WILSON'S DISEASE

Hepatolenticular Degeneration

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The inclusion of a rare neurological disease in an issue of this journal devoted to disorders of the liver would seem to warrant some explanation for although cirrhosis of the liver is an integral part of the syndrome of Wilson's disease, it accounts for an insignificant proportion of all patients suffering from hepatic cirrhosis. However, although quantitatively unimportant, its significance reaches beyond the rigid confines of a medical curiosity, for a study of this disease has posed problems in genetics, in trace metal metabolism, in protein metabolism and in renal tubular transport, to mention only a few of those aspects which have been investigated during the past decade with particular vigour. In this article some of these newer aspects will be discussed against the backdrop of knowledge which has accumulated steadily during the past four to five years. But enthusiasm for the newer knowledge should not automatically repudiate the old, and although our understanding of the disease has increased enormously there seems little likelihood that the clinical description of the disease by Kinnier Wilson in 1910 will be bettered.¹ Although Kinnier Wilson recognized and delineated the syndrome called hepatolenticular degeneration or, more commonly, Wilson's disease, it is of interest that Frerich described a case of cirrhosis in 1886 which seems to have been a case of Wilson's disease.² In his classic treatise on liver disease, Frerich described how Carl Zeppner, a peasant's son, suffered from severe liver disease associated with violent tremors and convulsions and died at the age of 10. An autopsy revealed hepatic cirrhosis. The age of the patient, his sex and the characteristic symptoms make the diagnosis of Wilson's disease, if not certain, at least highly probable.

Genetic Considerations

The application of Mendelian genetics to human disease was initiated by Sir Archibald Garrod over 50 years ago in his classical studies on alkaptonuria and other inborn errors of metabolism. Wilson's monograph appeared four years after

Garrod had delivered the Croonian lectures at the Royal College of Physicians, and it is noteworthy that Wilson regarded the familial aspect of the disease sufficiently important to include it in the full title of his monograph, 'Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver.'¹ The occurrence of the disease in families was well recognized by Wilson, although, curiously, he did not regard the disease as being truly hereditary. The probable reason for his view was based on the knowledge that, although the disease was present in siblings, the parents of the affected persons were free from the disease. However, this observation, which has been confirmed repeatedly, merely excludes the possibility of the disease being inherited in a dominant fashion and does not exclude—indeed, it favours—the disease being recessively inherited. In any rare, recessively inherited disease the proportion of cousin marriages in the parents of those individuals afflicted will be much greater than in a control group of subjects, and, further, the rarer the disease the greater will be the incidence of consanguinity in the parents. For a person to develop the disease he must inherit the gene for Wilson's disease in a double dose, since there is no evidence that patients who are heterozygous for the Wilson's disease gene develop clinical symptoms. If one parent is heterozygous for the Wilson disease gene, he will only have children with Wilson's disease if he marries someone who is also heterozygous for the abnormal gene. Since the gene frequency is extremely rare, perhaps 1/1,000, the chance of his marrying an individual who is also heterozygous will be greatly increased if he marries a close relative. It can be shown that if an individual who is heterozygous for a rare gene marries his first cousin the chance that his first cousin will also carry the abnormal gene is 1/8, whereas the chance of meeting the gene in a random marriage will be the gene frequency of the abnormal gene. Inquiry into a recent series of cases with Wilson's disease revealed a first cousin consanguinity in the parents of those afflicted with

37.5 per cent.,³ whereas the consanguinity rate for the general population is only about 0.6 per cent. Most of the cases seen by the author have occurred in Eastern European Jews and Italians from the southern part of Italy. Both these racial groups are considered to have an increased consanguinity rate and thus the figure of 0.6 per cent. is inapplicable to these genetic 'isolates' in whom the true consanguinity rate is probably very much higher. The detection of carriers of the gene by means of specific biochemical tests has not yet been possible. However, detection of specific biochemical abnormalities in asymptomatic siblings has recently been demonstrated and will be discussed later.

Clinical Aspects

From a clinical point of view, patients with Wilson's disease commonly fall into three broad categories and, although considerable overlap occurs, the following crude clinical classification may be helpful:

Acute Form

This variety of the disease was well recognized by Wilson in his classical monograph and has been observed many times subsequently. Characteristically, the disease occurs in adolescence and is commoner in boys than girls. The onset is usually fairly abrupt and rapid progression of the disease is the rule. A fatal termination is usual within a few months or years. The early symptoms are usually referable to the central nervous system; a mild flexion extension tremor of the wrist, unnatural grimacing, dysarthria or, more rarely, dysphagia may herald the onset of the disease. During the closing months of the disease the clinical picture is tragically memorable. The patients lie helpless in bed, their facial expressions vacuous and fixed. Continuous drooling at the mouth frequently accentuates their evident misery. More rarely tremor dominates the clinical picture and, although minimal at rest, the slightest attempt to execute any movement results in a wild thrashing tremor of the arms. A high fever accompanied by drenching sweats is a common terminal event, but may be present for many months. The cause for the fever is obscure.

Neurological Form

Within this broad group two varieties may be distinguished: those in whom tremor is predominant and those in whom rigidity is the outstanding neurological symptom. Frequently, of course, both tremor and rigidity are present to a varying extent in the same patient. The tremor can usually be exaggerated by the execution of voluntary movements. Although commoner in

the upper extremities, particularly at the wrist, may start in the lower limbs. Titubation may be exceedingly troublesome in some patients. Although these patients may have a progressive course, many appear to develop the disease slowly and a mild tremor may persist relatively unchanged for many years. One of the author's patients, a dental surgeon, noted at the age of 30 some difficulty in manipulating a dental drill. With perseverance, but it may be remarked, with increasing discomfort to his patients, he remained at work for a further five years, when he was forced to retire. He is now aged 57 and, although the tremor has slowly worsened and he has slight dysarthria, he continues to lead an active though restricted life. Occasionally the disease may begin with choreiform movements of the arms; less commonly the legs are also involved. The occurrence of spontaneous movements may lead, particularly in the case of a child, to the presumptive diagnosis of Sydenham's chorea. In most cases the presence of a Kayser-Fleischer corneal ring will lead to the correct diagnosis. In a few instances the only reliable means of differentiating Sydenham's chorea from Wilson's disease is the performance of specific diagnostic biochemical tests. Spontaneous movements of an athetoid type may occasionally dominate the scene. Frank euphoria is not very common, though lack of insight and general evidence of cerebral deterioration is a frequent finding. Rarely the disease is ushered in by a rapidly progressive dementia. Two of the author's patients were institutionalized within a few months of the apparent onset of the disease.

Hepatic Form

Although it is probably true that over 95 per cent. of patients with Wilson's disease have cirrhosis of the liver, the cirrhosis is well compensated and does not usually give rise to ill effects. In the majority of patients with Wilson's disease the liver function tests conventionally employed in clinical medicine are normal. The most sensitive index of abnormal liver function in Wilson's disease is an elevation in the bromsulphalein retention test. If the test is properly controlled, even minor degrees of elevation are significant. In a few instances an aspiration liver biopsy will reveal hepatic cirrhosis when all the biochemical tests of liver function are normal.

There is one group of patients with Wilson's disease in whom decompensated cirrhosis of the liver occurs without any neurological signs or symptoms. These patients have all the classical signs of cirrhosis and may die in hepatic coma or from the effects of portal hypertension before the disease is suspected. Rarely rupture of oeso-

phageal varices may occur early in the disease; ascites is uncommon and only rarely causes significant distress. The diagnosis of those cases of Wilson's disease in whom cirrhosis of the liver is the sole manifestation present a difficult diagnostic problem. There is no doubt, however, that increasing awareness of the disease in this form will result in the correct diagnosis being made more often. All cases of familial cirrhosis in young adult males should arouse the suspicion that the underlying cause may be Wilson's disease. When there is consanguinity in the parents the suspicion should be increased. If Kayser-Fleischer rings are present, the diagnosis of Wilson's disease is secure.

Kayser-Fleischer Rings

So-called pathognomonic signs in various disease states are usually more seductive than reassuring, for exceptions seem to prove the rule with singular regularity. However, classical Kayser-Fleischer rings have not been reported in any other clinical condition. They can usually be seen most clearly by shining a light obliquely on the cornea from above. Traditionally the greyish-green corneal ring is best seen by means of a slit lamp, but in well over 90 per cent. of cases the ring can be seen with the naked eye. Although the absence of a Kayser-Fleischer ring does not exclude the presence of Wilson's disease with certainty, it makes the diagnosis highly improbable.

Disturbances in Copper Metabolism

In the old German literature references to a possible disturbance in mineral metabolism in Wilson's disease can be found. Unfortunately, largely due to methodological difficulties, a precise relationship of copper metabolism to Wilson's disease was never clearly established. Indeed, at one time the disease was considered to be due to silver intoxication. A chance observation by Mandelbrote and co-workers at Oxford that a patient with Wilson's disease excreted an increased quantity of copper in the urine provided impetus to further investigation.⁴ Largely as a result of the work of Cumings, it has become clear that the total body copper in Wilson's disease is increased.^{5, 6} The excess copper is fairly widely distributed in the tissues and is not confined to the liver and regions of the basal ganglia of the brain. Despite an increased urinary excretion of copper on Wilson's disease, the serum copper is usually greatly decreased. This apparent anomaly has been clarified by recent investigations on the nature of the serum copper. Copper is normally present in the serum tightly bound to an α_2 globulin.⁷ The copper forms an integral part of the protein, and it has been shown that each protein molecule contains 8 atoms of copper. This protein, which

has been named ceruloplasmin, shows oxidase activity toward a variety of artificial substrates, and measurement of this oxidase activity provides one of the ways of measuring the level of serum ceruloplasmin. The copper content of ceruloplasmin accounts for about 95 per cent. of the serum copper. The remaining 5 per cent. of the serum copper is loosely bound to serum albumin and this fraction of the serum is relatively increased in Wilson's disease.^{8, 9} Patients with Wilson's disease appear to be unable to synthesize ceruloplasmin.¹⁰ In normal subjects, following the administration of radioactive copper, the radioactivity can be shown to be associated with the albumin component of serum. Within a few hours the radioactivity is associated with the α_2 globulin ceruloplasmin and very little remains bound to serum albumin. It is apparent that serum albumin has merely functioned as a transport system whereby the copper can be delivered to the sites at which the ceruloplasmin is normally synthesized. In patients with Wilson's disease the situation appears to be different. The radioactivity is again initially associated with serum albumin, but little or no uptake into ceruloplasmin occurs. The copper remains bound to the albumin and the quantity of copper bound is greater than in normal subjects.^{8, 9} This copper albumin complex is a very loose bond and the copper can be easily dissociated from the protein moiety. The increased copper content of the urine in Wilson's disease is now no longer anomalous, since, although the total serum copper is diminished, the copper bound to serum albumin is actually increased and copper will be excreted in the urine. It is of interest that in patients with nephrosis in whom proteinuria is present ceruloplasmin appears in the urine. The continuous loss of ceruloplasmin from the body by this route may cause secondarily a diminution in the serum copper in this disease. Under normal conditions ceruloplasmin is not present in the urine in significant amounts. The deposition of copper in the tissues occurs as a result of a similar mechanism. The perfusion of tissues with blood containing an increased quantity of copper attached to albumin permits the deposition of copper whenever there are substances in the tissues which have a greater affinity for copper than serum albumin. The deposition of copper in the tissues may cause damage directly by virtue of its 'irritant' effect or, more likely, by interfering with essential enzyme systems. Since the total body copper is high in Wilson's disease and because there is an increased excretion of copper in the urine, an increased absorption of copper must occur. Recent experiments using Cu^{64} have demonstrated conclusively that an increased absorption of copper in Wilson's disease does occur.^{8, 9, 11}

A deficiency of ceruloplasmin has been observed in asymptomatic siblings of patients with Wilson's disease without any other biochemical defects. Whether these individuals will eventually develop the clinical manifestations of Wilson's disease is still uncertain and careful follow-up studies will be required to answer this question.

Renal Abnormalities

In 1948 Uzman and Denny-Brown reported the exciting finding that patients with Wilson's disease excreted an increased quantity of amino acids in their urine.¹² This observation was not entirely new, since Dent had examined the urine from two patients with Wilson's disease in 1947 and had also noted an aminoaciduria.¹³ The plasma level of amino acids is not increased. Although the aminoaciduria is moderately generalized, certain amino acids are excreted in excess of others. The excretion of threonine and cystine is greatly increased, and in some instances the latter is excreted in quantities which equal those found in patients with cystinuria. Serine, glycine, asparagine, valine, tyrosine and lysine may also be greatly increased.¹⁴ Early in the disease, however, excessive aminoaciduria may be absent. As the disease progresses the aminoaciduria increases. Eventually, as much as 18 per cent. of the amino acids filtered by the glomerulus are excreted in the urine (normal 1 to 3 per cent.)¹⁵

Recently other renal defects have come to light and it has become apparent that additional tubular transport systems are defective. Glycosuria, which occurs in some instances of Wilson's disease, is associated with a normal fasting plasma glucose level and a normal glucose tolerance curve. However, loading experiments with glucose revealed a considerable diminution in glucose T_m , which in some instances was reduced to at least 30 per cent. of the normal value.¹⁵ The tubular transport of p-aminohippuric acid (PAH) is also impaired in some patients with Wilson's disease and the maximum capacity of the tubules to secrete PAH may be greatly decreased. Uric acid excretion is also increased in Wilson's disease.¹⁶ In some patients, particularly those in whom the disease has been present a long time, nearly 50 per cent. of the uric acid excreted by the kidney may be lost in the urine, whereas normally at least 90 per cent. is reabsorbed by the tubules and only 10 per cent. excreted in the urine. This drain of uric acid from the body results in a diminution in plasma urate which may be reduced below 2 mg. per cent. Recently phosphate, another substance normally reabsorbed in the proximal renal tubules, has been found to be excreted in abnormal amounts.¹⁵ The plasma phosphate is frequently decreased. This defect in phosphate metabolism may be related to

the occasional occurrence of osteoporosis and spontaneous fractures in patients with Wilson's disease. There is a striking similarity between the renal lesions in Wilson's disease and those found in Fanconi's syndrome. Recent work has indicated that the renal response of patients with Wilson's disease to an acid load (ammonium chloride) is normal. However, clinical acidosis commonly found in Fanconi's syndrome is not seen in Wilson's disease. Further work is required to determine whether under the stress of an acid load inadequate acidification of the urine occurs. No swan neck anomaly of the proximal renal tubules has been seen in the kidneys of patients with Wilson's disease studied thus far.¹⁷ It seems possible that all the renal defects may be caused by an increased copper deposition in the proximal renal tubules, which in turn leads to progressive inhibition of specific enzyme systems responsible for tubular transport. In this way the renal lesion in Wilson's disease would be analogous to those found in poisoning with other heavy metals.

Treatment

The chief biochemical defect in Wilson's disease appears to be a defective synthesis of the specific serum copper carrying protein ceruloplasmin, which leads to the accumulation of an increased quantity of copper in the tissues with consequent tissue damage. Logically, therapy should include the replacement of serum ceruloplasmin and the elimination of the excess tissue copper by the use of a specific chelating agent for copper. Unfortunately, neither of these two ideals have been realized and, although considerable strides have been made in the treatment of Wilson's disease during the past few years, treatment remains unsatisfactory.

The replacement of the deficiency of ceruloplasmin by regular infusions of the protein is unfortunately impracticable. The concentration of ceruloplasmin in normal human serum is about 25 mg. per cent. and thus represents only 0.4 per cent. of the total serum protein.¹⁰ The isolation and purification of such a protein is clearly no mean task. Even if it were possible to obtain large quantities of the protein in a form suitable for intravenous injection, the short half life of the protein would prevent the maintenance of the serum ceruloplasmin at a normal level without recourse to very frequent infusions.

A variety of chelating agents have been used during the past decade. BAL,^{18, 19} versene (ethylenediamine tetra-acetic acid)³ and, more recently, penicillamine ($\beta\beta$ dimethyl cysteine)²⁰ have been advocated as effective agents. BAL has been shown to be fairly effective in those cases in whom the disease is long standing and characterized chiefly

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by tremor. The drug must be given daily for many months. Tolerance to the drug varies. Some patients can be given doses up to 300 mg. per day; others will develop toxic reactions and prolonged therapy is not possible. Versene, although effective, has the disadvantage of requiring intravenous administration. Intramuscular versene is painful and not very effective; oral versene is ineffective. Penicillamine appears effective by mouth and, provided it can be produced cheaply, will undoubtedly prove of great value. All patients should be given a high protein diet, since the resultant increased amino acid excretion will itself increase the urinary excretion of copper. Ideally, the total copper content of the diet should be kept as low as possible. A diet containing less than 1 mg. per day of copper is rather unpalatable, and it is often simpler to compromise and merely exclude those articles from the diet which have a high copper content.

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