tion of red cells as a result of adsorption of antibody, it may be argued that the antibody in these cases is some product of the malignant tissue, or of reaction to this tissue.

Alternatively, the abnormal tissues may destroy excessive numbers of red cells, and thus provoke haemolytic antibody production. Whether this is the first step may depend on the type of reticulosis. Erythrophagocytosis is a usual and pronounced feature of histiocytic medullary reticulosis and an occasional finding in Hodgkin's disease ; it occurs rarely if ever in significant degree in lymphosarcoma, while in carcinomatosis the abnormal cells have no phagocytic ability. In the last-named types, therefore, some factor other than phagocytosis must initiate the haemolytic process. The early appearance of haemolytic signs is also more readily understood on the basis of an antibody mechanism.

Summary

Four cases of haemolytic anaemia are described. They were associated with different types of reticulosis.

The type of anaemia and possible mechanisms of haemolysis are discussed.

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On June 19 Tiverton and District Hospital celebrated its centenary. It was first opened as a dispensary for out-patients and intended for the relief of the sick poor. In 1865 additional wards were built and the whole converted into an infirmary for accident cases. The infirmary received its first in-patient in 1868. A children's ward of four cots, an isolation-room, and additional rooms for out-patients and nursing staff were added in May, 1892. In commemoration of Queen Victoria's diamond jubilee £1,700 was collected and spent on pay-wards for private patients and a new operating-theatre. Further gifts of land and money made it possible for more extensions and improvements. In 1932 Sir John Amory presented the hospital with a portion of the site, until then occupied by brewery premises. These were demolished and an extension built at a cost of £6,500, comprising a new kitchen, staff quarters, and other improvements. This was completed and brought into use in 1933. Finally, in 1947 the remainder of the old brewery premises was purchased and the accommodation for nursing staff enlarged. When the National Health Service started the hospital was placed under the authority of the Exeter and Mid-Devon Hospital Management Committee. It has 50 beds, of which four are for private or semi-private patients, and also a nursery with 11 cots. Since its foundation the work of the hospital has increased enormously. During the first 16 years of its existence 7,090 out-patients were treated, while during the year 1951 alone 5,595 out-patients were treated, involving a total of 14,847 attendances. There were also 1,703 in-patients admitted during the year, while the maternity department dealt with 241 births.

UNUSUAL FEATURES IN A FATAL CASE OF INFECTIOUS MONONUCLEOSIS

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[WITH SPECIAL PLATE]

Infectious mononucleosis is generally recognized to be an acute infectious disease characterized by enlargement of the lymphatic glands, changes in the blood cells, especially mononucleosis, and a uniformly favourable course (Tidy, 1945). Fatalities from the disease have been rare. Bernstein (1940), in a comprehensive paper, stated that no one has ever died of uncomplicated infectious mononucleosis, and maintained that most of the fatal cases that have been reported were probably not examples of infectious mononucleosis at all, but rather of generalized sepsis with general gland enlargement. Of the fatalities dealt with in his survey some occurred from associated pulmonary disease (bronchopneumonia and empyema) and one from asphyxia following a ruptured retropharyngeal abscess. In another case a " delicate child " died while convalescing from scarlet fever (no further details are given).

Lassen and Thomsen (1940) recorded a mortality of about 1% in 500 cases admitted to the Blegdam Hospital. They reported two fatal cases due to degenerative processes in the central nervous system, localized apparently selectively to the respiratory centre and thus producing a central respiratory failure. Ziegler (1944) and Smith and Custer (1946) recorded fatal cases due to rupture of the spleen ; the latter authors also reported deaths due to nasopharyngeal haemorrhage and laryngeal oedema (Custer and Smith, 1948). Two fatal cases presented as the Guillain–Barré syndrome (Ricker, Blumberg, Peters, and Widerman, 1947). Jersild (1942) performed a necropsy on a patient who died of myocarditis attributed to infectious mononucleosis. So far as we know there have been no reported fatalities from infectious mononucleosis which have been associated with severe jaundice and renal failure.

That liver-cell damage may be a cause of clinical jaundice in infectious mononucleosis was first demonstrated in 1942, when a liver punch biopsy showed focal acute hepatitis, and it was further observed that there was a rough correlation between the severity of the disease and the degree of hepatic impairment (Kilham and Steigman, 1942). However, as early as 1928 it was realized that liver changes, apart from those consequent upon obstruction from enlarged glands at the porta hepatis, occurred in glandular fever. It is now thought that some hepatocellular damage occurs in all cases of infectious mononucleosis, including those which exhibit no overt jaundice. Cohn and Lidman (1946) have described 15 cases without jaundice but all showing impairment of liver function as demonstrated by more than one chemical test. Hall (personal communication), in Liverpool, followed 12 cases with liver biopsies, but actual

necrosis of liver cells similar to that observed in infective hepatitis was not seen, although the possibility of permanent liver damage was discussed.

The incidence of nephritis in glandular fever is said by various authors to be up to 6%. Bernstein states that oliguria is exceptional and that there is neither oedema nor nitrogen retention. Renal function remains unimpaired, the course is benign, and recovery is rapid and invariable. He goes on to speculate that increased capillary permeability of the renal capillaries, which, as in anaphylactic purpura, could account for the urinary abnormalities, is merely a manifestation of the haemorrhagic diathesis that is not infrequently associated with glandular fever. Wechsler et al. (1946), in a study of 556 cases seen during an epidemic, reported abnormal urinary findings in 17 cases. The abnormal constituents were red and white blood cells, albumin, and hyaline and granular casts. The same uniformly benign course with rapid return to normal was noticed. Custer and Smith stated that the renal lesion of infectious mononucleosis is essentially an interstitial nephritis.

The purpose of reporting the following case is to show that, contrary to present conceptions, the hepato-cellular and renal damage in infectious mononucleosis may be associated with a fatal termination.

Case Record

A male art student aged 23 was admitted to the Rush Green Hospital on November 24, 1950. For the three weeks before admission he had complained of feverishness, especially in the afternoons, often accompanied by rigors and sweats. For the preceding 10 days he had suffered from a sore throat, arthralgia, headache, photophobia, nausea, anorexia, and constipation. The day before admission a rash had appeared on his abdomen and he had become jaundiced. On specific interrogation he admitted that his urine was "a dark-red colour" and his stools were "beige." He also affirmed that he had had some upper abdominal discomfort during the past few days. He had previously had excellent health apart from a mild paratyphoid B infection, contracted whilst in France, for which he was admitted to this hospital fourteen months previously. At that time the organism was isolated from the stools, and the Widal test was positive.

Examination showed that he was of excellent physique, though jaundiced and looking ill. His temperature was 102.8° F. (39.3° C.) and pulse rate 88. A red macular rash was present on the trunk and to a less extent on the arms, where it was mainly papular. There were no abnormalities in the cardiovascular and respiratory systems. The fundi were normal, Kernig's sign was negative, neck rigidity was not present, and the remainder of the central nervous system was intact. The liver and spleen were not palpable and were not enlarged to percussion. Several mobile enlarged glands, firm and not tender, were palpable in both groins and well above the inguinal ligament on the right side. There were similar glands in both axillae and the lateral chest wall on the left side. There was a large mass of glands in the anterior cervical triangle and submandibular area on the right side, and similar glands were present in the neck on the left side. The tonsils were enlarged and covered with exudate, which also spread on to the posterior pharyngeal wall. There was very little fetor oris. A provisional diagnosis of glandular fever was made, and in view of the history of dark urine and beige-coloured stools an obstructive lesion in the form of enlarged glands in the porta hepatis was postulated.

For the next three days he remained ill with a high continuous fever (103° F.—39.4° C.—although his pulse rate never rose proportionally), a slight increase in his jaundice,

and biliuria. This biliuria persisted throughout his illness, although the loose stools which he passed contained bile.

On the fourth day "aureomycin" was given, and for the next two days there was some remission in the temperature and slight amelioration of symptoms; the lips, however, became tense and swollen at this time, but the swelling subsided in a few days. The concentrating power of the kidneys began to fail, as evidenced by the early morning specific gravity, which became fixed at 1010.

On the seventh day some fresh tender papular lesions appeared on the chest and back and the temperature was again raised; penicillin, 250,000 units four-hourly, was now given. He began to vomit brownish fluid and the spleen became palpable, although the superficial lymph nodes had been regressing in size.

On the eighth day the liver edge was palpable one finger-breadth below the right costal margin. On the ninth day the jaundice deepened to a golden bronze and the patient began to hiccup. The urinary output had fallen despite attempts to restore fluid loss, and the blood urea was 210 mg. per 100 ml. On the twelfth day the patient became frankly delirious, this condition alternating with periods of lethargy and semi-coma. Large quantities of brown fluid containing reduced blood were vomited and passed per rectum. His respirations had become deep and slow. The presence of free fluid in the peritoneal cavity was suspected.

In view of the rather sudden change in his mental condition—that is, the alternating coma and delirium, the persistent vomiting, the deepening jaundice, the haemorrhage from mucous membranes, and the fact that his liver, palpable the previous day, could no longer be felt—a provisional diagnosis of acute hepatic failure was made and the "intravenous liver regime" was begun—10% dextrose in normal saline with vitamin supplements. However, he failed to rally, and died on the thirteenth day.

Laboratory Investigations

1st Day.—R.B.C., 4,300,000, no malaria parasites seen; Hb, 81%; W.B.C., 3,900 (polymorphs 10%, lymphocytes 80%, monocytes 2%, atypical monocytes 8%). Paul-Bunnell, 1:256 (antibody not adsorbed with guinea-pig kidney).

Widal test: *Salm. typhi* O, positive 1:50; *Salm. typhi* H, negative; *Salm. paratyphi* B O, positive 1:25; *Salm. paratyphi* B H, positive 1:250; non-specific salmonellae, positive 1:250. The Widal reaction on his previous admission (September 27, 1949) is given for comparison: *Salm. typhi* O, negative; *Salm. typhi* H, negative; *Salm. paratyphi* B O, negative; *Salm. paratyphi* B H, positive 1:250+; non-specific salmonellae, positive 1:125. Throat swab, heavy growth of coagulase-positive *Staphylococcus aureus*. Stools, no pathogens present. Chest x-ray film N.A.D.

2nd Day.—Paul-Bunnell, 1:256 (antibody not adsorbed with guinea-pig kidney).

3rd Day.—Mid-stream specimen of urine: bile ++; albumin ++; large number of granular casts, with a few red cells, white cells, and renal cells; culture sterile.

4th Day.—Blood culture, sterile aerobically and anaerobically.

5th Day.—W.B.C., 3,600 (polymorphs 43%, lymphocytes 36%, monocytes 1%, atypical monocytes 20%). Mid-stream specimen of urine: albumin +; bile +; occasional red cells. Paul-Bunnell unchanged.

8th Day.—W.B.C., 5,400 (polymorphs 52%, lymphocytes 27%, monocytes 8%, eosinophils 2%, atypical monocytes 11%); van den Bergh, biphasic reaction; serum bilirubin, 24 mg. per 100 ml.; serum alkaline phosphatase, 60 (King-Armstrong) units.

10th Day.—Stools still negative for paratyphoid and other pathogens. Blood urea, 100 mg. per 100 ml.

11th Day.—Blood urea, 210 mg. per 100 ml.

12th Day.—Blood urea, approximately 300 mg. per 100 ml.

Post-mortem Examination Within Twelve Hours of Death

The body was that of a well-built young man. The skin was deeply and uniformly icteric. *Head and Neck:* Swelling of the lips, otherwise nothing abnormal. No cervical glands seen and throat quite clear. *Chest:* Both pleural sacs contained clear bile-stained fluid. No adhesions present. *Heart:* Pericardial effusion, bile-stained. Otherwise heart muscle, valves, and vessels appeared normal. *Lungs:* Healthy, and no enlarged lymph nodes found in the thorax. *Abdomen:* Large collection of bile-stained ascitic fluid. *Stomach:* Large and empty. *Gut:* General distension, the lower ileum containing altered blood and mucus. The coeliac glands were enlarged, pinkish, and of a rubbery consistency, and matted together, though easily separated. *Liver:* Slightly enlarged (not weighed) and gave a gross appearance of subacute yellow atrophy (hepatitis). Regular and diffuse yellow and pinkish mottling throughout the organ. The hilar glands were large, rubbery, and oedematous, resembling those of the coeliac group. No apparent abnormality of the gall-bladder noted, nor any obstruction of the bile ducts. *Spleen:* Enlarged to about four times normal (not weighed), with a well-marked anterior notch. Smooth and regular, with a tense capsule. Pulp firm and dark in colour with diffuse mottling. No infarcts. *Pancreas:* No gross abnormality. *Kidneys:* Both showed engorgement and moderate cloudy swelling. *Adrenals:* Nothing abnormal noted.

Permission for examination of the central nervous system was refused.

No other important features were seen. Histological sections were made from the liver, coeliac glands, spleen, and kidney (haematoxylin and eosin, Leishman, and iron-staining).

Histological Reports

Hilar gland (Fig. 1, Special Plate) shows follicular and sinus infiltration with numerous lymphocytic cells, many of which are primitive ? lymphoblasts. Some possess irregular mottled nuclei and resemble the abnormal " monocytes " of the blood. Giant cells and macrophages are fairly numerous, and some contain regular granular yellowish pigment. Most of this gives a negative Perles reaction for iron, though some irregular haemosiderin deposits are present in the stroma. Patchy oedema with capillary engorgement and haemorrhages are seen in the medulla, besides the " monocytic " infiltration. Some sinus reticulosis is also present.

Liver (Fig. 2).—Moderate perilobular fibrosis. Infiltration, most pronounced in the periportal areas, but also pericellularly, with lymphocytes and ? abnormal monocytic cells, and a few giant cells. Suggestive of leukaemic picture, but the cells are less uniform and show irregularities in the shape and staining of the nuclei. The liver cells show some cloudy swelling. Areas of necrosis are a noteworthy feature, though this is not extensive in degree. Hyperplasia and regeneration are both seen, but are not pronounced.

Spleen (Fig. 3).—General engorgement; capillary haemorrhages and granulations under the rather thin capsule. Numerous pigment-containing macrophages. Pulp and sinuses show numerous lymphocytic and atypical cells.

Kidney (Fig. 4).—Glomerular engorgement, but little other change in the cortex. Tubular degeneration, with cloudy swelling, is general. Blood casts and a few granular casts seen. Medullary oedema and intertubular collections of cells similar to those seen in the lymph nodes.

Discussion

It is submitted that the diagnosis of this case as infectious mononucleosis is valid, as it satisfies the accepted criteria—namely, the clinical presentation, the presence of atypical monocytes up to 20% in the peripheral blood, the presence of heterophil agglutinins in a titre over 1 : 128, the agglutinins not being adsorbed by guinea-pig's kidney, and the existence of the infectious mononucleosis cells in necropsy material. The unusual features are: (1) the degree of hepatic impair-

ment as observed clinically and the finding of necrosis of liver cells on post-mortem examination ; (2) the degree of renal impairment ; and (3) the fatal outcome.

It may be argued that in view of the high serum bilirubin and raised serum alkaline phosphatase and the necropsy finding of the enlarged glands in the porta hepatis, the jaundice was solely obstructive in nature. Cohn and Lidman (1946) have noted the serum alkaline phosphatase to be abnormally high in those cases of infectious mononucleosis even without clinical jaundice. It must be remembered that while the patient observed his stools to be " beige-coloured " before admission, all specimens examined whilst he was in hospital (including those examined in the laboratory for paratyphoid) contained bile pigment. The explanation of this is probably that the enlarged glands in the porta hepatis which were found at necropsy were of a size sufficient to have caused bile-duct obstruction at a time before his admission, but they later, in company with the superficial lymph nodes, subsided. Bile pigment was obvious in all urinary specimens, but bilirubinuria was the rule in all the cases investigated by Cohn and Lidman (1946) although they had a normal serum bilirubin. Our patient's van den Bergh reaction was biphasic, for what it is worth. Notwithstanding all this the clinical picture was rather more severe than the actual hepatic damage would suggest.

The nature of the lesion causing the uraemia is more conjectural. At first we postulated a " cholaemic nephrosis." This condition is often present in diseases characterized by jaundice and liver failure ; the kidneys are found to be swollen and the epithelium of the convoluted tubules shows a variable but often considerable degree of necrosis, which is rapidly followed by regeneration. It is supposed that the necrotic process is due to toxic substances absorbed from the bowel which the severely damaged liver has failed to destroy. In the series investigated by Lucké (1944), however, liver damage was described as acute massive necrosis.

Doubtless extrarenal factors—continued fever, vomiting, and the alimentary tract haemorrhage—contributed to the azotaemia, despite measures adopted to offset these. These factors nevertheless do not explain fully the renal pathology found. In addition it is to be noted that failure of concentrating power, albumin, blood, and granular casts appeared in the urine before the extrarenal factors (except fever) were operative. One is left, therefore, with the speculation whether the " infiltration " with normal and abnormal lymphocytic and monocytic cells has caused the renal damage and subsequent failure.

Summary

A brief review of the nature of the fatal cases of infectious mononucleosis in the literature has been made, with special reference to the hepatic and renal changes.

A fatal case is recorded in which death was due to liver and kidney failure and in which there were more pronounced pathological changes in these organs than have previously been noted.

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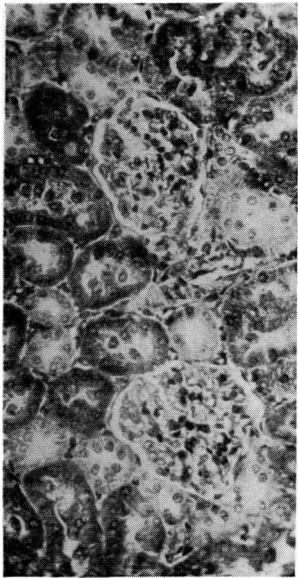
R. PLATT: ADAPTATION IN RENAL FAILURE

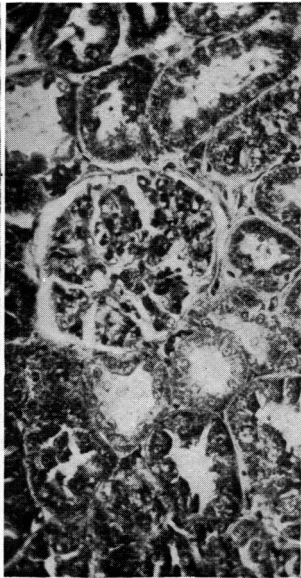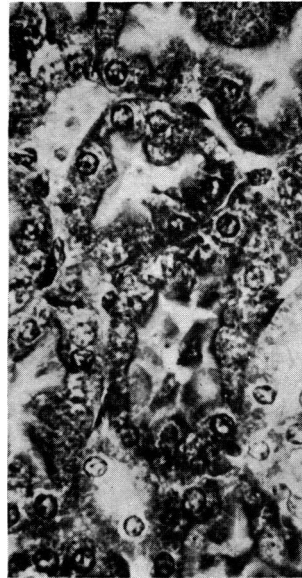FIG. 1a   FIG. 1b   FIG. 2a   FIG. 2b

FIG. 3a   FIG. 3b

FIG. 1.—(a) Normal rat kidney; (b) renal remnant (see text), showing hypertrophy of glomerulus and tubules. (Masson's trichrome. ×220.)

FIG. 2.—(a) Intermediate part of proximal tubule (normal rat); (b) same from renal remnant, showing hypertrophy and dilatation. (Masson's trichrome. ×450.)

FIG. 3.—Human chronic pyelonephritis. (a) Tubules showing hypertrophy and (b) dilatation with flattened atypical epithelium. (Masson's trichrome. ×220.)
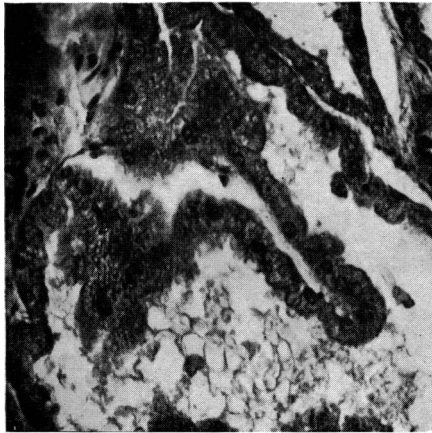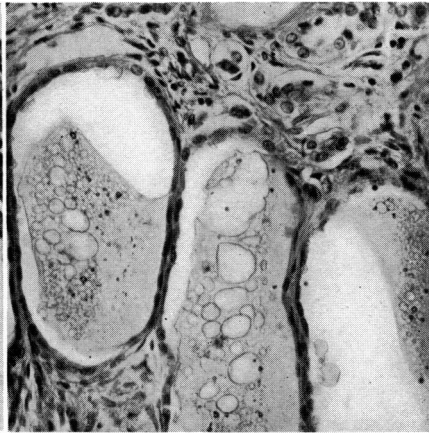
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CASE OF INFECTIOUS MONONUCLEOSIS
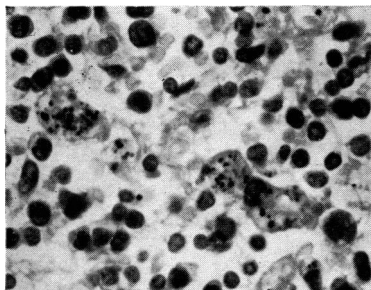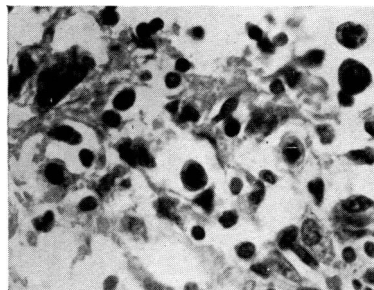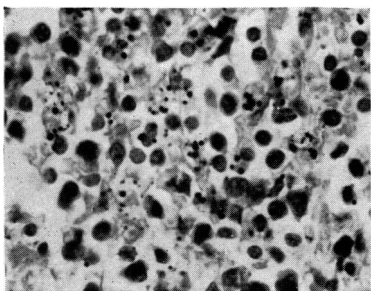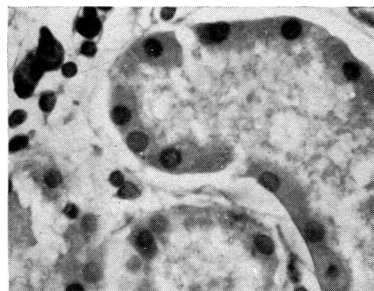
H. J. RICHARDS:
DUPUYTREN'S CONTRACTURE

FIG. 1   FIG. 2   FIG. 1
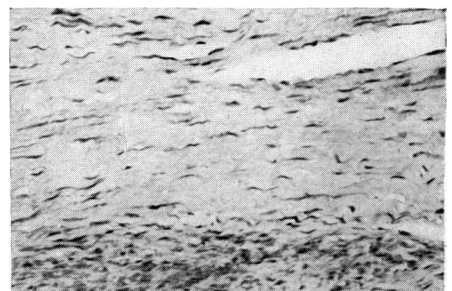
FIG. 3   FIG. 4   FIG. 2