Dr Brian Gibberd (1931–2006): a pioneering clinician in Refsum’s disease

A.S. Wierzbicki† and M.D. Lloyd‡
†Refsum’s Disease Clinic, Chelsea and Westminster Hospital, London SW10 9NH, U.K., ‡St Thomas’ Hospital, London SE1 7EH, U.K. and §Department of Pharmacy and Clinical Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, U.K.

Abstract
Branched-chain fatty acids are common components of the human diet (phytanic acid) or are produced endogenously (bile acids), and are also used as medicines (ibuprofen). Owing to their branched-chain structure, they are metabolized in peroxisomes. In the case of phytanic acid, the presence of a 3-methyl group prevents β-oxidation, and instead it undergoes one round of α-oxidation to allow further metabolism. Defects in this process give rise to neurological diseases and cancer. Dr Brian F. Gibberd was one of the first U.K. physicians to recognize the importance of these peroxisomal metabolic pathways in clinical medicine, and pioneered their study. This obituary recognizes his many achievements in neurology and especially in the treatment of peroxisomal disorders. The following four papers from this mini-symposium entitled ‘Advances in peroxisomal α-, β- and ω-oxidation’ describe work done in this area as part of a collaborative study in which Dr Gibberd played a key role. This work was presented as part of the Cardiovascular Bioscience focused topic at the Life Sciences 2007 conference, and this mini-symposium was dedicated to Dr Gibberd and his important contributions to this field.

Dr F. Brian Gibberd (Figure 1) was well known to all in the field of clinical neurology in London and worldwide for his work on Refsum’s disease. He died on 20 February 2006 on his way to work in the unique specialist Refsum’s Disease Clinic that he had created at the Chelsea and Westminster Hospital, at the age of 75. Brian had a long and distinguished career, being the youngest graduate of Westminster Medical School (1957) to be appointed as a consultant in 200 years when he was appointed as consultant general physician and neurologist to Queen Mary’s Hospital, Roehampton, and the Westminster Hospital in 1965 at the age of 34. He was one of the last neurologists to continue doing general medicine until his retirement from the National Health Service. He carried on his research work following the move of the hospital to the Chelsea and Westminster site in 1993 and even after his nominal retirement from active clinical medicine. He was active in Committee work and his appointments included being chairman of the Royal College of Physicians’ standing committee in 1970, and a council member, censor and examiner for the College for 25 years. He also served on the General Medical Council and was president of the Harveian and Hunterian Societies and an active member of the Society of Apothecaries.

His research career started, as with so many, with a case description when a junior doctor in 1963 [1] and rapidly progressed to a description of cases of ophthalmoplegia in the Lancet [1], Brain [2] and the prominent Scandinavian journals of the day. He developed an early interest in familial neuropathies and retinitis pigmentosa syndromes and found time to do some basic clinical pharmacology and publish on epilepsy [3,4] and therapeutic drug monitoring while remaining an active service clinician. His interest in Refsum’s disease was sparked in 1979 by the presentation of two patients with a constellation of signs including retinitis pigmentosa, anosmia, polyneuropathy and ichthyosis [5]. He not only made the diagnosis, but also surveyed the literature and found the papers from Dan Steinberg describing the basic biochemistry of the disorder [6,7]. He prompted the chemical pathology department under John Billimoria to assay the plasma for phytanic acid to make the definitive diagnosis and then initiated the acute management of the disorder by plasmapheresis [5]. Further reading in the area prompted the collaborations between Brian, John, David Burston, Gill Bannerjee and Maggie Hancock to measure the phytanic acid content of food as the original description of phytanic acid was a trace fatty acid present in sheep milk in New Zealand and dietary therapy had previously been attempted [7]. This work led to the development of a specific diet for Refsum’s disease [8,9] that, with slight modifications and updating [10], is still in use today. He was one of the first clinicians to state that Refsum’s disease could be treated by diet rather than lifelong plasmapheresis [11] and the >10 year follow-up data from the clinic on which he was working at the time of his death confirm this [12]. His interest grew, and he actively solicited patients with Refsum’s disease from colleagues around the country and initiated the first Refsum’s disease clinic in the world. This became so well known that it received referrals from not only Britain but also Europe and the U.S.A. This cohort of 48 patients later provided the basis for the definitive clinical descriptions of the ophthalmological [13], radiological [14], audiological [15], dermatological [16] and

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Abbreviations used: PhHy, phytanoyl-CoA hydroxylase; RCDP, rhizomelic chondrodysplasia punctata type 1.

*Refsum’s Disease Clinic, Chelsea and Westminster Hospital, London SW10 9NH, U.K., †St Thomas’ Hospital, London SE1 7EH, U.K. and ‡Department of Pharmacy and Clinical Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, U.K.

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osmic [17] features of Refsum’s disease and their response to dietary and plasmapheresis therapy. All of this work was performed with the collaboration of his wife Margaret (Sidey). Brian suggested that screening all patients with retinitis pigmentosa for Refsum’s disease by measurement of phytanic acid should be performed as this was the only treatable environmentally induced retinitis syndrome and that early detection could improve prognosis [18]. More than 20 years later, this remains an aspiration, as systematic screening for Refsum’s disease is still not performed in ophthalmology clinics in patients with retinitis pigmentosa. He began to gather families and identify heterozygotes clinically well before the molecular genetic technology to investigate them in more detail became available [19]. When such techniques were available, he interested a chemical pathology senior registrar with a background in the new science of molecular biology (Tony Wierzbicki) to collaborate with Jackie de Belleroche at the Charing Cross Hospital and her group working on the genetics of motor neurone disease in the newly merged medical school (Charing Cross and Westminster) to work on the genetics. Although the molecular defect in Refsum’s disease mutations in phytanoyl-CoA hydroxylase (PhyH) was discovered simultaneously in 1997 by the two major peroxisome groups in the Kennedy-Krieger Center at Johns Hopkins [20] and the Emma Children’s Hospital at Amsterdam Medical centre [21], the U.K. group was able to show that Refsum’s disease was actually a syndrome and that a second locus existed [22]. This work started collaboration between the α-oxidation groups in Europe, Minne Casteels in Leuven, Ron Wanders in Amsterdam and the U.K. clinical group, which later led to the identification of the second locus as a variant of RCDP (rhizomelic chondrodysplasia punctata type 1) caused by mutations in peroxin 7 [23]. Ironically, the first case of Refsum’s disease [24] ever described turns out to be a RCDP patient rather than a PhyH [25]. A casual conversation about the α-oxidation reaction in an Oxford College bar prompted the interest of Matthew Lloyd and Chris Schofield from the oxygenase group in the Dyson Perrins Laboratory in Oxford in PhyH [26]. They identified it as a 2-oxoglutarate-dependent oxygenase and decided to employ a D.Phil. student (Mridul Mukherji) to study the enzyme further. With funding from the Biochemistry and Biological Sciences Research Council and a collaborative grant from the European Union, the stage was set for a major investigation of the α-oxidation pathway [27,28]. This grant led to the prediction of the biochemical phenotype of the mutations in PhyH [29], its cofactors [30] and later its crystal structure [31]. The cDNA was used to identify another oxygenase relevant to transplantation and ischaemia when Mridul identified a novel oxygenase that acted as an oxygen sensor [32]. Hypoxia-inducible factor is now a widely investigated molecule with considerable pharmaceutical potential given its relevance as a switching protein coupled to effector pathways responding to hypoxia. Other work in the collaboration clarified the function of the lyase enzyme [33], identified the enzymes involved in the ω-oxidation pathway [34] and the role of phytanic acid and its conversion into phytanic acid in Sjogren–Larsson syndrome [35]. In the clinical field, Brian’s investigations within the European Union grant highlighted its potential clinical relevance of ω-oxidation as a drug target for the therapy of Refsum’s disease [36].

All of this work in the field has been presented at numerous neurological meetings and those of the Society for the Study of Inborn Errors of Metabolism. The collaborative group was invited to form the faculty for the first International Refsum Disease Workshop meeting in Berlin in 2005 which has prompted the setting up of Refsum’s disease services in Germany and Belgium. This meeting was also an opportunity for patients from numerous countries to meet up and meet the scientists and clinicians involved in their disease. An active Refsum’s disease discussion group exists (http://health.groups.yahoo.com/group/refsums_discussion) and information gathered from the collaborators has been consolidated in a Refsum’s disease website (http://www.refsumdisease.org). Brian always thought that Refsum’s disease might have a wider relevance to medicine, but even he was surprised that this pathway should turn out to lead to research in neuroophthalmology, oxygen physiology and even cancer biology. The finding that expression of an α-oxidation enzyme is increased in prostate and some other cancers [37] and high levels of phytanic acid (the fatty acid accumulated in Refsum’s disease patients) in the diet increased prostate cancer risk in men [38] has brought the work to a much wider audience.

A major interdisciplinary grant funded by the European Union was initiated in 2002 and continued until the end of 2005. The grant was remarkable in the breadth of expertise brought together. The first paper in the ‘Advances in peroxisomal α-, β- and ω-oxidation’ mini-symposium, part of the Cardiovascular Bioscience focused topic at the Life Sciences 2007 conference, describes the in vivo and clinical chemistry studies performed by the group of Professor Ron Wanders in Amsterdam [39] (pp. 865–869). On pp. 870–875, Professor Christopher J. Schofield from Oxford [40] then describes how use of chemical biology and structural biology
gave insights into the α-oxidation pathway and the functional effects of clinical mutations found in the enzyme catalysing the first step in the pathway. Professor Minne Casteels from Leuven goes on to describe the work done in her laboratory on a remarkable TPP (thiamin pyrophosphate)-dependent lyase [41] (pp. 876–880), which catalyses the second step in the α-oxidation pathway. Finally, Dr Anthony Wierzbicki from the Chelsea and Westminster Refsum’s Disease Clinic [42] reports on clinical management of α-oxidation diseases and promising new avenues of treatment (pp. 881–886). We dedicate this mini-symposium and the papers from it to our colleague, Dr Brian Gibberd, whose contribution made this work possible.

We thank all of the doctors, scientists, dieticians, students and patients who have collaborated with Brian and Margaret in their work on the clinical and biochemical description of Refsum’s disease over the last 30 years. Many organizations have funded Refsum’s disease research over the years, but we especially acknowledge the Trustees of Westminster Hospital funding clinical studies, the Biotechnology and Biological Sciences Research Council (BBSRC), the European Union (Refsum’s disease: Diagnosis, Pathology and Treatment, QLG3-CT-2002-00696) for post-doctoral funding, and the Felix Foundation for a studentship to Mridul Mukherji.

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