

BIMDG Bulletin

British Inherited Metabolic Diseases Group



Winter bulletin 2019:

Changes to medical training: Paediatric and adult

Cambridge 2019: Photos galore!

Workshops and symposium 2020: Save the dates

Winter/Autumn update! Message from the Chair

Elaine Murphy

This issue focuses on the planned changes to paediatric and adult medical training in IMD and how these will affect recruitment and training to the speciality in the coming years. It may be that paediatric and adult training schemes will continue to differ in their approach – see the articles by Saikat Santra, Andrew Hutchesson and Peter Galloway for details on the complex changes proposed, the timelines for change and the training options that may be considered.

We are grateful to Tim Hutchin for his great photos of the symposium in Cambridge 2019 – many of you will recognize familiar faces! The medication and dietary supplements formulary is in the final stages of completion and proofreading – and we hope to have it available on the website by the new year. Next year is a busy year for members – with two workshops, a session at the Cambridge Science Festival and the symposium already timetabled – for more details and to register to attend events please keep an eye on the website.

Wishing you all a peaceful break over Christmas and the new year.

Cambridge science festival

Elaine Murphy

Together with the Newborn Screening Laboratory at Addenbrookes Hospital, the BIMDG is planning to run a session at the Cambridge Science Festival on Sunday March 22, 2020 (Mothers' day!). The focus will be on IMD identified by newborn screening and we plan some brief multidisciplinary talks and an interactive exhibition. If you are a keen and lively science communicator (prepared to face tough questions from 10 year olds!) then do volunteer to help us out on the day. Or simply come along to support your colleagues.

Email if you wish to volunteer – elaine.murphy8@nhs.net

BIMDG dietitians update

Rachel Skeath

Harriet Churchill (Charles Dent Metabolic Unit, London) has replaced Kit Kaalund-Hansen as the adult dietitian representative on the BIMDG committee. We thank Kit for her contribution over the last couple of years on the committee and wish her well with her move to work with Vitaflo.

BIMDG psychologist's group update

Lynne Aitkenhead

In June members of the BIMDG Psychologists Group held an event together with service users to explore the best ways that psychological services can be provided for people with Inherited Metabolic Disorders (IMDs). Dr Anne Marie Walker and Louise Robertson from University Hospitals Birmingham discussed some examples of effective multi-disciplinary working in their service. Dr Lynne Aitkenhead shared data on current psychology provision and on service user needs, preferences, and experiences. Espen Johnson, service user, screened his prize-winning film *My complex relationship with my disability*. Dr Robin Lachmann, Chair of the Metabolic Clinical Reference Group (CRG), gave an update on changes to broader IMD service models. Finally, Dr Imogen Newsom-Davis from Great Ormond Street Hospital facilitated a workshop entitled *Psychology services for metabolic disorders: What does good look like?*

The BIMDG Psychologists Group would like to improve access to psychological support for people living with IMDs. We welcome contact from any team considering creating a case for psychology provision within their service and are able to share supporting data and guidance.

Stuart Forshaw-Hulme has replaced Collette Stainforth as the Co-chair of the BIMDG nurses' group and representative. We thank Colette for her contribution over the last six years (as she served two terms) on the committee. This year two successful study days were held. One in Manchester with an LSD palliative care focus, organised and chaired by Jane Roberts and one in Leeds with a General metabolic focus, chaired by Collette Stainforth. The BIMDG nurses group will run two study days in 2020 & would like to hear from the membership regarding any topics of interest. There is a map of BIMDG nurses working in the UK, available in the nurses section on the BIMDG website. If anyone requires adding, please contact Nicky Munford, BIMDG nurse secretary. The BIMDG nurses group have also opened a Slack channel for communication. If any nurses would like adding to the group, please contact Rachel Gould (Rachel.gould1@nhs.net).

New BIMDG lay trustee

Bernadette O'Reilly

I am delighted to be asked to serve as a lay trustee for the BIMDG. I do not have a medical background but, as a user of medical services and a private client lawyer working in private practice in Cambridge and London, I hope to be able to contribute to the group's work from a different perspective. Over the years I have worked for a wide range of individuals, trusts, charities and other organisations and I hope that these experiences will help me to make a valuable input to the BIMDG's work.

BIMDG symposium 2019 - Homerton College - Cambridge



This year's BIMDG summer symposium was organised by Addenbrookes Hospital BIMDG members and hosted in the verdant campus of Homerton College, Cambridge University. Situated in south Cambridge and surrounded by leafy college gardens, sports fields and an orchard, Homerton college is a picturesque setting with the stately Cavendish building at its centre. Although originally a Calvinist college located in London, Homerton college moved to Cambridge in 1894 before specialising in teaching and pedagogy. Notable alumni include the abolitionist Samuel Morely, the poet laureate Carol Ann Duffy, and the serial monarch impersonator Olivia Coleman.

Given the continuing progress in the routine use of next-generation sequencing with Addenbrookes and the Sanger institute being a major hub for this emergent NHS service, this year's symposium gravitated towards discussions on how these technologies and services can be provided to the field of metabolic disease. With this said, there was still a broad range of topics pertinent to wider aspects of metabolic disease, with specialist talks from clinicians, scientists, nurses, dietitians, pharmacists and psychologists.



Wednesday morning was kicked-off with a parallel session for the various vocational specialist meetings, adult IMD and the trainee medical and scientific meeting where early-career scientists and clinicians present metabolic cases that are of particular interest. These talks displayed a diverse range of topics from speakers from a wide variety of backgrounds.

The winner of the best trainee clinical/scientific talk was awarded to Erin Emmett, principal clinical scientist from St. Thomas's hospital, London. In brief, Erin discussed a neonate with profound hyperammonaemia that subsequently resolved following medical management. Initial metabolic investigations were normal (although sample deterioration may have occurred) while other clinical/laboratory investigations ruled out other common non-hereditary causes. A diagnosis of transient hyperammonaemia of newborn (THAN) was subsequently made, unusually however; one crisis urine organic acid sample showed significantly increased levels of orotate and uracil (typically indicative of a urea cycle defect). A urea cycle defect gene panel showed heterozygous mutations for *ASL* and *CPS1*, however; these should not have been sufficient to cause the observed hyperammonaemia. As such, this case highlighted that during the metabolic decompensation (or possible reduced hepatic blood flow) that occurs during a THAN episode, abnormal biochemistry can sometimes be misleading and needs to be considered in clinical context.

The afternoon session was chaired by notable geneticist and occasional BBC Horizon presenter, Dr Giles Yeo and commenced with an update by Dr Sarah Bowdin on the national genetic testing service. Outlining the ongoing reconfiguration into 7 regional Genomics Laboratory Hubs (GLH), this new structure is intended to deliver a vision of the NHS as world leading healthcare system in the use of cutting-edge genomic technologies that can predict and diagnose metabolic conditions. Sarah went on to list some of the tangible outcomes already generated from this this new national strategy, including:

- Establishing a whole genome sequencing pipeline.
- [PanelApp](#), a public database and crowdsourcing tool that allows the creation of virtual gene panels that can be stored and queried, providing an opportunity to build consensus and standardise future gene panels.
- Developing new clinical interpretation tools.
- Establishing new clinical working groups.
- Publishing a national [Genomics test directory](#) for rare and inherited diseases and cancer genomics.



The second talk of the session, nutrition and genomics, was a fascinating discussion by Dr Patrick Deegan on “Nutrigenomics” – the interaction between food, nutrition and genes, a potential future area of interest for personalised nutrition and therapeutic interventions. Dr Deegan outlined a theoretical framework of “very rare variants with large effects”, these would include classical IMD’s and monogenic obesity where carrier states are typically selection neutral in a given population; “Common variants with minor effects”, these can be identified via GWAS studies but have little therapeutic value and a final category he was interested in identifying, “relatively frequent variants of moderate size and effect” which may confer a positive selection bias in heterozygotes.

Nutrigenomic variants could confer a food related advantage for macronutrient availability, intermittent food availability or any other diet related selection pressure. A well-known example of this phenomenon includes lactase persistence, although generally lost after weaning in mammals it is retained in around 90% of Europeans and 50% of Mediterranean’s and enables the use of non-human milk as a foodstuff in adulthood. A less known example outlined by Dr Deegan included the possible advantage conferred by the common hemochromatosis conferring HFE variant, C282Y, that may have provided a thermoregulatory advantage to heterozygous humans during the neolithic period as they spread to colder and colder regions of Europe.



Professor Lucy Raymond's talk, 'Future Challenges of whole genome sequencing', started by stating some surprisingly stark statistics highlighting the critical need for better diagnostic and therapeutic interventions for rare childhood diseases. Rare disease (incidence below 1 in 2000) accounts for 35% of all deaths of children under 1 year of age, 30% of all children with a rare disease die within 5 years of onset while rare disease variants may be observed in as many as 6% of the total population.

Given the urgent need to correctly diagnose critically ill metabolic patients promptly, Dr Raymond's group has established a rapid whole-genome sequencing (trio analysis) approach for neonates and paediatric patients in intensive care with a suspected monogenic disorder. To date they have recruited 320 families and provided a genetic diagnosis for 18% of patients enrolled from NICU and 28% of those enrolled from PICU. Professor Raymond went on to describe the often-complete lack of correlation between the "text-book" phenotypes described in OMIM for a particular genetic disorder and those identified by this agnostic approach, further highlighting the importance of these comprehensive genetic technologies.



The afternoon session, chaired by Dr Robin Lachmann, showcased three talks on developments in gene therapy, illustrative of how mature and widely adopted this technology has become. Professor Brian Bigger discussed his groups work using hematopoietic stem cell gene therapy (HSC-GT), a technique which (unlike many gene therapy approaches) can cross the blood-brain barrier and so potentially be used to treat genetic disorders with a neurological component. Their group has developed a HSC-GT strategy for MPSIIIA wherein patient hemopoetic cells are mobilized and CD34+ cells taken up and transduced with a lentiviral vector so that they express functional N-sulphoglucosamine sulfohydrolase enzyme. These cells can then be cryopreserved and sent back to the patient for transfusion.

The final talk of the day was by professor Tim Cox on gene therapy in central nervous system, specifically Sandhoff and Tay-Sachs disease. One recent survey of UK patients with progressive neurodegeneration (n=1,164) found around half were the result of a lysosomal storage disorder with Sandhoff/Tay-Sachs accounting for 10-20% of the lysosomal subset. Professor Cox outlined that part of the difficulty in a gene therapy for Tay-Sachs was that although causative

mutations only occur in the HEXA gene, the resultant hexosaminidase-A alpha subunit must then dimerise with the endogenous beta-subunit. Despite this potential hurdle and difficulties with production of sufficient quantities of AAV vector, this approach has been able to mitigate disease progression in murine and feline models of the disease and has now been moved into an adapted clinical trial format in human patients, focusing on the youngest/most severe presentations before moving onto more milder examples.

The Thursday's morning session, chaired Dr Elaine Murphy, focused on movement disorders and psychiatric manifestation of inborn errors of metabolism. A fantastic talk from Dr De Koning showed some highly illustrative videos of hallmark movement features associated with various metabolic defects. This was followed by a comprehensive discussion on behavioral management strategies for metabolic disease patients by Dr Paramala Santosh.

The second session was given over to 15-minute BIMDG member submitted oral presentations. Dr Mildred Yeo presented clinical audit findings from GOSHH on the effect of newborn screening (NBS) for glutaric aciduria type-1 (GA1). Prior to the introduction of screening they had 18 GA1 cases (10 acute, 4 insidious, 3 via sibling-testing and 1 incidental) of those, 6 subsequently died, median age of 36 months. Following the introduction of screening they have had 9 GA1 cases: 6 via NBS, 2 via sibling testing and 1 false negative with the initial C5DC of 0.51 but subsequent repeats ranging from 0.19-0.34. All were treated successfully with a lysine restricted diet. This talk exemplified the reduced mortality brought about by to the introduction of screening but also highlighted that cases can still be missed and require fibroblast enzyme activity studies.

The winner of the best oral paper presentation was awarded to Dr Gauri Krishna for their study investigating psychological outcomes in adults that were identified and early treated for PKU (ETPKU). This study of 119 adult patients (mean age 32 ± 9) showed ETPKU patients showed only a slight underperformance in cognitive speed and executive function vs. neurotypical controls and comparable quality of life scores - a fantastic win for those responsible for the early diagnosis and dietary management of PKU.



The Thursday afternoon session moved away from typical BIMDG territory by discussing skeletal health in inborn errors of metabolism. Dr Mirjam Langeveld discussed some of the nutritional and lifestyle considerations for optimizing bone health in IMD. Of note, 10-25% of galactosaemia patients have a significant reduction in bone mineral density (BMD), osteoporosis is a salient feature of lysinuric protein intolerance and low BMD is also a concern in various GSD's (particularly 1 and 2). General recommendations included weight-bearing exercise, whereas; activities such as swimming and cycling were less beneficial. Other advice included increasing daily vitamin D dosages from 200 IU per day to 600-800 with adequate intake of calcium. Dr Langeveld also noted the recent interest in Vitamin K2 to bone health and in preventing vascular calcification.

The final talk of the day was delivered by BIMDG summer studentship recipient, Emma Procter, discussing her project at the university of Warwick. Emma showed data from cultured neuronal cells (SHS-5Y), where treatment with methylmalonic acid appeared to decrease mitochondrial respiratory chain enzyme, coenzyme Q₁₀, indicating that this mitochondrial energy generation dysfunction may play a role methylmalonic aciduria pathophysiology (see *BIMDG 2018 winter bulletin for the full report*).

The symposium was brought to a close with the prize awards to the best trainee clinical scientific talk (Erin Emmett) and members oral presentation (Dr Gauri Krishna). The winner of the best poster went to Dr Nour Elkhateeb for his case report series on six cases of SLC35A-CDG. This rare congenital disorder of glycosylation presents with global developmental delay and epileptic encephalopathy. While challenging to diagnose, this disorder is notable as it may be treatable with oral galactose supplementation.

To conclude, this year's summer symposium was a timely deep dive into the progress made by the national genomics service and its potential to revolutionise the diagnosis and understanding of metabolic disease. After many years in development, these services are now finally becoming usable as a routine service. Furthermore, advances in gene therapy have continued apace and now represent a near-future treatment for numerous inherited metabolic diseases. See you all at BIMDG's next summer symposium in Manchester!

Greg Toulson, Clinical scientist & BIMDG bulletin Co-editor

The future shape of chemical pathology training

Andrew Hutchesson
& Peter Galloway

In 2002, the Royal Colleges of Physicians and Pathologists (RCP and RCPPath) agreed a sub-accreditation programme for Metabolic Medicine. One of the drivers (among others) for this was a perception of the need to train adult physicians in the care of Inherited Metabolic Diseases (IMD), as it became progressively more inappropriate for paediatricians to provide care to adult patients. The sub-specialty was conceived as a group of five topics where an understanding of biochemistry is useful; these were Nutrition (including Obesity), Lipids and Cardiovascular Risk, Diabetes, Metabolic Bone Disease, and IMD. Programmes were developed to link Metabolic Medicine with either General (internal) Medicine or Chemical Pathology. Only one programme with G(I)M was established, with only two trainees ever completing (only Dr Robin Lachmann (Queen Square) practices in IMD), and the overwhelming majority of those trained in Metabolic Medicine have a CCT in Chemical Pathology. This option requires trainees to complete Core Medical Training and obtain MRCP(UK) before they commence Chemical Pathology training. It remains possible to train in Chemical Pathology alone, without Metabolic Medicine, with entry directly from foundation training; but overall the introduction of Metabolic Medicine has substantially expanded the experience of most trainees compared to the previous predominantly lipid-only experience ^(Ref 1).

With the expansion of adult services in IMD, a group of clinicians, who predominantly had had additional medical training, obtained sub-accreditation in metabolic medicine and were appointed to posts with IMD roles. There are 210 chemical pathologists in the UK; of these about 9 specialise entirely in the clinical care of IMD patients, about 10 combine “generalist” clinical IMD roles with laboratory roles and about 5 specialise in particular conditions (e.g. porphyrias, alkaptonuria or Wilson’s disease). Thus, from the cohort recently trained, fewer than 10% have any significant IMD role. Over the same period, the complexity of IMD care has increased, with the introduction of enzyme replacement therapy and other new agents (some of these may also have a role in other areas of Metabolic Medicine; for example siRNA agents are being trialed in lipidology).

When Metabolic Medicine was first introduced, it was possible to advertise a training post in Chemical Pathology “with or without” Metabolic Medicine. This allowed the most suitable trainee to be appointed, and an appropriately-qualified trainee was then able to add training in Metabolic Medicine. Following *Modernising Medical Careers* and the introduction of centralised recruiting a decade later, this flexibility was removed. In any one sitting, posts are advertised nationally for entry at ST3 to Metabolic Medicine. This is seen as limiting the pool of potential trainees to those with MRCP and CMT experience. None the less, it remains possible for individual training programmes to recruit to Chemical Pathology at ST1 level; a significant minority of trainees continue to enter Chemical Pathology training via this route, and some have valuable experience in other specialties ranging from general practice to surgery.

The GMC currently requires all curricula to be rewritten. This has provided an opportunity to address some of these issues. The RCP and RCPATH agreed it would be possible to broaden the entrance to those who complete core training and gain the appropriate college examination in: Medicine, Paediatrics, General Practice and Anaesthetics. The Metabolic Medicine curriculum is being incorporated into the overall Chemical Pathology curriculum; at present the name remains Chemical Pathology, but it is planned to review this to reflect the Metabolic Medicine content. The 2-year

CMT programme has now been replaced by a 3-year IMT curriculum, but it has been agreed that Chemical Pathology should be a “Group 2” specialty (along with others without an Acute Medicine component, such as Neurology), allowing trainees to be recruited after completing 2 years; this means that the overall length of the programme to CCT remains unchanged.

Assessment has also been reviewed as part of this. At present Metabolic Medicine is assessed entirely through workplace-based assessments, and it was considered whether to develop a Specialty Certificate Examination. However, the FRCPATH examination in Chemical Pathology is already an exit examination taken towards the end of training, and it was decided it would be more appropriate to increase the Metabolic Medicine content of this for medical trainees (it is also taken by clinical scientists).

The SAC in Metabolic Medicine will continue to review the progress of current trainees in Metabolic Medicine. In the long run, it will be merged with the equivalent committee for Chemical Pathology, administered by the RCPATH but with joint RCP/RCPATH oversight to ensure standards in clinical training are being met. This mirrors the current arrangements for clinical haematology and immunology, save that for those specialties the immediate administration is via the RCP.

For IMT, the aim of the new curriculum is to ensure individuals are exposed to laboratory issues of service and to their clinical management. The current minimal clinical attendance of approximately 25 clinics was not altered. Patients with IMD who become acutely unwell do not always present conveniently to specialist centres, and this curriculum should provide individuals with the skills to guide initial investigations and management and to obtain appropriate specialist support. It should also allow individuals the scope to develop an interest in particular disorders (e.g. porphyrias) if they wish.

Adult physician members of the BIMDG committee and CRG have expressed views that the current Chemical Pathology/Metabolic Medicine training scheme isn't adequate for training needs in IMD. The problem remains that very few centres in the UK have large numbers of patients so experience is variable. Moreover, the range of conditions and of treatments available continues to expand. Most clinicians specialising full-time in clinical IMD have undergone some post-CCT experience, and it appears sensible to formalise this. The GMC has now published the results of its consultation on post-CCT credentials and is piloting these with a few specialties. While they have indicated they will not support any further developments until the results of these pilots are known, IMD appears a prime candidate, in the words of their 4th criterion "extending and enhancing skills for specialists that are not covered in training sufficiently and where there is a patient need". The entry requirements and curriculum for such a credential would need to be defined – some individuals with a background in, for example, neurology or hepatology might be interested – and we would anticipate the BIMDG taking a leading role in this. The GMC has stated that credentials will need to undergo essentially the same approval process as that currently being applied to specialty curricula, and the RCPATH may be able to help with this. Issues about funding for credentials have been passed to the UK medical education reference group and we await more information about this.

For an individual trainee wishing to develop further, options include using the final year of Chemical Pathology training to expand clinic experience, choosing a project and audits related to IMD or seek OOPR/OOPE in IMD. If CCT-credentialing comes to fruition, trainees should have audit/research in IMD plus 1-2 years clinical experience allowing them to apply for these posts.

IMT was introduced in August 2019, and the first cohort of trainees will complete 2 years' training in 2021. We are therefore aiming for the new Chemical Pathology curriculum to be implemented from August 2021 with transitional arrangements covering all current "pure" chemical pathology trainees (i.e. those not including Metabolic Medicine). This means that the first cohort of trainees to be recruited to this curriculum will complete it in 2026. This should give adequate time for the results of the GMC pilots on credentialing to become available, and for a new GMC-regulated credential in IMD to be developed.

<u>Core Training Programme</u>		<u>Speciality Training</u>
IMT (2 years minimum)	Obtained relevant college exam	5 years with requirement to complete FRCPATH
Paediatrics (4 years)		
Anaesthetics (ACCS) (3 years)		Final year can be IMD related with project/audit and 1 year clinics in IMD clinics in first 4 years
GP (3 years)		

Ref: 1) Clinical experience of trainees in chemical pathology: a survey of junior medical staff in the United Kingdom. Galloway P J, Bayly GR, Badminton M. J Clin Pathol 1998, **51**: 711-2

The Future shape of paediatric metabolic training **Saikat Santra**

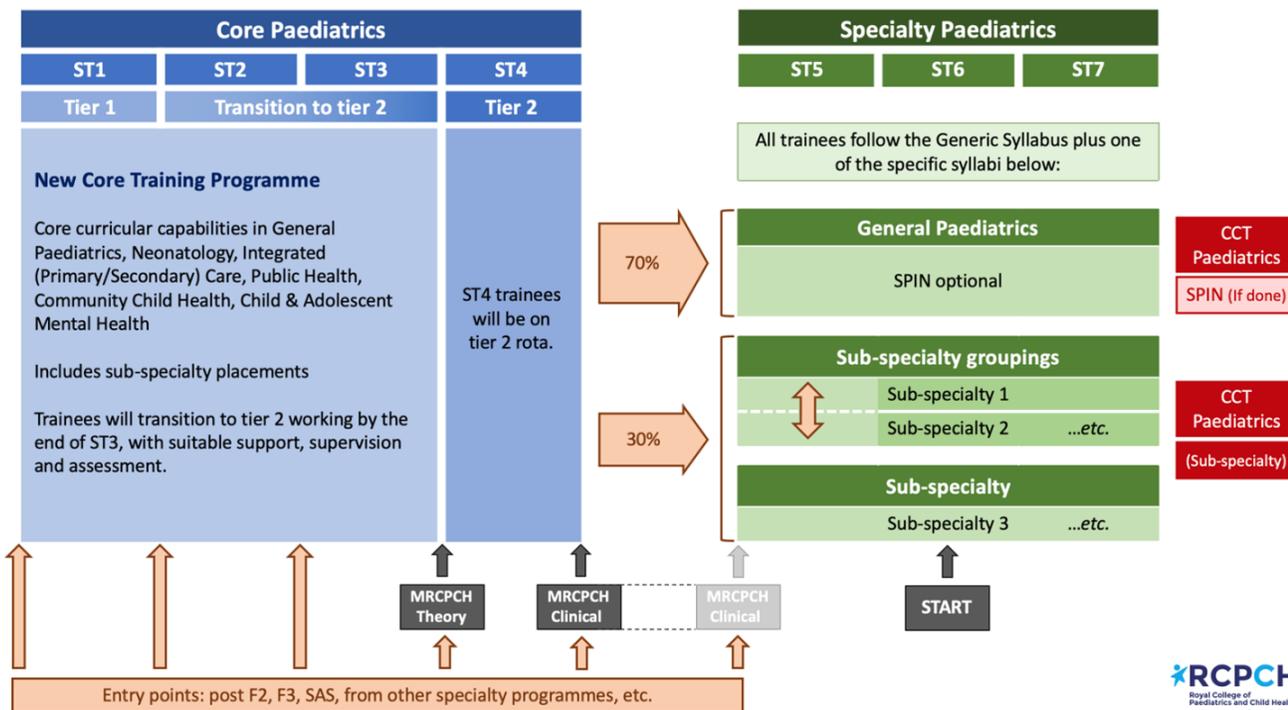
The way all doctors in the UK are trained is in a constant state of flux but one of the more radical shake-ups of medical training is currently in the process of being finalised and it might be useful for BIMDG members to know how this is likely to affect future trainees in Paediatric Metabolic Medicine.

Professor David Greenaway's report into the Shape of Training, published in 2013 (and accessible to all at <https://www.shapeoftraining.co.uk>) recommended a range of changes to the way that all doctors are trained after medical school and each Medical Royal College has been tasked with reviewing their training programmes in light of these recommendations. The Shape requirements are summarised as five key principles, such that any new training pathway must:

1. Take account of and describe how the proposal will better support the needs of patients and service providers.
2. Ensure that the proposed curriculum to CCT (certificate of completion of training) equips doctors with the generic skills to participate in the acute unselected take and to provide continuity of care thereafter.
3. Where appropriate describe how the proposal would better support the delivery of care in the community.
4. Describe how the proposal will support a more flexible approach to training.
5. Describe the role that credentialing will play in delivering the specialist and sub-specialist components of a curriculum.

The RCPCH has been developing its response to the Shape of Training review over the last five years and the proposed model has undergone a number of revisions. As one of the smallest paediatric sub-specialities, the Metabolic Medicine CSAC has had to be quite vocal in this process as the overwhelming theme of the review is that medical training programmes need to produce more generic doctors more quickly as this is what patients and the NHS are perceived to need more of. As a subspeciality trying to train a small number of people in a highly specialised area of medicine, this goes rather counter to this overall direction of travel. Indeed one of the earliest proposals was that all paediatric trainees complete much shorter training only in general paediatrics with anyone wishing to develop a subspeciality interest only doing so after their CCT. Thankfully this proposal was rejected early on (although were it not for the vocal contributions of the metabolic medicine CSAC and other small specialities, our subspeciality may have been earmarked as an area suitable for so-called post-CCT "credentialing").

On March 26th 2019, the RCPCH held a consultation with representatives from all CSACs (attended for the metabolic CSAC by Maureen Cleary, Shamima Rahman and Arunabha Ghosh) and following this the proposed model below appears to be crystallising:



Some of the key changes that you will note from this are that:

- Indicative training time has reduced for all paediatricians. There is now no “ST8” year – most paediatricians will come out in 7 years rather than 8 years.
- There is now no “middle tier” of training which in the past corresponded to ST4/ST5 and before that to “Core Registrar” training. Trainees will now complete 4 years of “core training” (corresponding to what many of us will remember as SHO training together with at least one year of working as a middle grade).
- Trainees no longer have to pass their MRCPCH clinical exam to work on a middle grade rota – but they will need to have done this before embarking on higher speciality training – which will either be in general paediatrics or a subspeciality.
- Core training still includes the possibility of sub-speciality placements, but there will also need to be more generic/integrated exposure to such areas as community paediatrics, child mental health, public health and primary care.
- It is proposed to promote flexibility in training by allowing trainees in more naturally allied groupings of specialities to transfer at ST5 between training programmes if (RCPCH’s words) they “may have re-evaluated the wisdom of their original choice”! Thus it might be possible for someone who started out in say Paediatric Neurology, Hepatology or Palliative Care Medicine for example to transfer into Paediatric Metabolic Medicine (and vice versa). This wouldn’t be an automatic right, however, and any transfer would need to be subject to placements being available and subject to a further sub-specialty application and appointment in open competition, to ensure equity amongst ST4 and ST5 applicants.

You might be wondering how that might affect future training in paediatric metabolic medicine and we can foresee a few things to be aware of:

- Centres which currently host “SHO” level trainees in metabolic medicine may find themselves under pressure to keep those posts given that core trainees now have a much broader curriculum to follow. Although the pathway states that subspeciality attachments can still be included in core training – they may become fewer and farther between and may need to be shared with other specialities or other aspects of core training.
- Trainees will need to decide whether to train in metabolic medicine earlier than they do now and most likely without previous experience. At least in England, Health Education England is considering developing another category of out-of-programme training called OOP-P(ause) to enable interested trainees to apply for up to 2 years between ST4 and ST5 to get experience in subspecialities that will help them make informed decisions about applying for GRID training. Expect trainees thinking about this to be asking for clinical fellow-type posts to help them make up their mind. In Scotland, Wales and Northern Ireland it is likely that deaneries will do a similar thing within existing OOP-E(xperience) and OOP-T(raining) guidelines. Also core trainees will be encouraged to apply for study leave to have “taster days” in different specialities which may be another way to attract good trainees into metabolic medicine. Please do consider how your department could showcase the speciality in a day if a trainee asked for a taster day with you.
- Metabolic trainees will not be expected to cover the same curriculum as general paediatric trainees (which is already now the case with the RCPCH Progress curriculum) but this may leave them less able to take up a Consultant post as a general paediatrician after CCT. It will be increasingly important for trainee numbers and expected consultant numbers to be closely matched.
- Trainees will be on middle-grade rotas earlier as the transition to tier 2 working is a key feature of core training. Consultants should be mindful of this when discussing cases with middle-grade trainees. RCPCH is developing a new type of workplace-based assessment called Entrustable Professional Activities (EPAs) to help evidence that trainees are capable of tier 2 responsibilities. Please do engage with these if asked to do so.

- RCPCH anticipates that this two-level pathway, along with a curriculum which is assessed by outcomes/capabilities rather than just time spent, will suit academic trainees and facilitate taking time out for research. OOP-R(earch) is expected to continue operating as it does.
- Trainees will be increasingly reliant on workplace-based assessments to evidence their training and it is really important that anyone involved in assessing trainees does so promptly and constructively.

Finally credentials aren't completely dead and buried. It is likely that things that are currently offered as SPIN (SPecial INterest) modules will eventually also morph into something that could be offered post-CCT to someone wanting (and more importantly needing for local service provision) to develop expertise in. There are no metabolic SPIN modules although the CSAC is producing a document along these lines that could be used to help general paediatricians who wish to be local links into a regional metabolic network and this may in due course become a post-CCT credential. Credentials may also in future offer a route for formal accreditation for clinical fellow-type training posts which is something we currently can't offer.

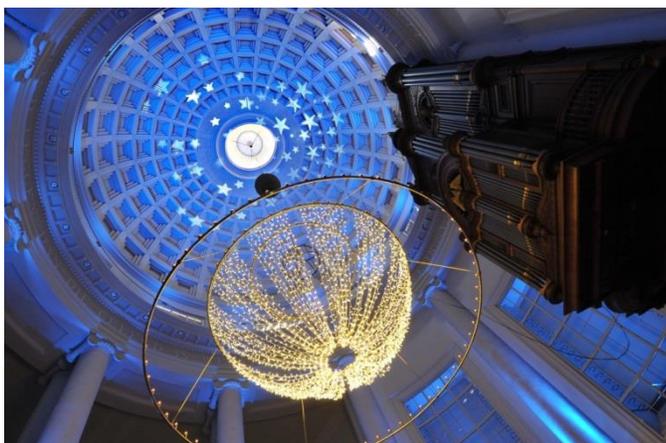
The RCPCH hope to implement the new pathway from August / September 2021, subject to GMC approval....but you heard it here first!

Saikat Santra
Consultant – Birmingham Children's Hospital
RCPCH Paediatric Metabolic Medicine CSAC Chair

Meeting report: INFORM Symposium – Amsterdam Sept 2019 **Joanne Croft**

I attended the 6th Annual International Network meeting for Fatty Acid and Oxidation Research and Management (INFORM) at which 25 countries were represented by over 120 attendees. The meeting was held in Amsterdam in the Koepelkerk Conference Centre, a beautiful 17th century domed church which is used for weddings as well as for conferences.

The meeting started late Sunday afternoon with the Keynote presentation given by Professor Deborah M Muoio from Duke Molecular Physiology Institute entitled 'Research on Fat Metabolism, Carnitine and CrAT'. Her presentation covered the role of CrAT (carnitine acetyltransferase) and Sirt3 (Sirtuin 3) in the deacetylation of mitochondrial proteins, acting to mitigate mitochondrial lipid stress via negative feedback on fatty acid oxidation.



Picture: Koepelkerk Conference Centre

Following this there was a networking reception, including poster presentations, during which the 5 authors short listed for the poster prize gave a short oral presentation on their work. I was particularly interested in the poster which concerned a retrospective study on patients diagnosed with multiple acyl-CoA dehydrogenase deficiency (MADD) in the Netherlands. A MADD disease severity scoring system was developed which was based on clinical symptoms and FAO flux assay results. The hope is this may be useful in improving early prediction of disease severity in order to start preventative treatment and follow up appropriately. This is especially important in countries where MADD is included in newborn screening programs. The author was one of 2 joint winners of the poster prize.

The meeting resumed early Monday morning with the first session entitled 'FAO Outside the Box'. Presentations included the impact of HADHA (trifunctional protein alpha subunit) on cardiolipin metabolism, metabolic control of neural stem cell activity in the brain and SIRT5 involvement in hepatic metabolism of medium chain fatty acids. I was particularly interested in a presentation concerning the enhancement of VLCAD activity in VLCAD knockout mice using mRNA technology, as this may have potential as a future treatment option.

After coffee break the theme was 'Novel Aspects of Fatty Acid Oxidation'. Presentations included one by Dr Mike Bennett from the University of Pennsylvania School of Medicine who talked about novel physiologic roles for acylcarnitines. He presented evidence that circulating acylcarnitines are not just a metabolic overflow but are likely to play a signalling role in the body as well as providing an energy source for peripheral tissues.

Monday afternoon began with a presentation by Melanie Gillingham concerning the use of essential fatty acid measurement in assessing deficiency in FAODs. Patients with a long chain FAO defect are treated using low fat diet; therefore it is important to ensure these patients do not become deficient in the essential fatty acids. Clinical sequelae of deficiency include decreased growth, impaired immune and retinal function and skin rashes. She showed that the method for measuring the essential fatty acids e.g. either by qualitative or quantitative assay, is important in the diagnosis of deficiency. Use of qualitative analysis, which uses ratios to assess deficiency, can be unreliable in the context of a very low fat diet.

Following this a 21 year old patient with trifunctional protein deficiency gave a talk about aspects of having to live with his condition, especially since he left home to go to University. He was not diagnosed until around 9 years of age when an anaesthetist decided to send off the relevant tests and the cause of his repeated episodes of severe rhabdomyolysis was established. At University he has to be very careful to listen to his body and not to always try and keep up with his peers.

The last session of the day covered inflammation and FAODs. This included a fascinating presentation given jointly by Jean Bastin and Jerry Vockley on the control of regulation of fatty acid oxidation and the treatment of FAODs with peroxisome proliferator activated receptor (PPAR) agonists. PPAR agonists, including REN₀₀₁, have been shown to modulate expression of genes for fatty acid oxidation enzymes, leading to increase in protein, enzyme activity and a decrease in cellular stress. PPAR agonists therefore have potential in the therapy of FAODs.

I noticed throughout the meeting that use of the Seahorse XF analyser (Agilent) is becoming more widespread. This analyser is a very sensitive means of assessing oxygen consumption and mitochondrial stress in cultured cells.

We are very interested in obtaining a Seahorse analyser for developing assays at Sheffield Children's NHS Foundation Trust but unfortunately it is not easy to obtain the finances to support this at the present moment.

I wish to thank the BIMDG for awarding me a grant enabling me to attend this meeting.

Joanne Croft

Principal Clinical Scientist, Sheffield Children's NHS Foundation Trust

BIMDG Travel grants

To help assist members attend conferences, meetings or workshops in the area of inherited metabolic conditions, the British Inherited Metabolic Disease Group (BIMDG) will consider travel grant applications. This is limited to a maximum of £500 pounds and is restricted to individuals who have been members of the BIMDG for 2 or more years. To apply, follow the contacts list on the BIMDG website members area and email an application to general contacts, including the name of the meeting and the cost of travel.

A workshop on Molybdenum Cofactor Deficiency, led by Bernd Schwahn, will take place in Manchester on Thursday October 1, 2020. Further details will appear on the website next year

SAVE THE DATE

BIMDG ANNUAL CONFERENCE - 2020

British Inherited Metabolic Diseases Group

**CONFERENCE 2020
MANCHESTER**

THURSDAY 25TH & FRIDAY 26TH JUNE

Venue : Pendulum Hotel & Conference Centre
Accommodation : Pendulum Hotel & Conference Centre

Symposium Dinner : Thursday 25th June
Same Venue

Pre-BIMDG event : Further details to follow in
December
Wednesday 24th June from 5pm-9pm
including supper

REGISTRATION OPENS PRE-CHRISTMAS

**FOR FURTHER DETAILS ON THE PROGRAMME &
ABSTRACT SUBMISSION VISIT**

www.bimdgconference.com

Jacqui McAleer, JM Associates conference organiser for BIMDG

Email : jmassociates1@me.com; Tel : +44 (0) 7836650782

Register now on the BIMDG website for a workshop on gyrate atrophy which will take place in London on **27th March 2020**. Registration fee: £25 (members) or £35 (non-members). Full programme available on the BIMDG website.

Topics to be covered:

- Pathophysiology of gyrate atrophy
- Eye disease in gyrate atrophy
- The role of NGS panels in the diagnosis of gyrate atrophy
- Dietary challenges in the management of gyrate atrophy
- Body composition as a tool to assess myopathy in gyrate atrophy
- Creatine supplementation and monitoring in patients with gyrate atrophy
- Pregnancy outcomes in women with gyrate atrophy
- Gyrate atrophy registry

BIMDG studentships

The British Inherited Metabolic Disease Group (BIMDG) will consider supporting undergraduate students to gain valuable experience in the area of inherited metabolic disease. A stipend of £200 a week, for a maximum of 8 weeks, is available. It is anticipated that up to two studentships will be awarded each year.

Applications are invited from disciplines relevant to patients with inherited metabolic conditions.

Students will need to identify a supervisor or vice versa. Potential supervisors should apply by submitting a one-page (A4) project proposal that includes background, aims and approach to be employed. A statement of how the project will benefit patients with inherited metabolic disorders should be included. A CV of the prospective student must also accompany the proposal.