EDITORIAL

Published as The inborn factors in disease (Oxford at the Clarendon Press, 1931), and building upon his classic Inborn errors of metabolism. Being the Croonian lectures of 1908 (Oxford Medical Publications 1909; second and updated edition, 1923), (Sir) Archibald Garrod (1857–1936) wrestles in his Huxley lecture for 1927, delivered at the Charing Cross Hospital (London, UK), with the concepts of ‘diathesis’ and ‘abiotrophy’.

The concept of morbid predispositions and temperaments, developed towards the end of the 18th century, recognized that some individuals are more and others less liable to develop a particular condition; and that disease may be handed down from parents to child. ‘Διάθεσις’, the arrangement of objects in space and hence predisposition, was much used in French schools of medicine throughout the 19th century. But in time, diathesis came merely to denote the mechanisms of disease—purulent, haemorrhagic, calcareous, saccharine, fatty and fibrinous—by virtue of which several organs might simultaneously or in succession become the seat of affections, spontaneous in their development and identical in nature even though presenting at separate times and under different circumstances. Contrary views in England emanated from Edinburgh and were much influenced by Jonathan Hutchinson (1828–1913) who used diathesis to indicate a condition of the body rendering it liable to certain diseases but nonetheless latent and needing to be exposed. For Hutchinson, diathesis was synonymous with chronicity. Garrod considers that ‘his oral teaching and writings…outstripped the knowledge of his day and…he fell into errors on that account’.

WH (Walter Hayle) Walshe (1812–92) refined the concept of diathetic maladies as those ‘generated and sustained by an intrinsic blood-poison resulting from some perversion of the nutritive processes of the individual’. Although Garrod considers this to be the founding statement of biochemistry, Walshe’s list includes tuberculosis and leprosy, leukæmia and cyanaemia, oxaluria, phospahturia and scurvy, and the more general diatheses such as ‘arthritism’ in which several strumous and dartrous disorders share a common cause leading to ‘slackening of the metabolic processes’. Here too, Garrod concludes ‘that theory ha[s] quite outstripped fact’. Later (Charles-Joseph) Bouchard (1837–1915) proposed an underlying chemical basis for predisposition to gout allowing Garrod to point out that the relevance of uric acid had been suggested 30 years earlier—as it happens by his father, Sir Alfred Barings Garrod (1819–1907), physician to King’s College Hospital. Further progress was made when Emil Fischer (1838–1914: Nobel Prize for Chemistry, 1902) showed that proteins are degraded not as a whole but as individual amino acids by specialized enzymes; and RJ (Reginald John) Ryle (1853–1922) defined diathesis as ‘a transmissible variation in the structure or function of tissue[s] rendering them peculiarly liable to react in a certain way to certain extrinsic stimuli’. Now the time was ripe for the opening of Constitutional Clinics in New York, Berlin and Turin. These enshrined a broader concept than diathesis that included all aspects of the individual determining whether a disease happens and how its course is shaped: ‘the reaction of the patient, his protest against the attack and his devices for repulsing it; including the inborn factors in connexion with morbid states and the idiosyncrasies of the individual…wittingly or unwittingly, the practitioner of medicine is constantly engaged in the study of constitutions and predispositions, and of reactions to environment. He must, throughout his active life, be a student of the inborn as well as of the external factors in disease’.

Garrod’s 1927 lecture also considers hereditary maladies or tissue defects, perhaps of embryological origin, that may not manifest until many years after birth. These develop when a progressive morbid process is superimposed on a congenital defect. Reprinted in the Lancet on 12 April 1902, and republished in his second series of lectures on Diseases of the nervous system (subjective sensations of sight and sound, abiotrophy, and other lectures, 1904), (Sir William) Gowers (1845–1915) delivered a lecture at the National Hospital for the Paralysed and Epileptic, Queen Square, Bloomsbury, on 21 February 1902 entitled ‘Abiotrophy: diseases from defect of life’. His thesis is that health, and hence disease, reflects the interplay of somatic forces present in the blood and the intrinsic vitality of individual organs that may degenerate slowly, at different rates, and for different reasons including ‘a defect which seems to be inherent, the tendency thereto inborn’…‘I do not like new words – indeed I dislike them – but if we have a conception for which no name exists… it is not wise… to shrink from an attempt to give it a name… what we need is to insert the root of μορφή after the negative participle in “atrophy”; this gives us abiotrophy’. And in a footnote Gowers concedes that the root of his word [without the initial ‘a’(briotrophy’)] was used by Georgias Pisides (NK), a Byzantine writer, in 620AD. Gowers considers disease of muscle in young people (‘pseudo-hypertrophy’: a form of muscular dystrophy credited to Duchenne de Boulogne (1806–75) but, as Gowers emphasizes, first described by Edward Meyron (1807–80), and on which Gowers lectured as assistant professor of clinical medicine at University College to the National Hospital in 1879), spinal muscular atrophies, hereditary spastic paraplegia, Friedreich’s disease and familial and toxic amblyopias as good...
examples. But abiotrophy may also manifest later in life as toxin-related conditions such as syphilis and diphtheria, and degeneration of spinal and bulbar motor neurons, paralysis agitans and dementia. Gowers chides his audience for too easily attributing the many degenerative diseases of the nervous system that result from a defect in vitality (abiotrophy) to ‘disseminated insular sclerosis, often assumed to exist when the symptoms afford no justification for the opinion and in cases where the assumption is disproved by the future course of the disease’. Perhaps confusion arose from Gowers’ concept that generic pathological processes such as ‘sclerosis’ underlie many of the abiotrophies. Garrod acknowledges Gowers’ lecture and borrows the words ‘inborn’ and ‘abiotrophy’ but challenges his account of the ‘wasting away of tissue, as of plants without soil, and its replacement by fibrous tissue, “tissue weed” as ‘not altogether a happy one, for the fibrous tissue may be more aptly described compared to the rubble with which a breach in a fortress wall has been repaired. It represents an attempt to mend; the best that Nature can do to make good the loss’.

Adding the spectrum of myotonic dystrophies to Gowers’ list, Garrod turns to Gaucher’s disease, another borderland malady on the frontier of structural and biochemical anomalies. This is unique amongst the abiotrophies in having a defined error of chemical structure as the proven basis for defective make-up of the affected tissues. First described as a condition of primary epithelioma of the spleen characterized by large hyaline cells, with time it became clear that the morbid changes are by no means limited to the spleen. The liver undergoes great enlargement and haemopoietic tissues including the bone marrow become involved. It occurs in several members of a sibship, usually females, inherited as a Mendelian recessive. Commencing during childhood, the malady advances ‘at a snail’s pace through decades of the victim’s life’. The hyaline swollen appearance is due to the presence of a chemical not found in normal tissues but constituting up to 10% of dry weight. This is kerasin, allied to cerebrin, a member of the galacto-lipins first identified by (Johan) Thudicum (1829–1901). Garrod concludes: ‘maladies which only manifest...some years after birth, or even during adult life, may have their origins in some peculiarities of the germ plasm which may be completely latent in the earlier years of life’. Our anonymous reviewer of ‘The inborn factors in disease’ (Brain 1931; 54: 240–1) raises an eyebrow at the chapter on the chemical basis of individuality: ‘the physician whose conception of a disease is dominated by its aetiology...will find much food for thought...the author’s bias towards biochemistry is everywhere apparent. It is disappointing that the word abiotrophy is used without any attempt to explain it in terms of metabolism. Obviously it is too early yet for us to envisage life altogether in terms of chemistry but the author sees in biochemistry the best approach to the study of mutations and hereditary predispositions’. As set out in From the Archives (see page 1658), the subsequent history of the lipidoses is one of significant therapeutic success through collaboration between academics and the pharmaceutical industry.

The book essay in the present issue also reflects involvement of the pharmaceutical industry with the practice of neurology. In ‘Stroke as an emergency: Semmelweis revisited’, Jan van Gijn reviews tPA for stroke: the story of a controversial drug by Justin A Zivin and John Galbraith Simmons (Oxford University Press, 2010).

Introducing his characters in the tradition of a good novel, or thriller, before revealing the plot, Professor van Gijn takes us from the cloning of recombinant tissue-type plasminogen activator and the demonstrations of lysis in the systemic venous and coronary arterial circulations, to the possibility of a role in ischaemic stroke and the frustrated efforts of one of the book’s co-authors to manage the clinical trials programme. We read of the author’s perception of being distanced from the applications of his own research; handing over the project to parvenus and those with vested interests; the struggle of publishing the data; difficulty in overcoming the reservations of opinionated nay-sayers; slow uptake through delays in marketing; reluctance of insurance companies to reimburse these interventions; and belief that the evidence for efficacy had been undermined. To anyone who has travelled the route from molecular concept through the uncertainties of experimental medicine studies and then successfully negotiated the stochastic forces on which oscillate the reliable demonstration of efficacy and accurate documentation of adverse effects (real and perceived; and, here, quite likely to prove a deal-breaker in terms of increased risk of cerebral haemorrhage) in Phase 2 and 3 trials, these are familiar cries of distress from clinician scientists confident that their early open-label studies were reliable predictors of advances in treatment that address important unmet needs in clinical medicine. Jan van Gijn proposes a metaphor that likens what happened to thrombolysis for stroke to a football match in which, despite one team having dominated the play, the final whistle goes with the score 0–0 and all that can be done is to replay the match rather than declaring a winner based on a revised outcome measure such as the number of free-kicks awarded to either side during the game; and an impression as to which is the better side. Professor van Gijn declines to take a position on the suggestion made by the authors that, in deferring the decision for licensing by insisting on another trial, the referee was nobbled behind-the-scenes; that is, coercion between the Food and Drugs Administration and the National Institute of Neurological Disorders and Stroke who sponsored the study. Although positive, debate continued for some time on the merits and demerits of the outcome measure adopted; just how secure was the evidence for efficacy; and the reality of significant risk. With time, the critical issue of timing with respect to administration of recombinant tissue-type plasminogen activator emerged; uptake became exponential; and the confidence of the early investigators was vindicated. As is his wont, Jan van Gijn takes us back through history to other lessons of medical society proving slow to adjudicate between the messianic urgings of experimental prophets and the seductive cries of Siren Sisters enticing prescribers to ignore risk. With others, Professor van Gijn writes Stroke: practical management (3rd edn., 2008): he was professor and chairman of the University Department of Neurology, Utrecht University, The Netherlands from 1983–2007; and has served as associate editor of Brain since 2004.

Amongst papers in the present issue that deal with stroke, Susanne Siemonsen and colleagues from Hamburg (Germany) and Århus (Denmark) use multiple imaging modalities to chart the progress of lesions over time following attempted thrombolysis, concluding that the familiar increase in T2-weighted values seen as
part of the natural history of stroke in untreated cases does not reliably identify tissue that is irreversibly damaged being identical in cases dichotomized according to the success or otherwise of recanalization (page 1981). Nichola Lax and investigators from Newcastle-upon-Tyne (UK) consider the vascular lesions seen most typically in the syndrome of mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and conclude that, using the cerebellum as tissue of interest, microangiopathy is a feature of this and several other mitochondrial cytopathies due to increased mitochondrial mass in endothelial and smooth muscle cells that loosens tight junctions and leads to local break-down in integrity of the blood–brain barrier (page 1736).

It follows that modulation of vascular function is one potential means for limiting the damage in the mitochondrial cytopathies. In 2011, Western Europe took fright following the outbreak of Shiga-toxin-producing *Escherichia coli* infection in northern Germany, 22% of the 3842 affected individuals developing haemolytic uremic syndrome. Now, Tim Magnus and a team from Hamburg (Germany) describe neurological manifestations of the episode involving 104 affected individuals (page 1850). The picture is of encephalopathy with aphasia, seizures and cognitive impairment; transient symmetrical focal imaging abnormalities in the brainstem and thalamus; and, despite a good overall prognosis, some neuropathological evidence for astrocyte and microglial reactivity indicating a mixed toxic and inflammatory disease mechanism but without primary vascular changes.

The modern era in the epidemiology of multiple sclerosis began at the Veterans Administration Hospital in the Bronx (New York, USA) during October 1953 when a nurse alerted John Kurtzke to the fact that a patient with paraplegia due to chronic multiple sclerosis had moved his legs after receiving isoniazid. After observing the effects in other patients, it became clear there were no published means for assessing changes in multiple sclerosis objectively. This led to development of the ‘Kurtzke Disability Status Scale’, first used in a preliminary and apparently positive trial of isoniazid (Kurtzke and Berlin, *American Reviews of Tuberculosis* 1954; 70: 577–92). To confirm these findings, 11 Veterans Administration Hospitals carried out the first double-blind, placebo-controlled, randomized, multi-centre study in multiple sclerosis in the USA during October 1953 when a nurse alerted John Kurtzke to the fact that a patient with paraplegia due to chronic multiple sclerosis had moved his legs after receiving isoniazid. After observing the effects in other patients, it became clear there were no published means for assessing changes in multiple sclerosis objectively. This led to development of the ‘Kurtzke Disability Status Scale’, first used in a preliminary and apparently positive trial of isoniazid (Kurtzke and Berlin, *American Reviews of Tuberculosis* 1954; 70: 577–92). To confirm these findings, 11 Veterans Administration Hospitals carried out the first double-blind, placebo-controlled, randomized, multi-centre study in multiple sclerosis—the results of which [see *Journal of the American Medical Association* 1957; 163: 168–72] could hardly have been more negative’. But, over a beer, it occurred to principal investigators from the Veterans Administration Multiple Sclerosis Study Group (Benedict Nagler, Gilbert Beebe and Leonard Kurland), together with Kurtzke, that World War II and the Veterans Administration provided a unique opportunity to study the natural history of the disease. A cohort of 762 veterans with onset whilst serving in the Armed Forces was identified; later the numerator for service-related cases was extended to all veterans of World War II and the Korean conflict—a denominator of 16535 000 personnel enlisted from 16 September 1940 to 25 July 1947 as part of World War II and 6807 000 in Korea from 27 June 1950 to 31 January 1955, of whom 1476000 served in both conflicts. Case-control comparisons identified a relationship between risk of multiple sclerosis and higher socio-economic status and education, and a latitudinal gradient for place of residence at entry into the Military.

In one of only two articles by John Kurtzke previously published in this journal, *Brain* picked up the tail-end of the many papers reporting on these cohorts (see *Brain* 2000; 123: 1677–87). Until then, Dr Kurtzke had not considered that *Brain* would be interested in such musings from the colonies. On that, he now reflects: *per aspera ad astra… dum spiro spero* (‘through hardship to the stars… while I breathe, I hope’). Happily, Dr Kurtzke breathes on; and we publish the first of his papers on cases identified as part of the Veterans Administration Hospitals responsibilities for the Gulf war cohort (see commentary page 1663; and 1778). Amongst five other papers on inflammatory brain disease Christina Elliott and colleagues from Glasgow (UK) and Heidelberg, Bochum, Martinsreid and Munich (Germany) and Stockholm (Sweden) test the relevance of antibody found in the cerebrospinal fluid for the pathogenesis of multiple sclerosis; 50% of patients have immunoglobulins that bind oligodendrocytes and myelin causing complement-dependent demyelination of co-cultures in *vitro* and with axonal loss in a smaller number of samples; they conclude that this provides evidence for mechanistic (but not necessarily aetiological) heterogeneity explaining the beneficial response to antibody-depleting therapies in some patients (page 1819).

Ronald Postuma and investigators from Montreal and Toronto (Canada) hypothesize that the study of patients with idiopathic rapid eye movement sleep disorder can be used to study the prodromal phase of parkinsonism (page 1860); they show that bulbar and facial akinesia predate awareness of the motor disorder by almost 10 years with later emergence of rigidity and impaired arm function and gait. Objective measures are more sensitive for early detection than clinical observation; and even a global measure such as the Unified Parkinson Disease Rating Scale detects disease 5 years ahead of presentation. Amongst the parkinsonian disorders, dementia with Lewy bodies has a slower evolution than Parkinson’s disease. Using 

Returning to neurogenetics and inborn errors, we publish two papers reporting mutations of *TTN* in hereditary myopathy with early respiratory failure (see pages 1682 and 1695; Commentary, page 1665). And on page 1724, Einat Vitner and colleagues from Rehovot (Israel) propose the cytotoxic role of microglia and involvement of inflammatory cytokines in response to release of glucosylceramide as the main mechanism of tissue injury in neuronal forms of Gaucher’s disease. In From the Archives, we review ‘The lipidoses and the central nervous system’ by Alan Bird (*Brain* 1948; 71: 434–450).

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