INFECTIVE HEPATITIS AND CATARRHAL JAUNDICE.

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In the past hundred years there have been few wars in which jaundice has not been responsible for sickness. Blumer (1923) goes so far as to say that, with the possible exception of the War of Independence, jaundice has inevitably appeared in every campaign in which the American army has taken part. In the American Civil War six separate outbreaks were recorded, and in the Franco-Prussian, the Spanish-American, and the South African wars, jaundice in epidemic form was by no means uncommon.

The true character of all these outbreaks cannot now be determined since it was only in 1912 that Cockayne pointed out that there are at least two forms of infective jaundice, one characterized by high fever and considerable mortality, the other almost afebrile and relatively benign. The cause of the severe form was proved by Inada and Ido (1915) to be a leptospira and it is, therefore, known as leptospiral jaundice or spirochætosis icterohæmorrhagica, sometimes unfortunately as Weil's disease. During the World War of 1914–18 this infection occurred on the western front. The milder form of infective jaundice, for long known as epidemic catarrhal jaundice, comprises, it is now generally agreed, at least two separate conditions: (1) a true catarrhal and obstructive jaundice, and (2) infective hepatitis.

Catarrhal and Obstructive Jaundice.

The view that epidemics of mild jaundice are due to a catarrhal condition of the mucous membrane of the duodenum with consequent swelling of the ostium of the common bile-duct can be traced back to Bamberger (1855). Pathological evidence in favour of this theory was brought forward by Virchow (1865), who at post-mortem had seen a case of jaundice in which the terminal portion of the common bile-duct was plugged by mucus. Since then a small number of cases have been recorded in which at death jaundice has been associated with obstruction of the common bile-duct. Eppinger (1908), for instance, reported the case of a girl aged 19 who fractured her skull and died as a result of jumping out of a window the day after admission into hospital for treatment of a typical attack of catarrhal jaundice, the jaundice being preceded for a few days by symptoms of gastro-intestinal catarrh. The liver showed no histological changes but the mucous membrane of the stomach and duodenum was swollen, and the papilla of Vater was unduly prominent, the mouth of the common bile-duct being completely blocked as a result of inflammatory swelling of its wall. More recently Hurst and Simpson (1934) and Barber and Osborn (1939) have recorded somewhat analogous findings. A number of cases of jaundice have also been described as a result of obstruction following inflammation of the lymph

nodes lying in close proximity to the bile-ducts (*cf.* Brulé, 1938). Much has been made of the association of jaundice with intestinal catarrh during the Gallipoli campaign, but in this instance the population was so saturated with bacillary dysentery and paratyphoid infections that the presence of intestinal catarrh is hardly surprising. Apart from this one outbreak, the ætiology of which can now never be determined, there is no record of a true catarrhal jaundice ever appearing in epidemic form. Sporadic cases of true catarrhal jaundice may, however, occasionally result from ascending cholangitis in association with a duodenitis or from inflammatory changes in structures such as the pancreas or lymph nodes, which lie in close relation to the bile-ducts.

Clinically there are no symptoms by which a true catarrhal jaundice can be differentiated from infective hepatic jaundice, or as it is more simply termed, infective hepatitis. Laboratory tests also fail to separate the two conditions, although Payne (1939) has suggested that in purely obstructive conditions the quantitative van den Bergh and the plasma phosphatase values rise and fall together, whereas in cases of infective hepatitis there is no such parallelism.

Infective Hepatitis.

Proof that the mild form of infective jaundice is in reality a hepatitis, a view first promulgated by Stokes (1839), is obviously dependent, in the absence of definite clinical symptoms or conclusive laboratory tests, on pathological evidence alone. Despite the low mortality such evidence is by no means lacking. Martin (1918), for instance, in reporting on the pathological changes in certain fatal cases of jaundice occurring at Gallipoli, found necrosis of the parenchymatous cells of the liver and came to the conclusion that the jaundice was due to a hepatitis following a systemic infection rather than to a primary catarrh of the bile-ducts. In a small number of cases it has been possible to examine the condition of the liver within ten days of the onset of so-called "epidemic catarrhal jaundice." Thus Morgan and Brown (1927), during an extensive epidemic of jaundice occurring in the midland and eastern counties of England, observed one fatal case in a small girl whose death took place nine days after the onset of illness and eight days after the appearance of jaundice. The stomach and duodenum were normal, but the liver showed degenerative changes in the parenchymatous cells with round-celled infiltration in the portal spaces. Wallgren (1930) described two fatal cases in a large epidemic in Gotenburg in a 3-year-old girl and a 2½-year-old boy, both of whom died on the twenty-fourth day of illness. No changes were seen in the bile-ducts or duodenum, but again there was great degeneration of liver cells and round-celled infiltration in the portal spaces. Schrumpf (1932) performed a biopsy on a woman eight days after the onset of so-called catarrhal jaundice. The duodenum and bile-ducts were normal, but the liver was necrosed. Similarly Hurst and Simpson (1934) found in a boy of 16, who died eight days after the onset of jaundice, no lesions in the stomach, duodenum or bile-ducts, but necrosis

of the parietal zones of the liver lobules with increased round-celled infiltration in Glisson's capsule.

Perhaps the two most striking cases, however, are those reported by Gaskell (1933) and, more recently, by Barber and Osborn (1939). Gaskell's case was that of a 5-year-old girl who died on the third day of illness from hæmorrhage after an operation for the removal of tonsils and adenoids four days previously. Twenty-four hours after the operation she had developed jaundice. At death the bile-duct system throughout was normal and not involved in any inflammatory process, but the liver itself showed acute hepatitis with much cloudy swelling and an inflammatory exudate at the periphery of the lobules. The girl came from a village where an epidemic of jaundice was occurring among the children. The case described by Barber and Osborn (1939) was that of a man aged 38, who felt unwell in the morning with nausea and flatulence. He thought he might walk it off, but on returning from a short walk he was quite exhausted and was left lying on a couch. About twenty minutes later he was found lying unconscious at the foot of some stone steps with his nose bleeding. On the third day of admission to hospital he vomited and the urine became dark in colour, while on the fourth day he was obviously jaundiced. He died on the tenth day after admission, the seventh day of the jaundice, the essential cause of death being hæmorrhage and fracture of the base of the skull. The stomach, intestines, and bile passages were healthy, but the liver showed clear evidence of a hepatitis affecting most severely the central zone and to a lesser degree the mid-zonal region of the lobule.

No definite line of demarcation can be drawn between these early cases of acute hepatitis and those dying at a somewhat later stage in which, as a result of efforts at regeneration on the part of the liver cells, the pathological process must be termed subacute necrosis. Such cases, dying two to three weeks after the initial illness and clearly associated with epidemics of, for the most part, mild jaundice, have been described in Great Britain by Okell (1931) and Findlay and Dunlop (1932), in the U.S.A. by Klemperer, Killian and Heyd (1926), and in France by Troisier, Albot and Netter (1938). In Sweden during the great jaundice epidemic of 1925–27, Bergstrand (1930) saw no less than ninety-seven cases of subacute liver necrosis. In the Lebanon, Yenikomshian and Dennis (1938) reported an outbreak of non-spirochætal jaundice in which there were seven cases of subacute necrosis; of the five female patients all were pregnant.

Sufficient evidence is thus available to show that the mild form of epidemic jaundice is in reality a hepatitis; there is no conclusive proof that a true catarrhal jaundice ever occurs in epidemic form and thus it would be advisable to abandon the use of the term "epidemic catarrhal jaundice."

The Ætiology of Infective Hepatitis.

Numerous unsuccessful attempts have been made to isolate specific bacteria or spirochætes from the blood, fæces, and urine, while efforts to

reproduce the disease in laboratory animals have also failed. Andersen (1937) and Andersen and Tulinius (1938) believe that they have transmitted the disease to pigs by feeding them with the duodenal contents of patients with infective hepatitis and by injections of blood. A form of porcine hepatitis is not uncommon in Denmark and it is suggested that outbreaks of infective hepatitis in man are due to eating the contaminated tissues of pigs. Up to the present no confirmation of these results has been obtained in this country, where hepatitis in pigs is a very rare disease. On occasions, however, it has been possible to cause a short febrile reaction in rhesus monkeys eleven to fourteen days after feeding them by stomach tube with blood taken from patients during the first seven days of illness. Further experiments are being undertaken to determine the specificity of this reaction in monkeys. The failure to cultivate any specific organism from cases of infective hepatitis suggested the possibility of a virus ætiology, especially after the accidental infection of a laboratory worker while working with sera from patients suffering from infective hepatitis (Findlay, Dunlop and Brown, 1931, cf. *also* Loeper 1937 and Cullinan 1939).

Further evidence in support of the virus ætiology of infective hepatitis came from a somewhat unexpected direction in the occurrence of jaundice after immunization against yellow fever both in this country (Findlay and MacCallum, 1937 and 1938), and in South America (Soper and Smith, 1938). For immunizing against yellow fever an attenuated pantropic virus is cultivated in a liquid medium consisting of one part of filtered human serum and nine parts of Tyrode solution with a small amount of minced chick embryo tissue. When first employed in 1935 no cases of hepatitis were noted, but early in 1936 reports began to be received of jaundice with symptoms similar to those of infective hepatitis. Of 96 patients with jaundice one died with lesions of subacute necrosis of the liver. Jaundice continued to occur despite various changes in the tissue culture medium. In November, 1937, another strain of attenuated tissue culture virus was employed and since then no cases of jaundice have been noted in more than 8,000 persons immunized. Since cases of jaundice were occurring for nearly two years in persons injected with different batches of vaccine, it was obvious that some hepatotoxic agent was being subcultured. The first explanation which naturally suggested itself was that the onset of jaundice, on an average two to three months after immunization against yellow fever, was caused by some modification of the particular strain of virus (17 EC) then employed. That the hepatitis was not directly due to the yellow fever virus was shown by the following facts :—

(1) The symptoms differed entirely from those of yellow fever.

(2) The virus of yellow fever could not be isolated from patients with post-inoculation jaundice at any stage of the disease.

(3) The yellow-fever-immune body titre in patients with jaundice remained constant during and after the disease and showed no tendency to rise as it does after reinoculation with the yellow-fever virus.

(4) Hepatitis occurred in persons who were injected with the yellow-fever

vaccine 17 EC but who were already immune to yellow fever as a result of either naturally acquired infection or previous immunization.

(5) Jaundice occurred in South America in persons injected with the yellow-fever vaccine who did not become immune to yellow fever owing to a defect in the vaccine.

Since the agent responsible for the jaundice was not the yellow-fever virus but was being carried over in the tissue cultures with the yellow-fever virus, steps were taken to explore other possibilities (cf. Findlay, MacCallum and Murgatroyd, 1939). By a process of elimination the only possible source of the agent appeared to be the pooled and filtered human serum which had been employed in the tissue cultures from 1935 to October 1, 1937. By this latter date, instead of using pooled sera obtained from donors whose past and future medical history could not be accurately obtained, a panel of donors had been built up, consisting chiefly of medical students and laboratory technicians. All these donors could state definitely that they had never suffered from jaundice. In addition the serum obtained from each individual was not used in the culture medium for at least thirty days after it had been withdrawn, and only when evidence was forthcoming that the donor had remained in perfect health since the withdrawal of blood. This precaution did not immediately stop the occurrence of hepatitis, for from October 1 to November 11, 1937, there were ten cases of jaundice among 291 persons immunized. Nevertheless when combined with the use of a new strain (17 D) of yellow-fever virus from November 11, 1937, it has been sufficient to prevent the occurrence of any further cases of jaundice among the eight thousand persons since immunized against yellow fever.

The evidence derived from these observations may be summarized as follows :—

(1) An agent causing symptoms and lesions in man indistinguishable from those found in infective hepatitis was capable of being propagated in a serum-Tyrode medium containing chick embryo tissue, the serum being either of human or monkey origin.

(2) The agent produced no visible growth when cultivated aerobically and anaerobically on a number of different bacteriological media.

(3) The agent was not visible with the highest powers of the ordinary microscope.

(4) The agent was freely filtrable through Seitz EK filters.

(5) The agent withstood freezing and drying for many months when kept at 4° C.

An agent having the above characteristics would normally be classified as a filtrable virus.

Nevertheless proof was lacking that cases of post-inoculation jaundice could give rise to ordinary infective hepatitis in contacts. Evidence on this point came from a different source. Propert (1938) reported that seven children housed in one block of a large institution for mental defectives were injected with pooled convalescent measles serum to protect them from measles, with which disease they had recently been in contact.

Each child received 4·5 c.c. of the same pooled serum which had been filtered, phenolized, and tested for bacteriological sterility. After an interval of between seventy-eight and eighty-three days all these seven children developed jaundice and three of them died with lesions typical of acute necrosis of the liver. No bacteria or leptospira were isolated. No other children in the institution developed jaundice at this time, but just two months later two other children who had been contacts with the first seven jaundice patients, but had themselves not been inoculated with the pooled serum, developed jaundice. Their illness was indistinguishable from that of infective hepatitis; no other children in the institution, with the exception of these contacts, developed jaundice. According to MacNalty (1938) between 82 and 109 persons were inoculated in various parts of the country with this same pool of measles-immune serum: 37 developed jaundice and seven died with acute liver necrosis. No leptospira nor specific bacteria were isolated. More recently jaundice has followed the injection of another bacteriologically sterile batch of pooled measles-immune serum.

Since therefore pooled human serum may contain a filtrable agent capable of causing in man a syndrome clinically and pathologically indistinguishable from that of common infective hepatitis, it seems highly probable that the cause of infective hepatitis is an agent possessing the characteristics of a filtrable virus.

One moral to be drawn from these observations is that human serum should not be used for purposes of immunization till at least one month after its withdrawal, the donor having remained in good health for this period.

The Control of Infective Hepatitis.

Infective hepatitis is a widely distributed disease by no means uncommon in Western Europe and America, as well as in West Africa and the near East; comparatively few records of its occurrence have come from India. It is most commonly seen in partially closed communities such as schools, barracks, and hospital wards. In country districts in Great Britain the village school not infrequently acts as the focus of infection, the disease dragging on through neighbouring villages for months or even years at a time. Special interest attaches to the frequency with which the disease appears in out-patient departments. Outbreaks have been recorded in a diabetic clinic (Graham, 1938), in patients treated with acriflavine for gonorrhœa (Murray, 1930) and in numerous treatment centres for venereal disease among patients receiving injections of the arsphenamines or bismuth. The fact that such outbreaks have often involved attendants and others who were not receiving antisyphilitic treatment is evidence that the drugs were not the primary cause of the jaundice, although the administration of hepatotoxic medicaments may naturally predispose to liver damage.

Infective hepatitis is most frequently seen in children and young adults, though older persons are by no means exempt; when such older persons are attacked the symptoms may be of long duration and considerable severity.

The view that jaundice is a contagious disease is of long standing, for Zacharias who was Pope from A.D. 741–752, in writing to Boniface, who was canonized for his efforts to convert the Germans to Christianity, strongly recommended that patients with jaundice should be segregated lest others catch the contagion (Migne, 1844). Infection is spread not by food or water, but rather by direct contact, probably as a result of droplet infection. In some outbreaks nasal catarrh is a common occurrence. It is not uncommon to see one member of a family after another succumb to infection. Epidemics have been successfully brought to an end by preventing overcrowding in hospital out-patient departments, but in view of the recent isolation of poliomyelitis virus from the stools the possibility of fæcal contamination in infective hepatitis cannot be entirely excluded.

There is now general agreement that the incubation period is in the neighbourhood of four weeks, with a possibility in some instances of an even greater extension. This long incubation is suggestive of a virus infection for there are a number of virus diseases with incubation periods of many months. The period of infectivity is probably short although patients on the fifth and seventh days of illness have proved infectious (Pickles, 1939). It must also be remembered that patients are infective during the pre-icteric period which may last from one to at least ten days, while in any large epidemic there are always some individuals in whom jaundice is never noted clinically, although the urine may be dark in colour for a day or two. The possibility that carriers exist cannot be entirely ruled out (Newman, 1939). A quarantine period of fourteen days is sufficient to prevent spread of infection.

The diagnosis of infective hepatitis, when it occurs in temperate climates and in mild form, is not difficult despite the absence of any definite laboratory test. The absence both of high fever and of a polymorphonuclear leucocytosis serves to differentiate the disease clinically from leptospiral jaundice. Failure to isolate leptospira, to infect guinea-pigs, or to detect agglutinins against leptospira gives definite laboratory proof. The total and differential blood-count usually shows a slight leucopenia with a relative decrease in the number of polymorphonuclear leucocytes and in some cases an increase in the large mononuclears (cf. Findlay, Dunlop and Brown, 1931). The mononuclear increase is never as great as in glandular fever but as cases of glandular fever associated with jaundice have recently been described by de Vries (1938) the sheep cell agglutination test of Paul and Bunnell should be carried out in any doubtful case.

In France another condition has not infrequently been termed catarrhal jaundice. In this syndrome, which appears to be of an allergic nature, the jaundice is associated with rheumatic pains, skin rashes, and very frequently severe migraine (cf. Caroli, 1938).

Owing to the fact that symptoms of liver insufficiency may occur suddenly after very mild prodromal symptoms, all cases of infective hepatitis should be given glucose by the mouth. If there are signs pointing to acute liver insufficiency, isotonic (5 per cent) glucose should be at once given intravenously, not more than 500 c.c. being injected in the twenty-four hours.

The administration of 5 to 10 units of insulin in the same period frequently aids in the assimilation of the glucose.

Conclusions.

Evidence is brought forward to show that so-called epidemic catarrhal jaundice is in reality an infective hepatitis.

There is reason to believe that infective hepatitis is due to a filtrable virus.

The control of infective hepatitis is discussed.

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