ME Research is suffering from inaccurate diagnosis

Research into the lifelong, uniquely disabling illness, myalgic encephalomyelitis (ME), is in danger due to the illness regularly being redefined and subsumed under the label of 'Chronic Fatigue Syndrome' (CFS). CFS is a non-specific term for a *heterogeneous* patient population suffering from various syndromes of chronic fatigue, whether organic or psychiatric in nature, only one of which is ME. These inappropriate re-definitions give the inaccurate impression that *all* syndromes of chronic fatigue have a *psychiatric* aetiology, whereas ME has been formally classified in the International Classification of Diseases (ICD) by the WHO as a neurological disorder since 1969. No one, however, disputes that, as in all serious illness, *some* sufferers may exhibit psychological morbidity, including emotional lability.

Accurate disease diagnosis and classification are essential for real progress to be made in understanding ME and it must not be confused with non-specific states of ongoing, medically unexplained, fatigue. The latter are classified in the ICD under Mental and Behavioural disorders at section F48.0, a category from which ME is expressly excluded. Confusingly, however, 'chronic fatigue syndrome' is listed in the ICD as a term by which ME is also known and the international research community now use the term CFS instead of ME. Unhelpfully, some UK psychiatrists who specialise in chronic fatigue refer to medically unexplained fatigue as 'CFS' without differentiation, so it is imperative to be aware that the term 'CFS' can mean different things to different people. It is crucial that a means of definitive differential diagnosis is developed to obviate further misunderstandings.

To this end, there is an ever-increasing body of evidence from international centres of excellence for a variety of biomarkers for ME. These exist, for not only neurological deficits, as demonstrated by nuclear medicine techniques such as SPECT and MRS scans (which demonstrate cerebral hypoperfusion), but also for endocrine dysfunction (disturbance of the HPA axis), immune dysfunction (evidence of an unusual and inappropriate immune response) and vascular disturbance (evidence of disrupted biology of blood vessel endothelium), together with evidence of mitochondrial abnormalities in muscle. Indeed, these findings support a biological basis for ME and examples of these have been presented at international research and clinical conferences in both the US and Europe for well over a decade. For example, at the recent AACFS conference in Virginia, USA (2003), Scottish researchers Drs Vance Spence and Gwen Kennedy (Vascular Diseases Research Unit, Dundee) presented novel findings of a prolonged action of acetylcholine in the microvasculature and of increased plasma isoprostanes as markers of oxidative stress in ME/CFS. In addition, they showed evidence of increased neutrophil apoptosis (programmed early cell death) in ME/CFS and higher levels of TGF-b1, which may be indicative of a persistent viral infection or a toxic state. Of special significance is the work of Professor Robert Suhadolnick (Temple University, Philadelphia, USA), who gave an excellent overview of the many biological and biochemical processes which are known to be altered and implicated in the pathoaetiology of ME/CFS, including: oxidative stress (nitric oxide / peroxynitrite); 2-5A synthetase / RNase L; p68 kinase (PKR); the mechanisms involved in apoptosis; skeletal muscle function; mitochondrial function and brain metabolism. Indeed, the abnormal 2-5A synthetase/RNase L pathway may soon be regarded as a diagnostic test for the disorder. A full report on this conference can be viewed at www.meresearch.org.uk

Much more work needs to be undertaken to build upon these findings in order to better understand the aetiology of ME and isolate potential treatment strategies. The UK ME community, however, is aware that certain important grant awarding bodies are apparently ignoring the large body of international biomedical evidence of serious organic pathology in ME, preferring to allocate research funding to re-evaluate the effectiveness of psychological management strategies more appropriate to aberrant illness belief. It is our view that future funded ME research should proceed along well-established biological routes – to do anything else would not only be misleading but would waste the already limited funds.

Yours sincerely

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[Ed: Please send your views and ideas on this subject and any other that you feel might be of interest to readers of Biologist *to the Letterbox. I welcome letters from readers on all aspects of biology.]*

Avery and colleagues paved the way for Watson and Crick

The 50th anniversary of the elucidation of the DNA double helix has prompted many fascinating articles, those in the April issue of *Biologist* among them. In taking as their *raison d'etre* the 1953 paper in *Nature* by Watson and Crick, they will doubtless ensure that a new generation of biologists understand that in putting forward the double helix model, Watson and Crick discovered the secret of life.

It is a view already familiar to readers of *The double helix*, Watson's personal account of the breakthrough, in which he recalls Crick bounding into a Cambridge pub 'to tell everyone within hearing distance that we had found the secret of life'.

As a sound-bite, this clearly takes some beating. Even so, it is hard to reconcile with the historical and biochemical facts. To see this, one must ask why Watson and Crick were studying DNA in the first place. As Watson makes clear in *The double helix*, the pair were led to view DNA as biologically important by the work of Oswald Avery and his colleagues Colin M MacLeod and Maclyn McCarty, at the Rockefeller Institute. It was Avery *et al.*, who, in 1944, published the first hard evidence that the long-sought carrier of genetic information came in the form of DNA.

Had it not been for this work, Watson and Crick might instead have spent fruitless years investigating the seemingly more plausible hypothesis that genes were made from proteins (if, indeed, they had worked on the problem at all). In the event, they took findings of Avery *et al.*, seriously and delivered powerful vindication of it by showing that DNA had a structure appropriate for the carrier of genetic information.

The operative word here, however, is *vindication*. The work of Watson and Crick (along with that of Wilkins and his colleagues, and others, such as Hershey and Chase) undoubtedly added impressive *additional* weight of evidence in favour of DNA being the key to the secret of life. Yet the fact remains that it was Avery *et al.*, who first directed serious attention towards DNA as the carrier of genetic information.

As such, I would argue that it is Avery and his group, rather than Watson and Crick, who should be credited with having found the secret of life. One may, of course, argue over the precise meaning of 'the secret of life'. Those who would argue in favour of Watson and Crick's discovery will find, however, that it is far easier to explain the fundamental processes of life without making reference to 'double helix' than it is to omit the term 'DNA'. Certainly, a recent analysis of papers published between 1953 and 1960 (*Nature*, **421**, 402-405, 2003) suggests that the main consequence of Watson and Crick's paper was to boost still further attention on DNA rather than on its structure, the latter being regarded as of secondary, albeit confirmatory, importance.

Since the mid-1970s it has been fashionable to focus on the lack of recognition afforded Rosalind Franklin for her role in determining the structure of DNA. Yet the injustice of her case pales in comparison to that of Avery *et al.*, whose seminal work was not even referenced in any of the seminal *Nature* papers of April 1953. Like Franklin, the untimely death of Avery in 1955 denied him (and, thereby, his colleagues) the Nobel Prize. Unlike Franklin, however, the now-ubiquitous focus on the double helix as the 'secret of life' has also robbed Avery *et al.*, of their rightful status in the story of modern biology.

The story of how Watson and Crick discovered the structure of DNA is an inspiring object-lesson in the role of chutzpah in