THE WIGHTMAN PRIZE IN CLINICAL MEDICINE 1971

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INTRODUCTION

The following five cases are presented as examples of different diseases which have in common an involuntary movement as part of the presenting clinical picture. Various aspects of the management of each case are discussed.
This patient is a 13 year-old school-girl, the daughter of a miner, who lives at home with her parents, four brothers and two sisters.

PAST HISTORY

She was admitted to the Royal Hospital for Sick Children, Glasgow, on the 16th of December 1967 three years previous to her present admission. At that time the patient exhibited choreiform movements, and a raised ASO titre suggested a rheumatic origin. There was no artritis, no carditis, no erythema marginatum, and no subcutaneous nodules. She was treated with chlorpromazine 25 mgs t.i.d. and penicillin G 250 mgs b.d. The choreiform movements had not entirely disappeared when the patient was discharged on the 6th of January 1968 after a three week stay in hospital. However, she was readmitted four weeks later, "... paralysed all over... I couldn't move my arms or legs." This is probably a graphic description of paralytic chorea in which muscle weakness is extreme, but complete paralysis never develops so that interference with breathing does not occur. Unilateral paralytic chorea has been misdiagnosed on occasions as hemiplegia due to intra-cranial lesions (1), but the chorea does not usually completely disappear in paralytic chorea.

The abnormal movements settled on chlorpromazine 50 mgs t.i.d. She was discharged on the 24th of April with no evidence of chorea on penicillin G 250 mgs b.d. as prophylaxis. The family moved from Glasgow to Edinburgh several months later, the patient exhausted her supply of penicillin and the prescription was not renewed with their new family doctor.

PRESENT HISTORY

From then until September 1970 the patient was in good health, but on the 29th of September 1970 she was readmitted to hospital at the request of the general practitioner. On admission she was complaining of spontaneous involuntary movements of the right hand, right arm, and right shoulder which had been present for about three weeks. The patient's mother had also noticed twitching of the patient's face, slurring of the patient's speech and disturbance of her gait for about the same period of time. The patient described the former involuntary movements as, "... writhing of my hand when I went to lift something... I kept knocking things over the table." Now the movements were not brought on by volitional movements as three years previously, but were exaggerated when the attention of the observer was focussed on her. She did not complain of having a sore throat, joint pains, skin rashes or skin nodules within the preceding three months.

EXAMINATION

On examination, she was a shy, quiet girl and was intelligently co-operative.

She exhibited repetitive, stereotyped, abnormal movements consisting of elevation of the right shoulder, flexion of the right elbow, adduction of the right thumb and little finger, flexion at the right knee, dorsiflexion at the right big toe, twitching of the
right corner of the mouth, and a predominantly right-sided tremor of the tongue.

The right arm and leg were markedly hypotonic, but neither the upper nor lower limbs showed any defect of co-ordination. The posture of the outstretched arms showed a flexed right wrist, and extended right metacarpo-phalangeal and interphalangeal joints. This characteristic 'dinner-fork' attitude of the hand is an exaggeration of the normal posture due to hypotonia of the antagonistic muscles. The right arm was pronated when both arms were raised above the head which is characteristic of chorea (1).

The power in all the major muscle groups was symmetrical in isometric contraction against a moderate opposing force. There was no obvious muscle wasting or fasciculation. The tendon jerks were symmetrically brisk in all four limbs, Hofmann's sign was bilaterally undemonstrable, and both plantar responses were flexor. Sensibility to light touch and pin prick, joint position and vibration were all intact.

The radial pulse was of good volume and regular in time and volume. The apex beat was not palpable and there were no heaves or murmurs felt over the precordium. Heart sounds 1, 2, 3 were heard together with a pansystolic murmur, grade 2 out of 6, heard best at the apex, radiating to the left axilla and not varying with posture or respiration. The heart rate was 68 per minute and during the whole of the three week stay in hospital the patient's heart rate remained less than 80 per minute.

The temperature was normal and remained so for the duration of the patient's stay in hospital. There were no subcutaneous nodules and no erythema marginatum.

INVESTIGATIONS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>11.4 g%</td>
</tr>
<tr>
<td>M.C.H.C.</td>
<td>32.3%</td>
</tr>
<tr>
<td>W.B.C.</td>
<td>5,500/cumm. (neutrophils 72%, lymphocytes 25%, monocytes 3%)</td>
</tr>
<tr>
<td>E.S.R.</td>
<td>6 mm in the first hour on admission and 4 mm in the first hour 10 days later.</td>
</tr>
<tr>
<td>The AP chest X-ray was normal, and neither obliques nor laterals showed evidence of selective chamber enlargement.</td>
<td></td>
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<tr>
<td>The ECG showed sinus rhythm with a PR interval of 0.12 seconds and a calculated/observed QT interval ratio of 0.39/0.36 seconds</td>
<td></td>
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<tr>
<td>Throat swabs yielded a light growth of upper respiratory tract commensals.</td>
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<tr>
<td>The ASO titre was 100 Todd units/ml.</td>
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</tbody>
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CLINICAL COURSE

The patient was treated for a recurrence of rheumatic fever with penicillin V 250 mgs t.i.d. On discharge after three weeks in hospital on 19th of October 1970 she was given benzathine penicillin 1 mega unit intramuscularly. Since she defaulted on previous treatment, her prophylactic therapy will be supervised on an out-patient basis. She will be asked to report monthly for an intra-muscular injection of 1 mega unit of benzathine penicillin as prophylaxis against any further recurrence of rheumatic fever.

DISCUSSION

In London schoolchildren the annual death rate from acute rheumatism
has been falling over the years from 67 per million in 1900 to 2 per million in 1965 (2). In a review of this aspect of diminishing severity, Bywater noted that rheumatic fever comprised 5% of admissions to Guy's Hospital, London in 1914, but by 1952 this figure was reduced to 0.23% (3). However, the declining severity and mortality of rheumatic fever does not imply a massive reduction in prevalence. Woaler reported from Bergen on 219 patients who were discovered to have rheumatic heart disease at necropsy between 1941 and 1955. He found no overall reduction in the incidence of rheumatic heart disease during the fifteen year study although the clinical severity had diminished. This suggests that subclinical or atypical forms of the disease may be commoner than realised (6).

Florid, acute rheumatic fever with classical flitting polyarthritis and a high temperature has become a relative rarity in the economically advanced countries, but is still seen frequently in the materially less prosperous societies. Diagnostic criteria used at present consist of modifications of the Duckett Jones criteria (7). Major criteria are carditis, polyarthritis, chorea, erythema marginatum and subcutaneous nodules. Minor criteria are a history of previous rheumatic fever or rheumatic heart disease, arthralgia, fever, a raised ESR, the presence of C-reactive protein, leucocytosis, and a prolonged PR interval on ECG. A diagnosis of rheumatic fever may be suspected if there are two major or one major and two minor criteria. The diagnosis is then strongly supported by evidence of a previous streptococcal infection such as a raised or fourfold rise in the ASO titre.

The original diagnosis of rheumatic fever was made on the evidence of chorea and a raised ASO titre i.e. a single major criterion only. Chorea occurs in girls with rheumatic fever three times more frequently than boys, and about 15% of girls with rheumatic fever present with chorea only and with no evidence of carditis or arthritis (9).

During her recent admission the patient once again displayed involuntary movements, but these were not the classical quasi-purposive choreiform movements. However it was not thought that these were movements of habit spasm with a subconscious motivation.

No evidence of carditis was found during the original episode of rheumatic fever, but a cardiac murmur was noticed during her present admission. This was a pansystolic, soft, blowing murmur, grade 2 out of 6, heard loudest at the apex, radiating to the axilla, and not significantly variable with position or phase of respiration. Innocent functional murmurs occur frequently in febrile or anxious children and are usually heard in the pulmonary area radiating to the neck, or at the left sternal edge radiating to the apex. Furthermore, functional murmurs usually vary with position or respiration. On the other hand, murmurs recently appearing or changing in character during or soon after an attack of rheumatic fever are probably due to valvular pathology. Significant mitral murmurs are high-pitched, blowing, present throughout systole, radiate to the axilla and vary little with posture or respiration. This patient also had
A prominent 3rd heart sound heard best at the apex. An accentuated 3rd heart sound at the apex is produced by a rapid flow of blood from the left atrium to the left ventricle and may have been due to mitral incompetence (7). The PR interval was within normal limits at 0.12 seconds, but the usefulness of this sign as an indication of carditis has been disputed (7,8). A prolonged PR interval on ECG is a nonspecific sign occurring frequently in streptococcal infections and other inflammatory responses. A persistently raised pulse rate is taken as a useful sign of carditis. This patient's pulse rate remained below 80 per minute for the entire three weeks stay in hospital. Auscultation is the most reliable method of diagnosis (12).

The diagnosis of a recurrence of rheumatic fever is suspect without evidence of previous beta haemolytic streptococcal infection. Throat swabs from this patient were negative for streptococci on culture and the ASO titre was within normal limits at 100 Todd units per ml. However, this patient presented with chorea and chorea is a late manifestation appearing up to two to three months after the original streptococcal infection. The ASO titre may have been raised in this patient and returned to normal before the appearance of chorea.

This patient then, probably suffered a recurrence of rheumatic fever originally manifest by uncomplicated chorea, but developed a significant murmur before the second attack or developed carditis at the recurrence. Recurrences of rheumatic fever are common. In a study of 1033 cases with a follow-up of between 5-40 years started by Dr Carey Coomb in 1924 and continued by Dr Bruce-Perry until 1964, the total incidence of recurrence was 47%, and 31% of second attacks occurred within four years. The frequency of recurrence has been declining so that in 1939 44% had only one attack but 91% with an onset after 1955 suffered only one attack (9).

The clinical features of the recurrence are similar to the first attack, but there is a higher incidence of carditis and valvular heart disease (10). Roth reported 149 children with polyarthritis and no carditis but found that 51/149 had carditis at the second attack (11). In the Carey Coomb study, 67 out of 117 children who presented with uncomplicated chorea had a recurrence during which 27 out of these 67 developed carditis at recurrence (9).

Bland and Jones commenting on the prognosis of carditis during rheumatic fever reported that of a series of 653 patients recovering the initial attack who had unequivocal signs of heart disease, 108 (16%) had normal hearts after 20 years. Conversely, 67 out of 387 (17%) of those with clinically normal hearts after the first attack developed heart lesions, (13), and 10 out of the 387 (3%) were dead. Bruce-Perry reported 211/274 (77%) who had no clinical carditis at the first attack, had normal hearts at ten-year follow-up, and 50 (18%) developed established heart disease, but 217/701 with obvious carditis at the first attack lost all signs of carditis at follow-up (9). May Wilson stresses the relationship between the number of recurrences and a mortality of 20% with one attack and
with four or more attacks. The recurrence of rheumatic fever in this patient, therefore is made prognostically less favourable by the development of a significant mitral murmur.

Hitchens studied the declining notifications of rheumatic fever and compared these with the notifications of scarlet fever. The actual incidence of scarlet fever diminished from 1926 onwards, but mortality rates changed more noticeably at a later date, falling from 0.47 to 0.12 per 100 cases between 1935-1942 (4). This corresponded closely to the diminishing crude death rate for acute rheumatism (5). The reduction in severity of both conditions was attributed to a change in virulence in the beta haemolytic streptococcus and to improved resistance of the host attendant upon improved social conditions coming about at this time (5,6). The incidence of recurrence has been falling steadily since 1939 but was reduced dramatically since 1955 (9). A vigorous campaign was introduced at that time of using penicillin as prophylaxis against subsequent infection and therefore against recurrence. Prophylactic penicillin now has an established place in the long term management of rheumatic fever. Since this patient previously defaulted on prophylactic penicillin treatment, her treatment in future will be supervised more strictly. She will be asked to report monthly as an outpatient for an injection of a long acting intramuscular depot penicillin.
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This 55 year old patient has been a barman since he left the armed forces 35 years ago. He described himself as "a boozers mate" and has a long history of many years excessive alcohol ingestion. He had been drinking both beer and spirits particularly heavily for a few months before admission.

FIRST ADMISSION.

CLINICAL HISTORY.

This patient had noticed distention of the abdomen which had been increasing more rapidly in size over the three months previous to admission. He also complained of a dull ache in the lumbar region radiating to both groins particularly to the right side. This had been present intermittently for several years. Episodes of vomiting 2-5 times had been occurring every few months for the previous ten years. The stools were occasionally straw coloured and the urine was at times dark in colour but the patient denied ever having been frankly jaundiced. Weight had been steady in the past although the patient was not a big eater.

Seventeen years previously the patient underwent partial gastrectomy for peptic ulceration of the duodenum.

EXAMINATION.

On examination there was an obvious coarse temor of both hands with an occasional flap. Several spider naevi were present on the neck and shoulders, and there was obvious gynaecomastia and palmar erythema. The abdomen was tense and distended. Abdominal shifting dullness was present and a fluid thrill was elicited. Pitting oedema was present in both lower limbs to the knee, but there were no clinical signs of pleural effusion. After vigorous diuretic therapy the spleen and a smooth firm liver were palpable. The liver was palpable four finger breadths below the right costal margin.

INVESTIGATIONS.

Hb. 100% 
MCV 34% 
WBC 9,000

Serum folic acid 4.4 mug/ml (normal range 4.5 - 180 mug/ml)
Serum B12 assay greater than 1000 uug/ml (normal range 170 - 1000 uug/ml)
Liver function tests indicated a degree of parenchymal cell damage.

Bilirubin 3.2 mg./100 ml. serum.
Alkaline phosphatase 190 in/ml.
SGPT 12 units/ml.
Thymol turbidity 12 (normal range 0-4)
Cephaline cholesterol +4 (normal -)
5 - nucleotidase 18

Serum protein values were typical of hepatic cirrhosis.

Total serum protein 7. 0G/100 ml. (normal range 6 - 8 G/100 ml)
  Albumin 40.9%  "  "  57 - 68%
  a1 Globulin 2.8%  "  "  1.0-5.7%
  a2 Globulin 7.0%  "  "  4.9-11.2%
  b Globulin 8.8%  "  "  7.0-13.0%
  g Globulin 40.5%  "  "  9.8-18.2%

Serum amylase 86 units/100 ml.  "  "  60-180

Glucose tolerance test showed diabetes mellitus.

Time (hrs) 0 ½ 1 1½ 2 2½
blood glucose 118 232 272 248 216 160
The ESR was 89 mm in the first hour on admission and 106 mm in the first hour six weeks later. In view of this persistently raised ESR a liver scan was performed to exclude that remote possibility of a hepatic neoplasm. The liver scan showed diffused reduced uptake of radio-isotope consistent with diffuse hepatic cirrhosis but no single focal lesion was demonstrated. Furthermore, the serum foetoprotein test was negative. The presence of foetoprotein is diagnostic of a hepatoma but its absence does not necessarily exclude hepatic neoplasm.

A barium swallow and follow through showed coarse mucosal folds at the distal end of the oesophagus consistent with the presence of oesophageal varices. A partial gastrectomy of the Polya type was demonstrated on the follow through.

TREATMENT AND CLINICAL COURSE.

A diuresis was established with spironolactone and fruseamide given with oral potassium supplements. The patient lost 11.9 Kg. in weight over the next six weeks. In view of the hypoproteinaemia, diabetes mellitus, and ascites, the patient was started on a high protein, low carbohydrate, salt-restricted diet. He was discharged from hospital six weeks after admission on this dietetic regime together with bendrofluazide 10 mg. daily and Kloref 2 tabs. t.i.d.

SECOND ADMISSION.

Three months after discharge the patient was readmitted. His abdomen had been increasing in girth during the previous two weeks. He had not had any abdominal pain, haematmesis or melaena stool but had been off his food for about ten days and had vomited two or three times three days before admission. The vomitus was not of the "coffee grounds" type and contained no blood or bile. The patient also developed a tremor of his hands and probably the legs since he had been stumbling and falling when he tried to walk.

On examination he was confused and responded poorly to commands. He had a gross flapping tremor of the jaw and both hands, and had demonstrable clonus at both ankles. The abdomen was distended (girth 45½") but there was no ankle oedema. There was marked foetor hepaticus and extensive areas of bruising around the sites of injury sustained during his stumbling and falling.

The patient had been taking Narphen (phenazocine) 5-6 tablets in all during the four days before admission for back pain and was at the time complaining of severe R. subcostal pain radiating into the back. This pain was constant and aggravated by the patient sitting up but did not radiate to either leg. He was given pethidine and cyclizine on one occasion and Fortral (pentazocine) on several occasions for this pain.

INVESTIGATIONS.

Investigations were carried out to determine the site of origin of this pain.

During an intravenous cholangiogram, neither the gall bladder nor the biliary system were outlined by contrast medium at 120 min, but this may have reflected liver disease and not gall bladder pathology since the liver function tests at the time were grossly abnormal (serum bilirubin 2.3 mg./100 mls, alkaline phosphotase 188 iu/100 mls, SGPT 21 units/ml, thymol turbidity 12 units).

Barium meal investigations once more demonstrated oesophageal varices and a Poly-type gastrectomy but there was also a persistent fleck of barium beyond the stoma of the duodenum which was thought to represent a stomal ulcer.

The lumbar and thoracic spine showed early degenerative changes but the disc spaces were intact.
Ten days later the patient suffered another episode of acute back pain which was associated with a serum amylase level of 292 units/100 mls in the acute phase falling subsequently to 119 units/100 mls (normal level 60 - 180 units). A pancreatic scan showed patchy uptake of radioactive material in the area of the pancreas which was not outlined clearly. These findings suggested a degenerative change in the pancreas probably chronic pancreatitis of alcoholic aetiology.

A EEG showed a slow dominant rhythm with temporal theta waves presumably reflecting liver damage.

CLINICAL COURSE AND TREATMENT.

In view of the encephalopathy demonstrated on EEG, the patient was started on Duphalac (laevulose) 20 mls t.i.d. He was given Alcin prn. for the stomal ulcer and subsequently for the relief of back pain, probably of pancreatic origin. DF118 was used with considerable success. Vigorous diuretic therapy was instituted with frusemide and spironolactone and the patient's weight fell by 7.6 Kg. during his seven week stay in hospital. He was started this time on a low protein diet (30G/day) with salt restriction. Kanakion (vit K) was given by intramuscular injection because of his easy bruising tendency and Parentrovite intravenously. He was discharge on Aldactone A 50 mg. t.i.d., Fursemide 120 mg. daily, Aneurine Co. forte tabs 2 t.i.d., Kloref tabs. 1 t.i.d. Calcium Sandoz tabs. 2 t.i.d., Duphalac 20 ml. t.i.d., Alcin tabs. prn.

THIRD ADMISSION.

Three weeks after discharge and ten days before his third admission, the patient became confused and forgetful after taking his first walk out of doors. He denied that he had been to the pub for a drink. He also developed a shake and just before admission his eyes had started to roll. His tremor had become so bad that he was unable to take his pills or dress himself.

On admission he had a pronounced flapping tremor of both hands and jaw, mild scleral icterus, and was more pigmented than on previous admissions. The abdomen was again grossly distended (girth 46") . This time ethacrynic acid was substituted for frusemide in the diuretic regime which produced a prompt diuresis so that he lost 3.1 Kg. body weight and 3" girth of his waist in three days. He once again received Parentrovite and Kanakion injections.

FOURTH ADMISSION.

After only four days out of hospital, the patient was readmitted for the fourth time, in a confused and disorientated state with a marked flapping tremor. He had developed an itch three days previously and had vomited "coffee grounds" type vomitus two days previously. The patient had taken little fluid during the 24 hrs. prior to admission and was clinically dehydrated so a 5% laevulose intravenous drip was set up. The brown vomitus probably indicated alimentary bleeding, so neomycin was started as a supplement to Duphalac although the FOB was negative. He had eaten little for four days but this had included chicken soup and a ham sandwich. He was once again started on a 20 G./day protein diet.

His mood was variable for the following two weeks and he had marked flapping tremor at times which was successfully treated with intramuscular Valium.

This patient died two days after developing a cough. The necropsy showed evidence of hepatic cirrhosis and widespread bronchopneumonia.
DISCUSSION.

Some patients with hepatic cirrhosis are apt to develop bouts of confusion and stupor (hepatic delirium) under certain well defined circumstances including alimentary haemorrhage, infection, abdominal paracentesis, constipation, uraemia and excessive dietary protein intake. A relatively high dietary protein intake in excess of 20 G/day preceded the hepatic coma which necessitated this patient's third hospital admission. Furthermore, chronic portal-systemic encephalopathy may be induced experimentally by the intravenous injection of urease or glycine and by the administration of ammonia liberating cation resins or ammonium salts. It would seem that portal-systemic encephalopathy (PSE) is caused by nitrogenous substances from the intestine and admitted directly into the systemic circulation by portal-systemic shunts or surgically formed shunts. Ammonia or ammonium producing substances are capable of producing PSE although other substances may also be responsible (1).

Adams and Foley (2) first described the flapping tremor of advanced liver disease as "....... a characteristic type of involuntary movement seen especially when the arms were held out with the fingers spread, consisting usually of lateral deviation of the fingers, flexion-extension of the fingers at the MP joints and flexion-extension of the wrist. The movements were rapid and arrhythmic and one phase was always more rapid than the other". They indicated that this was an important but not diagnostic sign of liver failure since they also observed similar tremor in two patients with uraemia and three patients with polycythaemia (2). Since that time, flapping tremor has been reported in other patients with no evidence of hepatic disease. Cook recorded flapping tremor in one patient with severe malnutrition and in three patients with steatorrhoea (3) and Smythe reports a similar tremor in a young woman with SLE and azotaemia, and in a young man with hypertensive cardiovascular renal disease and respiratory distress (4). Retention of ammonia is recognised as a closely correlated factor with the degree of hepatic coma (5), and the arterial level of ammonia correlates well with the degree of neurological disturbance (6), but it is not known whether the flapping tremor is related to the same metabolic derangement. However, the tremor closely resembles other neuromuscular disorders having origin in the basal ganglia, and the description of astrocytic proliferation in the basal ganglia in patients dying of hepatic coma is evidence of the special sensitivity of this area of the brain to the abnormal metabolic process in PSE (2).

Bircher first described the use of lactulose in two patients with hepatic disease (7). Lactulose is a synthetic disaccharide which is neither hydrolysed nor absorbed in the small bowel. The success of lactulose in the treatment of patients with PSE has been attributed to the replacement of proteolytic bacteria such as Esch. coli, Proteus, Bacteroides, in the colon with fermentative acidophilic organisms such as Lactobacilli lacking in urease and other ammoniagenic enzymes (8,9). Elkington recently described the first controlled trial of the value of lactulose in patients with PSE. In five out of seven patients lactulose resulted in improved clinical and laboratory indices. Long term lactulose treatment prevented hepatic coma in four patients, and reduced the frequency and severity of hepatic coma in three patients. Bircher could not demonstrate a decrease in the urease activity of the stool in treated patients despite a decrease in Bacteroides (10) but Castell showed that ammonia absorption from the isolated colon in patients with ileo-sigmoidal anastomoses decreased as the pH of the colonic contents decreased (11), and Elkington reported in the controlled
clinical trial that clinical improvement in patients with PSE receiving lactulose treatment correlated closely with effective faecal acidification (1). At the lower colonic pH more ammonia exists as the non-diffusible ammonium ion $\text{NH}_4^+$ and so the colonic absorption of ammonia is reduced. The patient described here was treated with lactulose after an EEG recording showed changes of PSE but any therapeutic benefit was difficult to assess since lactulose was used only during the last three months of his illness.

Certain drugs, including potent diuretics (12), hypnotics, sedatives and analgesics, have been implicated in precipitating hepatic coma in patients with pre-existing liver disease. Since morphine is conjugated by the liver before it is excreted (13) and morphine conjugation and urinary excretion is reduced in animals with liver failure (14), morphine must be used cautiously in patients with liver failure. Fagin (15) reported that coma followed the administration of morphine by a few hours in six out of fifteen patients dying of liver failure, and as little as 10 mg. of morphine induced coma for up to three days before death. This effect was ascribed to the reduced ability of the diseased liver to metabolize morphine.

Ladilaw and Sherlock (16) demonstrated that therapeutic doses of 12 mgs. morphine intravenously did not affect the EEG readings of patient free from liver disease, but in patient in pre-hepatic coma, this same dose of morphine produced changes in the EEG similar to the changes observed in patients with liver disease passing spontaneously into hepatic coma. The patient described here received several analgesics for episodes of acute back pain from bouts of chronic pancreatitis. These included pethidine, pentazocine, phenazocine, and DF 118, and various sedatives including chlorpromazine and Valium for agitation and disturbing flapping tremor. One episode of hepatic coma was preceded by ingestion of 5-6 tablets of Narphen (phenazocine) over the previous four days. Both phenazocine and pentazocine are synthetic narcotic analgesics derived from the benzomorphine nucleus (17). The manufacturers (18) of these two analgesics advise caution in their use in liver disease, and recently Prescott (19) stressed the importance of avoiding both Fortral (pentazocine) and Narphen (phenazocine) in patients with advanced liver disease. Since this episode of hepatic coma was probably precipitated by Narphen, DF 118 was used in subsequent bouts of back pain with success and without precipitating other episodes of hepatic coma (20). Sedatives were used also to control agitation and hepatic flapping tremor although both Valium (21) and chlorpromazine (22) have been shown to cause liver cell damage.

This case illustrates the difficult therapeutic problem posed by a patient with advanced liver disease requiring heavy sedation and powerful analgesia.
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CASE No.3

CLINICAL HISTORY.

This eighteen year old girl has had a tremor in both hands for as long as she can remember. Her tremor is worse when observed or when excited but is also present with no diminution in intensity when she is alone. She says that this tremor in no way interfered with her life at home, at school or at work until about 2½ years ago when she noticed that it was getting worse. She was working then at a wool spinning factory and part of her job entailed threading needles with wool. The increase in her tremor prevented her from doing this efficiently, so she then took a job in a paper mill. Her new job includes folding sheets of paper but she is able to do this quite satisfactorily.

She is not unduly clumsy and has no difficulty fastening even small buttons when dressing. She has no abnormality of gait, no other involuntary movements, no numbness, no paraesthesia, no loss of motor power, no headaches, no blurred or double vision, and has had no faints, blackouts, or fits.

There is no family history of tremor to implicate a genetic or metabolic cause, and no past history to implicate a traumatic or toxic cause.

She was treated by her general practitioner with Phenobarbitone 30 mg. t.i.d. for four weeks, followed by phenobarbitone 30 mg. t.i.d. and Librium 10 mg. t.i.d. for seven months, and then Stemetil 5 mg. t.i.d. for three months but there was no improvement of her tremor.

She was then admitted to hospital for assessment of her tremor and for a possible trial of Tetrabenazine.

EXAMINATION.

On examination the patient had a fine tremor of the right hand which was slightly exaggerated on voluntary movement. A cup and saucer rattled as she picked them up and held them in her outstretched right hand. There was a barely perceptible fine tremor of the left hand which was not noticable unless the hands were outstretched. There was no tremor of the head, tongue, lower jaw or legs. There were no other abnormal movements, no muscle wasting, weakness or fasciculation, and no clinically detectable abnormality of muscle tone. Tendon jerks were symetrically brisk, Hoffman's sign was not present in either upper limb, plantar reflexes were bilaterally flexor, abdominal reflexes were symetrical in all four quadrants, and a jaw jerk was not elicited. No abnormality of the cranial nerves were detected on clinical testing.

The thyroid gland was not enlarged.

INVESTIGATIONS.

- Hb. 95%
- ESR 6 mm. in the first hour
- WBC 8,700 (normal differential count)
- LFTs normal
- PBI 5.8 ug/100 ml.
- Chest and skull x-rays showed no abnormality.

The rate and amplitude of tremor was measured with a torque generator described by Walsh (1). Each wrist was subjected to oscillations of known force and rate using the torque generator, and readings were made of spontaneous tremor, or changes in tremor induced by the application of rhythmically varying torques. There was a measurable tremor of 6-7 oscillations/sec at each wrist. The amplitude of tremor was greater at the right wrist. There was no evidence of a disturbance of the reflex mechanisms controlling the
Valium 10

DISCUSSION.

Dana (2) first described essential tremor in 1887 as "... a fine tremor, constantly present in typical cases during waking hours, voluntarily controlled for a brief time, affecting nearly all voluntary muscles, chronic beginning in very early life, not progressive, not shortening life, not accompanied by paralysis or any other disturbance of nervous function".

Sauvages (3) describes a child born with tremor to a woman who received a fright in pregnancy but essential tremor usually comes on in adolescence or early adult life and occasionally in old age. Contrary to common belief tremor is not a common feature of old age. Charcot in 1876 noted only 30 cases out of some 2,000 aged inmates of Salpetriere (3). Senile tremor then, seems to be essential tremor coming on in old age.

The progression of essential tremor is extremely variable. It may progress from one segment to another over a period of 2-3 years or suddenly progress rapidly (4). Greis (5) quotes a case of remission in a man with tremor whose mother and brother were similarly afflicted. The patient described here was reported as having an obvious coarse tremor of both hands at rest when reviewed at MOPD on 19.8.70, but on admission to ward three months later on 19.11.70 the tremor was fine and obvious only on voluntary movement. However, this cannot be called a spontaneous remission with any certainty since the patient was being treated at the time with Valium 10 mg. t.i.d., phenobarbitone 30 mg. t.i.d. and Stemetil 5 mg. t.i.d.

Tremor commonly starts in one or both hands simultaneously or in succession, and then progresses to the head, neck, jaw or some other part of the cranial musculature. Cranial involvement is diagnostically important, since such a mode of progression is unusual in Parkinsonism but is diagnostic of essential tremor (4). Tremor not only varies in site but also in intensity (amplitude and frequency) from one person to another, and may be slow and coarse (rate 4/sec) resembling Parkinsonism, or fine and rapid (rate 12/sec) resembling thyroid toxic tremor as in the patient described here. However, her PBI was 5.8 ug/100 ml. thus excluding a thyroid toxic aetiology.

Essential tremor is often absent at rest but develops in afflicted persons during excitement or observation for tremor, when uncomfortably cold or when muscle tone is otherwise raised. Flatau observing the existence of precipitating factors suggested the term "intermittent tremor" (6). The severity of this patient's tremor was susceptible to observation and was always worse after she had been in an argument. The tremor was also worse on voluntary movement and when the hands were outstretched, which is in accordance with similar observations made by Critchly (4).

Even the intention type of tremor may be momentarily inhibited during the performance of a delicate movement by a willed effort. Máro (7) describes a case of essential tremor in a watchmaker and Critchly describes a patient who was a surgeon (4). One of Haebler's patients was an accomplished billiard player (8). The patient here changed her job from a wool spinning factory to a paper factory because of her alleged inability to thread wool through needles. However it is possible that this unskilled patient was not as highly motivated to persevere at her work as a skilled watchmaker who developed tremor in middle-age when a change of occupation would prove more difficult.

In contrast to single movements, protracted movements such as handwriting can be seriously affected by essential tremor. In 1665 the Venetian Ambassador wrote of Oliver Cromwell who was reputed to suffer from essential tremor.
I have found Cromwell somewhat haggard in appearance and looking in not quite so good health .... the hand holding his hat was trembling. Cromwell's handwriting shows the obvious signs of tremor (see fig. 1). No micrographia occurs as in Parkinsonisms.

The morbid anatomy of essential tremor is not known nor is the nature of physiological disturbance although many theories have been advanced. Kreis (5) implicated a "... general inferiority of the nervous system", and Minro (7) asked "... could it be a forme fruste of some other disease characterised by tremor?" Taking up this question, Hanart suggested that essential tremor might exist as a partial Friedrich's ataxia since in the families which he studied many of the siblings had neurological disorders resembling this form of hereditary ataxia. More recently, Critchley (9) expressed the opinion that essential tremor might represent a forme fruste of one of the cerebellar atrophies, more particularly olive-ponto-cerebellar atrophy.

The familial occurrence of essential tremor was originally noticed by Most (10), and confirmed by Pintus (11) who published the pedigree of a Sardinian family with tremor: from 200 members belonging to seven generations 16 cases of tremor were traced. One (2) or two (12) generations may show no cases of tremor, and essential tremor along with other inherited neurological conditions is subject to the phenomenon of "anticipation" where the inherited condition appears earlier in successive generations (2, 12). Although one of the most striking features of essential tremor is its frequent family occurrence, the patient described here gives no family history of tremor. This case would seem to be one of the less frequent but equally well documented sporadic type of essential tremor.

The drug treatment of hyperkinetic syndromes to eliminate abnormal motor movements began with the use of reserpine in the treatment of Huntington's chorea (13). However in doses high enough to reduce choreiform movements, side effects in the form of drowsiness, depression, and gain in body weight occurred with high frequency. The search for a more effective drug with fewer side effects led to the introduction of tetrabenazine (14). Tetrabenazine like reserpine is a monoamine depletor but clinical effects follow more rapidly and the drug is usually eliminated in 48 hours, so dosage is easier to control (15). Apart from slight sedation no side effects have been encountered in the cases of hyperkinesia already treated.

Recently, Dalby reported a series of thirty patients with extra-pyramidal movements treated with tetrabenazine (16). The diagnostic classification was as follows:-- Huntington's chorea (8), cerebral arteriosclerosis (8), epidemic encephalitis (3), Sydenham's chorea (1), paralysis agitans (6), spinocerebellar degeneration (4). The movements were choreiform movements (14), dystonic torsion syndromes (2), intention tremor (4), parkinsonism tremor (6). In patients with choreiform movements whatever the aetiology, 203 days treatment with 150-220 mg. tetrabenazine each day produced a gradual decrease in the number and amplitude of involuntary movements. In all cases, dyskinesia returned when the drug was stopped.

In parkinsonism, reserpine produces an exaggeration of a moderate tremor but does not affect a severe tremor. (17). A similar effect was noticed by Dalby with the use of tetrabenazine in patients with Parkinsonism (16).

It has been suggested that the dopamine content of the caudate nucleus is reduced in Parkinsonism (18), but is still high enough to suffer the depleting effects of reserpine resulting in exaggerated clinical features particularly tremor. On the other hand the dopamine content of the caudate nucleus in the severe syndrome is too low to suffer any further depletion (19). Tetrabenazine may have a similar action, but the beneficial effect of tetrabenazine in hemiballismus and choreiform movements is difficult to
explain since the dopamine content of the caudate nucleus has not been reported to be abnormal in these conditions.

The use of tetrabenazine in the treatment of essential tremor has not been reported in the English speaking literature during the last eight years. Lingjaerde reports an incidence of 8-85% tetrabenazine induced Parkinsonism syndrome in a group of psychotics treated with tetrabenazine. The incidence of this side effect was dose related(20). Furthermore, Calne reports that the tremor invariably develops on cats when tetrabenazine was given in a dose of 20mg./Kg. body weight(21). The use of tetrabenazine in the treatment of essential tremor would seem to demand caution.
REFERENCES.


(9) Critchly M. (1948) "Olivo-ponto-cerebellar Atrophy" Brain 71, 343 364.


(14) Brossi A. Helvetica Clinica Acta 41, 119

(15) Plesoher A. International Review of Neurobiology. 4, 275 (1962)


CASE No.4

CLINICAL HISTORY.

This 39 year old man was admitted as an emergency after being found unconscious in the street at 8 p.m. in the evening. The person who found him said that "... he was shaking all over". The patient could remember nothing of that day except getting up from bed in the morning until he came round in the ambulance on his way to hospital. He denied any previous hospital admission or ever having had a fit before. He said that he "like a pint" but had no recollection of drinking that day.

EXAMINATION.

The patient was fully conscious and orientated, and answered questions intelligibly. He had no evidence of injury to any part of the body, had not bitten his tongue and had not been incontinent. His B.P. was 160/110 but this fell subsequently to 140/75 whilst in hospital. His pulse was rapid (125/min.), totally irregular and of small volume. An E.C.G. tracing revealed atrial fibrillation. The apex beat was located in the 5th intercostal space in the mid clavicular line, there was no heaves or thrills. Heart sounds 1 and 2 were heard and no murmurs or added sounds were heard. There were about 5-10 dropped beats/min. There was no carotid bruits and chest x-ray was normal.

The patient was jumpy on examination. There was a marked tremulousness of the cut stretched hands which were warm and sweaty with nails bitten right down. All the tendon jerks and the abdominal reflexes were symmetrical and hyperactive. Both plantar responses were flexor. There was no lid lag, lid retraction, exophthalmos or palpable thyroid.

The patient's brother indicated that the patient had been in the habit of drinking about a bottle of whisky each day for the last 2-3 years and he thought that the patient had had previous blackouts, amnesic episodes and fits.

CLINICAL COURSE AND TREATMENT.

Carotid sinus pressure failed to revert the arrhythmia so the patient was started on digoxin 0.5 mg. orally. However, the atrial fibrillation had reverted to sinus rhythm within the next hour so the digoxin therapy was discontinued.

In view of this history he was given parentrovite i.v. stat. and multivite 3 tabs. t.i.d. orally with chlorpromazine 50 mg. stat i.m. and 50 mg. i.m. t.i.d. The following evening he was given chlorpromazine 100 mg. i.m. at bed time but in spite of this the patient became restless and began to pace the ward after disengaging himself from the E.C.G. monitor. He was given paraldehyde 10 mls. i.m. stat. at 7 a.m. without effect, and chlorpromazine 200 mg. i.m. at 9 p.m. Inspite of all these doses of sedatives the patient remained agitated and very tremulous. On two occasions that morning he was brought back from the hospital corridor and front porch after trying to make his escape in his pyjamas and bare feet. At mid-day he became disorientated for place and time but not for person and began to use obscene language. He was given Sodium Amytal 200 mg. orally stat. without effect and shortly afterwards, after the psychiatrist had expressed the opinion that the patient was not certifiable, he took his own discharge.

DISCUSSION.

The observation that seizures in the alcoholic do not occur in the period of intoxication but after the cessation of drinking can be found in the literature of the last century (1) and has been documented by present day authorities (2). In an experimental study Isbell (3) demonstrated the role of alcohol in the production of seizures in two volunteers who drank
between 400 and 500 mls. of 45% ethyl alcohol for periods of 47 and 78 days respectively. One volunteer developed a grand mal convulsion 41 hours after abrupt cessation of drinking. The other volunteer had seven grand mal fits between 12 and 36 hours after alcohol withdrawal following which he developed delirium tremens. More recently, Victor (4) reported on a series of 241 chronic alcoholics who presented after seizure. In 213 (90%) of the patients seizures began in adult life, were grand mal in type and occurred after a chronic period of intoxication. The temporal relationship between the onset of seizures and the cessation of drinking could be determined accurately in 162 cases. In 50% of cases, the onset of seizures occurred between 13 and 24 hours after cessation of drinking, and over 90% occurred between 7 and 48 hours. The convulsive episode consisted of a single seizure in 100/241 cases, 2-4 seizures in 133/241 cases, and 8/251 cases seizures took the form of status epilepticus. EEG recordings were taken in 125 patients in this group shortly after convulsion (within 24 hours in 55% of patients in this group) and showed definite abnormalities in only 12 (9.2%) cases. A sub-group of 21 patients had a history of head trauma before the onset of chronic alcoholism and seizures. Seizures occurred in 14/21 of these patients only after drinking, and were focal in nature in 8 patients with appropriate EEG abnormalities. A smaller sub group of 7/241 cases had idiopathic epilepsy and had become alcoholic after the onset of seizures. In both of these smaller sub groups seizures occurred with or without drinking but were more frequent in relation to drinking. The patient described here was a chronic alcoholic with no history of idiopathic epilepsy or severe head trauma and suffered a single grand mal convulsion within 24 hours of alcohol withdrawal after a period of heavy drinking. He therefore resembles cases in the major group of Victor's series described above (4).

In Victor's series, 75/241 (31%) cases developed delirium tremens. Invariably the seizures had subsided before the signs of delirium tremens became manifest. The alcohol withdrawal syndromes have been classified by Johnson (5) and Scultz (6) as follows:-

(a) tremulous states manifested by psychomotor agitation, confusion clauding of the sensorium (disorientation) without demonstrable auditory or visual hallucinations.

(b) acute hallucinosis with auditory hallucinations and a relatively clear sensorium.

(c) delirium tremens manifest by confusion, clauding of the sensorium psychomotor agitation, hallucinosis and delirium.

The patient in this case became increasingly agitated, confused, tremulous, and disoriented in time and place. He had developed a "tremulous state/ by the above classification.

The use of chlordiazepoxide and promazine in the treatment of alcohol withdrawal syndromes has been supported largely by uncontrolled studies (7) Some authorities have reported studies in which neither chlordiazepoxide nor promazine was any more effective than a placebo in the treatment of alcohol withdrawal syndromes (8). Travel (9) found no consistent relationship between the use of phenothiazines and reduction in mortality in delirium tremens. He attributed any reduced mortality to improved fluid and electrolyte therapy and to the early recogntion and treatment of complications. In a clinical comparative study, Colbert (10) treated 49 patients for tremulousness agitated states or acute hallucinosis, and 23 patients for delirium tremens with various therapeutic regimens.

The patients with tremulous states or acute hallucinosis were treated as follows:- (1) 12 patients were given 100% alcohol by mouth and 5% alcohol in 5% glucose solution by intravenous drip. 200 cc's alcohol were given in the first 24 hours, half orally, half intravenously. If necessary, the
oral and intravenous doses were increased hourly until agitation,
insomnia, or confusion were controlled. The alcohol was then withdrawn
over a period of not less than five days. Delirium tremens developed in
5/12 patients treated with alcohol.
(2) 12 patients were treated with chlordiazepoxide 100 mg. i.m. followed by
100 mg. four hourly by mouth. The dose was increased to a maximum of
100 mg. i.m. every hour and an additional 100 mg. orally or i.m. until restraints
could be removed. Delirium tremens developed in 6/12 patients treated
with chlordiazepoxide.
(3) 13 patients were treated with 100 mg. promazine (Sparine) i.m. followed by
100 mg. orally every four hours to a maximum of 100 mg. every hour and
an additional 100 mg. orally or i.m. every two hours if necessary.
D.T.s developed in 7/13 patients treated with promazine.
(4) 12 patients were treated with 10 cc’s paraldehyde orally or i.m. and
0.5-1G chloral hydrate orally. Paraldehyde was repeated four hourly and
chloral hydrate six hourly if required for agitation. When necessary,
the dose was gradually increased to a maximum of 10 cc’s paraldehyde two hourly
and 1G. chloral hydrate every four hours. D.T.s developed in only 1/12 patients
treated with paraldehyde and chloral hydrate.

Promazine was used initially in 12 patients treated for D.T.s but
was discontinued in 5 of these 12 patients because of therapy failure
and paraldehyde with chloral hydrate was introduced. The duration of
hallucinosis prior to the discontinuance of promazine in these five
patients was a mean value of 4.2 days, but after paraldehyde and chloral
hydrate were substituted for promazine, hallucinations cleared in all
five patients in less than 4.8 hours (mean 1.4 days). Two of the remaining
seven patients treated with promazine only died, and the mean duration of
hallucinosis in the other five was 5.6 days. A further 11 patients
with D.T.s were treated with paraldehyde and chloral hydrate. In all 11
patients hallucinations cleared in 24 hours, and there were no deaths or
complications. This small but controlled study would seem to indicate
the superiority of paraldehyde and chloral hydrate in the treatment of
alcohol withdrawal syndromes.

The success of paraldehyde and chloral hydrate has been attributed
to their physiological equivalence (9), and pharmacological similarity to
alcohol (12) whereas at present evidence suggests that phenothiazines
and chlordiazepoxides are non specific (11).

The patient in this series received 50 mg. chlorpromazine i.m. on the
night of admission before sleeping. Already he was showing signs of
restlessness, agitation, and insomnia. The following night at least 36 hours
after alcohol withdrawal he was agitated and confused. He disconnected
himself from the EEG monitor and began pacing the ward. He was given
chlorpromazine 50 mg. i.m. at 4 a.m. but remained agitated and became
disoriented. Not until 3 hours later at 7 a.m. was he given paraldehyde 10 ml.
i.m. and then chlorpromazine 200 mg. i.m. at 9 a.m. Finally at 12 a.m. just before
he signed his own discharge, he was given sodium amytal 200 mg. orally. An
alcohol withdrawal syndrome was anticipated in this case. Travel (9) recommends
that an alcohol withdrawal syndrome is avoided in a susceptible individual
by vigorous prophylactic treatment with doses of drugs large enough to
induce at first a state brodering on light sleep followed by gradual
reduction of the dose over the succeeding 7-10 days. In the patient described
here effective prophylactic doses of chlorpromazine were not given and
only after the onset of a tremulous agitated state an unplanned, belated
attempt was made to control them with inadequate doses of chlorpromazine.
REFERENCES.


CASE No. 5

CLINICAL HISTORY.

During the four years before admission, this 56 years old woman had suffered from a tremor of the right hand and right leg which had been slowly progressive in intensity. For about a year before admission she had noticed a similar tremor but of lesser severity in the left hand and left leg. Tremor is exaggerated when observed but disappears on voluntary movement.

She has also noticed a slowness of movement, and has had to rise earlier and earlier in the morning to prepare her husband's breakfast so that she was rising a full hour and a half earlier than four years previously. She has also had difficulty when walking in changing direction but did not complain of undue acceleration. Her walking was unsteady and she constantly tripped over small objects.

Her speech had become slurred and reduced in volume, and her writing had become smaller and less legible. She also noticed that on looking from the distance to a near object her vision was blurred initially but became clear on continued fixation.

There was no history of oculogyric crises or hot flushes but excessive salivation had been troublesome for about a year.

There was no history to suggest an encephalitic or arteriosclerotic aetiology.

She was being treated by her general practitioner for Parkinsonism with Artane 5 mg. q.i.d. and phenobarbitone 30 mg. t.i.d. and was admitted to hospital for assessment and treatment with L-dopa after a trial of Amantadine.

EXAMINATION.

The patient was a right handed, frail middle-aged woman, orientated in time and place and person, with marked gaitation hidden by a mask-like face and extreme poverty of movement. She was dysarthric and her voice was very weak, almost inaudible. There was tremor of both arms and legs but was more marked on the right side. The tremor was coarse and exaggerated when attention was drawn to it, but disappeared on voluntary movement. Cog-wheel rigidity was demonstrable in all four limbs at both wrists, elbows and knees, but was greater on the right.

The tendon jerks were symmetrically brisk in all four limbs, and the plantar responses were bilaterally flexor but there was a positive Hoffman's sign demonstrable in both upper limbs; and there was a marked glabellar tap.

The pupils were equally found and reacted to light and accommodation, but reacted less briskly on accommodation. There was no other abnormality of the cranial nerves on clinical testing.

The gait was small stepped and shuffling.

The clinical picture was one of arteriosclerotic Parkinsonism.

INVESTIGATIONS.

Hb. 13.2 gm./100 ml.
M.C.H.C. 31.7% 
W.B.C. 4,700
C.S.F. sugar 68 mg./100 ml.
protein 54 mg./100 ml.
3 cells, all lymphocytes
gold curve ccc000000
W.R. and Kahn both negative

ASSESSMENT.

The three cardinal features of tremor, rigidity and hypokinesia, although considered separately for diagnostic purposes, interact inseparable in the production of the motor deficit of Parkinsonism (1), such that tremor and
rigidity represents contraction of the same muscle groups. Rhythmically
interrupted contractions represent tremor, whilst sustained contraction
represents rigidity. Although rigidity impedes movement, there is a disparity
between the degree of hypokinesia and associated rigidity (2). Furthermore
delay in the initiation of voluntary movement is almost impossible to
distinguish objectively from the slowing of movements once initiated.
The above considerations make the critical evaluation of rigidity and
hypokinesia very difficult. Rigidity may be assessed by measuring the
resistance offered by a passively moved limb, but objective grading and
comparison at intervals is technically difficult. Tremor, too, is difficult
to compare at different times because of marked clinical variability
depending upon such things as drug treatment, temperature and anxiety.
As well as the inaccuracies and variabilities of clinical assessment,
there is also a marked discrepancy between the clinical grading and the
degree of functional disability in patients with Parkinsonism.

Clinical assessment of this patient was supplemented by estimations
motor function made by physiotherapists and occupational therapists who
recorded their findings under standard headings, and graded into four
degrees of severity the patient's ability to perform such daily activities
of living as dressing and feeding. The patient was also submitted to a
series of times dexterity tests some of which were performed with each
hand separately, whilst others tested bimanual co-ordination. Specimens
of handwriting were recorded.

The amplitudes and rate of tremor was measured by subjecting the wrist
to oscillations of known force and rate with a torque generator (4). Electronic
recordings were made of spontaneous tremor or changes in tremor induced
by the rhythmically induced torques.

Speech was assessed clinically by the speech therapist who determined
the degree of dysarthria, monotony of speech, delay in initiation and any tendency
to undue acceleration whilst speaking. A tape recording was made of the patient
repeating eight vowel sounds and a standard sentence. The recording thus
obtained was played through a condenser microphone and the voice volume
was measured in decibels on a sound pressure meter. The meter was standardised
so that the normal range of speaking voice was between -8 and +4 and a
change of one unit is a difference of one decibel. Meter readings were
taken every ten seconds during the reading of the standard passage and
the average values of voice volume were computed from maximum and minimum
sound pressure levels during successive 10 second periods during reading
of the standard passage.

The patient was also asked to report any subjective benefit from
treatment.

RESULT OF TREATMENT

Artane and phenobarbitone were withheld and the patient was assessed
before being given Amantadine 50 mg. b.d. for two days following by 100 mg. b.d.
until the completion of the three week course. The patient was again assessed
and L-dopa was substituted for Amantadine. The dose of L-dopa was increased
from 500 mg. b.d. by 1G every other day until the maximum tolerated dose
was achieved, in this case 1G t.i.d. The patient will be reassessed after
six months treatment with L-dopa.

(1) CLINICAL ASSESSMENT

Before the course of Amantadine the patient was virtually housebound.
She was confined to essential activities such as walking to the lavatory,
washing and dressing which she performed only with help. After Amantadine,
she was considerably more ambulant and began to walk about the ward as well
as washing and dressing herself unaided. Her gait was less shuffling and
had noticeably more associated movement of the arms.

(2) ASSESSMENT OF DAILY LIVING ACTIVITIES.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Pre Amantadine</th>
<th>Post Amantadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>EATING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eat with spoon</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Eat with knife and fork</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Able to cut meat</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Able to butter bread</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Able to drink from cup</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>WASHING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turn water taps</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wash and dry hands</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Wash and dry face and neck</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bath and dry self</td>
<td>Requires help</td>
<td>still needs help</td>
</tr>
<tr>
<td>Clean teeth/dentures</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Shave/use cosmetics</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DRESSING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underclothes</td>
<td>requires help</td>
<td>+ but slow</td>
</tr>
<tr>
<td>Shirt/blouse</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Trousers/skirt</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Jacket/overcoat</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Socks/stockings</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Shoelaces, buttons, zips</td>
<td>-</td>
<td>difficulty with small buttons</td>
</tr>
<tr>
<td>Turn door handle/knob/lever</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Insert doorkey and turn lock</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Manage book and turn pages</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>The patient was able to manage to dress herself after Amantadine.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(3) MANUAL DEXTERITY TESTS

<table>
<thead>
<tr>
<th>Task</th>
<th>Pre Amantadine</th>
<th>Post Amantadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexterity board replace 24 pegs</td>
<td>135 sec</td>
<td>59 sec</td>
</tr>
<tr>
<td>Open and close safety pin</td>
<td>15 sec</td>
<td>4 sec</td>
</tr>
<tr>
<td>Thread 12 nuts on road</td>
<td>70 sec</td>
<td>27 sec</td>
</tr>
<tr>
<td>Place 5 blocks on top of each other</td>
<td>49 sec</td>
<td>23 sec</td>
</tr>
<tr>
<td>Take match from box and strike it</td>
<td>43 secs</td>
<td>10 secs</td>
</tr>
<tr>
<td>Fold and envelope letter</td>
<td>106 secs</td>
<td>32 secs</td>
</tr>
<tr>
<td>Turn newspaper inside out</td>
<td>can't manage</td>
<td>18 sec</td>
</tr>
<tr>
<td>Take three coins from purse</td>
<td>25 secs</td>
<td>13 sec</td>
</tr>
</tbody>
</table>

Although the patient was R. handed she performed dexterity tests less well with the right hand before and after Amantadine because of the involvement of the right side of the body in tremor. However, both the single handed and the bimanual tests were performed more quickly after Amantadine therapy. The results of drawing tests also show improvement after Amantadine treatment (fig. 1) A specimen of handwriting is included for comparison. Writing was larger after Amantadine treatment and a standard sentence was copied more quickly (fig. 2).

(5) ASSESSMENT OF SPEECH.

After Amantadine there was no change in voice volume which remains reduced (pre-Amantadine decibel level -14.3; post-Amantadine decibel level -13; a change of 3 decibels is considered significant (5). The tone was still severely monotonous but there was some improvement in articulation. The patient remained moderately dysarthric with some festination present as well as slurring, but intelligibility had improved.

(6) ASSESSMENT OF TREMOR.

The coarse spontaneous tremor of 5c/sec frequency showed some diminution in amplitude after the course of Amantadine but was of a similar amplitude. Tremor is increased by anxiety and the slight improvement on retesting may
OCCUPATIONAL THERAPY DEPARTMENT - ASSESSMENT FORM 3.

NAME: AGNES HILL

CXR HANDED.

AMANTADINE

Pre-operative 6/10/70

AMANTADINE

Post-operative 27/10/70

1. Now in the time for all good men to come to the aid of the party.

2. Amnes 9 secs.

3. In the time all good men to come to the aid of the party.

54 secs.
NAME: AGNES HILL

AMANTADINE
Pre-operative 6/10/70

L.

R.

1 min. 5 secs.

AMANTADINE
Post-operative 27/10/70

L.

R.

21.5 secs.
have reflected the patient's decreased anxiety on increasing familiarity with the method and apparatus used in assessing the tremor.

**DISCUSSION.**

Amantadine was introduced at first as an antiviral agent (6,7) and was given to a patient with Parkinsonism who subsequently developed remission of her symptoms of rigidity, tremor, and hypokinesia. Schwab (8) reported a series of 163 patients with Parkinsonism who were given Amantadine in a dose of 100 mg. b.d. Varying degrees of improvement were noted in about 70% of patients, and this lasted for the 3-8 months of the trial period, although the beneficial effect declined after 408 weeks of treatment. Those patients who improved on Amantadine also responded favourably to L-dopa and in one patient the two drugs seemed to have an additive effect. Side-effects were reported in 22% of patients, and these included insomnia, dizziness, depression, confusion and a few cases of hallucinations. Convulsions were reported on a daily dose of 800 mg. The severity of side effects was decreased in some cases by dose reduction or concurrent medication with benzhexol. Similar results were reported by Parkes in a recent double-blind cross-over trial. Patients were given either Amantadine or a placebo for a two week period before cross-over. 26 out of the 37 patients preferred Amantadine and showed varied individual responses. The features of clinical examination showing most improvement were the patient's appearance, hypokinesia, and tremor. Rigidity seemed unaffected. No patient showed any improvement on the placebo, but they all suffered a deterioration in mood. Patients with previous thalamolysis were initially more disabled than the non-operated group and tended to show less improvement although this was not statistically significant. This patient showed marked clinical improvement after a three week course of Amantadine. She was more ambulant, less shuffling and her speech was more intelligible with less delay in initiation. She copied a standard sentence more quickly and her writing was larger and more legible (fig.2) She showed some improvement in daily living activities such as dressing and washing, and performed the manual dexterity tests more quickly and more efficiently (fig.1). The improvement in these activities probably represents a lesser degree of hypokinesia. The slight improvement in the amplitude of tremor was within the limits of the variability induced by an anxiety provoking situation, and could not be ascribed with any certainty to benefit of drug therapy.

These results are in keeping with the two previously reported series in which hypokinesia and tremor were reduced on Amantadine but rigidity was unaffected (8,9). She reported no side effects.

After the three week trial period, Amantadine was stopped and L-dopa was substituted in increasing doses up to 5 gm./day which was considered the optimal dose for this patient.

Carlsson (11) discovered that the putamen and caudate nucleus were rich in dopamine, a precursor of noradrenaline, though these structures contained little adrenaline (12). This suggested that dopamine itself might be physiologically active in this region. Ehringer (13) showed that the dopamine content of the caudate nucleus and putamen was greatly reduced in postmortem specimens from patients who had Parkinsonism. These observations prompted attempts to augment the dopamine content of the striatum in the therapy of Parkinsonism. Dopamine does not cross the blood-brain barrier, so its precursor dehydroxyphenylalanine (DOPA) was the substance used. Cotzias (14) reported marked improvement in patients with
Parkinsonism using a DL-dopa racemic mixture but showed later that the L-isomer was just as effective in half the dose without the danger of marrow depression attendant upon use of the DL-dopa racemic mixture (15). The similar range of activity which Amantadine and L-dopa display in the treatment of Parkinsonism suggests a similar mode of action of the two drugs, but at present, a direct or indirect effect of Amantadine in areas of the brain where dopamine is a transmitter cannot be inferred from present knowledge (10). Comparing the results of the activity of Amantadine and L-dopa, the improvement accompanying 200 mg. Amantadine/day seems less striking than that produced by the optimum dose of L-dopa. Schwab (8) reported that doses of Amantadine greater than 200 mg./day were not attended by further improvement but these observations require confirmation.

Calne (16) and Goodwin Austin (17) have shown that L-dopa is useful in treating Parkinsonism over a period of several weeks, and Mawdsley (5) has shown the effectiveness on a more long term basis of several months. Mawdsley reported that 9 out of 32 (28%) patients were markedly improved, and 12 more were probably slightly improved. Hypokinesis and rigidity were reduced more convincingly than tremor. This is in agreement with the observations of Cotaias (15) who reported that tremor was the last feature to show improvement. When this patient was started on L-dopa, she developed nausea for three days and vomited on the first and second days of treatment. This is a well documented side effect, and resulted in a complete unmasking of Mawdsley's double-blind trial (5) by all the patients involved who recognised the L-dopa tablet from this common side effect. This patient showed no evidence of postural hypotension whilst in the ward taking L-dopa, nor any of the other reported side effects such as oral dyskinesia (5,14). The full therapeutic effect of L-dopa is not seen until after about three months treatment (5) and it is impossible to predict which patient will derive benefit (5,15,16). This patient then, will be reassessed after six months to ascertain any improvement and to review the usefulness of continuing L-Dopa treatment.