concentration in the secreted bile at this site. The bile thrombi could therefore be the result of resorption of bile from change in membrane permeability rather than the actual cause of the jaundice by obstructing canaliculi. In the present state of knowledge, as the site of the lesion and the mechanism of the jaundice are still uncertain, it is unwise to call this condition "cholangiolitic hepatitis," and it is better described generally as hepatitis with features of prolonged bile retention.

The prognosis of our patients has been uniformly excellent, with complete clinical recovery and restitution of a normal liver histologically. This has been the opinion of others (Lipschutz and Capson, 1955; Johnson and Doenges, 1956), although their follow-up periods have been less than two months and they attribute remission to the use of steroids. Watson and Hoffbauer (1946) postulated the development in this type of patient of a cholangiolitic cirrhosis which they likened to primary biliary cirrhosis. Liver-cell damage, however, is so minimal and the essential zonal architecture of the liver so undisturbed that progression to biliary cirrhosis would be unexpected. The picture of primary biliary cirrhosis (Ahrens *et al.*, 1950; Sherlock, 1955) develops insidiously without acute prodromata and should not cause confusion. It is particularly important as regards prognosis to differentiate hepatitis with prolonged bile retention with a good prognosis from subacute virus hepatitis in which the zonal architecture of the liver is destroyed and which progresses to a post-necrotic or portal cirrhosis.

The value of biochemical tests in the differential diagnosis is limited, for identical results may be obtained whether the biliary retention is of intrahepatic or extrahepatic origin. Popper and Szanto (1956) found no essential difference in the biochemical features of intrahepatic and extrahepatic cholestasis, both being characterized by pale stools, absent or reduced urinary urobilinogen, and raised serum bilirubin, alkaline phosphatase, and cholesterol levels. In the present series, in the first six weeks of the illness flocculation tests were often positive, but with the increase of bile retention these reverted to normal. Negative flocculation tests should not exclude viral hepatitis as the cause of jaundice, particularly when the patient is first seen at a late stage of the disease.

Corticotrophin administration for four days has been advocated for the differential diagnosis of jaundice, the fall in icteric index in acute hepatitis contrasting with extrahepatic obstructive jaundice in which there is little change (Solem, 1957). A great decrease in serum bilirubin values strongly suggests hepatogenous jaundice, although there is much overlap and the usefulness of the method has been questioned (Chalmers *et al.*, 1956). In our Case 12 corticotrophin administration was followed by a dramatic fall in serum bilirubin values and the duration from peak to normal serum bilirubin values was the shortest in the series. Serial liver biopsies while on corticotrophin and prednisolone therapy, however, showed changes comparable with others in the series and the development of minimal portal zone scarring was not prevented. These hormones have a place in the treatment of virus hepatitis with prolonged biliary retention, as they shorten the period of jaundice and enable the patient to return to activity sooner. The sequence of events in the liver, however, is probably unaltered and steroids serve only as a convenient "whitewash." Relapses are likely if steroids are withdrawn too soon, and treatment should be given until the serum bilirubin level is normal and continued well into convalescence.

Summary

Twelve patients with virus hepatitis experienced an acute onset and then showed prolonged jaundice of obstructive type. Biochemical findings were often of little differential diagnostic value. In 10 patients liver biopsy showed histological evidence of hepatitis with additional bile-pigment retention. Three patients who

underwent laparotomy recovered very slowly. The prognosis in all the patients was excellent.

The differential diagnosis and the place of corticotrophin and prednisolone treatment are discussed.

REFERENCES

- Ahrens, E. H., jun., Payne, M. A., Kunkel, H. G., Eisenmenger, W. J., and Blondheim, S. H. (1950). *Medicine (Baltimore)*, 29, 299.
Chalmers, T. C., Gill, R. J., Jernigan, T. P., Svec, F. A., Jordan, R. S., Waldstein, S. S., and Knowlton, M. (1956). *Gastroenterology*, 30, 894.
Eppinger, H. (1937). *Die Leberkrankheiten: Allgemeine und spezielle Pathologie und Therapie der Leber*, p. 288. Springer, Wien.
Gall, E. A., and Braunstein, H. (1955). *Amer. J. clin. Path.*, 25, 1113.
Johnson, H. C., jun., and Doenges, J. P. (1956). *Ann. intern. Med.*, 44, 589.
Lipschutz, E. W., and Capson, D. (1955). *Ibid.*, 43, 1037.
Popper, H., and Szanto, P. B. (1956). *Gastroenterology*, 31, 683.
Saint, E. G. (1952). *Med. J. Aust.*, 2, 613.
Sherlock, S. (1955). *Diseases of the Liver and Biliary System*, p. 384. Blackwell Scientific Publ., Oxford.
Solem, J. H. (1957). *Gastroenterologia (Basel)*, 87, 23.
Watson, C. J., and Hoffbauer, F. W. (1946). *Ann. intern. Med.*, 25, 195.

AGRANULOCYTOSIS ASSOCIATED WITH INFECTIVE HEPATITIS

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The haematological changes in infective hepatitis are characterized by an early leucopenia, affecting neutrophils and lymphocytes, followed by a relative lymphocytosis and a return to normal by the end of the second week (Havens, 1948). The degree of leucopenia varies, the lowest count recorded by Thewlis and Middleton (1925) being 1,200 per c.mm. (47% neutrophils). Severe degrees of granulopenia appear to be rare, and the only reference to agranulocytosis accompanying possible infective hepatitis we have been able to find is a case report by Sabrazès and Saric (1935): since, however, the jaundice in their patient, a young woman, was preceded by diarrhoea and vomiting of one month's duration, the exact nature of the illness is open to speculation; the patient recovered completely.

In view of the apparent rarity of the association, we describe here a case of infective hepatitis complicated by fatal agranulocytosis.

Case Report

The patient, an undergraduate aged 22, was admitted to Addenbrooke's Hospital on April 29, 1955. Eight weeks previously he had become ill with depression, frontal headache, and fever, and when his doctor was consulted two weeks later jaundice and a dark urine were noted.

After a fortnight's rest in bed he felt improved, but developed a painful pharyngitis which responded well to treatment with penicillin lozenges. Two weeks before admission he returned to Cambridge for the beginning of term; he was now only slightly jaundiced. However, severe fatigue soon prevented work and games, and marked jaundice recurred, with clay-coloured stools and a slight aching pain below the right costal margin. He had lost in all 21 lb. (9.5 kg.) in weight. His previous health had always been good, apart from an attack of jaundice at the age of 7 years. He had had no injections in the recent past, and there was no suggestion of exposure to potentially toxic drugs or chemicals.

On clinical examination the patient was icteric and his liver was moderately enlarged and tender; the urine contained large amounts of bile pigment. There was generalized slight lymph-node enlargement, but no other abnormal physical sign. Blood investigations showed: haemoglobin, 10.9 g. per 100 ml.; total leucocyte count, 3,500 per c.mm. (47% neutrophils, 0.5% eosinophils, 48.5% lymphocytes, 4% monocytes); serum bilirubin, 6.3 mg. per 100 ml. The thymol turbidity test was normal, but the serum alkaline phosphatase was raised (14.7 Bodansky units per 100 ml.).

At first he was afebrile and, although ill and drowsy, had a good appetite. By May 6 the liver was smaller and the jaundice less, but he complained of a sore throat; the fauces appeared hyperaemic, with pus on the right tonsil, but a culture was negative for haemolytic streptococci. Thereafter the temperature gradually rose to 103° F. (39.4° C.). On May 9 the leucocyte count was 2,000 per c.mm. with only 1% neutrophils. At this stage the serum proteins totalled 6.1 g. per 100 ml., with a normal electrophoretic pattern, and the thymol turbidity test remained negative; the Paul-Bunnell test was negative. All subsequent leucocyte counts, taken on and after May 10, varied between 250 and 150 per c.mm., and neutrophils were completely absent, all the cells being lymphocytes. The haemoglobin level varied between 8.7 and 9 g. per 100 ml., with normochromia, normocytosis, anisocytosis, and poikilocytosis of the red cells, and platelets totalled 170,000 per c.mm. The sternal marrow was very hypocellular, with fair numbers of megakaryocyte fragments but scanty normoblasts and leucocytes, the latter chiefly lymphocytes and myeloblasts with very occasional later granulocytes.

Treatment for the agranulocytosis consisted of penicillin and, later, streptomycin injections, and of corticotrophin gel and pyridoxine, but swallowing became extremely painful and his general condition deteriorated. The jaundice seemed to diminish, but he lapsed into terminal coma and died on May 15.

At no time was a "flapping" tremor or the fetor hepaticus noted. Apart from the drugs already mentioned, the patient received during his time in hospital only magnesium trisilicate and a single capsule of pentobarbitone sodium, 1½ gr. (0.1 g.).

Necropsy Report

The body was that of a thin, jaundiced young man. The liver was firm, khaki-coloured, and moderately enlarged (weight 2,200 g.), with a slightly uneven surface showing wrinkled depressions in places; at three widely separated sites small superficial areas of liver tissue were light yellow and evidently necrotic. On section variable broadening of the portal tracts was seen and at places some wider grey-pink zones, but there was no obvious nodular hyperplasia of the parenchyma. The Prussian-blue test for iron was strongly positive. The gall-bladder and bile ducts appeared normal.

Histologically, a lobular pattern was still recognizable, but the lobules varied in size and shape, and the central veins were often eccentric, while in some parts regenerative nodules without central veins were present. The liver cells were large, with slight fatty change, and there were some bile "thrombi." Most of the portal tracts were widened, incorporating proliferated bile ducts, a moderate lymphocytic and plasma-cell infiltration, and numerous thin-walled blood vessels. The sublobular veins showed an endophlebitis. Here and there completely destroyed lobules were represented only by collapsed stroma surrounded by a ring of proliferated bile ductules (Fig. 1). There was extensive, probably agonal, centrilobular necrosis in the yellow areas, with no inflammatory infiltration.

The bone marrow of the sternum and vertebrae was pale and brownish, and haemopoietic marrow was present in the upper femur. Histologically the marrow was hypocellular (Fig. 2), with only scanty myeloid cells, mainly of the eosinophil series with rare neutrophils. Normoblasts, however, were relatively abundant in all stages of development, especially early forms, some of which were abnormal and

resembled plasma cells; there was an increase of true plasma cells and lymphocytes, while megakaryocytes were present in about normal numbers.

The spleen was moderately enlarged and congested (weight 405 g.). Microscopically, hyperplasia of reticulum cells was present, mainly in small foci in the pulp. The

FIG. 1.—Severely damaged area of liver, showing remnants of lobules, devoid of liver cells and outlined by proliferated bile ducts, on left, and surviving parenchyma on right. (H. and E. $\times 30$.)

FIG. 2.—Bone marrow from vertebral body. Clumps of normoblasts predominate. (Barrett's stain. $\times 90$.)

pulp contained occasional neutrophils, but phagocytosis was confined to a few red cells; there was some haemosiderin deposition.

The soft palate and pharynx, the lower oesophagus, and the respiratory passages were covered by a thick layer of shaggy, easily scraped-off, yellow exudate and the mucosa was necrotic but with a relatively slight inflammatory reaction, including very few neutrophils; bacteria were extremely numerous, and a fungal mycelium was present, in greatest quantity in the oesophagus. The lungs had a mottled red colour with large, yellow, necrotic bronchopneumonic foci in which the inflammatory reaction was mainly mononuclear with a small minority of neutrophils. Cultures from various sites grew predominantly *Staphylococcus pyogenes* (penicillin- and streptomycin-resistant) and also coliform bacilli, haemolytic streptococci, and *Candida albicans*.

Apart from some small haemorrhages in the pericardium and upper ileum and conspicuous reactive changes in the upper abdominal lymph nodes, there were no important changes in other organs.

Discussion

The clinical picture—a febrile illness followed by jaundice, with a relapsing course—is strongly suggestive of virus hepatitis. The necropsy and histological findings are those of liver scarring and regeneration following parenchymal cell loss, and are compatible with a viral aetiology (Lucké, 1944). A toxic origin would appear to be excluded by the negative history, and it therefore seems reasonable to regard the case as one of subacute infective hepatitis; homologous serum jaundice may give rise to identical pathological changes, but there was no story of an appropriate injection or transfusion. The changes in blood, bone marrow, and other organs leave no doubt that a severe agranulocytosis developed and was responsible for the fatal outcome. It remains to consider the possible cause of the agranulocytosis.

Drug toxicity can be excluded, for none of the drugs which are commonly responsible was administered. Barbiturates have only rarely been thought to cause granulopenia, and the single dose of pentobarbitone given can hardly be held to blame.

Overaction of the spleen is unlikely to have been present, for evidence of increased sequestration and phagocytosis of leucocytes in this organ (von Haam and Awny, 1948) is lacking; in addition, hypoplasia of the marrow is exceptional in hypersplenism. A pre-existing *chronic hypoplastic neutropenia* (Spaet and Dameshek, 1952) can be ruled out on account of the satisfactory past history.

The possibility of *hepatic failure* must be taken into account: Sherlock (1955) refers to a patient with cirrhosis in whom polymorphs were absent from the blood, returning as liver function improved. Our patient was drowsy, but in the absence of supporting evidence severe liver failure must be regarded as improbable.

Finally, a relationship with *infection* has to be considered. A similar question arises also with certain other fevers, including measles, mumps, and influenza (Whitby and Britton, 1953), in which agranulocytosis occurs as a rare complication; in each of these diseases, in common with hepatitis, a neutropenia is common in the ordinary course of the illness. Two possibilities suggest themselves: that the hepatitis virus alone may have caused the agranulocytosis, with secondary infection as a result, or that the secondary infection itself may have played some causative role. Robertson (1949) has emphasized the importance of infection in aggravating the granulopenia when marrow depression is due to drugs; he also refers to a case of glandular fever with moderate neutropenia, in which a streptococcal throat infection led to a severe drop in neutrophils, with prompt improvement after the start of penicillin treatment. In the present instance the first alternative cannot be excluded, but we suggest that the second offers a more attractive explanation—secondary infection occurring when marrow function was already depressed as a result of the virus disease, and in turn precipitating severe leucopenia. The failure of antibiotic treatment, which is usually so effective, can be attributed to the antibiotic-resistant staphylococci in the lesions, and it seems likely that these organisms were there from the earliest stages.

Summary

A case is reported of fatal agranulocytosis developing late in the course of severe hepatitis, thought to have been of viral origin. The agranulocytosis cannot be attributed to drugs, and a relationship with hypersplenism is improbable, while the presence of severe hepatic failure seems unlikely; it is suggested that it may have resulted from secondary infection occurring at a time when marrow function was already depressed as a result of the virus disease.

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REFERENCES

- Havens, W. P. (1948). *Medicine (Baltimore)*, 27, 279.
 Lucké, B. (1944). *Amer. J. Path.*, 20, 471.
 Robertson, K. (1949). *British Medical Journal*, 1, 799.
 Sabrazès, J., and Saric, R. (1955). *Angines lymphomonocytaires, agranulocytoses, leucémies leucopéniques*, p. 251. Paris.
 Sherlock, S. P. V. (1955). *Diseases of the Liver and Biliary System*, p. 82. Oxford.
 Spaet, T. H., and Dameshek, W. (1952). *Amer. J. Med.*, 13, 35.
 Thewlis, E., and Middleton, W. S. (1925). *Amer. J. med. Sci.*, 169, 59.
 van Haam, E., and Awny, A. J. (1948). *Amer. J. clin. Path.*, 18, 313.
 Whitby, L. E. H., and Britton, C. J. C. (1953). *Disorders of the Blood*, 7th ed., p. 479. London.

GLOSSOPHARYNGEAL BREATHING

ITS VALUE IN RESPIRATORY MUSCLE PARALYSIS OF POLIOMYELITIS

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In 1951 Dail, in the U.S.A., described the mechanism of this interesting and, for the human, abnormal form of breathing as observed in a series of 15 patients. A further report by Dail, Affeldt, and Collier (1955) brought the number under observation up to 100 with a correspondingly enhanced experience and comment. Our purpose is to bring to the notice of those faced with the problem of the respiratory muscle defect in the post-acute and chronic stages of poliomyelitis the experiences of the American observers, and also to describe the results of the attainment of this aid to breathing in a few of the patients in the respiratory unit of this hospital.

Description of the Technique

Glossopharyngeal breathing was so named by Dail because of the anatomical structures which take part in the process. It has also aptly been called "gulping" and "frog-breathing" because of its similarity to the breathing mechanism of amphibians. It has been stated that the method has been used by divers to allow for longer periods of submersion and may have been spontaneously developed by some poliomyelitis patients and used for years without recognition. Dail (1951) quotes the case of a patient whom he had observed to be using his mouth and throat in what appeared to be a swallowing action, but which further observations showed to be a gulping of air trapped by the pharynx and then forced through the larynx. It was later shown that each gulp could trap from 30–60 ml. of air and that from 10–20 or more of such gulps constituted a single inspiration. Breathing could continue in this fashion for minutes or hours.

In an excellent manual of instruction for glossopharyngeal breathing (G.P.B.) prepared by Dail, Zumwalt, and Adkins (1955) a description of the mechanism, based on observations and studies of more than 100 patients and 50 normal persons who had learned the technique, is summarized as follows: "There is a stroke-like action of the tongue together with constricting action of the pharynx pumping air through the larynx. The air accumulates step-like in the lungs. Each full 'inspiration' consists normally of about 10 or more such strokes, at the end of which air is released from the lungs in a manner similar to ordinary expiration."