Hepatolenticular Degeneration (Wilson's Disease)

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A Report of five cases, with Commentary

WILSON'S disease is a heredo-familial disorder, the essential pathological elements of which consist in a cirrhotic state of the liver combined with degenerative changes in the lenticular nuclei of the brain. The term "hepatolenticular degeneration" is therefore aptly precise, but affords little clue to the diversity of the clinical manifestations.

A logical survey of the latter should first emphasise the hepatic side of the picture, since all the evidence shows that the liver is affected long before recognisable nervous symptoms appear. During this "prodromal" phase various puzzling clinical states may present—in particular those of portal hypertension with jaundice and ascites, or of splenomegaly with anæmia and hæmorrhagic phenomena. Not infrequently, death occurs at this early stage and the correct diagnosis only becomes apparent if, and when, another member of the same family shows the fully-developed condition.

In patients who survive such early episodes the liver disease is prone to become quiescent, sometimes for years, before nervous troubles finally commence, and outward signs of hepatic damage are certainly inclined to be less prominent in the later phases of the disease. This adds further to the diagnostic difficulties for, once established, the neurological syndrome itself is easily capable of misinterpretation.

The classical features, originally described by Wilson (1912), are those of extrapyramidal motor dysfunction. This shows itself in the form of a coarse action-tremor of the extremities together with a plastic muscular rigidity, leading to contracture attitudes and, eventually, to true contractures. Pyramidal function remains intact, and there are no sensory disturbances. Dysarthria and dysphagia are prominent symptoms and there is habitually, some degree of emotional facility with a characteristic sustained grin or "spastic smile." Varying degrees of mental deterioration are frequently present. In this type of case, the nervous onset is in early youth or adolescence, and the downward progress rapid, leading to death after a few months or, at most, several years. Gross structural changes in brain tissue are usually found in such cases, including cavitation, or complete destruction, of the lenticular nuclei.

In others, the onset is much later in adult life, and the whole process more gradual and prolonged. Here, the outstanding symptom is tremor, without noticeable hypertonus, and without difficulties of deglutition or articulation, at least until the later stages. An immobile, Parkinsonian facies is common, and speech is monotonous. Involvement of pyramidal pathways, with corresponding physical

signs, may be evident. The cerebral changes tend to be more widespread, but less obviously visible, and may only be demonstrable histologically. Prior to Wilson's discovery of the disease, these cases were thought to be allied to multiple sclerosis, but lacking the characteristic pathology of the latter. Hence the term "pseudosclerosis," originally introduced by Westphal (1883) and Strümpell (1898), which is still sometimes used to distinguish this variety of hepatolenticular degeneration.

Yet another variation of the syndrome is exemplified by cases in which torsion dystonia is a prominent neurological feature (Thomalla; 1918, and others).

Various admixtures and intermediate forms of the above categories have frequently been described and, indeed, the neurological picture may, at times, display any of the characteristics associated with disorders of the basal ganglia in general. Consequently a diagnosis based solely upon neurological evidence is often extremely difficult.

There is, however, one pathognomonic sign which is common to all the aforementioned variants, and is present in about 80 per cent of cases—namely, corneal pigment—the so-called "Kayser-Fleischer ring." But it is not always possible to detect this by ordinary methods of examination and, without slit-lamp microscopy, it may be missed altogether. It is seldom searched for until the patient reaches the neurologist, but is present in some cases before nervous symptoms commence.

The fundamental mechanism responsible for the morbid processes of Wilson's disease is not yet fully understood. But, within the past few years, facts have been established which strongly suggest that it belongs to the group of inborn errors of metabolism.

Certain biochemical anomalies are now known to be constantly present — not only in fully-developed cases but also in the pre-neurological phase, and even in individuals where the liver itself is still apparently normal. Consequently it should in future be possible to identify potential victims. Moreover, there is evidence that a means of controlling these metabolic disturbances may be available. But treatment will require to be given early enough to forestall irreversible structural alterations in the affected organs. The diagnosis, hitherto of more academic than practical interest, has thus acquired a more urgent aspect.

The cases to be described here illustrate several of the clinical varieties referred to above, and provide a useful basis for some comments on the disease in general, and on the recent advances in diagnosis and treatment thereof.

Case Reports.

In a family, observed by the writer since 1938, there were three children — a girl (born in 1925) and two boys (born 1929 and 1937). The parents are alive and well, neither having suffered from any hepatic or neurological complaint.

Amongst the direct and collateral ascendants on the paternal side, however, there were numerous examples of degenerative nervous disorders, viz., senile Parkinsonism, senile dementia, post-encephalitic Parkinsonism, etc., as well as

cases of hepatic cirrhosis, jaundice, hæmatemesis, and sundry other abdominal complaints. On the maternal side neither hepatic nor neurological affections were notable, but the maternal grandmother and one aunt had pulmonary tuberculosis.

Case 1.—Joan C., the daughter, had died in 1936, at age 11. Only brief details of this case were available.

She developed jaundice forty-eight hours after tonsillectomy performed under chloroform anæsthesia. The jaundice rapidly became intense and was accompanied by ascites, hæmatemesis, and subcutaneous hæmorrhages. She died in coma on the fifth post-operative day.

Autopsy was not performed, but subsequent enquiries revealed the fact that ascites had been present prior to the operation. Death was, therefore, presumed to be due to acute liver necrosis precipitated by the effects of chloroform upon an already diseased liver.

Case 2.—John C., the second child, was healthy until aged 8, when he became vaguely unwell with headaches, anorexia, and occasional pyrexia. A year later he was seen by the writer for the first time, the outstanding symptoms being pallor, dyspnœa on exertion, and abdominal swelling.

His appearance was that of a profound toxic state, with ascites, severe anæmia, slight icteroid tinge, and a "swinging" pyrexia. There was œdema of the lower extremities, but no hæmorrhagic phenomena and no lymphatic gland enlargements. Liver and spleen were not palpable. Nothing abnormal was detected in central nervous system, cardio-vascular, or respiratory systems. The urine contained albumen but no bile, sugar, or blood. Ketonuria was absent.

Other findings included a blood sedimentation rate (B.S.R.) (Westergren) of 20 mm. in one hour and negative agglutination tests for enteric and abortus fevers. The blood picture showed R.B.C's. 1,550,000 cu. mm.; Hb.—35 per cent (Sahli); C.I.—1.1; W.B.C's.—25,200 cu. mm., and a normal differential count. Radiographs of the chest were normal.

The condition was thought to be tuberculous peritonitis (cf. — tuberculous history on maternal side).

Treatment in general lines (calcium; vitamins A and D; intramuscular liver) was followed by improvement and disappearance of ascites in six months. The anæmia responded satisfactorily, though tending to fluctuate from time to time in spite of continued treatment and the absence of hæmorrhages.

Leucocytosis persisted, and an increasing predominance of mononuclear cells was evident in successive blood films (reaching a maximum of 65 per cent at one period). This seemed to confirm the original diagnosis. The Paul-Bunnell test was negative.

General improvement was maintained until May, 1939, when he complained of pain and slight swelling below the left knee. X-rays revealed a spontaneous pseudo-fracture at the upper end of the tibia. Two further pseudo-fractures were detected during the following year (lower end of left femur and left fourth metatarsal). Intense osteoporosis of all the long bones was present, but there

was no disturbance of blood calcium—phosphorus balance (e.g., serum calcium 11.75 mg. per cent; inorganic phosphorus 2.5 mg. per cent).

Meanwhile (Jan., 1940) ascites reappeared and persisted for four months. Afterwards the liver edge was palpable at three finger-breadths below the costal margin and the lower pole of the spleen could be felt. Intermittent epistaxis was noted.

In 1941 (March-May) there were repeated attacks of diarrhœa and vomiting with lower abdominal cramps and pyrexia. Later in the year (November) he was acutely ill for four days with high fever, vomiting, diarrhœa, blurred vision, nystagmus and diplopia. No satisfactory reason for this episode could be found, and the symptoms disappeared quite suddenly, leaving no residual neurological signs.

He now remained well until January, 1942, when a transient attack of profuse hæmaturia took place. This left no evidence of renal damage. Gastro-intestinal symptoms continued to be troublesome during the year. The liver was becoming smaller and harder, but the spleen was still palpable. Leucocytosis had decreased (W.B.C's. 13,120 cu. mm.) and there was still a slight anæmia (Hb. 70 per cent —Sahli).

At age 14 (1943) there were signs of oncoming puberty. It was now noticed that his speech was dysarthric and explosive at times. Nothing further developed, however, until December, 1945, when a tremor of the left hand commenced. Shortly afterwards this affected the right hand, and his handwriting at school became quite illegible. The tremor was coarse in amplitude, exaggerated by voluntary movement, and accompanied by rigidity of the arm muscles. At the same time there was emotional instability with a tendency to laugh irrationally. Speech was monotonous, slurring, and explosive. Cranial nerves were normal, and there was no disturbance of pyramidal or sensory functions. The possibility of a post-encephalitic Parkinsonian state was considered (cf. episode of November, 1941, noted above), but progressive deterioration soon cast doubt upon this diagnosis.

Early on 21st November, 1946, he was found in a mentally confused state, with jaws tightly clenched, unable to speak. Involuntary micturition had occurred, and the plantar reflexes gave a temporarily extensor response. It was thought that an epileptiform attack had taken place. X-rays of the skull were normal, and the C.F.S. findings were as follows :—Protein 70 mg. per cent; globulin—nil; cells—nil; colloidal gold—negative; Wassermann—negative.

From this time onwards he became steadily worse. Rigidity and tremor began to affect the legs, and walking was eventually impossible. He came to adopt a more or less fixed posture in bed with asymmetrical contracture attitudes of the limbs. Kayser-Fleischer rings in both corneæ were discovered in April, 1947, thus establishing the diagnosis of Wilson's disease. Speech was reduced to a whisper, and he finally resorted to a system of signs to make known his wants. Dysphagia, commencing in the summer of 1947, resulted towards the end in

complete inability to swallow. A slow sustained smile was his usual response to questions, and he became mentally apathetic and disinterested in his surroundings. Pyramidal function remained intact and there was never any sensory impairment. Occasional incontinence of urine was probably due to inability to communicate his necessity quickly enough.

This neurological status remained practically unchanged from early 1948 until the time of his death, but his progress was punctuated, at intervals, by transient acute episodes. A feature of these, at one stage, was a series of torsion spasms affecting the muscles of the neck and causing violent spasmodic jerks of the head towards the right side. At other times, there were spasms of the whole skeletal musclature, producing momentary opisthotonic arching of the trunk. Repeated vomiting, hiccough, and pyrexia sometimes coincided with such phases and, in one instance, there was profuse sweating of the entire body for several days ("sudoral crisis").

During the last two or three years of his life the spleen could no longer be felt, and the liver was demonstrably reduced in volume.

Apart from the abdominal symptoms noted above, there were no other phenomena referable to liver disease with the exception of occasional epistaxis, and (on one occasion only) rectal bleeding from hæmorrhoids. The diarrhœa of earlier years gave place to persistent and obstinate constipation.

A series of liver function tests, repeated on five separate occasions between November, 1948, to November, 1949, failed to show any clear evidence of hepatic damage. The findings are summarised as follows :—

Bilirubin (mg. per cent)	...	ranging from ...	0.1 - 0.4	
Total plasma proteins (g. per cent)	,,	,, ...	7.0 -10.5	
Albumen (,,)	,,	,, ...	4.0 - 6.0	
Globulin (,,)	,,	,, ...	2.05- 5.3	
Thymol turbidity (units)	,,	,, ...	0.6 - 1	
Alkaline phosphatase (units)	,,	,, ...	5 -15	(King-Armstrong)

Takata-Ara—always faintly positive.

Serum colloidal gold; benzoic acid excretion; and lævulose tolerance tests all gave normal results.

On 27th October, 1949, he was dull and apathetic and had a rapid pulse with fever, and shallow respiration. Swallowing was impossible and the jaws were tightly clenched. Periodic twitchings of face and limbs occurred. There was no loss of consciousness. Glycosuria and albuminuria were present. Blood urea was 70 mg. per cent, and the liver function tests remained as before. Quantities of glucose and amino-acids were administered intravenously but without benefit. The blood pressure fell gradually and the pulse rate increased. Death took place five days later.

Autopsy.—A summary of the main findings is as follows :—

Liver—The surface was irregular and studded with nodules, and on section, a dense network of fibrous tissue was present throughout the organ. Microscopically, the appearance was that of a multiple nodular hyperplasia with minimal and terminal central zonal necrosis.

In the brain there were areas of destruction in the frontal cortex of both sides. Histologically, large cavities were seen bilaterally in the subcortical white matter of the prefrontal area. There were also a few cystic areas in the occipital lobes. The basal ganglia showed shrinkage on both sides, associated with compensatory dilatation of the third ventricle. In sections, there were focal areas of softening and status spongiosus. Minor degrees of damage were found in the thalamus and in the dentate nucleus of the cerebellum. A notable feature, throughout, was the absence of glial proliferation in any of the damaged areas. Alzheimer cells were not present. In the abdomen there was nothing to suggest a previous tuberculous infection.

Case 3.—Hugh C., the younger brother, was normal at birth and developed normally until aged 3, when he was found to have an enlarged, tender liver. From then onwards throughout his childhood, there was a more or less continuous tendency to looseness of the bowels, with spells of anorexia, pasty complexion, temporary loss of weight, and occasional pyrexia.

In March, 1948, at age 10 8-12, Kayser-Fleischer rings were found in both corneæ, and this was confirmed by slit-lamp microscopy. One month later there were signs of ascites with slight œdema of lower extremities, and minimal jaundice.

There was laboratory evidence of liver dysfunction, viz.—Thymol turbidity—10 units; Serum Colloidal gold—positive; Takata-Ara positive; total proteins —7.04 g. per cent; albumen 2.39 g. per cent; globulin 4.65 g. per cent.

Other findings were :— B.S.R. (Westergren) 30 mm. in one hour; blood picture—R.B.C.'s.—3,500,000 cu. mm.; Hb.—66 per cent (Sahli); C.I.—0.94; W.B.C.'s 5,500 cu. mm; lymphocytes 70 per cent.

There were no neurological signs or symptoms and the cerebro-spinal fluid was normal.

Ascites subsided after one month and has not returned since. A dietetic regime was instituted (May, 1948), and has been constantly maintained. It consists of a high protein-carbohydrate intake, with minimal fats. This is supplemented with Vitamins A, B-complex, C, and K. Weekly injections of Vitamin B_{12} (200 mgms.) are also given.

On this routine there was clinical improvement, shown by better appetite, gain in weight, and increased energy. But attacks of diarrhœa still took place intermittently, and liver dysfunction was still evident six months later (November, 1948), viz.—thymol turbidity—8 units; alkaline phosphatase—70 units; takata-ara + + + ; total proteins 7.5 g. per cent; albumen 3.4 g. per cent; globulin 4.1 g. per cent. Carbohydrate tolerance tests (galactose and lævulose) also gave positive results.

Slight hæmorrhagic tendencies had now become apparent—as shown by recurrent epistaxis, small crops of petechiæ, and excessive oozing from needle punctures. Blood coagulation properties were correspondingly deficient, viz.—prothrombin concentration 70 per cent; platelets 70,200 cu. mm. Coagulation time—11 minutes; bleeding time—7 minutes.

Fragility tests gave a trace of hæmolysis in 0.36 per cent Na Cl. — not complete in 0.28 per cent.

Treatment with dimercaprol ("BAL") was begun in May, 1949, and repeated courses of the drug have been administered (see discussion). Progress, to date, has been very satisfactory, and no neurological symptoms of any kind have been observed.

He is now aged 15, physically well developed, and intellectually well above the average. Signs of puberty are advancing. There are no outstanding hepatic symptoms and hæmorrhagic tendencies have receded. The liver remains palpable at two finger-breadths below the costal margin and is hard and slightly tender. The spleen is also slightly enlarged.

Laboratory tests for liver function show marked improvement, which has gradually emerged throughout regularly repeated enquiries, e.g., January, 1952—Bilirubin 0.4 mg. per cent; thymol turbidity—1.4 units; alkaline phosphatase 28 units; total proteins 6.49 g. per cent; albumen 4.4 g. per cent: globulin 2.0 g. per cent; takata-ara—positive; bromsulphthalein retention 9.4 per cent (normal 0—7 per cent).

Apropos of the spontaneous fractures which occurred in Case 2, it is of interest to record that this patient sustained a fracture of the left radius in May, 1950, due to a relatively slight injury. A second fracture, at exactly the same site, resulted from an injury in April, 1952. Radiographs showed normal bone texture. The serum calcium was 11.6 mg. per cent, and the inorganic phosphorus 3.5 mg. per cent. The blood sugar curve after dextrose (50 g.) indicated a normal response with no glycosuria. Acetone, however, was present in three urine specimens. There was no delay in bone union.

Case 4.—The following case was found in another, but unrelated, family in the same district.

Mary S., a married woman with one child (daughter aged 16, healthy). She herself was one of a family of three, of which the first (boy) was stillborn — cause unknown. A sister died at age 17 from liver failure with intense jaundice after one week's illness. Exact details are unobtainable. The parents are alive and well, having had no hepatic or nervous disorder. One paternal uncle died of hepatic cirrhosis.

The patient herself suffered from frequent epistaxis during school years. Otherwise she was quite healthy. She married at age 22 and had one normal pregnancy. No miscarriages. Following her confinement, menstruation became irregular and very infrequent, e.g., 3-6 months intervals, and recently only twice in two years. At age 28, an attack of jaundice took place, with vomiting and abdominal pain, lasting several weeks. This was diagnosed

in hospital as infective hepatitis. Shortly after her discharge from hospital a second attack of jaundice occurred and lasted one week. No ascites occurred on either occasion.

A tendency to bleeding gums was noticed at age 32, and severe hæmorrhage followed dental extractions. Her health then began to deteriorate generally, with loss of weight, anæmia, anorexia, recurrent epistaxis, bruising on slight injury, and intermittent spells of unexplained pyrexia.

In September, 1946, shortly after the dental hæmorrhages noted above, a coarse tremor commenced in the right hand, and soon afterwards in the left. The resulting disability persisted until, in 1948, she was admitted to the Royal Victoria Hospital for investigation (Dr. R. S. Allison). Physical examination gave the following findings :—

A marked tremor of the right hand at rest with a "pill-rolling" movement of the thumb and fingers. Tremor exaggerated by voluntary movement. A similar tremor in the left upper extremity. No muscular weakness anywhere. Movements of co-operation normal. No marked hypertonus in any of the limbs. Gait normal. No retropulsion. Tendon reflexes were all present and equal. Plantars both flexor. Bilateral ankle clonus. The cranial nerves showed no abnormality. The facies, however, was somewhat expressionless, the voice monotonous, and infrequent blinking was noted. No sensory impairment anywhere.

The liver edge was just palpable and the lower pole of the spleen could be felt. No jaundice, ascites, or œdema present. The other systems showed nothing remarkable. Kayser-Fleischer rings were detected in both corneæ and their presence confirmed by slit-lamp microscopy (Mr. F. A. McLaughlin), thus indicating the diagnosis of Wilson's disease.

Liver function tests, at this time, showed no evidence of hepatic dysfunction, viz.—Alkaline phosphatase 6 units; total proteins 7.0 g. per cent; albumen 4.8 g. per cent; globulin 2.2 g. per cent.

Blood picture—R.B.C.'s 3,710,000 cu. mm.; Hb.—99 per cent (Sahli); P.C.V. 45 per cent; W.B.C's. 3,550 cu. mm. (Lymphocytes 37 per cent). Films showed reticulocytes 2.5 per cent; red cell fragility normal.

Glucose tolerance test gave a normal response with no glycosuria.

On discharge from hospital her status remained unchanged, and when seen by the writer for the first time in September, 1949, the physical signs were identical with those described above, with the exception of a marked side-to-side tremor of the head which was now apparent. She was at that time not seriously incapacitated and was still able to do her housework. She evinced a complete aversion to any further investigations or treatment, and maintained this attitude until circumstances forced her to enter hospital in July, 1952.

Meanwhile, however, a gradual but marked deterioration ensued. Tremor of the upper limbs became so uncontrollable that she was unable to feed or dress herself. A similar state of the legs eventually made walking impossible, and she had been more or less bedridden from the summer of 1951. Speech was now difficult at times, but deglutition remained unaffected. Intermittent phases of

pyrexia, with temporary exaggeration of nervous symptoms, were noted and profuse epistaxis occurred from time to time. In the spring of 1952, abdominal swelling was noticed, and this became gradually worse.

She was admitted to Ards District Hospital, Newtownards, on 2nd July, 1952. The findings on admission were as follows :—

Marked ascites, œdema of legs from the thigh downwards, œdema of sacral region and back, extending upwards to the level of the ribs. The skin everywhere was sallow, but not jaundiced. Nipples darkly pigmented. Several dark pigmented moles on the trunk as well as a few minute angiomata. Elsewhere there were some patches of brownish pigmentation (abdomen and legs). Hirsutism was seen on the upper lip and chin. The tongue was raw and bright red. Salivation from both corners of the mouth, with perlêche.

Cardio-vascular system.—Soft mitral systolic murmur. Some tachycardia. Rhythm regular. Blood pressure 140/80 mm. Hg.

Respiratory system.—Dullness both lung bases with poor air entry and diminished vocal resonance. No adventitia.

Central Nervous System.—Facies expressionless, but mentally quite alert and co-operative. Speech somewhat dysarthric and monotonous, but intelligible. Deglutition normal. Constant side-to-side tremor of the head. Kayser-Fleischer rings in both corneæ. Fundi normal. Other cranial nerves normal.

The upper limbs showed little or no tremor at rest, but the least attempted movement caused a violent "wing-flapping" tremor at both wrists, rendering use of the arms impossible. Hypertonus of both upper and lower limbs was present but not excessive, and there were no contractures. The legs were quite powerless. Marked ankle clonus present. All tendon reflexes present. Abdominals not elicited. Plantars both flexor. No sensory disturbances. Incontinence of urine and fæces.

Urine, on admission, showed a heavy B. coli infection with pus and red blood cells present. No casts. A moderate evening pyrexia was noted. Streptomycin (1 gm. daily) was given, in accordance with results of sensitivity tests on the urinary infection.

Liver function tests indicated hepatic insufficiency :—Bilirubin—2.1 mg.; total proteins 6.5 g. per cent; albumen 2.7 g. per cent; globulin—3.8 g. per cent; alkaline phosphatase—8 units; thymol turbidity 5 units; total cholesterol 183 mg. per cent; cholesterol ester fraction 59.6 per cent. Blood urea—68 mg. per cent Blood picture normal. Blood sugar 115 mg. per cent; no glycosuria; no ketonuria.

A high protein-carbohydrate, minimal fat intake was inaugurated together with vitamin supplements. Abdominal paracentesis was performed and pale straw-coloured serous fluid withdrawn.

Two days later she became drowsy and apathetic. Speech unintelligible, deglutition difficult. Tissue jaundice became obvious and quickly deepened. There was continuous fæcal incontinence with diarrhœa. Coma gradually supervened, respiration became stertorous and the lungs œdematous.

Amino-acids and glucose were administered by slow intravenous drip, but without benefit, and on the second day of coma she appeared to be moribund. Nevertheless some improvement then became apparent and, after five days continuous coma, she regained full consciousness. Speech was now quite impossible, and deglutition extremely difficult. Tremor, which had been absent during coma, began to reappear. The urinary infection had disappeared and the temperature settled. Attempts to maintain an adequate protein-carbohydrate intake by tube feeding were made. Liver function tests showed similar findings to those noted above. Jaundice became intense and, on the sixth day after her recovery of consciousness, she again became comatose.

In this condition, death took place the following day (19th July, 1952). Autopsy was performed ten hours later.

The following is a summary of the findings :—

Liver. — Markedly shrunken (770 g. after fixation), and the entire surface nodular. Section showed advanced fibrosis. Histologically, the appearance was that of a multiple nodular hyperplasia, with large areas of regenerated liver tissue.

Spleen.—Was enlarged to about four times the normal size, and revealed chronic venous congestion, with some degree of fibrosis.

Brain. — Appeared generally small. No convolutional atrophy. On vertico-frontal section, there was visible atrophy in the head of the caudate nucleus and the putamen, with consequent widening of the internal capsules.

No cystic areas were found anywhere, but histological changes were widespread and characterised by nerve cell degeneration with glial proliferation, and formation of Alzheimer glial cells (type 2) in many areas, e.g., Putamen, globus pallidus, caudate, frontal and parietal cortex; in the cortex, there was diffuse loss of pyramidal cells.

There were no significant vascular changes in any area.

Case 5. — A third family, also from the same area, provided yet another case. This patient was not seen by the writer personally, but details were kindly supplied by Dr. Bryars, Ballywalter, Co. Down, and Dr. J. A. Smyth, who saw her in consultation.

The following is a short account of her history :—

Mrs. Emily C. was one of a family of six. Two brothers and three sisters, all healthy. Her mother died, aged forty-four, in the Royal Victoria Hospital, Belfast, with a cerebral tumour (Mr. C. A. Calvert). The father is alive and well.

Early in 1944 (aged 22) she noticed swelling of the legs and ankles. Menstruation ceased for several months, and there was a persistent cough. In May of that year she commenced to have crampy abdominal pains and frequent loose watery stools. She was admitted to hospital a short time later and found to have bilateral pleural effusions, ascites, œdema of the legs and lumbo-sacral region, with marked pyrexia. There was a slight anæmia—R.B.C.'s 3,860,000/c.mm.; Hb—72 per cent (Sahli); C.I. 0.94; W.B.C.'s 4,400/c.mm.; lymphocytes 41 per

cent; serum protein levels — total 4.58 g. per cent; albumen 2.45 g. per cent; globulin 2.13 g. per cent.

Fluid aspirated from abdomen and pleura gave negative results from biological tests for tubercle. The effusions disappeared with rest and general treatment and the temperature subsided. No satisfactory diagnosis was arrived at, and she was discharged from hospital, after about a month, apparently recovered.

About a year or so later she again felt vaguely unwell. The spleen was now enlarged and there was a leucopænia (W.C.B.'s—1,248 cu. mm). Pyrexia again evident. Widal—negative; Br. abortus—negative; Blood culture—negative; Van den Bergh — indirect positive; bilirubin — 1.6 units. Renal efficiency tests and blood urea were normal.

A considerable degree of hypothyroidism was evident, with B.M.R. minus 33 per cent—later, minus 40 per cent. Glucose tolerance test showed a fasting blood sugar level of 133 mg. per cent, rising to 285 mg. per cent in the first hour, but reverting to 125 mg. in two hours. No glycosuria was evoked.

Thyroid medication (gr. 6 daily) was instituted and, three months later, the basal metabolic rate was normal.

Neurological symptoms began in June, 1946, with a tremor in the left hand, shortly followed by an unsteady gait. Tremor then extended to the right hand and arm, and the head—and was noticeably exaggerated by voluntary movements. There was hypertonicity of the skeletal musclature, emotional instability, a spastic grin, and marked salivation. Speech was difficult and slurring, and there was some dysphagia. Reflexes were unaffected and there were no sensory changes. Rapid deterioration was observed. Speech became impossible and dysphagia extreme. Painful contractures developed in the legs and, by February, 1947, she was in a state of complete helplessness. She died from inanition a few months later.

Kayser-Fleischer rings were not found in this case, but there is no record of slit-lamp examination having been used.

Autopsy was not performed.

Discussion.

From a neurological aspect, the cases described here require little comment since they followed, for the most part, a very typical course.

Case 2 belongs to the category of "classical" Wilson's disease in conformity with the characteristics already mentioned. The same applies to Case 5, but the absence of other cases in this family, and the absence of corneal pigment rings in the patient, are noticeable. Clinical evidence requires to be unequivocal to justify a diagnosis of Wilson's disease under these circumstances, and anatomical confirmation is always desirable in such a case. Clinical evidence was, in fact, sufficiently convincing in this instance and the diagnosis was confirmed by Dr. Gordon Holmes, to whom the patient was referred. However, in view of present knowledge and for reasons which will be explained later, it becomes necessary

to consider whether cases of this kind can legitimately be classified in the same group as those with corneal pigment.

The severity of the damage to the frontal lobes in Case 2 was a notable feature of the anatomical findings, and was more obvious than the changes in the basal ganglia. But experience has proved, in other cases, that although the lenticular nuclei and neighbouring structures are never spared, there may often be profound and widespread destruction elsewhere. Richter (1948), for example, has drawn attention to the importance of cortical changes (the 'pallial component') and believes that these are almost as characteristic of the disease as are the lesions in basal ganglia.

Case 4 with its late onset, absence of extreme hypertonus, and relatively slow progression, illustrates the so-called "pseudo-sclerosis" type — a distinction to which Wilson himself (1940) was vigorously opposed, since he believed that such cases should be looked upon simply as a more benign and chronic expression of a process which is essentially the same in all variants of the hepato-lenticular group. Nevertheless many authorities (e.g., Denny-Brown, 1946) have recognised, and emphasised, the distinctive clinical features of this form of the disease.

Cases of hepatic cirrhosis, without neurological disorder, are not uncommonly found in "hepato-lenticular" families. In these the eventual onset of nervous troubles is to be expected, and there is no single instance on record where such a patient lived on to any advanced age with the nervous system still intact. But many have died whilst still in this pre-neurological phase — from hepatic failure precipitated either by the severity of the disease process itself, or by superadded noxious agents acting upon the liver, which is notoriously susceptible to them in Wilson's disease. The terms "abdominal Wilson" (Kehrer, 1930), or "forme portale" (van Bogaert and Willcox, 1936) have been used to denote the existence of such a type, also alternatively referred to as the hepatic "forme fruste." The present Case 3 is an example of the kind, and it is justifiable to place Case 1 in the same category—probably also the sister of Case 4.

When corneal rings are present (as in Case 3), and when one or more siblings have already displayed the complete picture, recognition is easy — as it was in this particular instance. But in the absence of these confirmatory data a correct diagnosis during life has hitherto been impossible. Nevertheless it is a type which probably occurs more often than is generally appreciated and a comprehensive survey of the literature supports this view, especially if one takes into account the numerous instances where siblings have died from causes evidently hepatic in origin but of no clearly proven nature — as in two of the families described here.

A much rarer occurrence is the splenomegalic variety. Minor degrees of splenomegaly—as noted in the present series—are quite usual, but sometimes the anatomical and functional disturbances of the organ are so prominent as to dominate the picture, which becomes that of a splenic anæmia with corresponding hæmatological features, hæmorrhagic tendencies, and so forth. These cases

constitute quite a distinct group, of which some twenty instances can be found in the literature. Those reported by Rystedt (1923); Halford (1933); Rabiner et al. (1941), and Richter (1948) may be cited as representative.

A diagnosis of Banti's disease has repeatedly been made in such cases and has been followed up by splenectomy in a number of instances—e.g., those mentioned above. This procedure is contra-indicated however since, although it has sometimes proved temporarily beneficial by way of improvement in the blood dycrasia and the hæmorrhagic phenomena, the onset of nervous symptoms is not correspondingly delayed or averted and has, in fact, often been accelerated afterwards. So far as the writer is aware, this syndrome is not mentioned in the literature on splenic anæmias or on splenectomy and its indications.

The prominence of hepatic symptomatology in the present cases is of some interest. It illuminates what has already been said in the introductory remarks on the importance, from a clinical viewpoint, of the hepatic element. This is a detail which has not often been sufficiently emphasised in standard text-book descriptions of the disease — most of which convey the impression that the hepatic element is seldom outwardly manifest, or at least only to a minor degree. This is an entirely mistaken impression which is attributable, one suspects, to the fact that the disorder is hardly ever systematically observed until such time as neurological disability has appeared, by which time — in many instances — the liver disorder has, indeed, become clinically quiescent.

It is certainly true that the more severe insignia of hepatic cirrhosis — e.g., jaundice and ascites — are relatively uncommon during the evolution of the nervous symptoms and death, from liver failure, such as occurred in Case 4, is not by any means usual in cases with advanced neurological troubles. On the contrary, inanition due to extreme dysphagia (Case 5), acute neurological exacerbations (Case 2), or intercurrent infection are more often responsible for death at this stage. It is, in fact, one of the distinctive features of the cirrhosis in Wilson's disease that advanced functional insufficiency with portal hypertension, appearing early in the course of the disease, can revert to a state of apparent normality and remain quiescent, thereafter, for many years (e.g., Case 2)—during which time all efforts to demonstrate dysfunction by laboratory methods may fail.

An analysis of almost all the existing case reports has been carried out by the writer (1950). This reveals that approximately 60 per cent of cases never exhibit outward evidence of liver disease after the onset of nervous symptoms. In the pre-neurological phase, however, one-third of all the cases had severe hepatic symptoms, many others showed lesser degrees of symptomatology referable to the liver affection, and in only about 25 per cent of cases was the liver disease completely asymptomatic. Jaundice, ascites, anæmia, gastro-intestinal symptoms, and enlargement of liver and spleen are the commonest of these manifestations.

Endocrine dysfunction is sometimes apparent — chiefly in the form of hypogonadism with delayed puberty, signs of sexual under-development, and

amenorrhœa in the female. A marked depression of basal metabolic rate combined with œdema has been recorded in a few instances — e.g., Cadwalader (1914) — Case 4 — in which a diagnosis of myxœdema was postulated, as in the present Case 5.

Another feature of the disease is cutaneous pigmentation, which has been frequently observed and was found to a slight degree in Case 5 also. It usually presents in the form of discrete patches varying in colour from brownish yellow to dark brown, or blueish-grey. Distribution follows no hard and fast rule, and it may appear anywhere on the body, sometimes being universal (e.g., cases of Halford, 1933; André, 1948—Case 5). Its precise nature has never been established, but its occurrence is of interest in view of the important role played by copper in the pathogenesis of the disease and the known influence of copper upon skin pigmentation processes in general (Dowling and Whitlock, 1952).

The metabolism of copper is markedly deranged in Wilson's disease, and it has long been known that it accumulates in the liver and brain (Haurowitz, 1930; Glazebrook, 1945). The question of its relationship to the disease process has been further clarified within the past few years as the result of enquiries in a number of cases, including three of those described here (Cases 2, 3 and 4). Details of the findings in the present cases are the subject of a paper which will appear elsewhere (Warnock and Neill, 1952).

The following is a summary of the facts already recorded in recent publications :—

Large quantities of copper can be recovered from liver and brain tissues at autopsy — particularly from the basal ganglia and other areas most affected by the disease. The amounts found are far in excess of the normal and of anything seen in other hepatic and neurological complaints. (Cumings, 1948; Warnock, 1950; Spillane, et al., 1952). This deposition constitutes a "biochemical lesion" which is potentially reversible — (Denny - Brown and Porter, 1951). Copper is excreted in excessive quantities in the urine, and this output can be still further raised by administration of dimercaprol ("BAL"). — (Mandelbrote, et al., 1948; Porter, 1949; Warnock, 1950). The mobilisation of copper, in response to dimercaprol, is followed by improvement in neurological symptoms and in liver dysfunction. (Cumings, 1951; Denny-Brown and Porter, 1951). Although relapses may occur, there is some evidence that repeated courses of the drug can control the progress of the disease. It is believed, however, that this is more likely in the chronic ("Pseudo-sclerosis") type than in the acutely progressive variety, since irreversible structural changes are more common in the latter (Denny-Brown and Porter, 1951).

Serum copper levels, though sometimes high, are not invariably so, and are of little diagnostic import. Hypercupricuria, on the other hand, is outstanding and has not so far been found in any other disease. Its detection is, therefore, of some diagnostic value. In the writer's Case 3 it has been shown to be present in the pre-neurological stage of the disease—a point not hitherto established.

Kayser-Fleischer rings, which are thought to be caused by copper deposition in the cornea, have been seen to diminish in colour after "BAL" treatment (Denny-Brown and Porter, 1951).

A second metabolic peculiarity has also been shown to be characteristic of the disease—namely, amino-aciduria. This was first described by Uzman and Denny-Brown in 1948. It is a "universal" amino-aciduria, not accompanied by any significant rise in blood non-protein-nitrogen content, and not confined to cases with severe liver dysfunction (Eckhardt, et al., 1948; Porter, 1949; Cooper, et al., 1950). Moreover, it exists not only in fully developed cases with neurological symptoms, but also in the purely hepatic form, and even in siblings with no demonstrable abnormality either in liver or C.N.S. (De Verdier, 1950; Hood and Fagerberg, 1951; Uzman and Hood, 1952). Dent and Harris (1951), however, claimed that amino-aciduria is absent in cases without corneal pigment. If this is true, it would be necessary to segregate these from all other cases of the group, as mentioned above.

The exact causal mechanism of this phenomenon is not, as yet, fully understood, but is seems likely that it is a "renal" amino-aciduria due to a defect in renal tubular reabsorption of amino-acids and comparable to that of the Fanconi syndrome (Dent, 1946; Dent and Harris, 1951).

So far, the relationship between this anomaly and the derangement of copper metabolism has not been explained, but it is clear that it is a constant association in these cases. The amino-aciduria is easily demonstrable by paper chromatography and gives a pattern which is quite characteristic. This was strongly evident in chromatograms done on the urine of the writer's cases 3 and 4 — the only two of the series in which it was possible to carry out the procedure.

Not the least important feature of these two chemical abnormalities is the opportunity they now provide of recognising the disease much earlier than has previously been possible, and of detecting potential victims in families where known cases already exist. Treatment could then be given at a time when it is most likely to be beneficial, i.e., before structural changes in the nervous system have begun. In most of the cases so far recorded the disease was well advanced —and the present Case 3 is the only one in which "BAL" has been given before the onset of nervous symptoms. It is believed, that in this case, the drug may be effective in permanently averting the onset of neurological symptoms, since it can reasonably be hoped that excessive deposition of copper in brain tissues will be prevented thereby.

One final point remains to be mentioned — namely, the occurrence of spontaneous fractures in Case 2. This has been known to happen before — e.g., cases of Economo (1918); Brückner (1925); Kehrer (1930); Lüthy (1931), and André 1948). Marked osteoporosis is found in such cases, and this is not necessarily the result of prolonged immobilisation in bed, for in the case of Economo, for example, a spontaneous fracture was the first sign of the disease. And in the writer's case, although the patient had been inactive for many months a high

intake of calcium and vitamin D had been maintained. Renal glycosuria, being one of the abnormalities not uncommonly found in Wilson's disease, can also be exhibited in conjunction with osteoporosis and amino-aciduria (e.g., case of Cooper, et al., 1950)—although, in fact, glycosuria was absent in the present case. But it may be pointed out that the picture, at the time of the fractures, was that of osteoporosis, enlarged liver and spleen, recent ascites and anæmia — but no neurological symptoms. Had the urine been subjected to the necessary tests at that time, there is little doubt that amino-aciduria would have been discovered. Thus, without attempting any explanation as to why such a state of affairs should arise, it is impossible to ignore the close clinical similarity to the Fanconi syndrome. Dent and Harris (1951) have already drawn attention to points of similarity between the amino-aciduria of the latter and that of hepatolenticular degeneration.

In summary and conclusion, therefore, one would emphasise that Wilson's disease is a condition which, in its earliest stages, may present itself as a perplexing diagnostic problem liable to be encountered by almost any clinician except the one to whom it is most familiar—namely, the neurologist. Yet the disease can be diagnosed, and is probably amenable to treatment, at this stage—but the key to the diagnosis is held by the biochemist.

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REVIEW

ATLAS OF HUMAN ANATOMY. By F. Frohse, M. Brodel and L. Schlossberg. (Pp. 88; figs. 71. 16s.). London: Allen & Unwin, 1952.

THIS "pocket size" Atlas of Human Anatomy is beautifully produced and contains more than seventy illustrations of the various parts of the human body.

Some of the coloured plates are miniatures of the Frohse-Brodel wall charts and are approximately one-eighth of the original size. This tends to make the detail very intricate, especially in the case of the nervous system.

Bones, muscles, the circulation, organs including the reproductive system and the endocrines are all dealt with in pictures with a numbered key along side. This is an excellent atlas for reference purposes, but it is rather difficult to use for teaching anatomy to physiotherapists. G. G.