ACD 46th ASM Conference Review™

Making Education Easy

19-22 May 2013, Sydney, Australia

In this review:

About Research Review

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Welcome to this Review of the 46th Annual Scientific Meeting of the Australasian College of Dermatologists, held in Sydney, Australia, from 19th to 22nd May 2013.

This event is attended by registered dermatologists and trainees and associated specialists, from both Australia and New Zealand, and from South-East Asia.

This Review provides a summary of significant clinical research presented at the Meeting, selected and reviewed independently by myself, Dr Amanda Oakley (Specialist Dermatologist, Hamilton) and Dr Samuel Zagarella (Specialist Dermatologist, Sydney), who both attended the Meeting. I also attended the joint conference hosted by the Asian Society for Pigment Cell Research (ASPCR) and the Australasian Society for Dermatology Research (ASDR), which was held in Sydney between 17th and 19th May 2013.

Links are available for both events: http://onlinelibrary.wiley.com/doi/10.1111/ajd.12051/pdf for the ACD 46th ASM and http://www.dermcoll.asn.au/public/meeting_and_conferences.asp for the ASPCR-ASDR.

I hope you find the Conference Review stimulating and I look forward to your feedback.

Kind regards

Amanda Oakley

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Distinct biologic subtypes and their impact on therapy and disease classification

Presenter: Prof. Boris Bastian, University of California, San Francisco

Summary: This presentation discussed recent findings providing strong genetic evidence of melanoma consisting of a heterogeneous group of diseases, characterised by genetic and morphological findings depending on the cell of origin, constitutional genetic and environmental factors. These associations are not only leading to changes in current melanoma classifications, but they also offer new opportunities for treatment and prevention.

Comment (AO): Prof. Boris Bastian gave a fascinating talk describing how distinct biologic subtypes of melanoma and melanocytic naevi are related to multiple causal pathways. Subtypes of melanocytes have differing susceptibility to genetic and environmental damage, giving rise to a range of diverse tumours.

The high naevus count, intermittent sun exposure type of melanoma loosely correlates with superficial spreading melanoma. It occurs disproportionately in young adults, predominantly on the trunk and proximal limbs. It is associated with *BRAF* mutation (70%). *BRAF* V600E mutation is also found in 90% of acquired naevi, suggesting clones of partially transformed melanocytes expressing BAP1 protein. Naevi mainly arise in the first two decades of life and are linked to the melanocortin-1 receptor (*MC1R*) gene. A second mutation may lead to a pink papule within a flat brown naevus, or a melanoma. Histopathological correlations for *BRAF* mutations are upward scatter of intraepidermal melanocytes, nesting and melanisation. Melanomas with *BRAF* mutations are more likely to metastasise. The origin of their neural crest precursor melanocyte is the ventral pathway.

The low naevus count, chronic sun damage melanoma affects older age groups and correlates with lentigo maligna and lentiginous melanoma. It is more common on the head and neck in people who also have solar elastosis and solar keratoses. *NRAS* or *KIT* mutations are found in 30–40%. *KIT* mutations are also associated with melanomas on glabrous skin, nail apparatus and mucosa. These tumours are histologically lentiginous, with a long *in situ* phase, and poorly circumscribed. Mucosal and acral tumours have marked (and different) genomic instability.

Nonepithelial melanocytes originating from the dorsolateral pathway of the neural crest give rise to blue naevi, dermal melanocytosis, melanocytomas and uveal melanomas. These are unrelated to sun exposure and often have *GNAQ* and *GNA11* mutations; the latter are more likely to lead to metastasis.

Spitzoid tumours appear to be unrelated to UV exposure. Nodular melanoma can arise from all the subtypes.

With free access through PMC, the review article on this topic is recommended.*

*David C. Whiteman, William J Pavan, and Boris C. Bastian. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Research 2011;24:879-897.

ASPCR-ASDR Conference. Keynote Session: Melanoma. Saturday 18 May.

http://www.aspcr-asdr2013.org/program-at-a-glance-2/detailed-program/

Melanomas of unknown primary have a mutation profile consistent with cutaneous sun exposed melanoma

Presenter: Dr Ken Dutton-Regester, Queensland Institute of Medical Research, Oncogenomics Laboratory, Brisbane

Summary: This presentation described investigations into exome sequencing data on 33 melanoma of unknown primary (MUP), in an attempt to better understand their mechanism of development.

Comment (AO): Metastatic MUP has an incidence of 3% and often presents with solitary lymphadenopathy. In general, MUP leads to better survival rates than known primary melanoma. Evaluation of oncogenic mutation profiles of lymph node metastases may help determine their origin. Metastases tend to have more mutations than primary tumours, and primaries arising in sun-exposed sites have more mutations than those from sun-shielded sites. Dr Dutton-Regester compared 101 MUP with 250 metastases from known primaries. MUP were often found in nodes around the head and neck (24% of the sample). Most MUP were associated with sun-exposed profiles including *BRAF* and *NRAS* mutations.

MUP may come from lower-risk sun-exposed primary melanoma that has regressed or a primary lymph node tumour that has arisen within migrated naevus cells.

ASPCR-ASDR Conference. Concurrent Session: Melanoma II. Saturday 18 May.

http://aspcr-asdr-2013.p.asnevents.com.au/event/abstract/5544

Pruritus: from bench to bedside

Presenter: Prof. Timothy G. Berger, University of California, San Francisco

Summary/Comment (AO): Tim Berger is an expert on complex medical dermatology and has an abiding interest in medical education. In his plenary presentation, Professor Berger pointed out that 2% of all medical visits in the USA are for itch. Itch affects quality of life to a similar degree as chronic renal failure for a patient on dialysis. Lack of sleep, ineffective treatments and lack of sympathy from others lead to a 'desperate helplessness'. He assesses severity of itch using the scale 0 (no itch) to 10 (worst itch imaginable). Itch can be classified into 3 types.

- Type 1 pruritus is itch on diseased skin and management involves treating the underlying skin disorder. Phototherapy may be useful.
- Type 2 pruritus or metabolic itch affects non-diseased skin and skin lesions are secondary to scratching. Investigations should consider likely causes: renal, liver and thyroid disease; iron deficiency, hypercalcaemia, and lymphoma, especially Hodgkin disease. Management depends on the underlying disease. Phototherapy and gabapentin help in renal disease; opiate antagonists and sertraline may be needed in severe liver disease; paroxetine helps itch of malignancy. Malignancy drives the Th2 pathway (allergy), leading to eosinophilic infiltration, which may be helped by topical steroids and phototherapy.
- Type 3 pruritus refers to localised itch without a primary skin lesion, where dorsal root ganglion and IL31-specific sensory itch nerves are hyperactive. Light touch triggers itch, leading typically to chronic lichen simplex, brachioradial pruritus, notalgia paraesthetica, prurigo and cutaneous amyloidosis. Topical treatment is not very effective, as the cause is neurological. Capsaicin may be useful. Physiotherapy of the spine and ergonomic improvements may help. Many patients need amitriptyline, and some do better with gabapentin, pregabalin or ketamine. Lumbosacral paravertebral injections can be used to counteract neuropathic scrotal itch, a chronic regional itch syndrome.

The June 2011 issue of Seminars in Cutaneous Medicine and Surgery was devoted to an extensive review of pruritus.

ACD 46th ASM Session: Keynote Session: From Bench to Bedside. Sunday 19 May.

ACD 46th ASM Conference Review

Independent commentary by Amanda Oakley

Professor Oakley is a specialist dermatologist in Hamilton and is an Honorary Associate Professor at Waikato Clinical School (Auckland University School of Medicine). Among her many other positions, she is President of the New Zealand Dermatological Society and the manager and chief editor of the Society's successful web site, DermNetNZ.org.

Daylight photodynamic therapy

Presenters: A/Prof. Pablo Fernandez-Peñas, Dr Diana Rubel, Dr Robert Salmon, Dr Jo-Ann See

Summary/Comment (AO): In this symposium several Australian dermatologists described their experiences in treating a field of actinic keratoses in a novel way.**

Results using daylight as a light source were as good as with conventional MAL-PDT using the Actilite® diode source of red light. Treatment can be undertaken during an overcast day in spring, summer or autumn in most parts of the world.

- The field to be treated is marked out.
- The keratoses are lightly scraped.
- A clear sunscreen is applied to all skin to be exposed to sunlight including intended treatment area.
- 15 minutes later, methyl aminolevulinate cream is applied to the field.
- Half an hour later, the patient should go outdoors to expose the treated area to shaded daylight.
- Two hours later, wash off the cream using saline.
- The patient should remain indoors for the rest of the day.

Tolerable inflammatory reactions, high cure rates and excellent cosmetic results were described. The procedure is apparently much less painful than conventional PDT and large areas of sun damage can be treated on a single occasion.

**Wiegell SR, Wulf HC, Szeimies RM, Basset-Seguin N, Bissonnette R, Gerritsen MJ, Gilaberte Y, Calzavara-Pinton P, Morton CA, Sidoroff A, Braathen LR. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012 Jun;26(6):673-9.

ACD 46th ASM Session: Industry symposium: Metvix Daylight Study results. Tuesday 21 May.

Dietary intervention in acne: Why does a dermatologist need to use and understand the evidence?

Presenter: Prof. George A. Varigos, The Royal Melbourne and Royal Children's Hospitals, Victoria

Summary/ Comment (AO): Prof. Varigos gave a highly entertaining presentation to convince dermatologists about increasing evidence of the importance of diet in the pathogenesis and management of acne. Each step in the pathogenesis of acne can be shown to be due to the effects of an overactive serine/threonine kinase mammalian target of rapamycin complex 1 pathway (mTORC1) via downregulated nuclear forkhead box transcription factor O1 (FoxO1). Other mTORC1-driven diseases include obesity, type 2 diabetes, cancer and neurodegenerative diseases.

Dietary glycaemic load augments the biological activity of free androgens, insulin and insulin-like growth factor-1 (IGF-1) leading to keratinocytic proliferation, seborrhoea and follicular occlusion.

Diets with minimum meat, milk, fat, alcohol and insulinotropic carbohydrates have been demonstrated to lead to decreased acne counts, weight reduction and improvement in insulin sensitivity. Anti-acne drugs including isotretinoin, benzoyl peroxide and metformin also act on the IGF-1 pathway.

Tell your acne patients to reduce total energy consumption, leucine in meat and protein supplements, milk, alcohol and sugar. Increase intake of fruit and vegetables.

An open-access review article on this topic is available on PMC: Melnik B. Dietary intervention in acne: Attenuation of increased mTORC1 signaling promoted by Western diet. Dermatoendocrinol. 2012 Jan 1;4(1):20-32.

ACD 46th ASM Session: Free Papers Session. Monday 20 May.

Inflammatory bowel disease and the skin

Presenter: Prof. Timothy G. Berger, University of California, San Francisco

Summary/Comment (SZ): The pathogenesis of IBD was discussed and the role of the immune system in reacting to bacterial flora in the gut. Genetic factors may also play a role in causing the immune system to mount an immune response, mediated by Th17, in the gut wall in these diseases. Some clinical presentations of cutaneous Crohn's disease were shown, including genital and perineal ulceration, and lip swelling. Treatment options for cutaneous Crohn's disease include oral metronidazole, prednisone, azathioprine, cyclosporin, TNF inhibitors, and combinations of these.

Neutrophilic dermatoses as an association of IBD were discussed. These reactions are part of the innate immune response, and may not correlate with the activity of the IBD. These reactions include erythema nodosum, Sweet's syndrome, pyoderma gangrenosum and oral aphthae. Pyoderma gangrenosum occurs in 1% of patients with IBD, affects ulcerative colitis and Crohn's disease patients equally, and is almost always on the lower leg.

IBD can cause dermatoses due to nutritional deficiency, including hair loss from iron deficiency, dry skin from essential fatty acid deficiency, and zinc deficiency dermatoses.

The side effects of TNF inhibitors were mentioned. Why can these drugs actually induce psoriasis and vasculitis and lupus in some patients? Perhaps it is because although they reduce TNF and Th1, Th17 cells at the target organ, there is a compensatory increase in Th1 and Th17 cells in lymph nodes, which can drive autoimmunity and psoriasis.

ACD 46th ASM Session: Dermatology and General Medicine. Monday 20 May.

BRAF new world

Presenter: Dr Nikolas K. Haass, University of Queensland

Summary: Novel therapies for metastatic melanoma were discussed, including the selective BRAF inhibitor vemurafenib and the CTLA-4 antagonist ipilimumab, as well as the newer BRAF inhibitor dabrafenib and the MEK inhibitor trametinib. The presentation acknowledged the need for novel drug targets, in the ongoing search for cure of this disease. Dr Haass discussed a new strategy for melanoma therapy: targeting the apoptosis pathways.

Comment (SZ): The role of basic research, translational research and actual bench-to-bedside research was discussed for the understanding of risk factors of melanoma, development of novel biomarkers and development and optimisation of targeted therapies of melanoma. The known risk factors for melanoma include the following:

UV exposure, complexion, naevus count, personal and family history of melanoma, and mutations (e.g. *CDKN2A*). In addition to this, there is now evidence that in patients with red hair and fair skin, the pheomelanin pigment pathway produces UV-radiation-independent carcinogenic contributions to melanoma genesis by a mechanism of oxidative damage. Although protection from ultraviolet radiation remains important, additional strategies may be required for optimal melanoma prevention.

We need biomarkers to help us determine the 5% of thin melanomas that will metastasise. Some research on the expression patterns of connexins has been done.

Regarding treatment of advanced melanoma, a new era has begun since the discovery of mutations in the *BRAF* gene in melanoma, which cause activation of the MAPK pathway, and development of drugs to block mutated *BRAF*. Vemurafenib and dabrafenib have shown unprecedented effects in shrinking *BRAF*-mutant melanoma in patients. However, after an initial response, drug resistance occurs through a number of mechanisms. In addition, melanoma cells bypass the intrinsic apoptosis pathway, hence avoiding cell death.

New research on drug combinations aims to sensitise melanoma cells to apoptosis by the BRAF inhibitors.

Finally, hot-off-the-bench research has identified individual subpopulations within melanomas that show different cell cycle behaviour. These differentially cycling subpopulations might respond differently to targeted therapy.

ACD 46th ASM Session: Melanoma Symposium. Monday 20 May.

Vascular birthmarks: Which ones to investigate?

Presenter: A/Prof. Orli Wargon, Sydney Children's Hospital

Summary: This session discussed some of the more unusual clinical presentations that have undergone investigations at a vascular birthmark clinic.

Comment (SZ): This was a very useful and important overview and crucial for those of us who may not see many paediatric cases regularly. The salient points follow:

Infantile Haemangiomas

If more than 5 skin haemangiomas are present, a liver ultrasound should be performed, as liver involvement can lead to consumptive hypothyroidism.
Large segmental haemangiomas over the mandible confer a 60% risk of subglottic haemangioma and require direct endoscopic visualisation.
Large or segmental haemangiomas can also be a marker for PHACES or PELVIS syndrome.

Vascular Tumours

One must differentiate between Kaposiform Haemangioendothelioma and Tufted Angioma. If the former is suspected, then check platelet, D-dimer and fibrinogen levels for Kasabach-Merritt phenomenon (consumptive coagulopathy); biopsy and MRI can be useful here.

Vascular Malformation Syndromes

Blue Rubber Bleb Nevus Syndrome has venous tumours in the gastrointestinal tract and mouth.
Cerebral cavernous malformations (CCM/OMIM 604214) are vascular malformations causing seizures and cerebral haemorrhages, with mean age at clinical onset of 29.7 years.
Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is characterised by AVMs in the brain and spine. It is autosomal dominant.

Multiple Mucocutaneous Venous Malformations

These require MRI investigations for extent of lesions and, if extensive, tests for D-dimers, platelets, fibrinogen and cardiac echo.

Facial Port Wine Stains – when to worry?

Very high neurological risk: complete unilateral V1 involvement; bilateral V1 involvement; combination V1, V2 and V3 involvement.
Very low or no neurological risk if V2 only or V3 only involvement.
Glaucoma develops in 3.9% with facial PWS and in 12.2% of V1 PWS.
All imaging (MRI, CT) with false negative results (later Sturge-Weber Syndrome and abnormal imaging) was performed in under 9-month-olds.

ACD 46th ASM Session: Vascular Update Symposium. Wednesday 22 May.

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Independent commentary by Dr Samuel Zagarella MBBS (Hons, Syd) FACD

Sam graduated with Honours from the University of Sydney Faculty of Medicine and in 1990 obtained his specialist Dermatologist qualification and became a Fellow of the Australasian College of Dermatologists.

He is now a Clinical Senior Lecturer and Senior Specialist Dermatologist at Concord Hospital in Sydney and is also in private practice in Ashfield, Sydney. Sam is also actively involved in supervising and teaching of Dermatology trainee doctors in Sydney and has been a past examiner for the final exams of the Australasian College of Dermatologists.

The spectrum of vascular tumours including borderline and malignant

Presenter: Prof. Luis Requena, Madrid

Summary/Comment (SZ): Prof. Requena gave an overview of vascular tumours and haemangioendotheliomas.

Dabska Tumour

Also known as Papillary Intralymphatic Angioendothelioma (PILA), it is locally invasive and can metastasise.

Retiform Haemangioendothelioma

It is a distinctive form of low-grade angiosarcoma. It contains elongated arborising vessels resembling the rete testis on pathology.

Kaposiform Haemangioendothelioma

Contains nodules of spindle cells, and areas of capillary haemangioma at the periphery. It may cause Kasabach-Merritt syndrome.

Epithelioid Haemangioendothelioma

This tumour is noteworthy, because it is a low-grade angiosarcoma, but the pattern of solid growth and epithelioid appearance of the endothelial cells frequently leads to a mistaken diagnosis of metastatic carcinoma. Although usually low-grade, metastases and death are reported, with mitotic rate and size being risk factors.

Cutaneous Epithelioid (Pseudomyogenic) Haemangioendothelioma

This is a little-known, low-grade, cutaneous vascular neoplasm. The tumour is multifocal, presenting with up to 15 nodules, some of which are painful. It may occasionally metastasise to lymph nodes or systemically, and death is reported.

Cutaneous Composite Haemangioendothelioma

Also described by Luis Requena, this tumour shows a mixed vascular picture and is a low-grade tumour that can metastasise to lymph nodes.

ACD 46th ASM Session: Vascular Tumours and Panniculitis. Wednesday 22 May.

Difficult cases from a male dermatology clinic

Presenter: A/Prof Anthony Hall, Deakin University, Victoria

Summary: A/Prof. Hall discussed some challenging clinical cases that he has encountered in a specialist male genital dermatology clinic over a 10-year period.

Comment (SZ): Most males with a genital dermatosis are concerned they have an STD, but in fact most cases are non-infectious genital skin disease. A/Prof. Hall's personal observation is that the commonest disease of the male genitalia is irritant contact dermatitis, a form of "intertrigo" in the uncircumcised. Nevertheless, it remains important to differentiate this from penile intraepithelial neoplasia (squamous cell carcinoma [SSC] *in situ*).

He showed a case of warty perianal lesions that failed to respond to multiple modalities for condyloma acuminata, and biopsy eventually revealed the diagnosis to be seborrhoeic keratosis.

Genital melanotic macules are often a concern for both patient and doctor, as they may mimic malignant melanoma. However, while biopsy shows an increase in basal keratinocyte pigmentation, there is no increase in melanocyte numbers and no increase in malignant potential.

The cause of Zoon's (plasma cell) balanitis is still unknown, but it is a condition that is chronic and exclusively occurs in middle-aged to elderly uncircumcised males. Although some texts advocate circumcision as the treatment, A/Prof. Hall recommends a combination of topical steroid and antibiotic cream, and biopsy and monitoring to exclude SCC.

The red scrotum syndrome, or "dysaesthetic penoscrotodynia", can be treated by amitriptyline, gabapentin, carbamazepine, or paroxetine.

ACD 46th ASM Session: Genital Dermatology Symposium. Sunday 19 May.

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