WILSON'S DISEASE

BY

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(RECEIVED FOR PUBLICATION JANUARY 15, 1962)

Wilson's disease (hepatolenticular degeneration) is a congenital metabolic disease which is characterized by an accumulation of toxic amounts of copper within the body. This is usually associated with a deficiency of a protein, caeruloplasmin, which is responsible for the transport of most of the serum copper. In addition there is an increased rate of absorption of copper from the intestine. Consequently copper is deposited in tissues, particularly the liver and brain, and in the cornea where it may be visible as a specific clinical sign (Kayser-Fleischer rings). Most of the signs and symptoms of the disease can be ascribed to the high tissue concentrations of copper occurring in these sites. Theories of the pathogenesis of this condition have been reviewed by Walshe (1957, 1959) and by Walshe and Cumings (1961).

Treatment aims to reduce the amount of copper absorbed and to remove the excess from the body by giving agents with which it will form soluble non-toxic complexes excreted by the kidney. The two most effective cupruritic drugs are dimercaprol (BAL) (Cumings, 1959) and penicillamine (Walshe, 1956a, 1956b). The latter appears to be the more effective (Walshe, 1960a), but relatively few reports have appeared on the results of long-term penicillamine treatment (Scheinberg and Sternlieb, 1960; Strong, Dempsey and Hill, 1961).

This paper records two cases of Wilson's disease in the same family, one severely affected, the other asymptomatic, and the good clinical response of the former to treatment with penicillamine over a period of four years.

A brief account of Case 1 is included in a review (Walshe, 1960a) on penicillamine treatment, where our patient is referred to as Case No. 16.

Case Reports

Case 1. E.M., a girl, born on July 1, 1945, was first seen at Chelmsford on July 19, 1957, at the age of 11. She was referred for consultation because she had developed 'symptoms of severe chorea with twitching movements and emotional instability' following a slight blow on the head.

She had had no serious illness until September 1952 when, at the age of 7, she developed a throat infection followed by jaundice with enlargement of the liver. Her urine contained bile but her stools were not pale. She was admitted to hospital where her jaundice fluctuated and she became so anaemic that she was given a blood transfusion. A diagnosis of Weil's disease was made and she was treated with penicillin. She was sent home in January 1953, looking well but with her liver still enlarged. A week later she became jaundiced again, and her liver and spleen had both increased in size. After temporary recovery jaundice reappeared, and she was then admitted to the Royal Hospital for Sick Children, Edinburgh, under Dr. D. M. Douglas. At this time she was jaundiced (serum bilirubin 7.0 mg./100 ml.), anaemic (Hb 9.2 g./100 ml. = 62%), and had a raised B.S.R. (20 mm./hour). Alkaline phosphatase was normal (4.5 K.A. units), but flocculation tests were positive (thymol turbidity 6 units; cephalin-cholesterol 4+). Serological tests (leptospiral agglutinins 1:10) were considered to confirm the past infection with leptospira icterohaemorrhagica. A liver biopsy (March 12, 1953) showed subacute atrophy with nodular hyperplasia, and considerable deposition of haemosiderin (Fig. 1). A section stained by Dobell's method was searched for leptospira without success. The jaundice cleared fairly rapidly, and her haemoglobin rose to normal, but her liver and spleen were still enlarged when she went home.

When seen by Dr. Douglas on June 8, 1955, her liver was enlarged three and a half finger breadths and her spleen two finger breadths below the costal margin. There had been no further episodes of jaundice.

The family moved to Essex in August 1955, where the child remained well until January 1957, when her parents began to notice a gradual change. Her speech became slurred and indistinct, and saliva began to drool from her mouth. She was clumsy and jerky in her movements. Her writing deteriorated and at times was almost illegible. She was careless and untidy with her belongings, and her temperament changed: she was excitable and difficult to handle, having outbursts of temper for little or no reason; and sometimes she would just be found crying.

Examination. She was a pleasant cheerful girl of normal physical development for her age (weight 83 lb. (37.6 kg.)). She was restless, excitable and obviously had some difficulty in fixing her attention. She complained of being unable to sit still. From time to time

FIG. 1.—Liver biopsy of Case 1 (March 12, 1953). ($\times 108$.)

she would burst into uncontrolled laughter for very little reason. When made to concentrate, as in writing, her features became somewhat fixed and expressionless, her mouth hanging slightly open with saliva drooling from it, so that she was constantly having to wipe it away with the back of her hand. Most of the time she appeared mildly euphoric, but her mood would change suddenly: she would then look solemn and anxious. 'Although the features of her illness made her appear somewhat childish and immature, she was in fact not so. Her general knowledge was excellent, and she was above average in intelligence' (Psychiatrist's summary).

Her speech varied greatly according to mood. When she was excited it was impossible to understand what she was trying to say, but when she concentrated and spoke slowly she formed her words and composed her sentences fairly well, although her speech remained slurred. There were no spontaneous involuntary movements as in chorea, but as soon as she got excited all her movements became clumsy. Conversely, she could control her movements to a certain extent by making a voluntary effort to suppress her excitement. Her gait was almost normal when she was walking slowly, but as soon as she became excited or tried to hurry she staggered and lurched into things, and as a result she had numerous bruises on her arms and legs. Her handwriting was untidy (Fig. 2). In spite of her clumsy movements her grip was constant, and there was no tremor.

Examination of other systems showed well-marked Kayser-Fleischer rings which were visible without the aid of a slit lamp (Fig. 3). The liver was firm and enlarged two finger breadths below the right costal margin; the spleen was enlarged two finger breadths below the left costal margin. There was no jaundice spider naevi or liver palms.

Investigations. Blood examination showed Hb 12.4 g./100 ml. (84%). The white blood cells, platelets, red cell fragility and B.S.R. were normal; the Wassermann reaction was negative. The cerebrospinal fluid was normal, with negative Wassermann and Lange reactions.

Liver function tests (bilirubin, alkaline phosphatase and flocculation reactions) were normal, but the prothrombin index was 75% and the bromsulphthalein test showed some delay in excretion (21% of the injected dye remained after 45 minutes).

Radiographs of skull and chest were normal, and no oesophageal varices were seen.

An electroencephalogram on October 18, 1957, was abnormal. It was dominated by an alpha rhythm of approximately 10-11 c./sec., with some theta activity. High voltage slow waves and sharp waves were superimposed upon these from time to time (Dr. S. L. Sherwood).

Her I.Q. on October 11, 1957, was 100 (Terman and Merrill, 1937 revision: Stanford Binet Scale).

*Pamela
by A. H. H. H.
=, Day is Saturday
July 27 1957*

July 27, 1957: before treatment.

*As quick as lightning
As sharp as a knife
As green as grass
As quiet as a mouse
As hard as wood*

July 15, 1958: in remission.

*Hyperbole means
exaggeration - for emphasis eg.
"O King live for ever";
The hairs of your head are numbered.
A Wordable - contradict itself*

June 5, 1959: in relapse.

*Lives on a lofty vases red
Where chimis gayer art had died
The azure flowers that blow
Demurest of the lolly kind
The penance Salome reckoned
gazed on the lake below.*

June 16, 1961: in remission.

FIG. 2.—Four specimens of handwriting from Case 1.

Diagnosis. The patient had presented with a chorea-like syndrome; but when it was found that she had hepatosplenomegaly, together with Kayser-Fleischer rings, a diagnosis of Wilson's disease was made. This was confirmed by two tests which together are specific. The serum *p*-phenylenediamine oxidase, which is a measure of caeruloplasmin (Ravin, 1956), was low (0.045 arbitrary units, normal 0.2-0.8), and the urine copper excretion increased (334 $\mu\text{g.}/24$ hours, normal less than 50 $\mu\text{g.}/24$ hours).

FIG. 3.—Kayser-Fleischer ring of Case 1 (1958).

Family History. The parents come from Scotland but are of French Huguenot extraction. They are first cousins and have three children: the patient, E.M., aged 12, a boy, A.M., aged 11, and another boy, R.M., aged 6. When it was found that the patient was suffering from Wilson's disease the family was investigated. The parents both had normal serum phenylenediamine oxidase levels. The elder brother, A.M., was found to have a normal serum oxidase of 0.35 units, normal urine copper excretion (36 $\mu\text{g.}/24$ hours) and no abnormalities on clinical examination. The younger brother, R.M., had the biochemical changes of Wilson's disease without overt clinical manifestations, and is described in detail below (Case 2).

The father was the fourth of five siblings, the eldest of whom, a male, had died at the age of 21 from a progressive nervous disorder with dysarthria which started when he was 11 years old. The symptoms of E.M. (Case 1) were thought by the family to be remarkably similar to those of her uncle. The youngest sibling, a girl, died at the age of 7 with ataxia following an illness lasting two years which was diagnosed as meningitis, although it was gradual in onset. The third sibling, a girl, also died as a child, but the cause of her death is not known. There is one surviving female who is normal. The mother was the third of three siblings. Her elder brother died at the age of 10 with nephritis; the other is alive and well. The family tree is shown in Fig. 4.

FIG. 4.—Family tree: cases of Wilson's disease are shaded.

Treatment. When the diagnosis of Wilson's disease was established, measures were taken to reduce the intake of copper and stimulate its excretion. She was put on a low copper diet which excluded cocoa products, nuts, liver, shellfish, mushrooms and spinach (Scheinberg and Sternlieb, 1960); this contained not more than about 1 mg. copper per day (by tables) compared with about 2 mg. in a normal diet. Specimens of tap water were analysed for copper. The results (Table) suggested that on a normal fluid intake the patient was unlikely to take in more than about 50 µg. copper per day in tap water, and no special measures were considered necessary to deal with this. Potassium sulphide (20 mg. t.d.s.) was given before meals in an attempt to reduce copper absorption by forming insoluble copper sulphide in the intestine (Cartwright, Hodges, Gubler, Mahoney, Daum, Wintrobe and Bean, 1954). This part of the treatment has been continuous.

It was decided to use D-penicillamine hydrochloride ($\beta\beta$ -dimethylcysteine) as the chelating agent to promote urinary excretion of copper. At the time little was known of the best dose to employ or the conditions under which it would be most effective. The urine copper excretion was, therefore, measured on at least two successive 24-hour specimens, in an attempt to assess the effectiveness of various forms of therapy.

Penicillamine was started on September 28, 1957. This was given at first in three doses daily, each of 0.3 g. by mouth after meals. As a result, the urine copper excretion increased and built up over about three weeks to about 2,000 µg./24 hours. The dose was then varied: as it was increased, at weekly intervals, from 0.3 to 0.6 to 0.9 g. daily, the urine copper excretion varied accordingly. There was, however, relatively little increase in copper excretion when the dose was increased from 0.9 to 1.2 g. per day, and it was concluded that 0.9 g. was the most efficient daily dose. When penicillamine was stopped copper excretion fell immediately to pre-treatment levels. These changes are illustrated in Fig. 5.

At first it was thought that penicillamine might easily be oxidized *in vivo* to the cystine derivative, which would be inactive (Walshe, 1956b). Ascorbic acid (500 mg. daily) was, therefore, given for a week with the penicillamine in an attempt to keep the latter in the active reduced form, but this resulted in no further increase in copper excretion. Scheinberg and Sternlieb (1960) have reported similar results.

It had been shown previously that the feeding of amino

TABLE
COPPER CONTENT OF TAP WATERS

Specimen	Copper Content (µg./100 ml.)
Hospital cold tap	2
Patient's home, cold tap	4
Patient's school, cold tap	10
Cold tap from a house with all copper plumbing	30

acids, such as glycine and alanine (Matthews, Milne and Bell, 1952), or a high protein diet (Bearn and Kunkel, 1954) increased the urine copper excretion of patients with Wilson's disease. The copper excretion of our patient was measured, over three-day periods, first when on a low protein intake (40 g. daily) and then on a high protein diet (100 g. daily). There was no significant difference between these two periods, and it was concluded that the addition of extra protein did not increase the output of copper whilst the patient was on penicillamine (Fig. 5).

By December 21, 1957, after three months of treatment, the patient had improved clinically and was sent home on 0.9 g. penicillamine daily, together with potassium sulphide and a low copper diet.

Progress. In April 1958, after continuous treatment with penicillamine 0.45-0.9 g./day, considerable improvement was noticed. Although still rather excitable, her behaviour had improved and her handwriting was clearer. There was no longer any difficulty in understanding her speech, and her gait was normal. Before this the electroencephalogram (February 18, 1958) had shown some improvement: it was a little more stable with fewer sharp waves. The liver function tests remained normal with the exception of the bromsulphthalein excretion which was still reduced (30% remained 45 minutes after injection), but the hepatosplenomegaly and the Kayser-Fleischer rings were unchanged.

In May 1958 she was able to return to school, and two months later she was clinically in remission and the excessive salivation had ceased. Her urine copper excretion had fallen from 2,000 µg./24 hours to 1,000 µg./24 hours; penicillamine was therefore stopped for a trial period of one month, although the potassium sulphide and low copper diet were continued. At the end of this break in treatment she was still clinically well, and on restarting penicillamine there was no marked cupropuriosis such as might have been expected if copper had been reaccumulating.

In October 1958, a year after starting treatment, her urine copper excretion had fallen to 300 µg./24 hours. It was decided, therefore, to stop penicillamine for a period of three months and to observe the child. Clinically she remained in remission, although her electroencephalogram (January 27, 1959) still showed some abnormal activity.

On restarting penicillamine in January 1959, there was again no marked cupropuriosis; and by February her

FIG. 5.—Initial response of Case 1 to penicillamine.

urine copper excretion had fallen to about 150 µg./24 hours. There seemed little purpose in continuing the drug since it was removing only small amounts of copper, and it was stopped on February 6. The patient was seen at frequent intervals, and at the end of June, when no penicillamine had been given for nearly five months, her parents reported that her condition had deteriorated during the previous three weeks. She was more excitable and her speech was less clear, although there was no return of the abnormal salivation. Her writing was again untidy (Fig. 2), her movements were less controlled, and she tended to walk with a rather stiff back.

Penicillamine was restarted and within a week her parents noticed an improvement in her behaviour: she had become calmer, her speech was clearer and her movements were more controlled. On restarting penicillamine her urine copper excretion was a little higher (900 µg./24 hours) than it had been after two previous breaks in treatment.

In September 1959 she was again in remission, but penicillamine was producing only minimal cupruresis. It was decided to stop the drug again to see whether the rather non-specific symptoms and signs which had occurred two months before were in fact directly related to cessation of this treatment. When seen three weeks later she was again excitable and emotionally unstable; her speech was slurred and she was beginning to drool saliva. Because of this second minor clinical relapse the penicillamine was restarted.

After this her clinical state was variable, but by February 1960 she had definitely deteriorated. Her parents then reported that her movements had become

incoordinated so that she was beginning to have some difficulty in feeding herself. She had become euphoric, and for the first time had developed a coarse tremor of her arms and hands when excited. She now had considerable difficulty in writing and saliva dripped from her mouth.

At this time it was thought that she was becoming resistant to penicillamine, and various measures were tried to increase the effectiveness of this therapy. Addition of ascorbic acid (500 mg. per day) to the penicillamine treatment for one week (as we showed earlier) produced no change in her clinical state or 24-hourly copper excretion. *In vitro* experiments had shown that the binding of penicillamine to copper was stronger in alkaline solution (J. M. Walshe, personal communication). She was, therefore, given sodium citrate with penicillamine for one week to make the urine alkaline, but this again produced no clinical or biochemical response. Penicillamine was first discovered in the urine of cases of cirrhosis who were receiving penicillin (Walshe, 1953), and it was thought that our patient might metabolize the latter compound to penicillamine, with a resulting cupruresis. She was given a short course of oral, and then intramuscular penicillin, together with penicillamine, but this produced no significant cupruresis.

Other penicillamine compounds were then tried. The isopropylidene derivative is hydrolysed *in vitro* to the free penicillamine (P. Eaglesfield, personal communication), but when this compound (0.9 g./day) was substituted for four days there was no biochemical change. Scheinberg and Sternlieb (1960) likewise noted that this compound was inactive. DL-penicillamine hydro-

chloride (0.45 g. daily) was given for four days, but this was no more effective than the D-isomer which had previously been used. Finally the patient was given 0.9 g. D-penicillamine intravenously, made up in a pint of sixth molar sodium lactate, over a period of six hours. The copper excretion during this day was no higher than it had been when the patient was on oral penicillamine hydrochloride.

In August 1960, following the failure of any of these measures to effect an increase in the 24-hourly copper excretion, she was admitted to Addenbrooke's Hospital, Cambridge, for copper clearance studies (Dr. J. M. Walshe). Her serum copper was found to be 42 $\mu\text{g.}/100\text{ ml.}$ (normal 68-165 $\mu\text{g.}/100\text{ ml.}$, Cartwright, Markowitz, Shields and Wintrobe, 1960), and after a single dose of 0.9 g. penicillamine her copper clearance rose from 0.3 to 17.3 ml./min. over a six-hour period (Fig. 6). It was concluded that the drug had not lost its cupruric effect, and that the failure of this to be reflected in the 24-hourly excretion figures might be due to depletion of the total copper pool (Walshe, 1960b). It was decided that treatment should be continued but with a larger dose, and in November 1960 this was increased to 1.2 g./day. When this was discussed with the family it was found that over most of the periods of treatment since January 1958 the patient had been taking only half the dose intended, namely 0.45 instead of 0.9 g./day. The mistake had arisen as a result of a change in the size of the capsules in which this drug was dispensed.

Within three weeks of increasing the dose her parents noticed an improvement, and this was confirmed when

she was examined on December 19, 1960. Since then there has been further improvement, and now she has lost her tremor and there are no neurological signs. The Kayser-Fleischer rings have become paler. A psychological report on April 13, 1961, gave her mental age as 15 years 9 months, and her I.Q. as 116. An electroencephalogram on March 20, 1961, was more stable than that of March 20, 1960. The hepatosplenomegaly and liver function tests have not changed, but no oesophageal varices have developed, and transaminase levels are normal.

When the results of copper analysis were re-examined, it was found that significant changes had occurred in the 'basal' copper excretion, i.e. the urine copper excretion when the patient had received no penicillamine treatment for at least five days (Fig. 7). Continuous penicillamine treatment at first produced a fall in basal copper excretion to almost normal values, but when treatment became intermittent and at a lower dosage the basal excretion rose again and symptoms returned. When intensive therapy was restarted the level slowly fell as the patient improved. These changes correlate well with her clinical condition, and the relapse is seen to be due to the inadequate dosage of penicillamine.

Case 2. R.M., a boy, born on September 30, 1951, was first seen in September 1957, when he was 6 years old, following the discovery that his sister (Case 1) had Wilson's disease. He had no symptoms and had never been jaundiced.

Examination. He was a quiet rather phlegmatic child of stocky build (height 49 in., weight 68 lb. (30.8 kg.)).

FIG. 6.—Copper excretion after single oral doses of D-penicillamine. The figures in brackets indicate the copper clearances (ml./min.) over each period.

FIG. 7.—Basal copper excretion and clinical response to penicillamine of Case 1. Each point is the mean of at least two successive 24-hour specimens collected after the patient had received no penicillamine for at least five days.

There were no signs of neurological disorder and no Kayser-Fleischer rings were seen on slit-lamp examination. The liver edge was two finger breadths below the costal margin and the spleen was just palpable; but there was no jaundice, spider naevi or liver palms.

Investigations. The serum *p*-phenylenediamine oxidase was 0.051 arbitrary units (normal 0.2-0.8), and the urine copper excretion 468 µg./24 hours (normal less than 50 µg./24 hours). Liver function tests (bilirubin, alkaline phosphatase, flocculation reactions and bromsulphthalein excretion) were normal, and the prothrombin index was 93%. A trial course of penicillamine (0.9 g. per day) produced a cupruresis of up to 1,770 µg. copper per 24 hours. An electroencephalogram (December 4, 1957) was normal, and his I.Q. was 109 (January 1, 1958).

Diagnosis. This patient had the biochemical changes of Wilson's disease but no symptoms. The presence of a low liver edge and palpable spleen was noted, but in a stocky child it was not considered to be sure evidence of hepatosplenomegaly.

Treatment. Penicillamine is expensive, and at the time of the diagnosis it seemed hardly justifiable to start such treatment in a case with no clinical evidence of disease. On the other hand it appeared reasonable to reduce the patient's intake of copper, so it was decided to put him on a low copper diet, to give him potassium sulphide (see Case 1), and to watch the course of events.

Progress. Although he remained free from symptoms,

and no corneal rings appeared, an electroencephalogram on April 12, 1960, was abnormal (Fig. 8), showing a spike focus in the right centro-parietal area (Dr. C. C. Evans). In October 1960, when he was 9 years old, and approaching the age at which signs of the disease might be expected to appear, he was admitted to hospital for special tests. These demonstrated the abnormalities in his copper metabolism: the liver uptake of injected radioactive copper (^{64}Cu) was low (Osborn and Walshe, 1958), the fasting plasma copper was reduced (59 µg./100 ml.), and there was a marked increase in copper clearance after a test dose of penicillamine (Fig. 6). Other tests confirmed that his serum caeruloplasmin was low [2 mg./100 ml., normal 27-38 mg./100 ml. (Cartwright *et al.*, 1960)]. There was no aminoaciduria, but the serum transaminases were raised (S.G.O.T. = 240 units; S.G.P.T. = 409 units; normal less than 40 units). It was decided therefore to do a liver biopsy (January 5, 1961). Sections showed early cirrhosis of the post-necrotic type (Fig. 9), similar to that described by Anderson and Popper (1960), although copper deposits could not be demonstrated on staining with rubeanic acid (Uzman, 1957).

In view of this evidence of liver damage, penicillamine was started on January 15, 1961 (0.9 g./day). Within three weeks the parents reported a change in his temperament: in retrospect he had been getting irritable and difficult to handle, but now he regained his normal placid disposition. In an electroencephalogram (March 20, 1961) the spike focus previously seen was no longer present, and the record (Fig. 8) showed no abnormality (Dr. C. C. Evans). His basal copper excretion and

FIG. 8.—Electroencephalograms of Case 2 before (April 12, 1960) and after (March 20, 1961) penicillamine treatment.

serum transaminase levels have decreased, but are still abnormal.

Discussion

Wilson's disease may be expected to present clinically at an age when copper has accumulated

in the body in amounts sufficient to produce signs and symptoms of toxicity. This process will presumably start at birth, and many factors, such as diet, will affect the rate of accumulation. In a review of 22 cases, Walshe (1960a) found that the average age of onset was 14.8 years, the youngest

FIG. 9.—Liver biopsy of Case 2 (January 5, 1961). ($\times 108$.)

being 8 years. Patients may therefore present as a paediatric problem in whom the diagnosis may not at first be obvious.

In Wilson's (1912) original account of the disease he described the association of hepatic cirrhosis with tremor, muscular rigidity, dysarthria, dysphagia and emotional disturbances. Later descriptions have shown that the clinical picture may be extremely varied and in some cases the liver involvement is unobtrusive. The commonest presenting symptom in Walshe's (1960a) series was tremor, often associated with dysarthria, Parkinsonism and choreiform movements. However, some cases may present with evidence of liver damage and never show neurological signs; Wilson's disease should therefore be considered in any patient with juvenile cirrhosis, particularly if a sibling has previously had liver disease (Chalmers, Iber and Uzman, 1957). The one pathognomonic sign—Kayser-Fleischer rings—is so important that it is worth examining the eyes with a slit lamp; but occasionally fully developed cases have been reported without corneal rings (Chalmers *et al.*, 1957; Lygren, Sörensen and Bernhardsen, 1959).

Thus the symptoms and signs are extremely variable. Case 1 was probably typical in that the diagnosis was not immediately obvious, but in retrospect the clinical picture was seen to be characteristic of the disease. The first relevant sign was fluctuating jaundice which, at the time, was ascribed to Weil's disease, but in view of later developments the correctness of this diagnosis is questionable. It seems more likely that the child had a haemolytic episode, similar to those recorded in patients with Wilson's disease (Cartwright *et al.*, 1954; Scheinberg and Sternlieb, 1960), and the finding of gallstones in a radiograph (1960) supports this contention.

The abnormalities of copper metabolism in this disease are shown in the low serum level and increased urine excretion. The former test is difficult and time consuming, and may not show a clear discrimination between the normal range (68-165 $\mu\text{g./100 ml.}$) and that in Wilson's disease (23-116 $\mu\text{g./100 ml.}$) (Cartwright *et al.*, 1960). The serum caeruloplasmin is usually proportional to the serum copper, but normal values have been reported in a small proportion of cases (Sass Kortsak, Cherniak, Geiger and Slater, 1959; Enger, 1959; Rosenoer and Franglen, 1959; Walshe, 1960a), although in some of these the concentration fell to abnormally low levels after penicillamine treatment (Walshe and Cumings, 1961). The urine copper excretion is invariably increased threefold, and the demonstration of this, together with

a low caeruloplasmin level, is probably the simplest diagnostic test for this disease.

The renal manifestations of Wilson's disease have received comparatively little attention. Copper deposition in the kidneys may result in a failure of tubular reabsorption. This renal involvement is best seen as a generalized aminoaciduria (Stein, Bearn and Moore, 1954), but there is no characteristic pattern, and it may not be seen in all cases. Bearn (1957) concluded that the lesion was similar to that of the Fanconi syndrome and suggested that this was the cause of the radiographic abnormalities seen in the joints of 13 out of 19 cases. However, a disturbance of calcium metabolism in the absence of renal damage has been observed in Wilson's disease (Playoust and Dale, 1961), and this might explain some of the radiological changes.

The genetic aspects of this disease have been summarized by Bearn (1953), who considered that it was inherited in an autosomal recessive manner. The family history is therefore an important factor in diagnosis. When a case has been discovered other members of the family should be examined and investigated. A number of authors have found siblings who were normal on physical examination but had some degree of biochemical abnormality, and the significance of this may be difficult to evaluate. Warnock and Neill (1958) considered that laboratory findings were seldom diagnostic in the absence of physical signs, and Cartwright *et al.* (1960) support this and suggest that corneal rings are always present in a true case of Wilson's disease, even before the appearance of symptoms. It is clear, however, that biochemical changes could indicate the presence of the disease which will inevitably appear in a clinical form. Thus Lygren *et al.* (1959) described a brother, aged 23, of an affected case, who was normal when first seen, although his serum caeruloplasmin was low. The disease first showed itself 14 months later and rapidly progressed to a fatal cirrhosis with the typical findings of Wilson's disease. Others have described similar cases diagnosed before the appearance of any signs or symptoms (Bickel, Neale and Hall, 1957; Walshe, 1960a), and one who was detected at the age of 10 months (Scheinberg and Sternlieb, 1960). In contrast to this, some relatives of patients with Wilson's disease may show single biochemical abnormalities, such as aminoaciduria (Soothill, Blainey, Neale, Fischer-Williams and Melnick, 1961), low serum copper (Soothill *et al.*, 1961) and low caeruloplasmin level (Vella, 1959; Cartwright *et al.*, 1960), without developing any other signs of the disease. This emphasizes the importance of using as many independent tests as possible.

We believe that biochemical tests are called for in all siblings of known cases of Wilson's disease. Those found to have a low caeruloplasmin and increased urine copper excretion should be investigated periodically for signs of neurological and hepatic disease. The following tests may be useful in providing this evidence:

1. Liver function tests, together with transaminase levels and bromsulphthalein excretion, may be abnormal.

2. A liver biopsy often shows signs of cirrhosis (Figs. 1 and 9) and excessive deposition of copper in that organ (Chalmers *et al.*, 1957).

3. Paper chromatography may demonstrate an aminoaciduria.

4. An electroencephalogram may show non-specific changes, such as those described above (Fig. 8) and by Hollister, Cull, Gonda and Kolb (1960).

5. A test dose of penicillamine should produce a marked cupruresis (Fig. 6).

6. The radioactive copper uptake may show characteristic changes (Osborn and Walshe, 1958).

Case 2 is a good example of this, and many independent lines of evidence now support the diagnosis of Wilson's disease. It is clear that the disease can be present in an active but silent form, whilst there are still no clinical signs or Kayser-Fleischer rings. We believe that such cases should be treated.

Penicillamine is probably the most effective chelating agent yet found for the treatment of this disease (Walshe, 1960a). Some cases fail to respond to this or other drugs, although they may have a cupruresis; this could be due to treatment starting too late. In many instances adequate doses of penicillamine bring about complete relief of symptoms; with our cases the parents often noticed the reversal of emotional behavioural difficulties within two to three weeks. Hollister *et al.* (1960) likewise noted that mental signs of the disease may precede the neurological signs, and that behavioural changes were not infrequent.

The dosage necessary to produce a remission will probably depend on the individual, and Case 1 clearly shows that relapses were due to inadequate amounts of penicillamine. Doses of up to 4.5 g. daily have been used in some cases (Fister, Boulding and Baker, 1958; Seven, Kliman and Peterson, 1959; Scheinberg and Sternlieb, 1960), but these may produce signs of toxicity, particularly if the synthetic DL compound is used. Our two cases have tolerated doses of up to 1.2 g. per day of the D-isomer without side-effects, and no vitamin supplements have been necessary.

The best biochemical index of response to treatment was found to be the basal copper excretion (Fig. 7). This probably reflects the size of the body's copper pool, which may still be relatively large when symptoms have disappeared. In some cases the copper deposits in the liver can be reduced or removed with effective treatment (Sherlock, 1960), but those in the cornea appear to be more resistant. The fading of the Kayser-Fleischer rings is a sure sign of long-term improvement, and is seen in relatively few cases (Fister *et al.*, 1958; Walshe, 1960a; Scheinberg and Sternlieb, 1960; Strong *et al.*, 1961).

Summary

The biochemical defect in Wilson's disease is present at birth, and in a high proportion of cases the earliest clinical signs of the disease appear in childhood, although their significance is not always recognized at the time.

A sister and brother with the disease are described. The former had an attack of jaundice five years before she presented with the typical picture of Wilson's disease. She was treated with penicillamine (0.45-1.2 g. per day), a low copper diet and potassium sulphide over a period of four years, with an excellent clinical response. Minor clinical relapses were shown to be due to inadequate doses of penicillamine.

The second child was diagnosed biochemically at the age of 6 when there was no other evidence of disease. Three years later no obvious symptoms or classical signs had developed, but there was evidence of liver damage, electroencephalographic changes and accumulation of copper. Many independent lines of evidence thus supported the diagnosis of Wilson's disease in an active but silent form, and the patient is symptomless after six months of penicillamine treatment.

Copper clearances were a better indication of sensitivity to penicillamine than were the 24-hour copper excretion figures. In the first case the best index of long-term response to treatment was the basal copper excretion, measured on urines collected when the patient had received no penicillamine for five days.

The difficulties of diagnosis in asymptomatic siblings of cases of Wilson's disease are discussed.

We wish to record our thanks to Dr. J. M. Walshe for his most helpful advice in the treatment of these cases, and for the radioactive copper and copper clearance results; to Dr. D. M. Douglas for supplying details of the early history of Case 1; to the Institute of Ophthalmology for the photographs of the Kayser-Fleischer rings; to the Distillers' Company (Biochemicals) Ltd., for gifts

of DL penicillamine and isopropylidene D penicillamine hydrochloride; and to Mr. P. Eaglesfield for advice concerning their use. Finally, we wish to thank the Distillers' Company (Biochemicals) Ltd., for their assistance in connexion with the printing of the colour plate for this article.

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