Guest Editorial

Inborn Factors in Disease: 1931-1981

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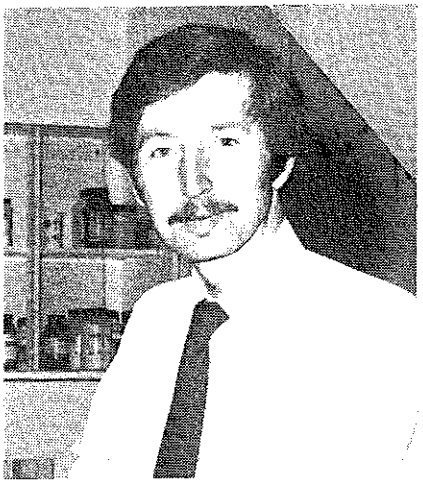

Dr. J.B. Whitfield

PROFILE OF DR. J.B. WHITFIELD

Dr. John Whitfield graduated in Biochemistry in 1964 from University of Bristol and then specialised in Clinical Biochemistry. He worked in Queen Elizabeth Hospital, Birmingham and Royal Post-Graduate Medical School, London, gaining his PhD in 1969 and Membership of the Royal College of Pathologists in 1972. In 1973 he came to Royal Prince Alfred Hospital as Deputy Director of Biochemistry. He was Secretary of the AACB from 1976-80 and has been actively involved in NSW Branch affairs.

Like other recent editorialisers, both here and overseas, I agree that it is time to examine where we have been, where we are, and (especially) where we are going. On this point, I am with the optimists; there is still a vast amount to be done and enormous satisfaction to be gained from doing it well.

The past 20 years have emphasised the chemical and technological aspects of our work, and our achievements have been impressive. We have now reached a stage where we can measure almost any chemical compound likely to be of interest, if money is no object, and many of them in large numbers at a reasonable cost. Development will, of course, continue in this way, and for the realisation of some of the opportunities before us new techniques will have to be adopted, but it is time to think further about biology. A biological revolution is in progress and technology is available for us to apply the new knowledge to the individuals who seek or need medical attention.

The greatest and most influential figure in the biological area of clinical biochemistry was Sir Archibald Garrod (1857-1936). His concepts of inborn errors of metabolism are familiar to all of us; their application in practice has led to biochemical investigations which reach to the heart of an important, but limited, group of diseases. The common diseases, however, appear in adult life and do not at first sight involve such 'inborn errors'. No one can doubt, however, that susceptibility to adult diseases varies between individuals. In many cases the differences in susceptibility have been shown to have a genetic component; this was suggested by Garrod in 'Inborn Factors in Disease' in 1931. These differences too would be of a biochemical nature, and inherited in the same way as the more extreme examples of inborn errors of metabolism.

Of course, differences in susceptibility to disease could have many causes, genetic and environmental, and probably in most cases a mixture of both. But considering for a moment the genetic aspects, how does this idea fit in with our other current concepts in biochemical genetics? It seems to me that a spectrum exists, and at least five main areas may be distinguished.

1. The most extreme situation is with inborn errors which are inevitably lethal in a shorter or longer time, and no modification of the external or cellular environment (short of restoring the missing enzyme activity) can be effective. Examples would include those where cell death occurs because of accumulation of macromolecules normally broken down by lysosomal hydrolases; almost certainly there are also inborn errors in enzymes so essential that even embryonic development cannot proceed, so that we are not aware of them.

2. Potentially lethal inborn errors can sometimes be treated by drastic modification of the environment. Examples include phenylketonuria and branch-chain aminoaciduria, where selective removal of aminoacids from the diet alters the internal environment; or severe combined immune deficiency, where attempts have been made to rear children in a sterile environment to prevent infection.

3. 'Conditional' inborn errors, which only become evident when an unusual environmental factor is encountered, include acute porphyrias, favism, and suxamethonium ("Scoline") apnoea. Here a chemical which is quite harmless to the majority provokes a life-threatening situation in a minority of people who had until then seemed totally normal. A particular genetic make-up is a necessary pre-condition for an unusual reaction to an environmental factor.

4. Differences in susceptibility are evident in many common diseases; the fact that not all smokers develop lung cancer, nor all drinkers cirrhosis, must mean that other factors protect or predispose. Whether these other factors are genetic or environmental is unknown but is amenable to experimental or epidemiological study in animals or man. It seems that there are examples of familial risk factors (although not necessarily genetic in origin) in breast cancer, neural tube defects, and sudden infant death syndrome. Striking case reports have appeared of families susceptible through several generations to some diseases, such as liver cirrhosis or malignant diseases, although whether the aetiology of their disease is the same as in the non-familial cases is unknown. Susceptibility to diabetes seems to be genetically determined: in Type II (maturity onset) the concordance in identical twins indicates a strong genetic component but in Type I

(juvenile onset) the concordance is much less and both genetic and environmental (viral?) factors must interact.

5. Biochemical individuality is manifested both qualitatively, as in allelic forms of plasma proteins, red cell enzymes, and blood group and transplantation antigens; and quantitatively in some biochemical components of plasma (and presumably tissues) such as creatinine, alkaline phosphatase, or cholesterol. Some of these are quite innocuous, as far as we know, but others such as cholesterol or some HLA types shade into the previous category.

The interaction of heredity and environment is well exemplified by cholesterol; different cultures or economic circumstances across the world show different plasma cholesterols, and movement of an individual from one country to another brings about change; nevertheless, there is wide variation in plasma cholesterol between individuals in the same country or social group and most studies have shown a significant degree of heritability.

If we accept this concept of variation in susceptibility to disease, then a number of implications for medical biochemistry can be seen. On the research side, there are implications for studies on the aetiology of many of the common adult diseases; in clinical laboratory practice, there is the possibility of finding markers to identify members of the population who are at risk with a view to defining what they should avoid. One research approach which could follow from this would be to concentrate on diseases where it is known that some environmental factor is involved but the disease does not appear in all exposed people (or it appears more slowly in some). This is the case, for example, with cirrhosis and other consequences of alcohol abuse; lung cancer and smoking; and arterial disease, hyperlipoproteinaemias, and diet. In each case large family or twin studies would be needed but because of the frequency of these conditions answers could be obtained within a reasonable time – perhaps five years, or less if a retrospective approach is acceptable. If it is known that there is an important genetic effect in any of these diseases then some protein/enzyme difference must be present and this can guide research planning. Alternatively, it could be found that familial environmental or random environmental factors are decisive; this also would be useful information.

Secondly, and closer to the work of most of us, markers might be found for a genetic susceptibility to a disease. What might these be? There are three levels at which a marker might be found, in metabolism, in proteins, or in the gene itself. So far most genetic disease has been detected by changes in metabolism, by the appearance of dark urine in alkaptonuria or by raised blood phenylalanine in phenylketonuria. It seems improbable that subtle genetic differences will be manifested in so obvious a way, so we must think of the protein and DNA sequences as more likely areas. The protein differences we have found so far have mostly resulted in reduced enzyme activity, or in the case of the abnormal haemoglobins altered oxygen affinity or stability; fairly obvious changes. We shall need to move beyond these to look at differences in co-enzyme affinity, or sub-unit binding, or allosteric activation and inhibition, before we have explored the full range of potential protein variations. Variation in regulatory genes can be expected also, governing the amount of enzyme protein and hence its activity.

Much interest has recently been focussed on one group of proteins, the HLA antigens, and their role in disease susceptibility. In many cases it seems likely that they are acting as markers only because of their proximity on the chromosome to the genes really producing the end result, and this approach of finding a readily detectable difference and exploiting its linkage with a 'disease-inducing' gene could be extended to other markers.

Finally, and until recently firmly in the realm of science fiction, is the possibility of determining the DNA sequence of the relevant part of the genetic material. It is already easier to isolate and sequence a gene than to isolate and sequence a protein, and there is the added advantage that the entire set of genetic information is available in easily accessible cells, such as the white blood cells, even when they do not express the variant protein which is being sought.

The economic and social consequences of any programme of this nature are large, and if these possibilities move closer to realisation we, and the whole community, will need to consider them carefully. What would be one's reaction, for instance, to the knowledge that one had a 90 per cent probability of developing cancer of the stomach? Presumably any programme would have to keep to the principle of only looking for conditions where treatment, or risk-reducing strategies, can be offered. Would people who were told they were 90 per cent certain to develop cirrhosis if they continued drinking, stop doing so? Would prophylactic hysterectomy in high-risk women be an acceptable procedure?

Whatever the problems which may arise, I hope I have shown you some of the ways in which biochemistry will continue to be exciting and clinically relevant, both in medical research and in clinical laboratory practice.

SIR ARCHIBALD GARROD

(1857 – 1936)

The front cover of this month's Newsletter features the first of our "Famous Figures in Medical Science". Sir Archibald Garrod was a physician who worked in a laboratory and made an outstanding contribution to the thinking of his time. The biographical notes on page 5 are taken from an article by Barton Childs in the New England Journal of Medicine (282, 1970, 71-77).

I am indebted to Dr. Bill Hensley for the photograph on the front cover also for the following quote and comment:

"If it be, indeed, the case that in alkaptonuria and the other conditions mentioned we are dealing with individualities in metabolism and not with the results of morbid processes, the thought naturally presents itself that these are merely extreme examples of variations of chemical behaviour which are probably everywhere present in minor degrees and that just as no two individuals of a species are ever absolutely identical in bodily structure neither are their chemical processes carried out on exactly the same lines. Such chemical differences will be obviously far more subtle than those of form, for whereas the latter are evident to any careful observer the former will only be revealed by elaborate chemical methods."

These thoughts were first made public in the Lancet of 1902 and developed to what was essentially a "one gene one enzyme" hypothesis by the Croonian Lectures in 1908. Beadle and Tate in accepting their Nobel Prize in 1956 intimated that they dotted the "i's" and crossed the "t's" of Garrod's hypothesis. Oxford University Press published the 2nd and final edition of his "Inborn Errors in Metabolism" in 1923.

Ed.