physiotherapy. Out of a total series of 15 patients this is an exceptionally high proportion to die because of this condition and under these circumstances. Whether the pulmonary embolism is related to the length of time taken at operation, or whether it may be connected with post-operative activity initiated after a very prolonged and markedly inactive pre-operative period, is not certain.

In the two patients in whom death was due to intracerebral haemorrhage it may be worth noting that the approach through the temporal lobe was used, and in both operations the method of coagulation was by the injection of alcohol. Two patients never recovered from the operation; in neither was the lesion large, nor was there any obvious reason why the patients did not recover.

Finally, in considering the operation as a factor contributing or leading to the death of the patient one point must be considered. In four patients (Cases 1, 3, 5, and 11) the pre-operative state was extremely poor, and as a result of increased experience with this type of operation it is doubtful whether such patients would now be accepted by the surgeons as reasonable operative risks.

Summary

The stereotactic lesions made by four different methods in 15 brains (16 sides) have been described in relation to their macroscopic location in the brain. In 13 cases the operation was performed for the relief of the tremor and rigidity of Parkinsonism, and in two cases to abolish the abnormal movements in Huntington's chorea and in hemichorea respectively. In 11 operations the target was the globus pallidus, and in five the thalamus. It has been found that there was a greater accuracy in placing the thalamic lesion than the pallidal lesion. The internal capsule was frequently involved, but it was rare for this to result in serious paralysis.

The location of the lesion is considered in relation to the clinical findings and to the cause of death. In six cases the results of operation were considered to be satisfactory; in two there was a little improvement; in two the immediate result, for a few hours, was satisfactory, then the patient deteriorated; and in six the result was bad. Good results were achieved with different lesions, both small and large, in widely scattered sites.

My most sincere thanks are given to all those neurosurgeons and neuropathologists who have so generously supplied this material. I also warmly thank Dr. E. A. Carmichael for his interest and the facilities he has provided. My thanks are due, and most heartily given, to Mr. K. L. Frampton for the photography, and to Miss Anne Ebborn for her technical work and help with the diagrams.

Requirements for Spencer Wells artery forceps (straight and curved) with box joints are specified in a new British Standard (B.S. 3355:1961). It is specified that the instruments shall be made of stainless steel in a range of sizes of 5 inches (12.7 cm.), 6 inches (15 cm.), 7 inches (18 cm.), and 8 inches (20 cm.) nominal overall length. The standard is one of a series dealing with surgical forceps of various types. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1. (Price 3s. each; postage extra to non-subscribers.)

PERSISTENT ACUTE VIRAL HEPATITIS

BY

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[WITH SPECIAL PLATE]

Viral hepatitis is usually a benign, short-lived disease with recovery occurring within one to two months from the onset of symptoms. However, in some patients recovery is delayed well beyond this period. The purpose of this paper is to present our experience with the latter group of patients, and to emphasize that complete recovery eventually occurred in each case, despite the presence of active disease for as long as three years. The term "persistent acute viral hepatitis" is used to describe this group, as the histopathological picture was that of acute hepatitis despite the length of the illness.

We have encountered five patients with such an illness, all of whom were females aged between 19 and 47 years. Each patient had an onset compatible with viral hepatitis with initial mild jaundice. Outstanding symptoms were nausea, malaise, anorexia, pain in the right upper quadrant, and, less frequently, poorly localized abdominal pain. Hepatomegaly was present in four cases and splenomegaly in two cases. The biochemical pattern was that of hepatocellular disease, and it returned to normal in the intervals between attacks. Filter-paper electrophoresis of serum from these patients revealed transient mild increases in gamma-globulin level. L.E. cells could not be demonstrated. Aspiration liver biopsies revealed the changes of acute hepatitis with variable degrees of cellular necrosis and intralobular and periportal inflammation. The duration of the illness ranged from eight months to three years, despite prolonged periods of rest in bed and the provision of an adequate diet. Corticosteroids were given to each patient in an attempt to shorten the illness, but variable responses were obtained. The criteria for recovery were the disappearance of symptoms and signs, return of liver function tests to within the normal range, and normal liver biopsy findings. An illustrative case history is provided.

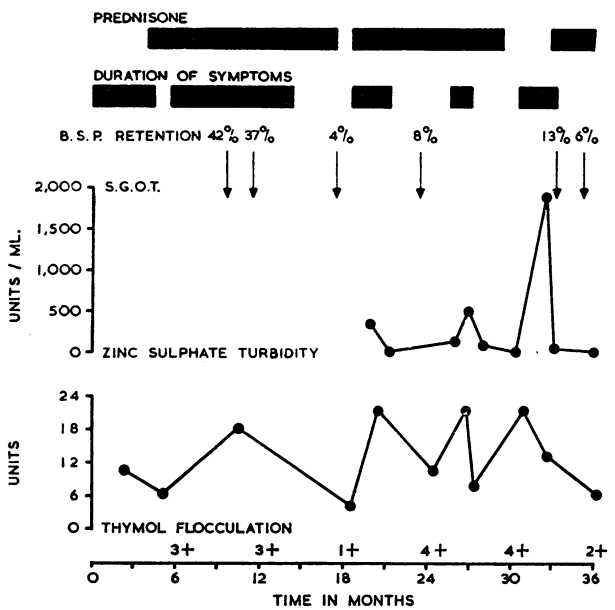
Case History (see Chart)

A 20-year-old female student began to complain of malaise and tiredness in April, 1958, and in the following week her urine darkened and she became jaundiced. Examination at this time also revealed tender enlargement of the liver, and viral hepatitis was diagnosed. She was treated with a high-protein diet and rest in bed, but she remained jaundiced and was seen by us in June, 1958. Abnormal physical findings persisted.

Investigation at this time revealed: Hb 15 g. per 100 ml.; white cell count 7,000 per c.mm. (polymorphonuclears 76%, lymphocytes 15%, monocytes 8%, eosinophils 1%); prothrombin index 100%. Serum bilirubin 2.5 mg. per 100 ml.; serum alkaline phosphatase 9 King–Armstrong units; thymol flocculation 2+ and zinc sulphate turbidity 11 units.

*Supported by the Bushell Trust.

Electrophoresis of serum revealed a mild increase in gamma-globulin. Examination of the blood for L.E. cells gave negative results. Liver biopsy material obtained by the percutaneous route showed a disappearance of cells from the centres of the lobules. The portal tracts were enlarged and there was a moderate infiltration of lymphocytes, neutrophils, and occasional eosinophils. The architecture of the liver was normal. The appearances were those of acute hepatitis (Special Plate, Fig. 1). Symptoms persisted despite continued rest in bed, and in August, 1958, prednisone therapy was begun in a dosage of 40 mg. daily. Rapid clinical improvement followed, and in September the dosage of prednisone was reduced to 15 mg. daily. However, malaise, nausea, and jaundice recurred and she began to



Showing course of illness in patient described.

complain of vague abdominal pain. The dosage of prednisone was increased to 60 mg. daily in December, 1958, as her symptoms had persisted and the results of laboratory investigations had remained abnormal despite prolonged rest in bed and maintenance corticosteroid therapy. "Bromsulphalein" retention after 45 minutes was markedly abnormal during this period, values of 42% and 37% being obtained in succeeding months. However, this had fallen to 4% by March, 1959, when she again felt quite well.

A liver biopsy in June showed no abnormality apart from a few residual inflammatory cells and fibrous-tissue strands within portal tracts. The dosage of prednisone was then reduced until the drug was withdrawn in August. Nausea and vague abdominal pains reappeared in October, but there was no jaundice until December, when the liver was again found to be enlarged. Prednisone therapy was restarted in a dosage of 40 mg. daily and symptoms subsided rapidly, but in February, 1960, she had another episode of hepatitis while receiving 10 mg. of prednisone daily. The dosage of prednisone was increased to 40 mg. daily and improvement followed. The serum bilirubin level fell from 6 mg. to 1 mg. per 100 ml., and serum glutamic-oxalacetic transaminase from 700 units to 60 units per ml. in the following week. Liver biopsy material obtained in May, 1960, appeared normal apart from the presence of a mild inflammatory infiltrate in the portal tracts (Special Plate, Fig. 2). Prednisone therapy was discontinued in September, 1960, but in January, 1961, she again became jaundiced, transaminase levels reaching 1,900 units per ml. Treatment with prednisone was resumed after a fortnight, as there had been no spontaneous improvement.

In May, 1961, liver biopsy was again performed when the patient was free from symptoms. The liver was no longer palpable, and tests of liver function, including bromsulphalein retention and transaminase estimation, gave normal results. Biopsy of liver tissue revealed no inflammatory changes. There was evidence of parenchymal regeneration and prominence of fibrous tissue about the portal tracts. Masson staining revealed normal liver architecture and no increase in fibrous tissue. There has been no recurrence during a follow-up period of six months.

In summary, this patient had five episodes of acute hepatitis during a period of three years. Repeated liver biopsy revealed either acute inflammatory changes or evidence of a subsiding hepatitis, and after three years there is no evidence of cirrhosis. Though symptoms and signs disappeared rapidly after starting corticosteroid therapy, renewed activity usually followed its withdrawal.

Discussion

The time taken for restoration of the normal histological appearance of the liver after uncomplicated viral hepatitis is variable, but in most cases this probably occurs within eight weeks. Mallory (1947) found that the hepatitis had almost cleared in liver biopsy material from two of his patients examined on the 32nd and 33rd days respectively after the illness began, and the histological appearances were normal in four patients observed between the 45th and 53rd days. However, in one patient studied on the 83rd day moderate activity was still present. Lucké (1944), who studied 14 patients who had had viral hepatitis and who died from unrelated illnesses one to 14 months after clinical recovery from the hepatitis, found the histology of the liver to be normal in each instance.

There is ample evidence in the literature that acute viral hepatitis can persist for long periods without the occurrence of permanent damage. Mallory (1947) describes recrudescences of this disease and recurrent attacks even after a prolonged interval of normal health. He described 40 patients who recovered despite the persistence of symptoms, signs, and abnormal liver function tests over long periods. Biopsies were obtained from 100 to 500 days after the onset of the acute attack. Biopsy findings were abnormal in 15 patients, with periportal and intralobular inflammation and focal hyaline necrosis—changes identical with those in our experience. Flood and James (1947) reported 12 patients in whom biopsy of the liver 73 to 761 days after the onset of the illness showed persistent acute hepatitis.

Smetana (1957) reported that a relatively small number of patients with hepatitis continue to suffer from indigestion, gastro-intestinal discomfort, and vague pains associated with abnormal liver function tests and biopsy evidence of subsiding acute hepatitis. He postulated that these changes are due to continued viral activity, as demonstrated by the presence of focal necrosis of liver cells. He indicated that in viral hepatitis periods of clinical activity are sometimes followed by temporary quiescence for long periods, the biopsy appearances always being compatible with those of viral hepatitis. Our experience parallels closely that of Smetana. The patient here described had repeated episodes of gastro-intestinal symptoms, vague abdominal pains, and liver tenderness with biochemical and biopsy evidence of liver disease during a period of three years. Another patient, after an illness of six months' duration, had a symptom-free period of eight months before a second episode occurred, the total length of the illness being 18 months. In the remaining three patients the illness was less protracted, the interval between the

onset of symptoms and recovery not exceeding eight months. We would agree with Mallory (1947) that in patients with persistent acute hepatitis the pathological changes are the same as those seen in the acute stage, though they are of a milder nature with focal hyaline necrosis of liver cells and periportal and intralobular inflammation. In the experience quoted (Mallory, 1947; Smetana, 1957) and in our own cases the architecture of the liver was not disturbed and cirrhosis did not occur.

A question which remains unanswered is: "What causes the persistence of the inflammatory state?" The protracted nature of this disease suggested to Smetana (1956) an analogy with the virus infection of oral herpes; he considered that the virus persists in the liver. Neefe *et al.* (1947) attempted to demonstrate this by injecting material from patients with persistent hepatitis into volunteers. The majority of these developed symptoms suggestive of hepatitis, but laboratory evidence was either absent or minimal. Liver biopsies were not performed. We are unable to clarify this problem, but agree that the persistence of the virus in the liver is the most likely explanation. While it will be noted that all our patients were females, the experience of the authors we have quoted indicates that this illness may run a similar course in males.

It is important to stress that persistent acute viral hepatitis differs from cholangiolitic hepatitis (Watson and Hoffbauer, 1946), recovered hepatitis with abnormal flocculation tests (Sherlock, 1957), the post-hepatitic syndrome (Sherlock and Walshe, 1946), and post-hepatitic or post-necrotic cirrhosis (Sherlock, 1948). Patients with cholangiolitic hepatitis usually have a mild febrile illness which is followed by protracted jaundice and pruritus. Liver function tests demonstrate an obstructive profile with a marked rise in serum alkaline phosphatase level and inconspicuous changes in the result of flocculation tests. While focal necrosis of liver cells may be found in biopsy sections, bile stasis and periportal inflammation predominate and eosinophils may be prominent. Patients who have made a clinical recovery after an attack of hepatitis, but in whom abnormal flocculation tests persist, lack confirmatory evidence of an active hepatitis such as abnormal bromsulphalein retention and raised serum transaminase levels, and changes in liver biopsy sections are confined to the portal tracts. Persistent acute viral hepatitis may also be distinguished from the post-hepatitic syndrome, as patients with the latter complain of languor and abdominal discomfort in the absence of laboratory and histological evidence of acute hepatitis.

Patients with post-hepatitic or post-necrotic cirrhosis usually develop more ominous signs of liver disease, such as ascites and evidence of portal hypertension, but in the early stages differentiation on clinical grounds may be impossible. However, the distinction can be made by histological means, as an active cirrhosis is present in this group at the time of the first liver biopsy. The absence of L.E. cells, minor changes in serum globulin level, and inconsistent liver biopsy findings make it clear that our group do not have "lupoid hepatitis" (Mackay *et al.*, 1956).

The normal liver biopsy sections from our patients show that cirrhosis has not developed. Smetana (1957) reported that in a study of 1,000 cases of viral hepatitis at the Armed Forces Institute of Pathology, Washington, from 1949 to 1955, histopathological evidence of portal cirrhosis was not observed in repeated biopsies performed on patients with hepatitis that had persisted for many years. A good prognosis can therefore be reasonably given to patients with this illness.

Despite the good outlook in these cases, their management poses problems. Symptoms may be so marked that rest in bed is appreciated, and relapses have been associated with increasing physical activity. We have chosen modified bed rest with gradual activity as improvement occurs. However, the length of the illness led to the use of corticosteroids in each of our cases, as there is some evidence that these drugs shorten the duration of acute viral hepatitis (Evans *et al.*, 1953; Huber and Wiley, 1955). Treatment with corticosteroids, in our experience, appeared to hasten recovery in three cases, but had no effect in a fourth. In the patient whose history is described it appeared to control symptoms, but relapses occurred as the dosage was diminished.

Summary

Reference has been made to five patients with an illness suggestive of acute viral hepatitis. This illness was noteworthy inasmuch as, though its duration ranged from eight months to three years, cirrhosis did not develop. Liver biopsy material obtained at varying stages of the illness revealed either persisting acute inflammatory changes or normal liver tissue. Persistent or recurrent illness led to a trial of adrenal corticosteroid therapy, but the results obtained were variable. Complete recovery from the illness occurred in all cases.

Dr. V. J. McGovern, of the Fairfax Institute of Pathology, and Mr. S. Woodward Smith, of the Department of Medical Illustration, University of Sydney, kindly helped in the preparation of this paper.

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"The Social Security Institute [Mexico] has made dramatic contributions to better housing for employees, constructing large units in several parts of the capital and other cities, which include medical centers, schools, and parks. The Institute provides medical care in its own clinics as well as compensation for accidents, disability, old age and death. In May 1961 it inaugurated the multi-hospital National Medical Center in Mexico City, which serves the 4,000,000 beneficiaries of the social security system. Mexico devotes 20 per cent. of the Federal budget to education, and somewhat more to transportation and communication. Social security and medical services are high in priority (14 per cent.), followed by agricultural development (10 per cent.)." (*New York Times*, supplement to international edition, March 2.)

MARION C. SMITH: LOCATION OF STEREOTACTIC LESIONS CONFIRMED AT NECROPSY

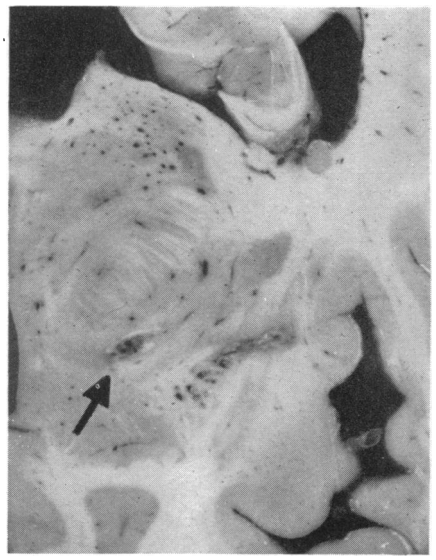

FIG. 1

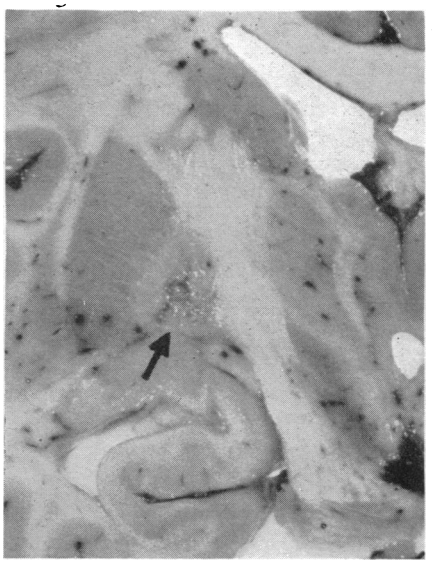

FIG. 2

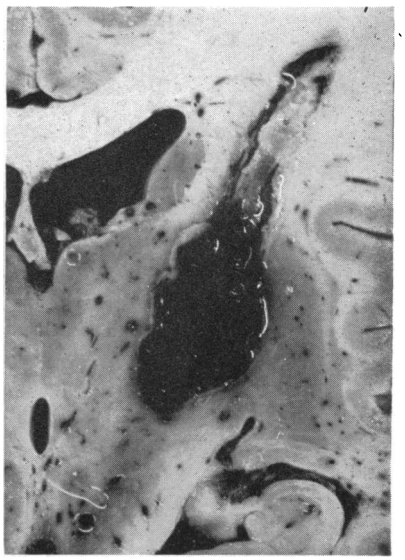

FIG. 3

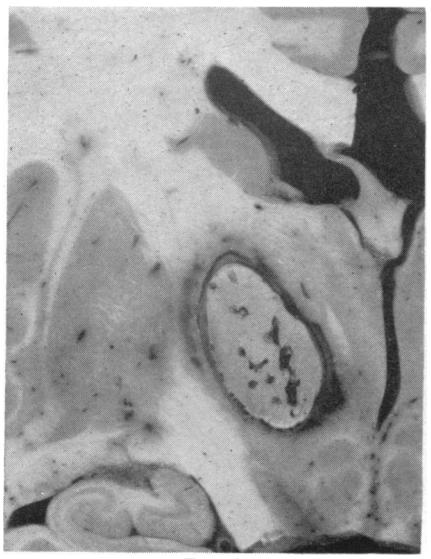

FIG. 4

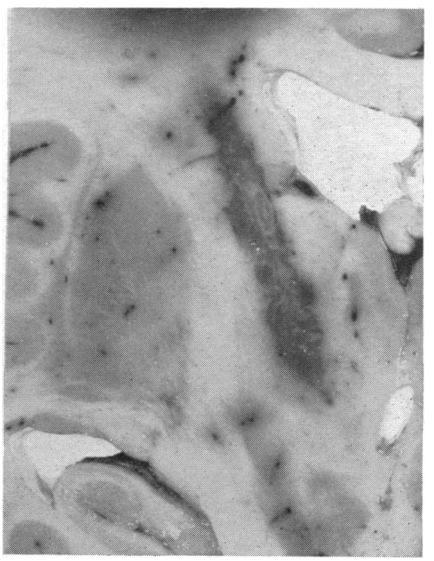

FIG. 5

FIG. 1.—Case 4 (left side). Horizontal plane. Lesion, produced by injection of absolute alcohol, in ansa lenticularis. Post-operative survival: 1 year.

FIG. 2.—Case 15 (left side). Coronal plane. Lesion, produced by Leksell's diathermy method, in globus pallidus. Post-operative survival: 10 months.

FIG. 3.—Case 2 (right side). Coronal plane. Lesion, produced by Cooper's balloon method, mainly in internal capsule. Post-operative survival: 3 weeks.

FIG. 4.—Case 9 (left side). Coronal plane. Lesion, produced by injection of etopalin and kaolin, mainly in lateral part of lateral thalamus, and in latero-ventral thalamus. Post-operative survival: 8 days.

FIG. 5.—Case 12 (left side). Coronal plane. Lesion, produced by two injections of etopalin, mainly in medial part of lateral thalamus. Post-operative survival: 11 and 8 days.

N. D. GALLAGHER AND S. J. M. GOULSTON: PERSISTENT ACUTE VIRAL HEPATITIS

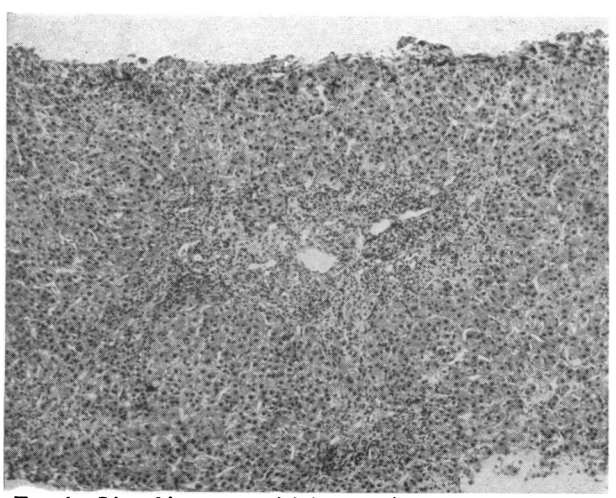

FIG. 1.—Liver biopsy material from patient described, showing marked inflammatory changes three months after illness began. (×50.)

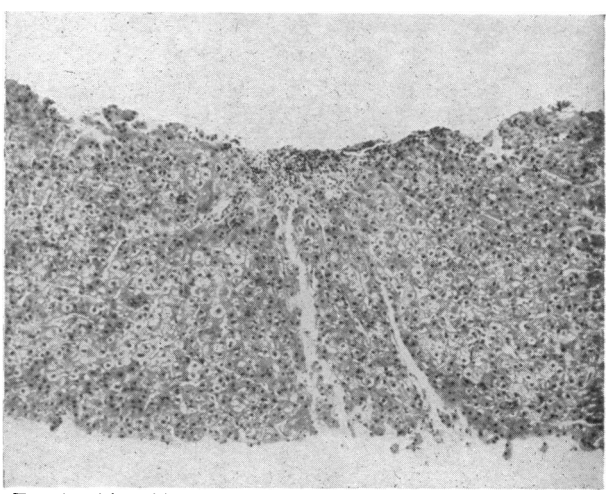

FIG. 2.—Liver biopsy material from patient described, two years after illness began. A few inflammatory cells remain. (×50.)