BIMDG Bulletin

British Inherited Metabolic Diseases Group

Winter 2020 bulletin

- 50 Years of PKU screening
- PKU - a patient perspective
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- Dates for your diary
- In memory of Maggie Lilburn

BIMDG
British Inherited Metabolic Disease Group

Message from the chair — Elaine Murphy

Well – it's nearly over – 2020 – a year none of us will ever forget. Traditionally this is a time to give thanks, so I am going to reserve my greatest thanks for our colleagues in science, the virologists and the vaccine developers.

The fantastic cover illustration of this bulletin by Taila Wallace reminds us that life goes on and despite everything, when all of routine medicine looked in danger of being overwhelmed, the newborn screening programme kept running thanks to the dedication and hard work of everyone involved.

I wish you all a peaceful Christmas break, hopefully with time to relax. Even if meeting with family and friends is difficult this year, we end the year with real hope that next year things will be better.

Bulletin editorial

In a break from the ongoing challenges that COVID-19 has presented to many in the metabolic field, this edition of the BIMDG bulletin will focus on the achievements of 50 years of newborn screening for PKU. Susanne Ford has been kind enough to write a short history of PKU screening, while our cover art by Taila Wallace and patient perspective article by Teresa Speer are both the work of PKU patients.

In what will be an ongoing feature of future bulletins, Springer publishing has allowed BIMDG readers to review textbooks that may be of interest to the metabolic community (an ideal Christmas present for a loved one!).

We would also like to thank BIMDG members for all of their efforts over the last year and wish you all a happy (and hopefully more normal) 2021.

BIMDG Specialist Nurses group update — Rachel Gould & Stuart Forshaw-Hulme

We hope all our Nursing colleagues are ok. It has been a difficult year due to COVID and we have not been able to meet face to face. To aid communication we have set up a Slack group for BIMDG nurses. Within the group, we have 2 channels (LSD & General), so nurses can chat with colleagues. If you are a BIMDG nurse member and want to join the Slack group, please email Rachel.gould1@nhs.net and you will be added. Additionally we will be arranging for a Virtual Nurse meeting at the Summer Virtual BIMDG meeting. Please email Rachel or Stuart (stuart.forshaw-hulme@nhs.net) any suggestions you have for discussion topics for the meeting. Take care and have a lovely Christmas.

Stuart & Rachel, BIMDG Nurse Group Co-Chairs

BIMDG Dietitian group update — Anne Daly

Despite the unprecedented times of COVID over the last year we would like to say thank you to all who have helped in a number of publications. Citrin Deficiency paper was published in 2020 alongside Development of national consensus statements on food labeling interpretation and protein allocation in a low phenylalanine diet for PKU. In addition the Dietetic Formulary together with the Medical Formulary was produced and is now accessible to everyone on with web site.Thank you again to everyone's help and commitment in getting this work produced.

There are plans moving forward to set up a working group on standardisation of protein values used in the other amino acid disorders. We look forward to moving these plans forward, maybe taking the good points of Zoom and Teams to aid collaboration and reduce CO2 !

BIMDG calendar for 2021

Now that we have all got to grips with various platforms for recording and sharing presentations, slides etc – we aim not to postpone any further events in 2021, but if they cannot be run in person to run them digitally. At present these are the events in the BIMDG calendar for 2021:

- How to Improve IMD Monitoring with Patient Collected Samples – Workshop – 12 February 2021 (digital only). See final page of bulletin for details.
- The Cambridge Festival, Spring 2021 – likely to be a digital only event – but we hope to participate.
- Gyrate atrophy workshop – will run in 2021 (either digitally or in person, details to be announced).
- Molybdenum cofactor deficiency workshop – 13 May 2021 (either digitally or in person, to be confirmed).
- BIMDG Annual Symposium, Manchester – will run in 2021 (as a one-day digital event, details to be announced).

Article: 50 (+1) Years of Newborn Screening, for PKU

Suzanne Ford
Dietitian Advisor for NSPKU

Newborn screening (NBS) for Phenylketonuria (PKU) is one of *the* most important public health interventions in the last 50 years and the screening programme in the UK was organized in 1969. This piece is a belated 50th birthday celebration of NBS for PKU and a reminder that there is still work to do to make uninterrupted treatment a reality in the UK.

PKU history started in Norway, 35 years before universal newborn screening when, in 1934 Dr Asbjørn Følling was approached by Borgny Egeland, whose two children were severely developmentally delayed. Testing urine with ferric chloride revealed phenylpyruvate – and from that Folling deduced phenylalanine was the cause of toxic metabolites affecting Borgny's children. Folling enlisted a geneticist and a medical student and found 420 children with developmental delays. There were 9 positive results on urine testing. He identified family links between these children and thus established a genetic basis for the disorder - Autosomal Recessive inheritance pattern.

In 1949 Horst Bickel, interested in PKU, proposed all "mentally retarded" patients attending Birmingham Children's hospital should be screened. In April 1951, the urine of the third child who was screened, tested positive. This was Sheila Jones, aged 17 months, could only sit and rocked continuously; her mother demanded a treatment be found. Louis Woolf, at Great Ormond Street, worked with Horst Bickel and Evelyn Hickmans (also of Birmingham) to contrive a means of removing phenylalanine from a casein hydrolysate using a charcoal column. The revolting result was given to Sheila from December 1951, reported in the Lancet (1) and there are videos on Youtube showing the difference this first protein substitute made to Sheila.

With a clinically effective treatment now available, the phenylpyruvate test was taken up widely. From 1957 to 1969 in the UK health authorities used this nappy test by means of ferric chloride impregnated strips – Phenistix. The test was only relatively reliable – some health authorities administered routine repeat tests in acknowledgement of this; urine reportedly needed to be fresh and cool for more accurate results. The 1963 MRC report from Moncrieff of GOS and others pointed towards improved outcomes with earlier diagnosis (2). (The diet continued to be quite a "palatability challenge" during this time).

In the States 1958 Robert Guthrie had a niece diagnosed aged 15 months old with PKU who was sadly, and it was then thought inevitably damaged. Dr Guthrie developed a bacterial inhibition assay using dried bloodspots on filter paper placed onto agar (3). This assay proved more sensitive and found more patients than the ferric chloride urine test when he compared the two. Guthrie immediately proposed the utility of testing babies on their day of discharge from the maternity hospital. After considerable campaigning, fending off those with commercial interests, Robert Guthrie himself produced the testing kits at a low cost and the concept of a screening scheme was agreed upon in America and in other parts of the globe.
Wilson and Junger were the first to describe the screening principles in 1968 (4). All subsequent principles of newborn screening have been a development from these, and they can be found on the World Health Organization website.
The principles of newborn screening are:

- Only worthwhile if a test is available with sufficient sensitivity and specificity to be applied with an acceptable positive predictive value, for diseases with
- Identified, effective treatment, *and*
- Early diagnosis and the treatment offer benefits, then:
- Cost-benefits could weigh in favour of screening.
- Review the expected incidence and "disbenefits" of false positive results.

In the 50 years since Newborn screening was launched over two and a half thousand babies have been detected with PKU; the annual cost of both the screening programme and treatment is about £8 million and the annual cost of residential care would be in excess of £60 million (5).

The UK positive PKU screen figures, currently unpublished (6), from 2018-19 are as follows:

	England	Northern Ireland	Scotland	Wales
Number of PKU screen positive babies	85	8	11	6

Effectiveness of treatment has improved in that prescribable low protein foods and protein substitutes have been developed into a range of *almost* palatable products which would astonish the PKU pioneers of the 50s and 60s. Multidisciplinary paediatric teams help parents come to terms with a positive screen result, and the National Society for Phenylketonuria aims to provide a community for peer support and reliable information from diagnosis onwards.
Of Note - accessing treatment via primary care means that, in a recent patient survey, **47%** of respondents experienced running out of treatment due to delays or obstructions (7). When we consider if the Wilson and Junger/WHO principles of newborn screening have been met, then, the answer is surely yes, but with a caveat that the processes in administering the treatment is that it is only effectively delivered without disruption for part of the time.

It has been an eventful 50 years and for PKU patients to get uninterrupted access to an effective treatment, then the next 50 will be just as eventful.

1. Bickel H, Gerrard J, Hickmans EM (1953). Influence of phenylalanine intake on phenylketonuria. Lancet 265:812-813
2. Treatment of Phenylketonuria. (1963). *British medical journal*, *1*(5347), 1691–1697.
3. Guthrie R, Susa A; A Simple Phenylalanine method for detecting phenylketonuria in large populations of newborn infants; Pediatrics Sep 1963, 32 (3) 338-343;

4. Wilson JMG, Jungner G. Principles and Practice of Screening for Disease. World Health Organization: Geneva, 1968. https://apps.who.int/iris/handle/10665/37650
5. Brown M. C. J. and. Guest J. F. Economic impact of feeding a phenylalanine-restricted diet to adults with previously untreated phenylketonuria; Journal of Intellectual Disability Research 1999; 43, 30-37
6. Personal Communication (Cavanagh C, Programme Manager - NHS Newborn Blood Spot Screening Programme, PHE Screening, to Ford 2020)
7. Ford S et al Prescribing issues experienced by people living with phenylketonuria in the UK; Molecular Genetics and Metabolism Reports 21 (2019) 100527

Article: a patient's perspective of PKU — Teresa Speer

My name is Teresa Speer (nee Side). I was born on 4th February 1969 at St Richard's Hospital, Chichester in West Sussex. I had the Guthrie test and when my results came back positive for PKU they sent them off again because they didn't believe the results as I was the first one to be diagnosed in Chichester! Mum and Dad were informed that I had Phenylketonuria when I was 8 days old . My Mum remembers being absolutely devastated, particularly as there was hardly any information they could give them about prognosis, treatment or outcomes! Mum was given a photocopy of a text book with some information, marked 'For medical use only!'

When meeting with the doctor and dietician when I was several weeks old they were told that there was a high risk of brain damage, death or severe mental and physical disabilities. My early days of diet, supplement and vitamin drops was fraught with me never being able to take all of it as it was so filling, this was very stressful for my Mum as she worried that I would have brain damage if I didn't stick to all the amounts that we had been told. When we moved to Plymouth when I was one year old there wasn't a dietician to start with and then with the paediatrician they didn't really know what to advise or give any help so Mum and Dad felt very much on their own.

Aminex rusks were the only food item on prescription at the time. There weren't any prescription milks then, and I would have half a weetabix with water. From about toddler age I would spit out my supplement and it would take 2 hours every meal time to get it into me!

Growing up the foods available on prescription were very limited and baking cakes, puddings etc was not always very successful. I remember having bread in a tin, which had to be boiled on the hob! I would have lots of fruit and vegetables, and at teatime use my exchange allowance up for crisps. My Mum was very strict with my diet and although I went to children's parties with my own packed tea it was difficult as I always felt different. I would have PKU fairy cakes that mum would make etc but there wasn't much variety on the exchange lists in those days. Family holidays would always be in the UK as it was considered too risky and difficult to manage the diet abroad.
At the age of 13 I was told I could ease my diet and had my exchanges doubled. The excitement as we left the clinic and went to the hospital café for a doughnut was amazing! Unfortunately, this was fairly short lived as I started to not feel well, not concentrating at school (in fact my worse term ever on my school report), headaches and emotional so that I asked the consultant if I could go back to my original number of exchanges. Later when I was older and had left college I eased it again and thought I was doing fine, until I enrolled in night school and found I couldn't remember what I had learned from one week to the next. With the help of my dietician I went back to 8-10 exchanges and stayed on that ever since, with the exception of pregnancy.

When I was pregnant I was able to eat lots of different foods in the later weeks which was lovely but I do find it more difficult now to stay good as I know all the things I liked!

The range of items available today is incredible compared to the early years and it is so much easier to manage the diet. The supplement is now nice to drink and not a torture to have at each mealtime. It is still very difficult to eat out and I am not very confident to ask about making changes to items etc as I don't like to draw attention to myself. Holidays are self-catering which I prefer as I can have total control, with a few meals out as a treat.

Now at the age of 50 it would be amazing to have a treatment which meant I could eat normally and would love my Mum to see that day come. My daughter, Kirstie isn't PKU but she knows she is a carrier. She is 23 and achieved a 1st class degree in Biomedical Science at university. She has now started her first job working for Public Health England. Maybe one day she will be involved in future development of treatments or a cure for PKU!

This article was originally authored for the national society for PKU (NSPKU).
Find out more about the NSPKU and how you can help support them as an organisation.

NSPKU

Meeting report: BIMDG trainees meeting, Mitochondrial Diseases

Dr. Sarah Hulley

In a year that has been blighted by cancelled meetings and the establishment of virtual conferences, we were extremely lucky that the 2020 BIMDG trainees meeting went ahead as planned! The Wellcome centre for Mitochondrial Research very kindly hosted the meeting in Newcastle-upon-Tyne.

The mornings first sessions were headed up by Dr Victoria Nesbitt and Dr Rob Pitceathly who had kindly joined us from the Rare Mitochondrial Disorders Service in Oxford and London respectively. The key message from Dr Victoria Nesbitt's talk on clinical presentation in children was: Any Age, Any Organ, Any Time. Case presentations demonstrated the broad spectrum of clinical symptoms associated with MTTL (m.3243A>G) and its association with several clinical syndromes (including Mitochondrial Encephalopathy, Lactic Acidosis & Stroke-like episodes (MELAS) and Maternally Inherited Diabetes & Deafness (MIDD)). Adult presentations were covered by Dr Rob Pitceathly. He illustrated previously unrecognised mitochondrial phenotypes (bowel dysfunction, lower urinary tract symptoms, vestibular dysfunction and mood disorders) that have been identified from the large, deeply phenotyped cohorts.

Professor Rob Taylor delivered an excellent session on the laboratory diagnosis of mitochondrial disease. In the current era, genetics is the first line investigation for suspected mitochondrial disease but functional validation of variants of unknown significance is becoming increasingly important. The outline of how this is achieved was very insightful.

Professor Bobby McFarland and Catherine Feeney then lead us through the reproductive choices for women with mitochondrial disease. Preimplantation genetics looks to identify embryos for transfer that have a heteroplasmy level of less than <30%. Mitochondrial donation (MD) was discussed and they are currently studying neurodevelopmental outcomes at 18 months of babies born using MD.

We were very fortunate that our meeting allowed us to coincide with a visit from Professor Laurence Bindoff (Bergen, Norway). His team has been developing a cellular model for POLG that mimics in vivo issues using iPSC derived stem cells. Their current model shows loss of complex 1, mtDNA depletion, loss of ATP, activation of mitophagy and changes in redox potential.

Dr Yi Ng started the afternoon session with some of the findings coming to light from the Mito cohort study, which has now recruited in excess of 1800 patients. Dr Grainne Gorman then got us thinking about the constraints of various mitochondrial clinical trials and the limitations of many of the outcome measures currently used. The afternoon was brought to a close following 4 very stimulating presentations by some of the trainees.

The trainees would like to extend their thanks to the team in Newcastle and to everyone who contributed to a very successful meeting.

Book Review: Varun Sethi
Atlas of Clinical Neurology, 4th Edition. Editor Roger N Rosenberg

The eBook of the 4th Edition of the Atlas of Clinical Neurology, like previous editions of this very comprehensive book, maintains its goals of providing a holistic and visual concept of neurological disease. Spread over a canvas organised into fourteen chapters that include developmental disorders, genetic diseases, neuroendocrine disorders, critical care neurology, cerebrovascular disease, dementias, behavioral neurology, neurooncology, movement disorders, epilepsy, neuromuscular diseases, infectious diseases, neuroimmunology, and headache, this book is a collection of excellent images and figures, where each picture is truly worth a thousand words.

Unlike other books in the field, this book brings together, in one place, images from clinical medicine, neuropathology and neuroimaging, and in addition has a constellation of cartoons, pedigree charts, and algorithms that express disease mechanisms, pathogenesis, diagnosis and treatment. In a career as a neurologist, the journey from day one of medical school to day one of being a neurologist, and beyond, may often still not allow us to see or examine disease rarities, even though the theoretical literature of these conditions is the substance of most textbooks. Seeing some very rare photographs allows us to visualise characteristic presentations and will certainly be a reminder to observe for these clinical findings more carefully. This is true in particular of the many presentations described in the chapter on developmental anomalies.

Sections such as cerebrovascular disease are predominantly a collection of images and pictures, whereas other chapters consist of text with more figures and tables. Some of the radiology images, are understandably rare, and thus of a slightly dated quality but in other sections this is compensated by information from research with up to date literature on FDG PET , fMRI studies and depiction of histopathology and electron microscopy describing newer concepts and findings.

An added advantage of seeing a very visual book as an e-book is the ability to zoom in to some of the photographs. I have never more clearly appreciated the Lisch nodules over the iris in neurofibromatosis 1. Neurocutaneous syndromes are well described. Movement disorders would certainly benefit from additional links to relevant video clips; this chapter in particular discusses treatment strategies in length, examining various medications and side effects. The association of vitamin deficiencies is not new in the field of neurology and perhaps there is room to add information on examination findings in these presentations. Clear examples of fundoscopy are highlighted in some sections but it would be helpful to also see images depicting eye movement disorders.

The reader will clearly benefit by seeing knowledge on disease conditions ‘come together’ in a concise collection of relevant photographs and images in this text. The pathological heterogeneity of frontotemporal dementias, for instance, is very well simplified with a combination of imaging and algorithms. A rare opportunity to find images on neurophysiological investigations and concepts, including NCS, EMG and EEG adjacent to relevant MRI and neuropathology will make this book a favourite to the keen resident or registrar in neurology. The guidelines for treatment are at places more generic and should be taken in context, and local practice guidelines must remain a reference.

A mammoth task like this, bringing together contribution from a long list of contributors, does come with an inherent heterogeneity in style and layout, but at large the book follows a systematic approach within each section. Numerous neurology topics are examined in this text and pictorial collection, thus there is some degree of overlap and duplication in the chapters. A homogenous colour tone across tables, algorithms, and images would allow for an easier organisation of thought and a section on key points per disease or chapter was also felt needed. Diagnostic criteria and classifications are also earmarked in some chapters. It is important that the reader remain cognisant of subtle differences in terminology within the same disease entity when being referred to in the context of a pathological classification vs. a clinical classification.

This book serves to draw in interest from the novice medical student and continue to be of relevance for residents and registrars in neurology, neuroradiology in particular, preparing for the exit exams or board certifications, and in addition reman an important reference for routine in-patient clinical ward neurology and outpatient neurology alike. Some sections are covered more in-depth than others, and thus this book remains an important adjunct to other standard review books. It fills an important void of having more visual reference texts in the field of neurology.

Book Review: Advancements in Mass-Spectrometry in Biomedical Research, 2nd Edition. Editors AG Woods & CC Darie

Greg Toulson

Mass-Spectrometry (MS) has been with us for more than 100 years, starting in earnest in with the discoveries of AJ Dempster in 1918 and FW Aston in 1919. It would not be an exaggeration to state that MS has contributed towards the understanding of nearly every discipline in pathology and basic biology. Given the (extreme!) maturity of this technology, when classified as a field unto itself, developments in MS as a discipline would be characterised as small, incremental technological advancements that then feed through to an exceptionally diverse array of specialist fields. This diversity makes forming a holistic view of the state-of-play extremely challenging, however; Advancements in Mass-Spectrometry in Biomedical Research strikes an interesting but somewhat lop-sided balance.

Now in its second edition, Advancements in Mass-Spectrometry in Biomedical Research comprises 46 separate chapters, the majority of which are self-contained review articles with a small number of notable journal articles that demonstrate novel methods or experimental designs. The latter do a good job at illustrating the diversity of the field from ‘analysis of breast milk for cancer biomarkers’ to a study on the ‘proteomic analysis of saliva from participants given an exercise in expending mental energy’.

While discussing (to various extents) the three major ‘omics’ fields where MS plays a significant role: proteomics, lipidomics and metabolomics; this book skews very heavily towards proteomics and the various methods for protein analysis. This is an area I knew little about before reading this text-book and its numerous chapters on the topic give a clear and comprehensive account of the technical and data-analysis strategies required. Although written in 2014, the approaches outlined remain at the core of proteomics. With this said, the field has progressed significantly in the intervening period, the human proteome project (HPP) having recently announced >90% identification completion rate for mapping the Human Proteome.

Unfortunately, metabolomics, a field that is probably more immediately relevant to IMD scientists, is not covered in any great detail in this book. The two chapters on the topic do offer a good introduction to the field while the second gives a crash course in data analysis. This short-coming is possibly due to proteomics being a more established field at the time of publication and I would hope that a future edition could devote a more time to the topic. I would direct BIMDG readers with an interest in the field towards the monthly newsletters from the metabolomics society, which each contain a list of new and interesting metabolomics papers.

As this book is focused on MS in research, diagnostics are not a focus and so many in the IMD field may not immediately find this book relevant; however, what this text does well is show how adaptable MS can be and how many applications can be paired with MS. This points to numerous future potential diagnostic paradigms that may prove useful, either independently or when used in combination with whole-exome sequencing data. These include analysis of post-transcriptional modifications by MS, immuno-capture MS and electrospray imaging by MS, opening a potential future door to MS utilisation in histology.

Overall, I would recommend this book to anyone with an interest in what is possible when using MS outside of the single analyte, quantitative assay paradigm that increasingly forms the bread and butter of laboratory medicine. Metabolic disease features rarely in this text book, however; it does a relatively good job at condensing MS developments in other fields and would make useful reading for anyone with a particular interest in protein analysis by MS

BIMDG Student Summership Report — Melissa Kuo

An *in vitro* proof of principle study to test the efficacy of translational read-through therapy for mitochondrial disorders

Student: Melissa Kuo[1]
Principal investigator: Shamima Rahman[2]

[1]Third Year Undergraduate, iBSc Paediatrics and Child Health, University College London, Gower Street, London, WC1H 6BT
[2]Professor of Paediatric Metabolic Medicine, Genetics and Genomic Medicine Programme, UCL Institute of Child Health, London, WC1N 1EH

BACKGROUND: Mitochondrial disorders collectively form one of the most common and severe inherited metabolic disorders (~1:5000 live births). Although best known for its role in oxidative phosphorylation, mitochondria contribute to a multitude of vital cellular processes including apoptosis and calcium homeostasis. Mutations across two genomes, and in over 350 genes, can result in debilitating, multi-systemic presentations; often targeting energy-demanding organs and particularly severe within the paediatric population. Biochemical, genetic and phenotypic heterogeneity pose challenges in therapeutic development; no cure is available and instead, patients rely on symptomatic management and unestablished treatments. Consequently, the overall prognosis is poor. Patients are often subject to long diagnostic odysseys and early mortality.

AIM: This project aimed to perform an *in vitro* proof-of-principle study to assess a novel pharmacological treatment strategy for mitochondrial disorders. Representing approximately 12% of monogenic disorders, and being the cause of some of the most severe genetic disorders, a potential approach is to specifically target bi-allelic nonsense mutations. This describes a genetic mutation causing a premature termination codon (PTC) being encoded within the mRNA transcript, which can result in a truncated or absent protein due to premature translation termination or nonsense-mutation-mediated decay (NMD), respectively. A class of drugs called translational read-through inducing drugs (TRIDs) can induce the cell's ribosome to skip the PTC and continue synthesising a full length protein. This project aimed to treat fibroblasts from two paediatric patients with mitochondrial disease with TRIDs, or NMD inhibitors (NMDIs), and determine whether transcript and protein levels can be restored.

METHODS: Treatment efficacy was investigated on two patient cell lines harboring a nonsense mutated mitochondrial disease gene (*COQ9*). Fibroblast cell lines were cultured and treated with TRIDs (PTC124 and RTC13) or NMDIs (Amlexanox). Protein and transcript restoration was determined subsequently, using western blotting and real-time quantitative PCR, respectively.

RESULTS: The obtained results suggest that PTC124, RTC13 and Amlexanox are unable to restore protein or transcript levels in fibroblasts containing *COQ9* mutations (figures 1 and 2).

DISCUSSION: The results suggest that TRIDs and NMDIs may not be effective in the treatment of mitochondrial diseases. However, in order to determine the true potential of TRIDs and NMDIs, these results need to be considered alongside experiments using a wider range of drugs and mutations.

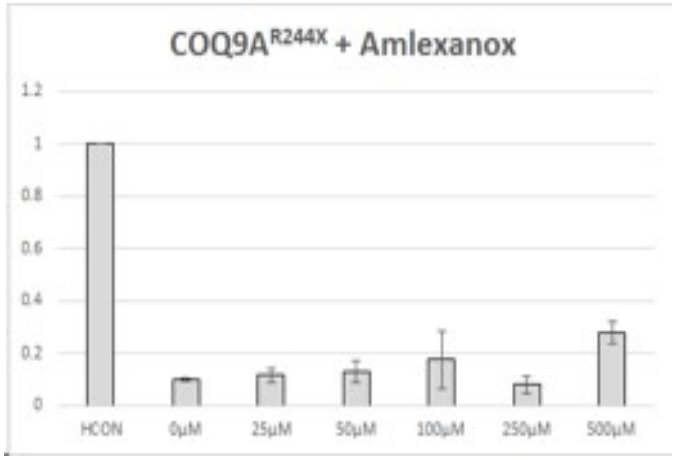
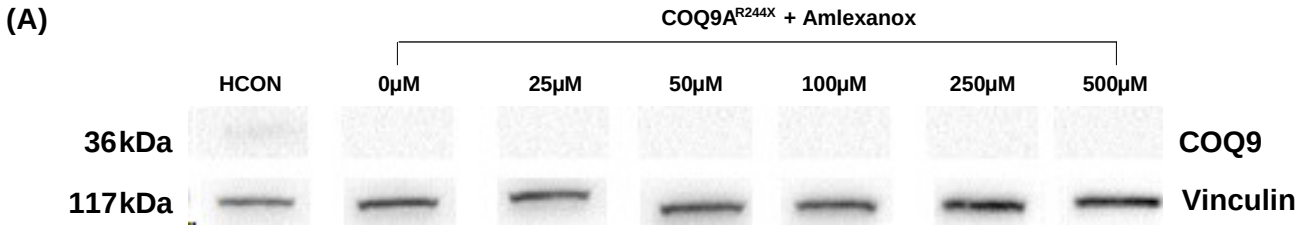


Figure 1. Effect of Amlexanox Treatment on *COQ9* Transcript Restoration in COQ9A^{R244X} Patient Fibroblasts. Bar chart of relative quantification of *COQ9* transcript in COQ9A^{R244X} patient fibroblasts treated with Amlexanox compared to the healthy baseline control (mean=1, SD=0). *COQ9* C_T value was normalised to *ACTB* and *B2M* and the resulting ΔC_T value was normalised to healthy control cells. Chart represents mean ± SEM (n=3).



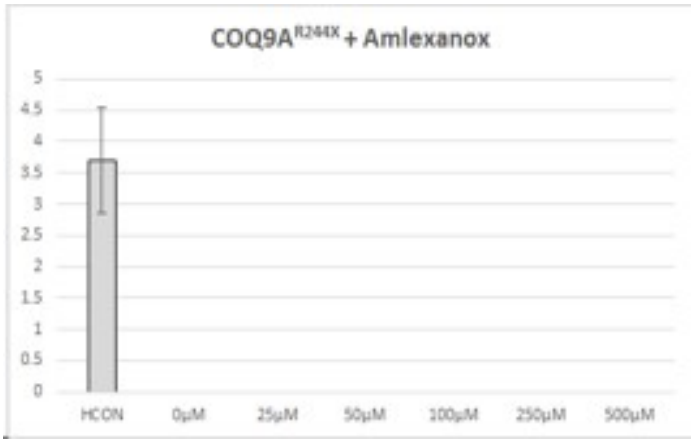


Figure 2. Effect of Amlexanox Treatment on COQ9 Protein Restoration in COQ9A^{R244X} Patient Fibroblasts. (A) Western blot of COQ9A ^{R244X} patient fibroblasts treated with Amlexanox using COQ9 and vinculin antibodies. (B) Bar chart of COQ9 protein band densities normalised to the vinculin control band density for COQ9A^{R244X} patient fibroblasts treated with Amlexanox. Chart represents mean ±SD (n=3).

Tributes to Margaret (Maggie) Lilburn (1942-2020)

Maggie (Margaret) Lilburn was a specialist dietitian in the field of inherited metabolic disease. She worked at the Charles Dent Metabolic Unit, University College London Hospitals, from 1966 until her retirement from clinical work in 2004, and remained involved in dietetic research until 2007. Alongside colleagues, she helped to set up a transition service for paediatric patients from Great Ormond Street Hospital, and was a pioneer in managing maternal phenylketonuria (mPKU) to allow women with PKU to have healthy children by following a very strict diet during their pregnancies. She went on to publish much of the key outcome data of these pregnancies that shapes and informs mPKU practice today, and was widely involved in clinical research in IEM. Maggie worked tirelessly to help improve the lives of her patients.

Acting as an advocate, she helped to drive innovative product development for adults living with metabolic conditions – which was at the time often considered a paediatric speciality. Her determination to ensure their needs and wants were met by dietary products has helped thousands of young adults around the world with their day-today dietary treatment. With dietetics being the translation of science into food, it is only right that the educational metabolic kitchen for patients and their families at UCLH is named in her honour. She was a kind and patient teacher, inspiring others to join her working in the field of inherited metabolic disorders. Her work was her life and love, and she gave her all to her patients. Maggie was a humble individual, and described by all who knew her as warm and with a very good sense of humour. She moved to be with her family later in life, and passed away with them close by.

Charlotte Ellerton,
Dietitian adult inherited metabolic disease,
Charles Dent Metabolic Unit, London

First printed in Dietetics Today, Oct 2020

“Most of us grow old with increasing regrets that we failed to say thank you enough to those we depended upon to achieve the things we were aiming for. I can look back with gratitude for Maggie's wonderful skills and personal qualities. Practitioners in the inherited metabolic diseases are frequently entirely dependent upon laboratory services and dieticians. Dieticians are key not just because of their knowledge and understanding of food sciences, their human interactions with patients and their families are crucial to success in getting dietary treatment started and adhered to.

I first met Maggie when I began as a research fellow in the laboratory of Professor Charles Dent working on Homocystinuria. Maggie was the metabolic ward's dietician doing all the dietary work, including meal preparation, for calcium balance studies which Charles Dent was doing on patients with metabolic bone disease. To keep an absolutely constant calcium intake for 4-6 weeks preparing and weighing all the food items and then making sure it was all eaten was very demanding. She was meticulous.

After the premature death of Charles Dent the calcium studies ceased but a new challenge arose when colleagues at Great Ormond Street and elsewhere realised that women with phenylketonuria needed to restart low phenylalanine diets before conception to prevent harmful effects in their offspring. When I was asked to help with adult dietary care of such patients I knew that Maggie was would be able to do it. She had the knowledge, skills and ability, and the warmth, kindness and devotion to bond with the patients. Her patience was inexhaustible, and I knew she would make herself available to encourage and support them. She was one of the first dieticians anywhere to be involved with adult phenylketonuric patients dieting during pregnancy. I owe her my own thanks for all she did. She was a star and I am sure her patients thought so too."

David Brenton
Emeritus Reader of Inherited Metabolic Diseases,
University College London

"I owe Maggie a huge debt. She patiently took me under her wing as a metabolic novice fresh from MRCP when I came to London in 1989. Sue Povey, my PhD supervisor, had put me in touch with David Brenton, knowing my preference for IMD rather than Clinical Genetics. So after a couple of clinics sitting in with both of them in the Cleveland Street outpatients at the Middlesex, Maggie and I did clinics together. I'm sure David knew that he could trust Maggie to keep me on the right track. That was the beginning of my dietetic education (which Mel, Nicola and now Rowan still have to struggle with!). Learning how to take an adequate dietetic history. How to count exchanges. How to get preconceptual patients back on diet. How to adjust diet as pregnancy progresses. All invaluable bread and butter with an expert and ever-patient teacher.

She was a workaholic, living just round the corner, seemingly spending all hours in her small office just next to the Outpatients (an old workhouse). The photograph of Charles Dent had pride of place, and she recalled fondly her work with him (and Dr Brenton) on the wards in the UCLH Cruciform Building (with the Margaret E Thompson tiles in the children's ward decorated with radioactive paint).

When I moved to Sheffield in 1998, additional dietetic support for PKU pregnancies was "bought in" from SCH at one session per week per pregnancy. When I told Maggie this, she smiled wryly, admitting that she was managing nine patients at the time, on top of her general metabolic workload. Periodically she was called on to cover general dietetics on top of all this: battles that she seemingly had to fight for years."

Godfrey Gillet
Consultant, Sheffield Teaching Hospitals

Diary Marker: BIMDG Workshop – February 12th 2021
How to improve IMD monitoring with Patient Collected samples

Prior to the COVID pandemic much work was progressing on the use of patient collected samples. The arrival of COVID has intensified the efforts we need to make to monitor patients effectively through alternative methods "at a distance" and thereby reducing the need to physically attend clinical out-patient settings. This BIMDG workshop sets the scene for the challenges we face in order to help assist develop a work-plan to take this important work and opportunity forward. Registration details will follow.

Friday 12th, February 2021

10-00 Welcome and Introduction – Dr Elaine Murphy, London

Morning Session – Chair: Dr Graham Shortland, Cardiff

10:15 – Getting the Sample

Mel McSweeney, London; Liz Morris, Cambridge

10:50 – Bloodspot quality and testing issues - Impact upon target treatment ranges.

Professor Stuart Moat, Cardiff

11:30 – Applying the results of Patient Monitored Samples to clinical practice – Strengths and Weaknesses

Dr Saikat Santra, Birmingham

12-05 – Chair summing up.

Afternoon Session – Chair: Dr Helena Kemp, Bristol

13-00 – New blood collection devices and laboratory technologies

Dr Rachel Carling, London

13-30 – 14-30 – Breakout – optional one of three workshops

1. Patient sample collection – Mel McSweeney, London; Liz Morris, Cambridge
2. Analytical/Laboratory aspects- Prof. Stuart Moat, Cardiff; Dr Rachel Carling, London
3. Clinical conditions reviewed – Dr Stephanie Grunewald, London

14:30 to 14:40 - Break

14:40 – All participants. Each session chair to feedback on their discussion.

15:30 – Session chair summing up

15:45 – BIMDG Chair Dr Elaine Murphy – next steps

16:00 - Close