Previous work has shown that a gamma-globulin fraction is responsible for the L.E. cell phenomenon of Hargraves, a part of which involves alteration of the nuclear material of white cells. This suggests that the L.E. cell factor is of an antibody nature, and the present demonstration in tissue-cell

FIG. 6.—Non-specific fluorescence of cytoplasmic granules in certain leucocytes (? eosinophils). Unfixed blood film pre-treated with normal serum, then stained with conjugate. Nuclei remain non-fluorescent. ($\times 480$.)

nuclei of a fixed globulin derived from L.E. positive serum adds support to this hypothesis.

The present work also confirms a recent finding of Mellors *et al.* (1957), who described specific localization of fluorescein-conjugated antiglobulin serum in the nuclei

of the white cells in an L.E. cell preparation. It thus seems very likely that the "L.E. factor" active against leucocytes is also the factor reacting with the tissue-cell nuclei reported here.

Further work may show whether the existence in lupus erythematosus of an immunological mechanism involving tissue-cell nuclei can account for the presence of altered nuclear material in this disease.

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REFERENCES

- Coons, A. H., and Kaplan, M. H. (1950). *J. exp. Med.*, **91**, 1.
 Friou, G. (1957). Communication to the ninth International Congress of Rheumatic Diseases, Toronto.
 Gueft, B., and Laufer, A. (1954). *A.M.A. Arch. Path.*, **57**, 201.
 Hargraves, M. M., Richmond, H., and Morton, R. (1948). *Proc. Mayo Clin.*, **23**, 25.
 Lee, S. L., Michael, S. R., and Vural, I. L. (1951). *Amer. J. Med.*, **10**, 446.
 Mellors, R. C., Ortega, L. G., and Holman, H. R. (1957). *J. exp. Med.*, **106**, 2, 191.
 Milgrom, F., Luszczyński, T., and Dubiski, S. (1956). *Nature*, **177**, 329.
 Rohn, R. J., and Bond, W. H. (1952). *Amer. J. Med.*, **12**, 422.

VIRUS HEPATITIS WITH FEATURES OF PROLONGED BILE RETENTION

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Atypical manifestations of infectious diseases are difficult to recognize when the causative agent cannot be identified. In epidemics their recognition is facilitated, but sporadic cases are always diagnostic problems. "Virus" hepatitis is a well-recognized clinico-pathological entity, although the causative virus still eludes us. Eppinger (1937) recognized that, in addition to a hepatocellular variety, infective jaundice might take a "cholangitic" form which was characterized by more prolonged, deeper icterus, clinical features of obstructive jaundice, and histologically a liver showing periportal cellular infiltration and bile stasis with little evidence of hepatocellular injury. Watson and Hoffbauer (1946) described the cases of eight patients who were exposed to hepatitis and whose illness began as a typical acute hepatitis, but who showed a prolonged course with features of

obstructive jaundice, and they introduced the term "cholangiolitic hepatitis" for such cases. This complication of acute hepatitis has subsequently been described by others (Saint, 1952; Lipschutz and Capson, 1955; Johnson and Doenges, 1956).

It is the purpose of this paper to review 12 cases of acute "virus" hepatitis showing features of prolonged bile retention, with particular reference to the difficulty in diagnosis, to the management, and to the prognosis.

Clinical Features (Table I)

The seven female and five male patients were aged 13 to 59 years (mean 40 years). Two had been in contact with hepatitis during the preceding two months and two had received blood transfusions three months previously. In the others the jaundice occurred sporadically. The onset was always acute with anorexia, malaise, nausea, and vomiting, and smokers developed a distaste for tobacco. Pain in the liver area was unusual. Following the acute prodromata, jaundice appeared and deepened progressively. After about three weeks pruritus was noted, lasting about three weeks, and two patients showed a generalized maculopapular rash which lasted two to three weeks. The liver was enlarged in seven patients, but tender in only three; in two patients the spleen was palpable. The urine showed bile pigment, and an initial urobilinogen excess was soon followed by absence of urobilinogen. Stools became acholic, but as the disease continued pigment was usually noted from time to time.

After the first three to four weeks the patients felt well, were afebrile, gained weight, and the spleen and liver could no longer be felt. Jaundice, however, deepened and lasted 8 to 29 weeks, with a mean of 13 weeks. In three patients the possibility of extrahepatic biliary obstruction was so strong that exploratory laparotomy was performed, but no bile-duct obstruction could be found. These patients made slow post-operative recoveries, one having a transient episode of liver failure with ascites and impending hepatic coma. All the patients made an eventual complete clinical recovery. In seven patients a cholecystogram or intravenous cholangiogram was performed, and this was normal. The patients have been followed up for one month to six years, no relapses or clinical progression to chronic liver disease being noted.

Biochemical Features (Table II)

The peak serum bilirubin level was reached within eight weeks, and averaged 17 mg. per 100 ml., with a range of 6.6 to 27 mg. per 100 ml.; it then fell fairly sharply and steadily but did not fall below 2 mg. per 100 ml. until about the thirteenth week. The urobilinogen returned to the urine about the eighth week with a range of 4 to 18 weeks. The serum alkaline phosphatase level was raised above 30 units per 100 ml. in only three patients, but showed a tendency to increase with the serum bilirubin level and fell some time after the serum bilirubin level was normal; in two patients it was still raised after one year. Serial changes in serum cholesterol values were not remarkable, but three patients showed an elevation at the onset, and one rose later. The serum albumin concentration was not significantly altered. There was a tendency to hyperglobulinaemia, with a proportionate increase in the α_2 - and β -globulin fractions (Fig. 1), which eventually returned to normal. During the first six to eight weeks the flocculation tests were positive in eight patients but became

FIG. 1.—Case 6. Electrophoretic pattern of the serum proteins, showing an increase in the α_2 - and β -globulin fractions.

flocculation tests were positive in eight patients but became

negative in six of these as the disease progressed and the α_2 - and β -globulins rose. The other patients showed negative seroflocculation tests throughout.

Haematological Features.—The leucocyte count was normal and the erythrocyte sedimentation rate was raised in only three patients. There was no significant anaemia.

Hepatic Histology (Table III)

Sixteen liver biopsies were obtained from 10 patients—3 at the time of operation and 13 by the needle method. The first biopsy was performed 5 to 17 weeks (mean 8 weeks) from the onset. Varying degrees of bile retention, parenchymatous damage, and portal zone infiltrations were constant.

Bile retention was shown by bile thrombi, bile staining of liver cells, and swelling of Kupffer cells with bile pig-

ment. This change was absent only in two biopsies taken late in the illness. Bile necroses or laking were not seen, and the distribution of the bile thrombi was not predominantly zonal. Bile-duct proliferation was not prominent.

In the three operation biopsies and in one needle biopsy centrilobular necrosis was definite and too conspicuous for simple extrahepatic biliary obstruction. In these patients the picture was easily recognized as that of virus hepatitis. A second needle biopsy from Case 11 eight weeks post-operatively showed a marked increase in hepatocellular necrosis, and this coincided with an episode of liver failure. One year later, however, the liver biopsy appearances were normal. In the remaining six patients the evidence of hepatocellular damage was less obvious. However, all six showed definite centrilobular eosinophilic change in the cyto-

TABLE I.—Clinical Findings

Case	Age and Sex	Type	Contact History	Weeks from Onset		Clinical Features						Laparotomy	Follow-up		Comment
				First Seen	Serum Bilirubin 2 mg./100 ml.	Onset	Rash	Pruritus	Faeces	Liver	Spleen		Duration	Cholecystogram or Biligrafin	
1	58 F	I.H.	—	4	11	Acute	—	+	Pale	0	0	—	3 months	Normal	Complete recovery
2	34 F	I.H.	—	3	11	"	+	±	"	0	3	—	7 "	"	Spleen impalpable. Complete recovery
3	44 M	I.H.	—	7	29	"	—	++	"	2	0	No extra-hepatic obstruction	6 weeks	—	Slow post-op. recovery
4	45 F	I.H.	—	3	9	"	+	++	"	4	0	—	5 "	—	Liver impalpable. Complete recovery
5	46 F	I.H.	—	2	10	"	—	+	"	3	0	No extra-hepatic obstruction	6 years	—	Slow post-op. recovery. Well 6 years later
6	13 M	I.H.	+	14	18	"	—	++	"	2	0	—	8 months	—	Liver impalpable. Complete recovery
7	37 M	I.H.	+	7	12	"	—	+	"	0	0	—	3 "	Normal	Complete recovery
8	39 F	I.H.	—	6	9	"	—	+	"	0	0	—	2 years	"	"
9	42 F	S.H.	—	8	13	"	—	+++	"	1	1	—	18 months	"	Liver and spleen impalpable. Complete recovery
10	59 F	I.H.	—	6	12	"	—	+++	Variable	2	0	—	16 "	"	Liver 1 cm. palpable. Complete recovery
11	21 M	I.H.	—	12	14	"	—	+	Pale	0	0	No extra-hepatic obstruction	1 year	"	Post-op. coma + ascites transient. Completely well 1 year later
12	45 M	S.H.	—	1	8*	"	—	+	"	2	0	—	6 weeks	—	Complete recovery

* Treated with corticotrophin + prednisone. I.H. = Infective hepatitis. S.H. = Serum hepatitis.

TABLE II.—Liver Function Tests at Time of Maximum Serum Bilirubin Contrasted with Those at Longest Interval after Onset (Biochemical Results per 100 ml. of Serum)

Case	Weeks from Onset	Bilirubin (mg.)	Alk. Phosphatase* (K.-A. Units)	Cholesterol (mg.)	Albumin (g.)	Globulin (g.)	Electrophoretic Globulin Pattern	Thymol Turbidity (Units)	Zinc Sulphate (Units)
1	4	12.5	13	266	2.9	3.5	$\alpha_2\beta$	12	9
	9	0.9	13	208	3.0	3.0	Normal	2	10
2	13	13.8	102	814	3.1	3.5	$\alpha_2\beta$	5	11
	40	0.4	10	266	4.4	3.3	Non-specific	1	4
3	10*	15	70	155	4.9	2.3	—	1	—
	44	1.4	16	158	4.5	6.1	—	4	—
4	3	19.6	28	520	3.4	3.4	$\alpha_2\beta$	4	8
	13	0.6	17	314	3.6	3.3	$\alpha_2\beta$	1	8
5	5*	26.6	20	189	2.6	3.2	—	9	—
	29	1.1	14	—	4.5	2.0	—	2	—
6	13	20	20	264	4.0	3.3	$\alpha_2\beta$	6	3
	52	0.4	36	175	3.7	3.2	$\alpha_2\beta$	2	4
7	7	9.0	22	412	3.7	3.2	$\alpha_2\beta$	1	8
	17	0.4	16	226	3.4	3.3	Non-specific	1	9
8	6	6.6	9	218	3.8	3.1	γ	11	4
	17	0.6	6	—	4.3	3.6	γ	2	—
9	8	10.5	16	213	3.0	3.2	$\beta\gamma$	15	18
	14	2.2	12	230	3.5	3.8	$\beta\gamma$	3	13
10	6	27	20	165	3.4	3.5	—	2	—
	12	1.6	14	380	4.9	3.0	—	1	—
11	4*	23	21	286	4.0	3.6	γ	9	8
	60	0.6	8	239	5.3	3.3	Non-specific	6	9
12	7	21.2	16	265	3.8	3.3	$\alpha_2\beta$	6	3
	12	0.5	5	281	4.0	3.1	Normal	3	4

* Post-operative levels.

TABLE III.—Liver Biopsy Findings

Case	Weeks from Onset	Liver-cell Changes				Portal Zone Cellular Infiltrate		Biliary Retention
		Centri-zonal Loss	Pyk-nosis	Eosino-philic Change	Multinucleated Cells	Degree	Cell Type	
1	6	+	+	+	0	+	Mono-nuclear	++
2	8	0	0	0	+	±	"	+
3	7	0	+	+	0	++	Polymorphs Lympho-cytes	++
4	9	+	+	++	+	++	Monocytes Lympho-cytes	++
5	5	++	++	++	0	++	"	+
6	18	0	0	+	+	+	Monocytes	++
7	9*	+	+	++	+	++	Polymorphs	++
8	18*	0	0	0	+	++	"	0
8	8	0	+	+	+	+	"	+
11	10	+	++	++	+	++	Lympho-cytes	++
12	18†	++	+	++	0	+++	"	0
	60	0	+	0	0	±	"	+
	7‡	+	+	++	+	±	"	++
	11‡	±	0	+	+	±	"	±

* Showed fatty changes not found in other specimens.

† A post-operative biopsy following transient liver failure.

‡ Biopsies during steroid treatment.

plasm of the liver cells, indicative of damage, and ancillary evidence of hepatocellular necrosis was given by pyknosis of nuclei and multinucleated liver cells.

Portal zone infiltrations, predominantly mononuclear, were always present. The reticulin pattern of the liver was normal.

Patient 7 was an obese man and showed fatty change in the liver cells in both biopsies; this was an atypical feature.

Case 6

A schoolboy aged 13. In November, 1955, three school-fellows developed infective hepatitis, and six weeks later, on December 31, the patient complained of headache, malaise, loss of appetite, nausea, and generalized weakness. On January 9, 1956, he was noticed to be jaundiced, with pale stools and dark urine. The appetite returned and he felt very well. On January 16 itching was noted, and, in spite of bed rest and a high carbohydrate diet, the jaundice deepened and the pruritus continued; he lost 14 lb. (6.4 kg.) in weight.

He was admitted to Hammersmith Hospital on April 17, not acutely ill but deeply icteric with many scratch marks. The liver was enlarged 2 cm. below the right costal margin, firm, smooth, and non-tender. The spleen was palpable. The stools were pale, and urine contained bile pigment but no urobilinogen. He was kept in bed without specific therapy. Urobilinogen appeared in the urine two days after admission, and during the next month the jaundice gradually subsided. Itching disappeared spontaneously three weeks after its onset. An aspiration needle biopsy of the liver performed five months after the beginning of the illness (May 15, 1956) showed residual bile thrombi with centrilobular multinucleated liver cells compatible with a healing hepatitis. He was discharged from hospital, having gained 6 lb. (2.7 kg.) in weight and having a normal serum bilirubin level. Eight months later he had gained a further 14 lb. (6.4 kg.), grown 2 in. (5 cm.), and was a well-developed boy. The liver was no longer palpable and there were no stigmata of chronic liver disease.

Comment.—Six weeks after contact with epidemic jaundice a typical onset of hepatitis was followed by prolonged icterus of obstructive type lasting five months, with final excellent recovery.

Case 11

A draughtsman aged 21. In June, 1955, while on holiday, he felt tired and ill, lost his appetite, and had nausea and occasional vomiting. Three days later the urine became dark and the motions loose and pale, and two days afterwards the eyes and skin were yellow and there was gener-

alized itching and a widespread rash. As the jaundice deepened he felt better, pruritus being the only symptom. After three weeks the jaundice was still intense and he was admitted to hospital, where he was found to be deeply icteric with a palpable spleen. The skin showed excoriations and a maculo-papular rash. Liver-function tests in July, 1955, showed: serum bilirubin, 19 mg. per 100 ml.; alkaline phosphatase, 16 King-Armstrong units per 100 ml.; serum albumin, 4 g.; serum globulin, 3.6 g.; thymol turbidity, 9 units. The urine contained bilirubin and no urobilinogen. X-ray examination of the abdomen revealed no calculi, and the Paul-Bunnell test was negative. The patient was kept in bed with a low-fat diet and the pruritus and rash cleared. However, after four weeks the jaundice had not altered significantly and the seroflocculation tests were now negative. The original diagnosis of infective hepatitis was revised, and an exploratory laparotomy was performed on July 27, eight weeks after the onset of jaundice. Apart from an enlarged spleen, no abnormality was found. A liver biopsy showed appearances consistent with a healing hepatitis (Table III).

Post-operatively the jaundice deepened and he developed ascites and ankle oedema. The ascites cleared quickly on dietary salt restriction and mercurial diuretics, but as the jaundice persisted he was referred to Hammersmith Hospital in September, 12 weeks after the onset. He was mildly icteric, with a palpable spleen but no other stigmata of chronic liver disease. A second aspiration needle biopsy performed two months after the first showed evidence of recent acute centrilobular necrosis with increase in reticulin, a few bile thrombi, and conspicuous portal zone cellular infiltration with some fibrosis; progression to cirrhosis seemed possible. During the next two weeks the jaundice cleared and he was discharged from hospital. In August, 1956, he was readmitted for assessment. He felt perfectly well and was leading a normal life. The spleen was no longer palpable, biochemical tests were virtually normal (Table II), and an intravenous cholangiogram showed a normal biliary system. Aspiration liver biopsy revealed normal liver structure.

Comment.—In this patient hepatitis started acutely but was followed by a prolonged phase of biliary retention. Following laparotomy, liver function deteriorated, ascites developed, and the liver lesion progressed. Ultimate recovery, however, was complete.

Case 12

A buyer aged 45. In November, 1956, following a car accident, he received blood and pooled plasma intravenously. In January, 1957, anorexia, nausea, malaise, loss of desire to smoke, with some fever, were followed several days later by dark urine and the eyes became yellow. On January 16, 10 days after the onset, he was admitted to Hammersmith Hospital. He was an ill-looking, moderately icteric man with marked fetor hepaticus and a tender liver edge just palpable. Bio-

chemical tests showed: serum bilirubin, 6.1 mg.; albumin, 3.9 g.; globulin, 3.6 g. ($\alpha_2\beta$ pattern); thymol turbidity, 6.5 units; zinc sulphate, 4 units; alkaline phosphatase, 37 units; cholesterol, 239 mg. per 100 ml. A diagnosis of serum hepatitis was made and he was treated with bed rest, glucose drinks, and a light diet. His appetite improved and he felt generally better, but jaundice deepened and two weeks after admission there was generalized itching. Six weeks after the onset he felt well, although his serum

FIG. 2.—Case 12. Effect of corticotrophin and prednisolone therapy on the serum bilirubin level.

chemical tests showed: serum bilirubin, 6.1 mg.; albumin, 3.9 g.; globulin, 3.6 g. ($\alpha_2\beta$ pattern); thymol turbidity, 6.5 units; zinc sulphate, 4 units; alkaline phosphatase, 37 units; cholesterol, 239 mg. per 100 ml. A diagnosis of serum hepatitis was made and he was treated with bed rest, glucose drinks, and a light diet. His appetite improved and he felt generally better, but jaundice deepened and two weeks after admission there was generalized itching. Six weeks after the onset he felt well, although his serum

bilirubin level had risen to 21 mg. per 100 ml. and the urine still contained no urobilinogen.

On February 16 corticotrophin gel, 40 units intramuscularly twice daily, was started, and within three days his bilirubin had fallen to 8 mg. (Fig. 2). The stools were darker and urobilinogen was present in the urine. Itching disappeared and the general well-being and appetite had greatly increased. After four days the corticotrophin was reduced to 20 units twice daily, and after nine days' corticotrophin therapy the serum bilirubin was 2.6 mg. per 100 ml. An aspiration needle liver biopsy was then performed which showed centrizonal liver cell necrosis, many bile thrombi, and Kupffer-cell pigmentation without distortion of lobular architecture and with a minimal lymphocytic infiltration in the portal tracts (Fig. 3). In spite of the

FIG. 3.—Case 12. Jaundiced for 51 days. Aspiration liver biopsy 1, showing centrizonal necrosis and giant liver cells with Kupffer-cell increase and many very dark bile thrombi. (Stained Best's carmine. $\times 92$.)

FIG. 4.—Case 12. Jaundiced for 81 days. Aspiration liver biopsy 2, showing residual portal zone cellularity and scarring and slight centrizonal rarefaction. The zonal architecture is preserved. (Stained Best's carmine. $\times 66$.)

corticotrophin therapy this biopsy did not differ from other comparable cases in the series, although perhaps the infiltration in the portal zones was less. The corticotrophin was now replaced by prednisolone, 10 mg. twice daily. Three weeks later there was no jaundice and his liver was no longer palpable. A second aspiration needle biopsy showed portal tract fibrosis with a few bile thrombi and several centrizonal eosinophilic granules (Fig. 4). This picture, with residual scarring, was comparable with our other serial biopsies on patients who had not received steroid therapy. The prednisolone was reduced to 5 mg. twice daily for one week and then discontinued. When seen on April 8 he felt perfectly well and was returning to work. Biochemical tests on liver function were normal (Table II).

Comment.—In this patient serum hepatitis was followed by a prolonged period of biliary retention. Steroid therapy induced an abrupt clinical relief of the biliary retention but did not seem to influence the sequence of histological changes in the liver.

Diagnosis

The exclusion of extrahepatic or surgical jaundice is essential, as laparotomy seems to affect the prognosis adversely. The history is all-important. In an epidemic, little difficulty should be experienced in the initial diagnosis, which should not be changed because jaundice is prolonged. In sporadic cases the diagnostic difficulty increases. However, the prodromal symptoms followed by the acute development of jaundice with recovery of appetite and well-being are typical of hepatitis. If, as was usual in this series, the patient is first seen several weeks after the onset of jaundice and after other medical opinions have been taken, the history can be misleading. Biochemical tests may not be helpful, although the occasional positive flocculation test, with hyper-gammaglobulinaemia and the frequent low serum alkaline phosphatase values, may support the diagnosis of hepatitis.

Intravenous and oral visualization of the biliary system is of no value, as the liver is unable to excrete the contrast media in the presence of jaundice. Plain x-ray examination of the abdomen may reveal opacities in the right upper quadrant, but undue emphasis should not be placed on their diagnostic value. A chest x-ray examination is routine, and further investigations may include a barium meal and stool testing for occult blood.

Aspiration liver biopsy is indicated when the clinical diagnosis cannot be made with certainty. In our series evidence of hepatitis was present in every case, and the criteria for diagnosis are well described by Gall and Braunstein (1955) as focal necrosis with eosinophilic hyaline bodies replacing liver-cell cytoplasm, ballooning of liver cells with ground-glass cytoplasm, nuclear vesicularity, and intralobular clusters of lymphocytes. They suggest that these lesions show no essential differences from typical hepatitis, but may be obscured by the additional features of biliary retention.

Certain drugs, especially chlorpromazine, methyltestosterone, and organic arsenicals, may occasionally produce jaundice characterized by bile retention without extrahepatic biliary obstruction. The clinical course, biochemical findings, and hepatic histological changes may closely mimic virus hepatitis with predominant bile retention, and the history of taking the drug is essential for diagnosis.

Primary biliary cirrhosis should present no diagnostic difficulty. The onset, usually in a middle-aged woman, is gradual, with pruritus and jaundice; hepatosplenomegaly is constant. The hepatic histology shows a proliferative portal zone lesion.

The subacute form of virus hepatitis may provide diagnostic difficulties. This patient, however, is predominantly suffering from failure of liver-cell function and feels and looks ill. Jaundice is rarely deep and waxes and wanes. Vascular spiders develop and the spleen is enlarged. The serum gamma-globulin level is always very high and the flocculation tests are strongly positive.

Occasionally diagnostic doubt continues, and it is then our policy to wait for a minimum of six weeks before considering surgical intervention. The intervening period is occupied by daily clinical assessment, weekly serum biochemical tests, and daily observation of the urine and stools. Liver biopsy is then performed, and if doubt still exists surgical exploration is undertaken. Little is lost by delaying operation in extrahepatic obstruction, but surgery may kill the patient with infective hepatitis.

Discussion

The mechanism of biliary retention without obstruction to extrahepatic bile ducts is uncertain and the site of the obstruction still unknown. It has been suggested that the abnormality is located in the cholangiole, the hypothetical connexion of the intralobular bile canaliculus with the bile duct in the portal tract. This might be a mechanical strangulation by portal zone infiltrations or a change in membrane permeability causing bile pigment to increase in

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 Biondheim, 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.