tissues

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Nuclear hormone receptors (NRs) are ligand-activated DNA binding proteins which function as physiological sensors to regulate gene expression. The NR4A family of orphan nuclear receptors includes three members, *Nur77, Nurr1* and *Nor-1*. The NR4As respond rapidly to a number of biological and physiological processes including cAMP, stress, fatty acids, growth factors, prostaglandins, peptide hormones, inflammatory cytokines, calcium, phorbol esters and neurotransmitters. Previously we have identified the rapid and robust induction of the NR4A subgroup upon beta-adrenergic stimulation in mouse skeletal muscle *in vitro* and *in vivo*. This was concomitant with several changes in gene expression implicated in lipid and glucose homeostasis and energy expenditure. In a comprehensive study, we have isolated several tissues (1-24 hr) after mice were injected intraperitoneally with isoprenaline. From these studies we have similarly identified the rapid induction (between 1-4 hr) of the NR4As in metabolic, cardiovascular, endocrine and gastrointestinal tissues. Moreover, we have utilized a candidate-based genetic screening approach (Taqman Low Density Arrays - consisting of several genes involved in metabolism and a number signaling pathways) to determine potential downstream targets of the NR4As. In these studies we have identified major changes in several genes involved in lipid, oxidative and glucose metabolism in major metabolic tissues. These studies support a role for the NR4As in the modulation of critical pathways of metabolism in several important tissue systems.

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RFRP-1 and -3 neurons are not hypophysiotropic gonadotrophin inhibitory neurons in the rat.

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An RFamide peptide named gonadotrophin-inhibitory hormone (GnIH), that directly inhibits gonadotrophin synthesis and secretion from the anterior pituitary gland, has recently been discovered in the avian hypothalamus. It is not known if the mammalian homologues of GnIH, RFamide-related peptides-1 and -3 (RFRP-1/3) act in the same way. We used a newly-generated antibody against the rat RFRP precursor combined with retrograde tract tracing to characterize the cell body distribution and fibre projections of RFRP-1/3 neurons in rats and mice. RFRP-1/3-immunoreactive cell bodies were found scattered between the dorsomedial and ventromedial hypothalamic nuclei, with a more dorsal distribution in mice. Immunoreactive fibres were observed in the septal-preoptic area, hypothalamus, mid-brain, brainstem and hippocampus, but not in the external zone of the median eminence. Intraperitoneal injection of the retrograde tracer Fluoro-Gold in rats resulted in the labeling of the majority of gonadotropin-releasing hormone (GnRH) neurons but no RFRP-1/3 neurons. In contrast, intracerebral injections of Fluoro-Gold into the medial preoptic area and CA3 hippocampus resulted in the labeling of 75±5% and 21±8% of RFRP-1/3 cell bodies respectively. To assess RFRP actions at the pituitary in vivo, RFRP-3 was administered as an intravenous bolus to ovariectomized rats and plasma luteinizing hormone (LH) concentration measured at 0, 2.5, 5, 10 and 30 minutes. RFRP-3 had no effects on basal secretion, but GnRH-stimulated LH release was reduced by ~25% at 5 minutes. Together, these observations suggest that RFRP-1/3 is not a neuroendocrine hormone in rodents.

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Loss of cytoplasmic membrane E-Cadherin is associated with nuclear accumulation of E-Cadherin in pituitary tumours

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E-cadherin is part of the cell adhesion complex and loss of the protein is associated with invasion and metastasis in a number of malignancies. Mutations in *CDH1*, the gene encoding E-cadherin have been identified in hereditary diffuse gastric cancer and lobular breast cancer. Loss of E-cadherin cytoplasmic membrane staining has been reported as a marker of invasion for prolactinomas but the mechanism of loss is unclear. Recent studies in other human tumours have reported nuclear E-cadherin associated with loss of cytoplasmic membrane staining suggesting nuclear relocation of the protein.

The objective of this study was to investigate E-cadherin status of pituitary tumours.

Immunohistochemistry using an antibody with specificity to the extracellular domain of E-cadherin was performed in 8 normal and 44 pituitary tumour samples. Strong cytoplasmic membrane staining was present in all normal pituitary samples with loss of membrane staining in 21/44 (48%) of pituitary tumours and weak staining observed in an additional 11 tumours. No nuclear staining was present. Immunohistochemistry using an antibody specific to the cytoplasmic domain identified nuclear staining was in 38/44 (86%) of pituitary tumours which was absent in normal pituitary tissue. Nuclear E-cadherin appeared to inversely correlate with loss of E-cadherin cytoplasmic membrane staining. In contrast to the aberrant protein expression, E-cadherin mRNA expression was reduced in only 2/46 (4%) samples, ascertained by RT-PCR. Pituitary tumours were screened for mutations in the 16 exons of E-cadherin to determine if the abnormal protein observed was the result of a mutation. Five known polymorphisms have been identified but no mutations were detected in 10 of the 16 exons examined to date.

In conclusion, frequent loss of cytoplasmic membrane E-cadherin was identified in pituitary tumours with evidence that this may be secondary to cleavage and translocation of E-cadherin to the nucleus. The mechanism of this is currently unknown.

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Cortisol responses to exercise, endotoxin and wetting stress in sheep: Importance of sex and type of stressor

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The magnitude of the cortisol response to stress in sheep depends on the sex of the animal and the stressor encountered. For instance, females had a greater cortisol response than males to isolation/restraint stress (1) and audiovisual stress (2) and males had a greater cortisol response than females to insulin-induced hypoglycaemia (1). Here, we extended these findings to test the hypothesis that there are sex differences in cortisol responses to exercise, endotoxin and wetting stress.

Blood samples were collected from gonadectomised Romney Marsh rams (n=6) and ewes (n=6) before, during and after imposition of exercise, endotoxin and wetting stress at weekly intervals. For exercise stress, sheep (unconditioned) were run three times around a 0.6km circuit (total 1.8km) at an average rate of 11km/h (first circuit: 3:38 minutes, second circuit: 4:07 minutes, third circuit: 4:51 minutes). For endotoxin stress, sheep were injected with endotoxin (400 ng Lipopolysaccharide/kg body weight i.v.; E. coli 0127: B8, Sigma, St. Louis , MO , USA). For wetting stress, sheep were housed indoors and were sprayed with water from a hand held hose for 30 minutes (rainfall equivalent 1ml/minute).

Females had a greater cortisol response than males to wetting stress (time * sex interaction: P=0.027) but there was no difference between the sexes in the cortisol response to exercise stress (time * sex interaction: P=0.993) and endotoxin stress (time * sex interaction: P=0.983).

These data show that there are sex differences in cortisol responses to wetting stress but not in response to exercise and endotoxin. This confirms that cortisol responses to stress depend on the sex of the animal and the stressor encountered.

(1) Turner AI, Canny BJ, Hobbs RJ, Bond JD, Clarke IJ and Tilbrook AJ (2002) Journal of Endocrinology 173: 113-121
(2) Turner AI, Rivalland ETA, Clarke IJ, Lambert GW, Morris MJ and Tilbrook AJ (2002) Neuroendocrinology 76: 373-380

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Effect of RFRP-3 on gonadotropin synthesis and secretion in ovine pituitary gonadotropes

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Gonadotropin–releasing hormone (GnRH) provides the primary stimulus for the reproductive axis, but recent work has also revealed the existence of gonadotropin inhibitory hormone (GnIH) that acts on pituitary gonadotropes. In sheep, GnIH properties are displayed by a hypothalamic dodecapeptide which is a member of the RF-amide family, namely RFRP-3 (1). One study has reported on the effect of GnIH on gonadotropin synthesis, using an avian form of the peptide (2). The aim of the present study was to determine the effects of ovine RFRP-3 on the expression of genes for gonadotropin subunits in ovine pituitary cells. Pituitary glands were collected from ovariectomized ewes and prepared for culture. The cells were plated at 4-6 x 10^6 cells/well and were treated with either vehicle or GnRH, with and without RFRP-3 treatment. GnRH was given every 8 h for 24 h and RFRP-3 was given for 24h (during GnRH treatment). The supernatant was collected for LH assay and the cells were extracted for semi-quantitative rt-PCR to measure luteinising hormone β (LH β) and follicle stimulating hormone β (FSH β) subunit expression. The experiment was replicated twice, with similar results and the data in table 1 are from one experiment.

Table1. Percentage change in expression in LH secretion, and LH β and FSH β subunit expression (relative to 18S) in pituitary cells treated with GnRH (10^{-9}M) and RFRP-3 ($10^{-9,}$ 10^{-12}M).

GnRH treatment	RFRP-3 Treatment	% change relative to control		
		LH in Medium	LHβ/18S	FSHβ/18S
0	0	-	-	-
10^{-9}M	0	702	627	311
10^{-9}M	10^{-9}M	250	108	22
10^{-9}M	10^{-12}M	356	152	19

We conclude that RFRP-3 acts on pituitary gonadotropes to reduce expression of the gonadotropin subunits.

(1) 1 Clarke et al. Endo, in press, (2008).
(2) 2. Ciccone et al. J Neuroendocrinol, (2004)

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A picture tells a thousand words The Insulin Tolerance Test – Getting the most from the data collected

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The Insulin tolerance test (ITT) is regarded as the 'gold standard' in assessing the hypothalamic-pituitary-adrenal axis in adults. It can be used to assess ACTH/cortisol reserve and growth hormone release which is used to aid decision making by clinicians regarding cortisol and growth hormone replacement.

Though recognized protocols exist for carrying out this dynamic test, this does not mean that staff feel comfortable performing it. The rate of change of blood glucose level (BGL) can be quite variable between patients, which results in staff needing to respond either with glucose to reverse the hypoglycaemia or more insulin to achieve the target.

This variability in individuals is what makes it a test that staff find stressful and anxiety producing and begs the questions:

Can we

- · feel more confident during the procedure
- · improve on the way we gather information
- · improve upon our reaction time
- · make our results more informative

To this end and in a setting of doing regular ITT's, an innovative method of graphing the rapid fall in blood glucose level has been developed. This tool has improved the staff confidence within the unit when performing the test as well assisting new staff to the area in learning about how to perform the test accurately and safely.

Further development has been the production of a 2 page report which details all aspects of the monitoring performed by staff during the test. As a part of this report, a numerical grading of symptoms has been introduced. This visually corresponds with bedside BGL's which ultimately assists in the final interpretation of the procedure.

This more accurate monitoring method has improved the staff confidence and importantly it has reduced the response times to BGL readings that do not follow the normal pattern of fall. An informative report can be produced either electronically or manually in any endocrine setting.

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The Syndrome of Generalised Glucocorticoid Resistance.

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Adrenocorticotropic hormone (ACTH) dependent cortisol excess in the absence of clinical features of Cushing's syndrome represents a diagnostic challenge. We describe two non-related subjects in whom a diagnosis of generalised glucocorticoid resistance has been considered. A 63yo male was referred for hypertension, whilst a 30yo female was asymptomatic. Neither subject manifested clinical features of Cushing's syndrome. Both had elevated cortisol and ACTH levels with an abnormal diurnal rhythm. Cortisol failed to suppress with a low dose dexamethasone suppression test, but did suppress with a high dose test. The rare syndrome of generalised glucocorticoid resistance is characterised by partial insensitivity to glucocorticoids in all tissues, associated in many cases with a mutation in the glucocorticoid receptor (GR) gene, NR3C1. GR is a ligand-dependent transcription factor that is ubiquitously expressed. It mediates negative feedback control within the hypothalamic-pituitary-adrenal axis by circulating glucocorticoids. The syndrome of glucorticoid resistance is therefore accompanied by a compensatory increase in cortisol, mineralocorticoids and adrenal androgens. This may either be asymptomatic or be accompanied by hypertension, hypokalaemia, and/or virilisation. Sequencing of the NR3C1 coding exons in both our subjects failed to identify a mutation. Absence of NR3C1 mutations has been well-documented in other cases of apparently sporadic glucocorticoid resistance, so that some as yet unidentified post-receptor defect in GR signalling may be responsible for the clinical and biochemical abnormalities in these patients. In conclusion, ACTH dependent hypercortisolism in an individual without Cushingoid features raises the possibility of generalised glucocorticoid resistance. An absence of clinical or biochemical progression in our subjects, as well as further functional GR studies, will allow increased diagnostic certainty.

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Blockade of gene expression modifies the acute inflammatory release of activin A in response to lipopolysaccharide

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Activin A, a dimeric protein in the transforming growth factor-β superfamily, is a critical component of the inflammatory response (1). Our previous work indicates that the bacterial cell wall component, lipopolysaccharide (LPS), can induce the release of activin A within 1 hour (1), and serum concentrations of activin A are increased in septicemia and other infections (2). In order to understand whether the release of activin A is from protein stored in cells or newly synthesised production, we treated adult C57Bl6 mice with the transcriptional inhibitor actinomycin D (act D, 5 mg/kg) or the protein translational inhibitor cycloheximide (CHX, 5 mg/kg) 60 min before an LPS (100 μg) challenge. Profiles were compared from mice challenged with LPS alone. Sera collected at various timepoints up to seven hours after LPS was assayed for activin A concentrations using a specific immunoassay. We found that act D and CHX inhibited the release of activin A one hour after LPS, by 50 % in both cases. Thereafter, CHX had no further effect on activin release following LPS, but act D progressively

increased serum activin A levels above LPS-treated levels from 3 hours. To assess whether this increase was due to a delayed effect of act D on activin A production, mice were injected with act D alone and blood was collected over the same period. Concentrations of activin A following act D injection alone were similar to those in untreated control mice. These findings indicate the release of activin A during acute inflammation is, in large part, from newly synthesised protein. They also highlight a novel interaction between inflammatory and gene synthetic pathways, where the release of activin A following LPS challenge is potentiated following actinomycin D exposure.

(1) Jones et al. (2007) Proc Natl Acad Sci USA 104: 16239-16244
(2) Michel et al. (2003) Eur J Endocrinol 148: 559-564

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Generation of normal ranges in serum for activin A, activin B and follistatin

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Activins and follistatins are now appreciated as having functions more diverse than their original description as reproductive factors. While they may be useful for diagnosis in inflammatory disorders (1) and other pathologies, careful determination of normal ranges has not been performed. Therefore, we determined serum concentrations from healthy adults representative of the general population. After written consent, non-fasting blood was obtained from participants of both genders. Exclusion criteria were a body mass index (BMI) >30 kg/m^2 (obese), statin medication, pregnancy, major hospitalisation within 3 years, current acute illness/injury or chronic inflammatory or neoplastic disease. A total of 144 participants (81 women and 61 men between 21 and 85 years) met the inclusion criteria. Serum obtained from participants was assayed for activin A (2), activin B (3) and follistatin (2) concentrations using specific immunoassays. The contribution of gender, age, ethnicity, BMI, smoking etc. was evaluated by multivariate regression analyses. Activin A concentrations were not different between sexes but increased significantly with age ($r = 0.50$, $P<0.0001$). Although not significant when using multivariate analysis ($P = 0.058$), univariate analysis detected there was a significant ($P<0.001$) effect of ethnicity, with Asians having lower activin A levels than Caucasians. For activin B, concentrations were lower ($P<0.05$) in participants in the 51-65 age group compared with younger or older adults. For follistatin, there were no significant differences with age or gender, but a significant correlation between follistatin and days since last menstruation ($r = 0.56$, $P<0.01$) noted in pre-menopausal women. Overall, these findings provide critical baseline data allowing the value of measuring these proteins in pathological conditions to be explored; the effect of ethnicity requires clarification.

(1) Michel et al. (2003) Eur J Endocrinol 148, 559-564
(2) O'Connor et al. (1999) Hum Reprod 14, 827-832
(3) Ludlow et al. (2008) Proc Endocr Soc, Abstract P3-77

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A comparative assessment of three cell lines for use in the E-screen.

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The original E-screen used estrogen-responsive MCF7 cells to measure the estrogenicity of endocrine disrupting compounds (EDCs). Cells were plated overnight, exposed to EDCs for 5 days and cell numbers determined. Various sublines of MCF7 are used, each with different proliferative responses. We found fold proliferation of low passage MCF7 was 3.07 compared to late passage cells 1.84. The aim of this study was to assess the use of ZR-75-1 and T47D cell lines in the E-screen.

5000 cells/well in 96 well plates were cultured for 5h, to allow adherence, or 24h to synchronise to G_0 in estrogen-free media. Exposure to 10^{-14}M to 10^{-6}M 17-beta estradiol (E_2) ± antagonist (Fulvestrant) followed for 3, 5, 7 days. Dead cells were removed and remaining viable cells were fixed (50% methanol) stained (0.5% Crystal Violet) and solubilised (33% acetic acid) before measuring optical density. Absorbance was modelled to a best fit sigmoidal curve to determine EC_{50} and a t-test applied to determine the lowest dose that was significantly different from solvent control ($n \geq 3$).

The best combination of low EC_{50} and high R^2 values was obtained with T47D cells after 24h pre-treatment and 5d exposure. The best fit EC_{50} was 7.35×10^{-12}M E_2 (R^2=0.81) and fold proliferation was 2.18. The lowest concentration of E_2 significantly different to the solvent control was 10^{-11}M. Antagonist EC_{50} was ~1×10^{-7}M E_2. MCF7 cells with 24h pre-treatment and 5 d generated a very low R^2 (0.19) which negates an accurate EC_{50} (3.2×10^{-12}M E_2). Fold proliferation was at most 2.89 . Antagonist EC_{50} was ~1×10^{-7}M E_2. ZR-75-1 data was between the other cell lines.

5hr pre-treatment gave higher EC_{50}s than 24h. Antagonist results show that proliferation was directly related to estrogen receptor activation. The best E-screen was obtained using T47D cells with 24h pre-treatment and 5 day exposure.

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Development of an *in vitro* assay to detect endocrine disrupting compounds (EDCs) using cryopreserved ovine luteal cells

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The blue-green algal toxin, cylindrospermopsin (CYN), inhibited basal and hCG-stimulated progesterone (P) production by luteinised human granulosa cells, independently of cytotoxicity[1]. CYN was therefore likely to disrupt endocrine function of ovine luteal cells. The EDC ethinyl estradiol (EE_2) acts via estrogen receptors, and should not affect ovine luteal cells. Cryopreservation of luteal cells would avoid seasonal unavailability of corpora lutea (CL) and improve applicability of the proposed EDC activity assay.

Aims were to examine effects of cryopreservation on responsiveness to LH, hCG, dbcAMP, 22OH cholesterol and P production, and characterise effects of EDCs.

1xCL preparation comprised ~40 abbatoir-derived CL disaggregated in 400U/ml collagenase. Half were stored at -80^{o}C in 10% DMSO+DMEM+10%FCS. 10000 fresh or thawed luteal cells/well were added to 96-well plates in DMEM+10%FCS for 24h before replenishment with medium supplemented with 5 to 200 ng/ml hLH, or 0.1 to 1000IU/ml hCG or 2 to 50uM 22OHChol or 0.1 to 10mM dbcAMP, or combinations of these, (n≥3) preparations. Cryopreserved cells (n=3) additionally cultured with 0.1 to 3uM CYN or 10^{-8} to 10^{-4}M EE_2. After 24h, media were collected for P measurement, and photomicrographs of cells taken before the MTT cell viability assay was performed.

None of the supplements affected 'fresh' or cryopreserved viable cell numbers. Both 'fresh' and thawed cells were seeded at 10000 viable cells/well, but 48h later numbers of cryopreserved cells were lower than 'fresh' for all supplements. For example, freeze-thawed viable cell numbers were 37% and 41% of 'fresh' after 24h with 0mM or10mM dbcAMP respectively. All 4 supplements caused dose-dependent increases in P production, but the increase was attenuated in freeze-thawed cells; 10mM dbcAMP-stimulated P production by cryopreserved cells was 27% that of 'fresh' cells. CYN caused dose-dependent cytotoxicity as expected, so did EE_2. Surprisingly, CYN did not inhibit basal P production. Conclude that EDC activity assay requires further characterisation.

(1) Fiona Young, Jasmine Micklem, Andrew Humpage (2008) Effects of Blue Green Algal Toxin Cylindrospermopsin (CYN) on Human Granulosa Cells in vitro. Reproductive Toxicology Vol 25 Issue 3 374-380

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The Effects of a Reproductive Homeopathic Remedy & Novel Anti-cancer Agents on Female Human Reproductive Cells

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Muricidae molluscs have been exploited for food, purple dye (6'6-dibromoindigotin), and the basis of a homeopathy remedy 'Murex Purpurea' to treat gynaecological disorders. Chemical analysis of muricids has identified the compounds tyrindoleninone and 6-bromoisatin which have anti-proliferation activity in human cancer cells. 6'6-dibromoindirubin has been isolated from muricids and indirubin is the active ingredient in a Traditional Chinese medicine for treating leukaemia. Chemical synthesis of muricid compounds is difficult however some structurally related indole derivatives are commercially available. This research investigated a range of commercial compounds as potential anticancer agents and/or their beneficial effects. Granulosa cells were isolated from the follicular aspirates of women (n=7) undergoing ART due to male infertility and compared to the choriocarcinoma JAr cell line. Granulosa cells (10,000 cells per well) were exposed to 5-bromoisatin, indirubin and the Murex Purpurea remedy at concentrations 0.1-100µg/ml for 24, 48 and 72hrs. JAr cells (20,000cells per well) were exposed to the same compounds + 6'6-dibromoindirubin at the same concentrations for 2, 4, 6, 8, 10 and 24hrs. Cell viability was determined using a crystal violet assay and hormones measured by radioimmunoassay. 5-bromoisatin was cytotoxic for granulosa cells at 100 µ g/ml after 24hrs and inhibited progesterone production at 100 µ g/ml after 48hrs. 5-bromoisatin was cytotoxic to JAr cells at 100 µ g/ml at ≥ 4hrs exposure. Neither Murex Purpurea nor indirubin affected granulosa cell viability or hormone production. Murex Purpurea remedy, indirubin and 6'6-dibromoindirubin had no affect on JAr cell viability or progesterone production at concentrations tested ≤ 24hrs exposure. 5-bromoisatin was the most promising candidate as an anticancer compound, although at concentrations tested it was found to be cytotoxic to human reproductive primary-derived granulosa cells. Overall, this preliminary study did not substantiated the use of Murex Purpurea remedy or brominated indoles for treatment of gynaecological disorders.

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In vitro characterisation of the rapid effects of estradiol-17β in ovine pituitary gonadotropes

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In addition to genomic effects, estrogens also exert rapid (non genomic) actions in several cells types. We used ovine pituitary cells in primary culture to investigate the rapid effects of estrogen on gonadotropes, including luteinizing hormone (LH) secretion, second messenger activation, intracellular free calcium (Ca^{2+}_i) levels, and membrane currents. After 72h of culture, mixed cell preparations received 10^{-9}M estradiol 17β (E17β) for 5, 15, 30 or 60min followed by a pulse (15min) of 10^{-9}M GnRH. Medium was collected for LH assay and cells extracted for estimation of phosphorylation of second messengers. E17β treatment for 5min induced phosphorylation of ERK-1/2 and reduced GnRH-induced LH release. GnRH (10^{-9}M) application for 30s increased Ca^{2+}_i which was abolished by 2min treatment with E17β or E17βconjugated to bovine serum albumin. Nifedipine, ryanodine receptor blockade and caffeine had no effect on the GnRH-induced increase in Ca^{2+}_i, but this was abolished by thapsigargin. Nifedipine (10^{-5}M) treatment (15min) lowered GnRH-induced LH secretion by 20%. This suggests that GnRH stimulates release of $Ca^{2+}_i$from inositol 1,4,5-trisphosphate 3-sensitive Ca^{2+}_istores, but release of LH requires some Ca^{2+}influx. GnRH (10^{-9}M) evoked plasma membrane depolarization which was associated with the activation

of several currents, including a cationic current. These currents were probably activated by the release of $Ca^{2+}$from intracellular stores. The depolarization increased the rate of firing of action potentials. E17β (10^{-9}M) treatment for 2min reduced the amplitude of the action potentials, which was explained by attenuation of the voltage-gated Na^{+}current by E17β . We conclude that the induction of pERK 1/2, inhibition of Ca^{2+}release and suppression of the action potential relate to the rapid effect of E17β on gonadotropes, which reduces the response to GnRH and rapid suppression of LH secretion.

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Women with Polycystic Ovary Syndrome (PCOS): Experiences with diagnosis and treatment options.

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Introduction: PCOS is a common endocrine condition (8-10% of women) with psychological, reproductive and metabolic implications. This study investigated the experience of diagnosis, resources/ information received and confidence in treatment in women with PCOS.

Method: Observational cohort study using comprehensive surveys in 37 Australian women with PCOS. Results: *Experience of diagnosis:* The majority of women (89%) saw more than one health professional before diagnosis was made, 49% took >6 months to be diagnosed (27% >2 years) and 41% were dissatisfied with the manner they were informed of their diagnosis. *Information received at diagnosis:* Nearly two thirds (62%) were not given resources about PCOS, despite evidence-based independent resources being avaialble[1]. When information was provided: 43% were dissatisfied with it. Many did not receive information about lifestyle management (36%), long term complications of PCOS (21%) potential difficulties with infertility (21%) and medical therapy (7%). *Confidence in treatment options:* Over half (57%) were extremely/very confident lifestyle changes would improve PCOS symptoms, 59% believed it would prevent long term complications, and 62% that it would lead to sustained weight loss. Only 32% were extremely/very confident medical therapy would improve symptoms, 13% that it would prevent long term complications, and 13% it would sustain weight loss. Conclusions: The experience of diagnosis for women with PCOS appears difficult. Limited information is currently provided regarding management, particularly in relation to lifestyle, yet many women believed lifestyle changes would improve symptoms, prevent complications and lead to sustained weight loss. Greater awareness, targeted education and resources are needed for women with PCOS and their health professionals.

(1) www.managing PCOS.org.au and www.jeanhailes.org.au

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The spectrum of thyroid disease following Interferon-α2β therapy for chronic hepatitis C infection

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Autoimmune endocrinopathies are common manifestations of hepatitis C infection, exacerbated by Interferon-based treatment. A small proportion of these patients develop thyroid diseases whilst undergoing treatment. However, the pattern of thyroid diseases in the short/medium term following the completion of IFN-based is relatively unknown and there are very few previous reports regarding the specific spectrum of thyroid diseases that may follow. We hereby report 3 cases which demonstrate the full repertoire of thyroid diseases that have incurred following interferon therapy. This sheds further information on the pathogenesis of these conditions in that there must be a triggering mechanism as the onset of thyroid diseases occur outside the pharmacokinetic of pegylated interferon. This report highlights the need to regularly follow thyroid status in IFN-treated HCV patients in the immediate period following the completion of therapy, certainly within the first 6-months.

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Transcriptional profiling of the mid-spermatogenic stages in the rat reveals mechanisms of hormone action

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Suppression of androgen and gonadotrophins arrests spermatogenesis and is a promising approach to male contraception. The mid-spermatogenic stages (VII and VIII in the rat) encompass several important processes, including remodelling of intercellular junctions and release of mature spermatids, and are well known to be particularly sensitive to hormone suppression. This study aimed to discover the genes and molecular pathways involved in the transition from stage VII to VIII of spermatogenesis, and the effects of acute hormone suppression.

Stage-specific seminiferous tubules were isolated from testes of normal adult rats (*control*) and those with acute (4d) androgen and FSH suppression (*hormone-suppressed*). Affymetrix GeneChip® Rat Genome 230 2.0 arrays were used to investigate global mRNA expression in stage VII vs VIII ± hormone suppression. 16,979 probe sets were expressed in >20% of samples, representing the "transcriptome" of the rat mid-spermatogenic stages. Differentially expressed genes were identified, and a cellular localisation in the testis was ascribed to 69% using microarray data from purified testicular cells[1].

Major findings include: 1) In stage VIII in controls, spermatid genes are preferentially and markedly down-regulated (indicating a cessation of transcription prior to elongation), spermatocyte genes are preferentially up-regulated, while Sertoli cell and spermatogonial genes are both up and down-regulated; 2) Genes showing stage-specific changes are largely hormone-responsive; 3) Hormone suppression partially reverses stage-specific transcriptional changes in spermatids and spermatocytes, such that stage-specific effects persist, but with a smaller

fold change. Thus hormone suppression "blunts" stage-driven expression changes in meiotic and post-meiotic germ cells; 4) Hormone suppression causes a more diverse transcriptional response in Sertoli cells and spermatogonia, and does not simply reverse stage-driven changes. Current analyses are investigating the functional pathways influenced by stage and hormones in each cell type, with the potential to reveal new targets for contraception.

(1) Chalmel et al 2007 PNAS 104:8346

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Effects of Human Chorionic Gonadotrophin on the Mouse Leydig Cell Proteome

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Leydig cells (LCs) reside in the interstitium between the seminiferous tubules in the testes. Their main function is to produce testosterone when stimulated by luteinizing hormone (LH) or its analogue human chorionic gonadotrophin (hCG) . However, little is known about proteins produced and/or secreted by LC's in response to LH stimulation. We are using a proteomic approach to identify unique secretory and cellular proteins produced by hCG stimulated LCs *in vitro* .

LCs from the testes of adult Swiss outbred mice (10 weeks old) were isolated by mechanical dispersion and purified by Percoll density gradient centrifugation. Cell purity was assessed by staining with the LC-specific marker 3β-hydroxysteroid dehydrogenase and DAPI. LCs were then incubated for 24 hours in DMEM/bSA 0.1% with different doses of hCG (0, 69, 208 or 625pg/ml), and their functionality assessed by testosterone radioimmunoassay. Both cells and culture media were harvested, and extracted proteins were labelled using CyeDye DIGE fluor saturation dyes. Labelled proteins were separated in 24cm immobilised pH gradients (pH 3-10) in the fist dimension, and 8-16% polyacrylamide gradients in the second dimension. Protein expression changes following hormone treatment were analysed using SameSpots software.

Isolated LC's were >80% pure as demonstrated by histochemical staining, and showed a dose-dependent increase in testosterone production in response to hCG stimulation. Of over 500 protein spots detected in the LC proteome, 34 were found to be significantly ($p<0.05$; ANOVA) differentially expressed between the treatment groups. The greatest response occurred in cells treated at the highest dose of hCG (625pg/ml), with 8 and 26 proteins up-or down-regulated, respectively. Differential protein expression also changed in a dose dependent manner, with a decreasing effect on protein expression changes noted as hCG dose reduced. Analysis of the culture media for secreted proteins, as well as identification of the proteins showing altered expression, is underway.

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The Intrauterine (Pro)Renin/(Pro)Renin Receptor System and its Role in Prostaglandin Synthesis During Pregnancy

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During pregnancy, the human intrauterine tissues and amniotic fluid contain large amounts of prorenin. Prorenin, by binding to a (pro)renin receptor (PRR), exhibits biological activity without proteolytic activation [1]. Renin stimulates the production of prostaglandins (PGs) in human amnion and decidua [2, 3]. The PRR may mediate the effects of prorenin and renin on uterine PG synthesis by influencing Prostaglandin H2 Synthase-2 (PGHS-2) expression, which is the key PG-synthetic enzyme in gestational tissues. To see if the PRR is co-localised with prorenin and PGHS-2, and if expression is altered following labour, term amnion, chorion, decidua and placenta were collected following elective caesarean section or after spontaneous labour, and prorenin, PRR and PGHS-2 mRNA were quantified by real time RT-PCR. PRR localization was examined by immunohistochemistry. PRR protein was highly expressed in the syncytiotrophoblast, decidua, chorionic trophoblast and, to a lesser extent, the amnion. Prorenin mRNA levels were highest in decidua whereas PRR mRNA was most abundant in placenta. After labour, decidual prorenin and PRR mRNA were reduced, as were levels of placental PRR mRNA. Placental prorenin mRNA was positively correlated with PRR mRNA after labour indicating a functional role for this system in the placenta. PGHS-2 mRNA was most abundant in the amnion and was increased in all tissues after labour. In decidua before labour, PRR mRNA was negatively correlated with PGHS-2 suggesting that the PRR system may inhibit decidual PGHS-2 expression. These results demonstrate that prorenin and PRR expression is altered during labour and the (pro)renin/(pro)renin receptor system may be implicated in the mechanism of term and preterm birth.

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A MODEL OF PREGNANCY INDUCED CHANGES IN ASTHMA

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The effect of pregnancy on maternal asthma remains unclear. However recent studies suggest that a higher proportion of asthmatic women experience at least one exacerbation during pregnancy with greater incidence occurring in the last trimester. An asthma exacerbation during pregnancy increases the risk of an adverse pregnancy outcome. Both asthma and pregnancy are conditions associated with a skewing of the immune response from T helper (Th) -1 toward a Th-2 response. Studies have reported changes in maternal immune cell profiles and chemo-attractant properties during normal pregnancy. Nevertheless, the mechanisms contributing to worsening of asthma during pregnancy have not been well characterized.

The objective of this work was to develop an *in-vitro* model to determine whether changes associated with pregnancy and maternal asthma modulate airway secretion of inflammatory factors known to mediate the pathophysiology of asthma. In addition we have also assessed maternal immune cell profiles and measured plasma cytokine levels using Luminex system. Peripheral blood chemotactic response to plasma from pregnant and non-pregnant asthmatic subjects was determined using a transwell chemotaxis assay.

The results of the study showed that pregnancy alone was associated with increased circulating neutrophils, increased airway production of interleukin (IL-6), regulated upon activation, normal T-cell expressed and secreted (RANTES) and suppressed chemotaxis. The presence of maternal asthma during pregnancy was associated with increased monocyte and neutrophil numbers, increased airway cell production of IL-8, sICAM-1, RANTES and increased chemotactic capacity relative to pregnant women without asthma. Maternal asthma during pregnancy was not associated with increased circulating proinflammatory and Th-2 cytokines. In combination, our data suggests that maternal asthma during pregnancy promote the release of chemotactic mediators and cell adhesion in the airways. This change in airway function, together with changes in number and recruitment of immune cells may be one mechanism that contributes to worsening asthma during pregnancy.

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Maternal parity and growth hormone administration differentially affect fetal growth and muscle development in pigs

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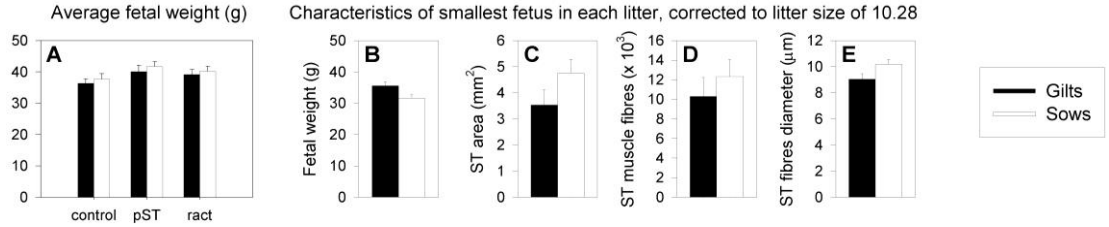
Fetal growth and birth weight predict neonatal survival, postnatal growth and function, but are constrained in pigs by litter size, adolescent pregnancy and nutrition. In growing primiparous pigs (gilts), daily maternal injections with porcine growth hormone (pGH) in early-mid pregnancy increase fetal growth, muscle fibre numbers and growth rates of progeny (1-3). Feeding the β-adrenergic agonist ractopamine to mature pigs (sows) during early-mid pregnancy may have similar effects (4). We therefore investigated effects of these interventions on fetal growth and muscle development.

Pregnant primiparous and multiparous pigs were injected daily with saline or pGH (14.7 ± 0.2 μg/kg/day), or fed ractopamine (20 ppm) from d 25 to 50 of gestation, when dams were euthanased. Cross-sectional area, fibre number and diameter were measured in fetal semitendinosus muscle. Effects of treatment and parity were analysed by 2-way ANOVA with litter size as a covariate. Results are mean ± SEM.

Litter size was higher in sows (12.7 ± 0.6) than gilts (9.7 ± 0.6), and was not altered by treatment. Maternal pGH increased (P=0.023) and ractopamine tended to increase average fetal weight (A, P=0.094), which did not differ between parities (P=0.38). For the smallest fetus of each litter, weight was higher in gilts than in sows (B, P=0.027), but semitendinosus area (C, P=0.15) and total fibre number (D, P=0.46) were similar between parities. Average fibre diameter tended to be greater in fetuses from sows than gilts (E, P=0.066). Maternal treatments did not alter muscle characteristics.



Maternal GH treatment increased fetal growth to a greater extent than feeding ractopamine. Larger fetal muscle fibres may contribute to greater progeny growth potential from sows. Maternal treatments did not alter muscle characteristics, suggesting that effects later in pregnancy contribute to improved progeny performance, and we are currently investigating effects on placental function and development.

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Maternal Circulating Antioxidant Levels In Pregnancies Complicated By Asthma

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Antioxidants such as tocopherols and carotenoids may confer a protective effect against the oxidative damage caused by normal metabolic processes and many diseases including asthma. While normal pregnancies are exposed to high levels of oxidative stress, it is not yet known if tocopherol or carotenoid levels are altered in pregnancies complicated by asthma. Therefore, maternal circulating levels of tocopherols and carotenoids were measured longitudinally in asthmatic and non-asthmatic pregnant women. Peripheral blood was collected at gestational weeks 18, 30 and 36 from pregnant asthmatic (n = 35) and non-asthmatic (n = 22) women. Maternal circulating plasma levels of α-, γ- and δ-tocopherols, and carotenoids (α- and β-carotene, β-cryptoxanthin, lutein and lycopene) were examined using high performance liquid chromatography (HPLC). Significantly higher α-tocopherol levels were found in the pregnant asthmatic group over time relative to controls (ANOVA, $p < .001$). In contrast, both the asthmatic (n = 16) and control (n = 5) groups showed reducing levels of total carotenoids (ANOVA, $p < .001$), and α-carotene (ANOVA, $p = .015$) over the three time points but no differences were found between the groups. Interestingly, these data suggest that reducing levels of total carotenoids and α-carotene may be due to their increased utilisation in the presence of free radicals. Additionally, there may be compensatory increases in antioxidant α-tocopherol levels in the presence of asthma during pregnancy. Such increases may prove important in the protection against asthma induced oxidative damage to the placenta and fetus.

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Presence of the novel membrane estrogen receptor G-Protein coupled receptor 30 (GPR30) a membrane estrogen receptor in human pregnant myometrium and its biochemical characterization

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Context: Estrogen is one of the most important female reproductive hormones. It has diverse roles in many aspects of physiology, including reproduction, the vascular system and the nervous system. Traditionally, estrogen binds to the nuclear receptors, ER a and ER b . Both of these receptors then bind to DNA to regulate gene transcription. Recently a novel cell surface receptor for estrogen, called GPR30, was identified in cancer cells.

Objective: Given the importance of estrogen in pregnancy, we investigated the presence and role of this novel receptor in human myometrium.

Methods: We collected myometrial tissues from elective or emergency cesarean sections. Tissues were immediately frozen in liquid nitrogen and were kept at -80° C. These tissues were used for RNA and protein extraction. We performed realtime quantitative PCR and western blot for GPR30.

Results: mRNA for GPR30 was detected in both labouring and non-labouring myometrium at term. Western blot analysis revealed that a monomeric ~38 kD protein band specific for GPR30 was expressed in the human pregnant myometrium at term. In addition, a trimeric form was also detected at ~120 kD. During Western blot analysis, detection of both the monomeric and trimeric bands were abolished by use of a blocking peptide. Furthermore, two-dimensional separation of proteins prior to Western blot analysis revealed monomer and trimer detection occurred at the expected isoelectric point (pI 8.6) for GPR30.

Conclusion: This study documents the novel detection of GPR30 in human myometrium, the physiological role of the receptor in this context remains uncertain.

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High prevalence of suboptimal Vitamin D in first-trimester pregnancy

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Introduction: There is growing evidence that vitamin D deficiency in pregnancy has adverse consequences including reduced intrauterine long bone growth, neonatal hypocalcaemic convulsions, rickets in infancy and reduced bone mass in childhood. Furthermore, maternal vitamin D deficiency may predispose to preeclampsia.

In Australia, maternal vitamin D deficiency is well recognised as a public health problem particularly in certain migrant populations. A Melbourne antenatal clinic found that 80% of pregnant women who are dark skinned and veiled are vitamin D deficient, however the prevalence of vitamin D deficiency in pregnant women in Western Australia is unclear.

Method: Vitamin D was measured on stored serum obtained from 485 consecutive women attending Western Diagnostic Pathology for first trimester screening during the summer month of February 2008. Vitamin D was analysed by chemiluminescent immunoassay using the DiaSorin Liaison Vitamin D Total kit.

Results: The average maternal and gestational ages at the time of serum collection were 30.9 +/- 5.5 years and 11.3 +/- 1.1 weeks respectively. Vitamin D levels ranged from 14.7 to 180 nmol/L with an average of 70.9 +/- 21.4 nmol/L and median of 99.2 nmol/L. There was no correlation between maternal age and vitamin D level.

Using the classification recommended by the ANZBMS published in MJA 2005 and the cut-off of 80 nmol/L (Hollis et al, 2005), the prevalences in each category are tabulated as follows:

Vitamin D level (nmol/L)	Number (%)
<25	5 (1%)
25 to 50	66 (13%)
50 to <80	265 (55%)
≥ 80	149 (31%)

Conclusion: Of first trimester pregnant women in Western Australia, 69% are vitamin D insufficient and 1% are moderately vitamin D deficient. This potentially has important adverse health consequences for their offspring. The generous support of DiaSorin and Immuno is acknowledged.

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Resveratrol, an activator of FoxO, inhibits LPS-induced cytokine and prostaglandin release from human gestational tissues.

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Background: A successful outcome to labour and delivery is dependent upon common proximal events that result in an increase in prostaglandins and cytokines. The mechanisms by which these processes are coordinated and coupled with fetal maturation (normal spontaneous delivery at term) or uncoupled from fetal development (preterm birth) remain to be fully elucidated. Upstream multifunction regulators may coordinate proximal labour-associated events, including nuclear factor-κB (NF-κB). In non-gestational tissue studies, forkhead transcription factor FoxO proteins acts as negative regulators of NF-κB signalling. Thus the aim of this study was to determine the (i) localisation of FoxO proteins in human gestational tissues and (ii) effect of FoxO activation by resveratrol on pro-labour mediators.

Methods: Immunohistochemistry was used to analyse the localisation of FoxO proteins in human term placenta, amnion and choriodecidua. A gestational tissue explant model was used to determine the effect of resveratrol on pro-labour mediators. Placenta and choriodecidua (n=6) obtained at term Caesarean section were incubated 6h in the absence (control) or presence of resveratrol (50, 100 and 200 μM) with LPS-stimulation (1 μg/ml). NF-κB, FoxO1a and FOXO3a nuclear protein expression was assessed by Western blotting. Pro-inflammatory cytokine (TNF-α, IL-6, and IL-8) and prostaglandin (PGE_2 and $PGF_{2\alpha}$) release was quantified by ELISA.

Results: Staining of FoxO proteins was localised to the nucleus and the cytoplasm of the amniotic epithelium and the trophoblast layer of the chorion. Decidua, where present, expressed positive pale FoxO staining. In placenta, there was strong nuclear staining of trophoblasts, scattered nuclear staining was observed within the villi, but no staining of the syncytial knots. Treatment of placenta and choriodecidua with the FoxO activator resveratrol dose-dependently decreased LPS-stimulated release of both pro-inflammatory cytokines and prostaglandins ($p<0.05$).

Conclusions: These data are consistent with the hypothesis that FoxO pathways affect the expression of proximal, labour-associated effectors.

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Tissue specific epigenetic regulation of CRH gene expression

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Corticotropin Releasing Hormone (CRH), derived from the hypothalamus/pituitary, orchestrates a series of neural and endocrine adaptations known as the stress response. CRH has also been identified in many tissues outside the hypothalamus; in particular, in the placenta during human pregnancy. Placental production of CRH has been linked to the length of gestation in humans with increased concentrations in maternal blood being associated with preterm delivery.

The steroid hormone receptors that we have previously shown to be important in CRH gene regulation are also known to be important factors controlling the extent to which chromatin is acetylated. We hypothesise that regulation of CRH gene expression is likely to involve the alteration of histone acetylation.

Treatment with histone deacetylase (HDAC) inhibitors increases the degree of acetylation of chromatin, allowing the transcription machinery access to the gene, and generally results in increased gene expression in most cell types. However, our data on CRH expression in placental cells compared to pituitary cells suggests that alterations in acetylation produced by HDAC inhibition produces opposite effects in these two cell types. The inhibition of HDAC activity in transfected AtT20 cells (a HPA model) resulted in the stimulation of CRH gene expression while, in contrast, CRH gene expression was suppressed by this treatment in transfected placental cells. We have confirmed by Q-RT-PCR that this suppressive affect of HDAC inhibitors also occurs on endogenous CRH gene expression in primary placental cells.

This result is consistent with a recent publication showing that epigenetic modifications of chromatin surrounding the growth hormone gene results in opposite effects on expression of that gene in placenta compared to the pituitary.

Understanding the regulation of CRH expression in different gestational tissues is important if we are to understand how subtle changes in programming can affect processes such as the timing of birth.

Phospho-Proteomic Determination of Contraction Associated Proteins in the Human Uterus

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BACKGROUND: During the onset of labour, the myometrium of the uterus is transformed from a quiescent, non-contractile phenotype into an actively contracting organ. The factors initiating the onset of labour remain unknown, however the sudden triggering of this event suggests that contractions are the culmination of a series of protein post-translational modifications, such phosphorylation and dephosphorylation events.

HYPOTHESIS/AIMS: We hypothesised that the onset of labour in humans is associated with the phosphorylation and dephosphorylation of a cohort of myometrial proteins, and that these phosphorylation events promote the contractile myometrial phenotype. We aimed to test this hypothesis through examining the phospho-proteome of myometrium prior to, and after the onset on spontaneous contractions in vitro.

METHODS: Human myometrial tissue was collected during caesarean section from term, non-labouring women. The tissue was dissected into strips and suspended in organ baths under tension. Transducers were then used to observe the gradual onset of spontaneous contractions. To highlight phospho changes associated with contractions, myometrial strips were snap frozen at specific stages, these included; (i) prior to the onset of any contractions, (ii) at maximum contraction, (iii) at maximum relaxation, and (iv) at tetanic contraction following treatment with oxytocin, a uterotonic used clinically in the induction of labour. Proteins were then extracted, separated by SDS-PAGE and subjected to phosphoprotein detection techniques.

RESULTS: Onset of spontaneous contractions was associated with up-regulated phosphorylation of 5 high molecular weight proteins, a prominent 50 kDa protein, and 3 lower molecular weight proteins. A complementary anti-phosphotyrosine analysis highlighted up-regulated phosphorylation of 4 high molecular weight proteins, including another prominent protein of 115 kDa.

CONCLUSION: Phosphorylation events occur in association with contraction in human myometrium. Identification of the modified proteins may allow a better understanding of the regulation of contraction and relaxation during human labour and guide the development of novel tocolytics.

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