Psychological Medicine, 1971, **1**, 353–355

EDITORIAL

Biochemical research in psychiatry

It is commonplace that over the 100 years or so since systematic chemical studies in mental illness first appeared biochemical research in psychiatry has become increasingly frustrating, both for biochemist and clinician. Biochemists in the field seem to divide their time between disproving the research of their less rigorous colleagues and adding to an increasingly long catalogue of essentially negative results; everyone regrets the failure of research in the field to contribute anything of significance to the pathology of the major mental illnesses and thus facilitate their diagnosis and treatment. It is important to recognize the magnitude of this failure. Contrary to a common view, much sound research into body chemistry in mental hospital patients was done in the first 40 years of the century. One need only mention the classic studies of Folin on the excretion of nitrogenous constituents (Folin, 1904) and in Great Britain the studies of workers at the Maudsley Hospital, whose contribution has been admirably summarized by McIlwain (1955). After the second world war technical advances in microanalysis and the discovery of new and more powerful psychotomimetic drugs stimulated a great increase in research in the field. Initially, much of this new work was poorly executed, repetitive, and contradictory, but recently the standard has greatly improved. For example, a survey in the *Index Medicus* of biochemical research into schizophrenia over the past decade shows that of the 500 or so papers published the number reporting sound research is surprisingly high. Perhaps it can now be reasonably said that many, if not most, of the more obvious biochemical approaches to the disease have been adequately explored with a negative outcome. Nor do we need to confine our attention to the major psychoses: the recent growth of interest in the chemical pathology of depressive illness, often employing approaches admirably related to fundamental knowledge, has so far produced disappointingly equivocal evidence. Thus a century after the appearance in 1867 of Maudsley's *Physiology and Pathology of the Mind*, with its remarkable emphasis on the importance of searching for 'a material basis for mental activity', we seem to have made remarkably little progress towards the core of the problem, at least as it affects the great majority of mentally ill patients in our hospitals.

In the face of this record there is not surprisingly a current tendency for research workers in the field to pause and take stock. For some this has led to a questioning of the whole value of continuing to apply to the investigation of mental illness the classic approach of chemical pathology—the comparative analysis of body constituents in normal and abnormal populations; for others to claim more firmly than hitherto that our knowledge of fundamental neurochemistry is still too meagre to enable us to formulate testable hypotheses to explain abnormal cerebral function. Both reactions are understandable and both, I believe, adumbrate the central issues involved. Relatively speaking, neurochemical research is only just beginning and at the present rate of progress the next few decades should see a tremendous increase in basic knowledge in the field which may well help us to see more clearly how to investigate more rationally the chemical mechanisms in mental illness. But it is, of course, a mistake to divorce fundamental and applied research and argue that one must wait on the other. In other areas of medicine the empirical observations of the chemical pathologist have often taken years to become explicable in terms of the basic biochemistry of the organs involved, but in the meantime they have contributed to diagnosis and treatment and have often stimulated the development of fundamental research.

Because of the failure of the empirical approach this has not yet happened in psychiatry, but it is well known that something like it is taking place in the related field of mental subnormality. For example, in the area of amino acid metabolism, research since 1950 has brought to light over 40 new inborn errors in subjects in whom cerebral dysfunction, usually that of retardation, is a prominent

sympton (Scriver, 1969). These are admittedly conditions in which the biochemical defect has a relatively simple genetic basis involving a deficiency of a single enzyme; interaction with environmental factors to give the phenotype occurs early in life before the vital post-natal period of brain maturation is complete. Their relevance, therefore, to the problems of biochemical research in psychiatry may legitimately be questioned. However, recent research has shown that there are instances in which the two areas appear less distinct. In a number of inborn errors the abnormality in enzyme function has been found to be only partial, leaving more scope for variation in environmental interaction, as is exemplified, for example, by the frequent ability of high doses of pyridoxine to correct the biochemical abnormality in homocystinuria (Kaeser, Rodnight, and Ellis, 1969). Of even greater interest for the present argument is the rare condition of Hartnup disease, where the subject matures relatively normally and suffers only intermittent symptomatology throughout childhood and early adulthood, sometimes with distinct psychiatric features, despite major and permanent defects in amino acid transport. A genetically determined constitution interacting with largely unknown environmental factors to yield intermittent symptoms which develop after structural maturation of the brain is a description which can also be reasonably applied to many mental illnesses; Hartnup disease is therefore a useful reminder that an inherited biochemical defect can result in a clinical condition with temporal features resembling those seen in the major area.

However, in the purely psychiatric field the problems are clearly of a different magnitude. The genetics of the major mental illnesses are complex (Slater and Cowie, 1971), and in the light of modern knowledge it is perhaps understandable why they do not result in a gross chemical pathology as so often occurs in conditions characterized by the recessive mode of inheritance. That more subtle genetically determined abnormalities in bodily chemistry do occur in mental illness remains an entirely rational postulate, but it is one which at this juncture raises the whole question of biochemical individuality in normal as well as abnormal populations. The remarkable increase in our knowledge over the past few years of the extent to which normal individuals vary in chemical make-up was foreseen by Garrod over 60 years ago (Garrod, 1909). It has, no doubt, been a factor in generating the reservations that some of us have about the value of much current biochemical research in psychiatry. Is it possible, for instance, that the differences in chemical make-up between mentally normal and abnormal populations are quantitatively no greater than between individuals within each group? Essentially qualitative group differences in the pattern of chemical constituents might still distinguish the groups, but if this is so we may need to develop entirely new approaches to demonstrate them. This would indeed be a formidable task, but with the help of automated analysis and computers to process data, it is conceivable. At all events there is a strong case, as Harris (1970) has emphasized, for studying chemical diversity in normal subjects in the hope of discovering in a small proportion of individuals characteristics that can be matched in mentally abnormal populations.

Against this background the recent publication by the Medical Research Council of a booklet entitled *Biochemical Research in Psychiatry: Survey and Proposals* (1970) was a timely venture. This consists of a report by the Council formulated by a committee of eight distinguished clinicians and medical scientists, although no neurochemist was included. The Council have been generous, if selective, in their support of biological psychiatry in the past and it is gratifying to learn from this booklet that they envisage continuing and even extending this support in the future. Most important also is their recognition of the continuing need for basic research in neurochemistry as the indispensable foundation for progress in applying biochemistry to the problems of mental illness. However, in other respects the publication is disappointing. Here one feels was a chance to consider the whole subject afresh and generate new ideas and approaches; instead we have a document much of which could equally well have been written a decade ago. Basic knowledge of brain biochemistry is summarized in a few paragraphs of amateurish writing which contain several factual errors and misstatements. The emphasis here is on descriptive rather than dynamic neurochemistry; only once in a short sentence on page 26 does the document refer to any of the current developments in neurobiology which are just beginning to show us a glimpse of how the brain functions as an organ, such as studies on sleep, adaptive behaviour, and the storage of sensory information. But it is in the

last section, where the recommendations for future work are made, that the MRC booklet is most disappointing. Considerable emphasis is rightly placed on the importance of 'bridging' studies and the role that psychopharmacology can play in bringing about collaboration between basic neurobiology and clinical studies. Beyond that we have a list of eight 'possible developments' in basic neurobiology, all of which are at present under active study in one centre or another of the western world. Similarly, in suggesting how research into the clinical aspects of the subjects should advance, the suggestions made largely reflect current activities in the field, although here some appreciation of how the subject could develop does creep in. One rather gets the impression that the authors were aware of the limitations of their approach but felt it was not their task to engage in any serious forward thinking on the subject. If this is so it is a great pity, because the status of biochemical research in psychiatry in this country will hardly be enhanced by this document, nor will it do much to attract serious biochemists to join the field.

RICHARD RODNIGHT

REFERENCES

Folin, O. (1904). Some metabolism studies, with special reference to mental disorders. *American Journal of Insanity*, **61**, 299–364.

Garrod, Sir A. E. (1909). *Inborn Errors of Metabolism*. H. Frowde: London. (1963). Reprinted with a supplement by H. Harris. Oxford University Press: London.

Harris, H. (1970). In *Chemical Influences on Behaviour. Ciba Foundation Study Group No. 35*, p. 122. Edited by R. Porter and J. Birch. Churchill: London.

Kaeser, A. C., Rodnight, R., and Ellis, B. A. (1969). Psychiatric and biochemical aspects of a case of homocystinuria. *Journal of Neurology, Neurosurgery and Psychiatry*, **32**, 88–93.

McIlwain, H. (1955). *Maudsley, Mott and Mann on the Chemical Physiology and Pathology of the Mind*. An Inaugural Lecture. Published for the Institute of Psychiatry. Lewis: London.

Medical Research Council (1970). *Biochemical Research in Psychiatry: Survey and Proposals*. Report. HMSO: London.

Scriver, C. R. (1969). Inborn errors of amino-acid metabolism. *British Medical Bulletin*, **25**, 35–41.

Slater, E., and Cowie, V. (1971). *The Genetics of Mental Disorders*. Oxford University Press: London.