Section of Neurology

President—W. RITCHIE RUSSELL, C.B.E., M.D., D.Sc., F.R.C.P.

[*March* 27, 1958]

DISCUSSION ON SOME CLINICAL, GENETIC AND BIOCHEMICAL ASPECTS OF METABOLIC DISORDERS OF THE NERVOUS SYSTEM

Dr. W. B. Matthews (Derby):

Metabolic Disease of the Nervous System: Clinical Aspects

Inborn Errors of Metabolism

It is not possible to discuss clinical aspects of inborn errors of metabolism without a brief incursion into biochemistry and genetics. Dent (1957*a*) has stated that if we believe in the genetic theory of inheritance it is not permissible to speak of inborn errors of metabolism of the nervous system, or of the renal tubule or of any other organ. The abnormal gene is universally distributed in the somatic cells. For the clinician this emphasizes the importance of recording associated abnormalities in inherited nervous disease. Numerous examples come to mind; it was pigmentation of the skin that first led to the suspicion of metallic poisoning in Wilson's disease. The recent report on the association of ichthyosis, mental defect and spastic paralysis (Sjögren and Larsson, 1957) shows that clinical observation may still have much to contribute.

There is general agreement that metabolic errors are the expression of defective or abnormal enzyme action. Much of the basis for this belief rests on elegant experiments on unicellular organisms. As far as I am able to understand this work it seems to contain certain valuable ideas for the clinician. It is probable that although the abnormal gene may be present in every cell the resulting metabolic error is only potentially present. It has been shown that in certain instances not only the action, but even the production of a genetically-induced enzyme may be controlled by the environment. A second significant finding is that enzyme abnormalities are not necessarily absolute; an enzyme may be reduced in quantity but not completely absent (Davis, 1954). If these findings can be applied to human disease they are of some importance as, at first sight, a disease due to an intracellular enzyme defect is not a promising therapeutic subject. It is through the environment that we can hope to exert any influence and there is strong evidence that in many instances it is environmental factors that are responsible for the production of symptoms. A puzzling feature of certain of these diseases is that, in spite of a presumably constant metabolic defect, symptoms are often episodic and sometimes very acute. Another feature is the great variation of clinical response to an apparently stereotyped biochemical disorder. Even in a single family great variation may occur and between families there are often wide differences in the age of onset and severity of symptoms. The interaction of the genetic defect, which may itself perhaps vary in degree from case to case, and the environment, is of vital importance.

It may one day be possible to classify inborn errors according to the enzyme at fault and to describe the manner in which the nervous system is affected. We are very far from this at present and even in apparently simple examples there is no agreement. In the condition of congenital methæmoglobinæmia a varying proportion of the hæmoglobin is unable to transport oxygen. The disease is characterized by fluctuating cyanosis and, in some instances, by mental defect and motor retardation. It is tempting to attribute the mental defect to anoxia, but here we meet a recurring theme in writing on hereditary disease, as it has been suggested that the cerebral damage is not causally connected with the metabolic defect but is separately inherited (Worster-Drought *et al.*, 1953). There is recent evidence that this may not be so. Dine (1956) reported a family in which the elder child was diagnosed

and treated with reducing agents at the age of 18 days and grew up retarded. The second child was treated at the age of 4 hours and has so far developed normally. Dine plausibly suggests that anoxia in the vulnerable neonatal period may be responsible for cerebral damage, when this is present. This introduces another complicating factor, the suggestion that the biochemical defect may only affect the nervous system at certain stages of its development.

The episodic nature of the symptoms found in certain metabolic errors is well shown by the recent description of Hartnup disease by Baron and others (1956). The symptoms are certainly suggestive of pellagra, although not thought to be entirely typical, and the rash and ataxia appear in acute episodes. Dent (1957*b*) has reported dementia in the older members of the Hartnup family, so that more permanent effects also seem to be produced. Dent considered the acute attacks were probably the result of environmental factors, but was not able to identify these, and could not be certain whether altering the environment by adding excess nicotinamide to the diet produced any therapeutic benefit.

This episodic clinical picture is shown even more clearly by acute intermittent porphyria and here some at least of the environmental factors are known. Garcin and Lapresle (1950) in their review of the clinical features of porphyria emphasize that *chronic* neurological and psychiatric disease does not occur. Certainly I have found that the routine testing for porphobilinogen in cases of organic dementia and chronic polyneuritis has been unrewarding. I have seen 2 patients who were incapacitated by a mild dementia following an acute attack, but, in general, the problem is that of prevention, detection and treatment of the acute attack. Dean and Barnes (1958) state that in the form of acute porphyria found in South Africa acute attacks are *always* precipitated by drugs, notably barbiturates. This form of porphyria is clinically and biochemically distinct from that usually found in this country and here it is certainly not always possible to incriminate drugs, but the exacerbation following heavy sedation with barbiturates when the diagnosis has been missed is only too well known. The full combination of abdominal colic, paralysis, fits and psychiatric symptoms is very characteristic, but the incomplete syndrome may be very easy to miss. My most recent case presented with a painless hæmatemesis followed by death within thirty-six hours. Detection of the symptomless affected relatives is important so that they can be protected from known environmental risks and here the Watson-Schwartz test for porphobilinogen (Watson and Schwartz, 1941) should not be relied on as it may be negative in patients who have not had an acute attack. Treatment of the attack has been based on supportive measures which may be life saving, but no rational attack on the biochemical disorder has been developed. There have been recent claims that BAL produces good clinical results, but the work requires confirmation and closer chemical control (Peters *et al.*, 1957).

An episodic history is, of course, typical of familial periodic paralysis. I am not qualified to comment on the recent advances in understanding this disease or group of diseases reported by Conn and others (1957). I mention it as an example of a condition where symptoms can be induced by changes in environment, either natural, such as a carbohydrate meal or even sleep, or artificial, such as glucose and insulin combined. Attacks can be prevented by the radical change in environment of a very low sodium diet.

A remittent history is not, of course, found in all inborn errors of metabolism. In certain instances the known environmental factor is constant daily exposure to an item of the normal diet that the patient is unable to metabolize normally. In galactosæmia there is a block in the metabolism of lactose leading to accumulation of metabolites in front of the block. Symptoms usually occur very early with intolerance to milk, vomiting and later mental defect and cataract. It is seldom likely to be seen by neurologists at this stage, but unsuspected cases may be found associated with mental defect in older children (Bergren *et al.*, 1958). There is again controversy about the relationship of the mental defect to the metabolic disorder. It is now possible, however, to establish the diagnosis in suspected cases by examination of the cord blood and to ensure that the child is never exposed to the noxious environment. The subsequent development of such children should settle the disagreement (Schwartz *et al.*, 1958).

Phenylketonuria is another example where the known environmental factor is exposure to a normal dietary constituent and, as might be expected, the disease is not characterized by acute attacks and remissions. The clinical picture is well known: relative lack of pigment, dementia and often epilepsy and evidence of injury to the basal ganglia. Although the great majority of cases are of very low intelligence, normal or almost normal intelligence may rarely be found (Coates *et al.*, 1957; Hsia *et al.*, 1957). This fact is of greater importance than its rarity would suggest as it raises the question of the cause of this great variation of clinical response. In this disease it is known that the metabolic defect can exist in an incomplete form, as clinically normal heterozygotes can be detected by chemical means (Hsia *et al.*, 1956). In affected homozygotes, however, no marked variation in the biochemical defect has been detected, even in cases with relatively normal intelligence

(Hsia *et al.*, 1957). Variations in the degree of genetic defect, which had seemed to me to be a possible explanation, do not appear to be significant and it is difficult to believe that exposure to phenylalanine can be very different from case to case. Unknown influences seem to be at work and, if treatment is to be fully effective, it is important to discover what they are. Determined efforts are being made to influence the disease by withdrawing phenylalanine from the environment. Recent reports suggest that if the environment can be controlled the genetic defect may even be harmless (Bickel *et al.*, 1954; Woolf *et al.*, 1958).

Much work has recently been done on the metabolic defect in Wilson's disease and I do not propose to discuss the chemical theories in any detail. The environmental factor appears to be a continuous one, namely that the normal diet contains more copper than the body requires. The nature of the genetic metabolic defect is still controversial, but most workers believe that the normal, but unknown, mechanisms preventing the absorption of unwanted copper are defective. It seems unlikely that these two factors vary greatly from day to day and yet acute clinical episodes are not infrequent. I may illustrate this by an example of a little-known clinical feature, hæmolytic anæmia. A girl of 6 was originally admitted to Burton General Infirmary under Dr. R. D. C. Johnstone, to whom I am indebted for the original notes. She had suffered from an attack of jaundice followed by ascites. When admitted the jaundice had almost cleared, but then returned suddenly accompanied by a severe fall in the hæmoglobin (Fig. 1). Recovery from the jaundice coincided with a rise in hæmoglobin. When I saw her three years later she had cirrhosis of the liver and corneal rings, but no neurological signs. This anæmia seems to parallel the hæmolytic crises that occur in sheep receiving too much copper in their diet (Marston, 1952). In these animals copper steadily accumulates in the liver and then, without any known environmental change, a hæmolytic crisis occurs accompanied by a rise in the blood copper. I do not know of any case of Wilson's disease diagnosed during a hæmolytic crisis, as they do not seem to occur late in the disease. The state of the blood copper would be of great interest and, in the present context, the anæmia illustrates a mechanism whereby a constant metabolic defect can produce an acute illness.

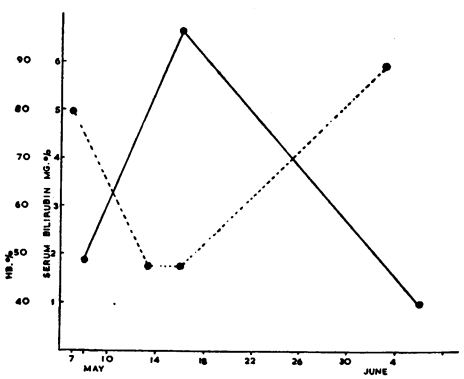

FIG. 1.—Hæmolytic crisis in Wilson's disease. Dotted line: hæmoglobin. Solid line: serum bilirubin.

In this disease an enzyme, cæruloplasmin, has positively been identified as deficient, but unfortunately the function of the enzyme is unknown. It has, however, led to a fundamentally different attempt at treatment of a metabolic error. Bickel and others (1956) have been able to raise the plasma level of cæruloplasmin to normal by injecting the substance. They have not so far been able to report any clinical benefit and the crucial experiment of determining whether absorption of copper is restored to normal does not appear to have been carried out. Treatment has otherwise been concentrated on removing excess copper from the body or on altering the environment by rendering the alimentary copper unabsorbable. Anyone with experience of treating children with BAL will welcome Walshe's (1956) discovery of a chemically effective oral agent, penicillamine. In my experience BAL has been disappointing in children and it requires a hard-hearted physician to persist with regularly repeated courses.

The clinical features are well known and often described. It is therefore surprising that in 5 cases the original hospital diagnoses were juvenile cirrhosis, adolescent scoliosis, schizophrenia, malignant hysteria and excessive maternal solicitude. The temptation to

ascribe peculiar movements to hysteria is often powerful, but is usually worth resisting. A further clinical point is the close resemblance between the clinical and pathological features of the more chronic forms of Wilson's disease and those of cerebral disease secondary to cirrhosis. This resemblance is so close as to have led so eminent an authority as Greenfield (1954) to doubt the specificity of Wilson's disease. There seems to be no doubt about the specificity of the metabolic defect, but our ideas of causation of symptoms may yet require revision.

I must omit certain important groups of diseases, largely because of ignorance. Advances in the understanding of the lipidoses have been limited by the relative ignorance of intermediate lipid metabolism in the brain. Progress is likely to accelerate, both in the discovery of "new" diseases and in elucidation of old enemies. Allan and others (1958) have described a family with convulsions, dementia and an obscure amino-aciduria. Dr. J. H. D. Millar has allowed me to mention that he has found a suggestion of a metabolic disorder in familial myoclonic epilepsy. I recently described a metabolic abnormality in a case of familial calcification of the basal ganglia with normal blood chemistry (Matthews, 1957). Dent has expressed the view that all genetically induced defects are the result of biochemical disorders. If so, such diseases as Huntington's chorea and muscular dystrophy present a formidable challenge.

Diabetic Amyotrophy

I would like now to speak briefly about one aspect of carbohydrate metabolism. Garland and Taverner in 1953 drew attention to a purely motor disturbance associated with diabetes. Briefly this is characterized by asymmetrical weakness, usually of the legs, with loss of reflexes, frequently with pain and very seldom with fasciculation. The prognosis is ultimately good although recovery may be long delayed. In a number of instances extensor plantar reflexes had been found and the condition was labelled "diabetic myelopathy". This has been amended to the less committal term of "diabetic amyotrophy" (Garland, 1955). No examination of the spinal cord has been reported.

An example of this condition was admitted to Dulwich Hospital under Dr. S. Nevin when I was working at King's College Hospital. I am indebted to Dr. Nevin for permission to refer to this case, which it is hoped to publish in full. A man of 52 had a five months' history of pain and progressive asymmetrical weakness of the legs, but no diabetic symptoms. He was grossly overweight and had marked weakness of all movements at hip and knee joints, absent ankle-jerks, flexor plantar responses and no sensory loss. The urine contained much sugar, a random blood sugar was 278 mg.% and the C.S.F. protein was 75 mg.%. He was treated with a low carbohydrate diet, but after three weeks he died suddenly of a pulmonary embolus. I carried out a post-mortem examination. Sections of the spinal cord at the most affected level show only a little chromatolysis of anterior horn cells, without any definite fall-out of cells. The impact of the disease certainly does not appear to fall primarily on the spinal cord.

Garland has always emphasized that not only may the diabetes be symptomless but that gross neurological defect may be present with diabetes that can only be detected by means of a glucose tolerance test, and perhaps only doubtfully then. He (Garland, 1957) mentions one patient with involvement of bulbar muscles and suggests that some patients with "motor neuron disease" may have diabetic amyotrophy and that the former disease may not be a distinct entity. This possibility had been brought to my attention by the following case. A woman of 60 had a six months' history of progressive asymmetrical weakness of the legs accompanied by pain. At this time weakness and wasting were confined to the legs, the tendon reflexes were absent, the plantars flexor and there was no sensory loss. Fasciculation was present but was not marked. The C.S.F. protein was normal. Among other investigations which were not helpful a glucose tolerance test was done and repeated (Fig. 2). It was slightly but definitely abnormal and of the steeple type specifically mentioned by Garland (1957). Treatment with carbohydrate restriction and later insulin was quite ineffective. The wasting progressed, and after a further four months caused her death from spinal respiratory paralysis. The spinal cord presented a very different appearance from that of the previous case, showing virtual destruction of the anterior horn cells typical of motor neuron disease. Although these two conditions may be clinically very similar, pathologically they appear to be distinct.

I have carried out glucose tolerance tests on 11 cases of motor neuron disease. This test is notoriously affected by factors such as preceding diet, infection, drugs, thyroid disease, the method of collection of specimens and of estimation of the blood sugar; in fact nearly every conceivable factor except the size of the patient and of the dose of glucose, which seem to matter little. These tests were done with 50 grams of glucose using the Folin and Wu method on capillary blood. In most cases pains were taken to exclude extraneous factors and the tests were repeated in the more abnormal cases. It can be seen (Fig. 3)

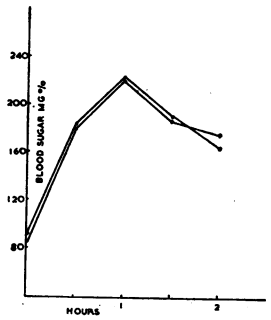

FIG. 2.—Glucose tolerance tests in a case of atypical motor neuron disease.

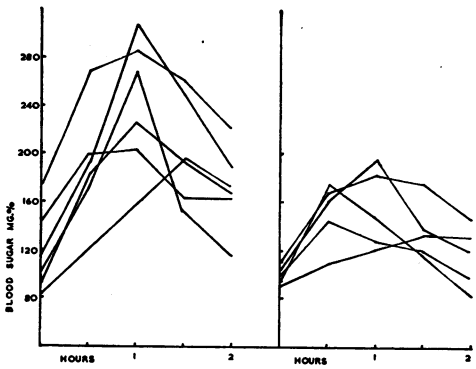

FIG. 3.—Glucose tolerance tests in 11 cases of motor neuron disease.

that although the fasting blood sugar was abnormal in only one case, approximately half the curves are abnormal. I have not found any correlation between the nature of the curve and any clinical feature. It is extremely doubtful whether these curves are of any significance in the causation of the disease and I have not yet carried the investigation any farther. Their immediate significance appears to be that it may not be wise to give a good prognosis in the presence of muscular wasting and an abnormal glucose tolerance curve. Most of the patients figuring on this chart are now dead.

In such investigations we are very much dependent on our biochemical colleagues. I do not think that this dependence makes the work of the clinical neurologist any the less important. It is necessarily the clinician who must pose the questions and to do this he must endeavour to understand, at least in broad outline, what the biochemist has to offer.

REFERENCES

ALLAN, J. D., CUSWORTH, D. C., DENT, C. E., and WILSON, V. K. (1958) *Lancet*, i, 182.
BARON, D. N., DENT, C. E., HARRIS, H., HART, E. W., and JEPSON, J. B. (1956) *Lancet*, ii, 421.
BERGREN, W. R., DONNELL, G., and KALCKAR, H. M. (1958) *Lancet*, i, 267.
BICKEL, H., GERRARD, J., and HICKMAN, E. M. (1954) *Acta pædiat., Stockh.*, **43**, 64.
——, SCHULTZE, H. E., GRÜTER, W., and GÖLLNER, I. (1956) *Klin. Wschr.*, **35**, 961.
COATES, S., NORMAN, A. P., and WOOLF, L. I. (1957) *Arch. Dis. Childh.*, **32**, 313.
CONN, J. W., LOUIS, L. H., FAJANS, S. S., STREETER, D. H. P., and JACKSON, R. D. (1957) *Lancet*, i, 802.
DAVIS, B. D. (1954) *Res. Publ. Ass. nerv. ment. Dis.*, **33**, 23.
DEAN, G., and BARNES, H. D. (1958) *Brit. med. J.*, i, 298.
DENT, C. E. (1957*a*) *Amer. J. Med.*, **22**, 671.
—— (1957*b*) *Arch. Dis. Childh.*, **32**, 363.
DINE, M. S. (1956) *Amer. J. Dis. Child.*, **92**, 15.
GARCIN, R., and LAPRESLE, J. (1950) *Sem. Hôp. Paris*, **26**, 3404.
GARLAND, H. (1955) *Brit. med. J.*, ii, 1287.
—— (1957) In: Modern Trends in Neurology. Editor: D. Williams. London; p. 229.
——, and TAVERNER, D. (1953) *Brit. med. J.*, i, 1405.
GREENFIELD, J. G. (1954) *Proc. R. Soc. Med.*, **47**, 150.
HSIA, D. Y.-Y., DRISCOLL, K. W., TROLL, W., and KNOX, W. E. (1956) *Nature, Lond.*, **178**, 1239.
——, KNOX, W. E., and PAINE, R. S. (1957) *Amer. J. Dis. Child.*, **94**, 33.
MARSTON, H. R. (1952) *Physiol. Rev.*, **32**, 66.
MATTHEWS, W. B. (1957) *J. Neurol. Psychiat.*, **20**, 172.
PETERS, H. A., WOODS, S., EICHMAN, P. L., and REESE, H. H. (1957) *Ann. intern. Med.*, **47**, 889.
SCHWARTZ, V., HOLZEL, A., and KOMROWER, G. M. (1958) *Lancet*, i, 24.
SJÖGREN, T., and LARSSON, T. (1957) *Acta psychiat., Kbh.*, **32**, suppl. 113.
WALSHE, J. M. (1956) *Amer. J. Med.*, **21**, 487.
WATSON, C. J., and SCHWARTZ, S. (1941) *Proc. soc. exp. Biol. N.Y.*, **47**, 393.
WOOLF, L. I., GRIFFITHS, R., MONCRIEFF, A., COATES, S., and DILLISTONE, F. (1958) *Arch. Dis. Childh.*, **33**, 31.
WORSTER-DROUGHT, C., WHITE, J. C., and SARGENT, F. (1953) *Brit. med. J.*, ii, 114.

Dr. R. T. C. Pratt (London) read a paper on *Genetic Aspects of Metabolic Disorders of the Nervous System.*