BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 27 1938

TOXIC AND INFECTIVE JAUNDICE *

BY

C. E. LAKIN, M.D., F.R.C.P.

Physician to the Middlesex Hospital and the London Fever Hospital

In opening this discussion on toxic and infective jaundice I am proceeding on the assumption, now pretty generally accepted, that the parenchymatous cells of the liver have nothing to do with the formation of bile pigment, that the pigment is derived from haemoglobin liberated from more or less effete red corpuscles, and that the transformation of haemoglobin into what I may call pre-hepatic bilirubin is attributable to the activity of cells of the so-called reticulo-endothelial system. In this conception the liver is regarded as playing the part of an excretory organ for bile pigment, though in passing through the liver cells some subtle alteration in the physico-chemical nature of the bile pigment takes place, since what may be termed post-hepatic bilirubin has slightly different characters from its pre-hepatic precursor.

The Three Types of Jaundice

Staining of the skin and tissues by bile pigment—for this is what is meant when we employ the word "jaundice" in clinical medicine—may arise in three different ways. The first is when some gross obstruction to the escape of bile into the intestine leads to the damming up of bile in the excretory ducts with subsequent absorption of bile into the blood stream—the so-called obstructive jaundice. Here not only is there absorption of post-hepatic bilirubin but of bile salts and cholesterol. Some observers have thrown doubt on the reabsorption of these substances, pointing out that when a pressure of from 250 to 300 mm. of water is attained in the bile ducts the excretion of bile pigment ceases, and that this is sufficient to explain the occurrence of staining of the tissues in obstructive jaundice. The second way is when excessive blood destruction leads to the accumulation in the blood stream of such a large amount of pre-hepatic bilirubin that the excretory function of even a healthy liver is overpowered—the so-called haemolytic jaundice. And the third way is when the liver itself is damaged, so that it becomes unable to work at its normal level—the so-called toxic or hepatogenous jaundice. It is with this last type of jaundice alone that we are concerned.

Among the poisons which act by damaging the liver cell are phosphorus, arsenic, antimony, chloroform, carbon tetrachloride, trichlorethane, toluylenediamine, aniline, benzene, cinchophen derivatives, and certain mushroom poisons. Microbic activity may be responsible, as in the

jaundice of pyaemia, septicaemia, pneumonia, and typhoid; or protozoal infections, as in spirochaetal jaundice, malaria, and syphilis. In other instances a virus may be the offending agent, as in yellow fever with or without a secondary microbial infection, while yet again some auto-genous toxin may be responsible, as in toxæmia of pregnancy, some cases of acute yellow atrophy, and perhaps Hanot's cirrhosis. Anoxaemia probably plays an important part in the jaundice of congestive cardiac failure.

Pathology of Toxic Jaundice

Whereas in obstructive jaundice the sufferer is likely to be more jaundiced than ill, in toxic jaundice he is likely to be more ill than jaundiced, though deep jaundice is sometimes seen. Except in the most severe cases the stools remain fairly normal in colour. Fever is usually an accompaniment of toxic jaundice, though in some of the most serious forms, such as acute yellow atrophy, the temperature may be subnormal. Varying quantities of bile may be found in the urine in addition to urobilin and albumin; bile-stained casts and sometimes red blood corpuscles are likely to be present, while the excretion of amino-acids may be raised. In severe cases the blood sugar falls, and in a case known to me in which severe liver damage ended in convulsions the blood sugar fell to nearly 70 mg. per 100 c.cm., while daily examination showed a steady fall of non-protein nitrogen, a condition reminiscent of Mann and Magath's experiments on dogs. In spirochaetal jaundice there may be an increase in blood urea owing to coincident damage to the kidney.

Pathologically the essential lesion in toxic jaundice consists in damage to the parenchymatous cells of the liver. In some instances there is an associated cholangitis. When the injurious agent acts upon the liver in massive doses acute necrosis of the parenchymatous cells results, and the case is usually referred to clinically as one of acute necrosis of the liver, acute toxic hepatitis, or acute yellow atrophy. When the injurious agent is less virulent and reaches the liver in smaller amounts over a greater length of time a much more gradual change is induced in the liver cell and a gradual replacement fibrosis results, with the production of chronic hepatitis or cirrhosis of the liver. Thus, according to present-day conceptions, acute yellow atrophy at one end of the scale and cirrhosis of the liver at the other fall into line. A great deal of variation is seen in the post-mortem appearances of fatal cases of toxic jaundice. Thus in cases of phosphorus poisoning when

* Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Plymouth, 1938.

the person has survived long enough to have developed jaundice the liver is usually greatly increased in size, doughy in consistency, and yellow in colour. When examined microscopically an excessive fatty infiltration, progressing from the periphery of the lobule towards the central zone, is the outstanding feature, and the liver cells, although undergoing autolytic and necrotic changes, are seen to retain their nuclei till a relatively late period. In acute yellow atrophy, on the other hand, the liver, except in the most virulent type of case, is found to be reduced perhaps to as much as a third of its normal size, and its capsule shows a wrinkled appearance. On section the normal liver pattern can be no longer distinguished, and, except in the most acute cases, red patches sharply marked off from the more general yellow groundwork are a noticeable feature. The older the lesion the greater is the predominance of these red areas. Microscopically the yellow portions are seen to consist of the remains of liver cells in all stages of disintegration, from parenchymatous and hydropsical swelling with bile precipitation to complete necrosis and fusion of cell remains in which no nuclei can be distinguished. The red areas show widely dilated capillaries, engorged and often ruptured, together with newly formed granulation tissue and groups of such liver cells as have survived showing active hyperplasia.

Catarrhal Jaundice : Obstructive or Hepatic?

Following the teaching of Virchow, ordinary catarrhal jaundice, till recent years, has been regarded as a form of obstructive jaundice. Its onset is frequently associated with gastro-intestinal disturbance, and it has been assumed that obstruction arises from inflammatory swelling of the mucosa at the ampulla of Vater or from infection ascending the common bile duct. In some cases of catarrhal jaundice ending in death from some other cause a plug of mucus capable of producing mechanical obstruction has been found on post-mortem examination. Sir Arthur Hurst has collected quite a few instances from the literature. It is pointed out that, while catarrhal jaundice shows itself mostly in the form of sporadic cases, instances of a disease indistinguishable from it clinically, yet occurring in epidemic form, are not uncommon. Several members of a family may be attacked, or it may break out in schools, institutions, or barracks. It is held to be an infective disease in which damage to the liver cells is the essential pathological lesion, though whether infection occurs by way of the common bile duct or by the blood stream has not been determined.

Perhaps I may be allowed to digress for a few moments to mention a few points worthy of consideration in connexion with the epidemic form of the disease. The incubation period has generally been regarded as one of a few days, but recent observations would suggest that an incubation period of from three to five weeks is more probable. In an outbreak among nurses at the London Fever Hospital in which five cases occurred, twenty-one days appeared to be its duration. It is not surprising, with an incubation period as long as this, that persons exposed to a common source of infection and who eventually develop jaundice within three or four days of one another should appear to have infected each other within those few days. In some epidemics nasopharyngeal catarrh has been noticed, and there is a certain amount of evidence to suggest that the infection is air-borne from case to case, though the actual nature of the infecting material is unknown. Cultures of blood, stools, and urine have so far failed to reveal any infecting organism. Dr. Alison Glover furnished an interesting account of an outbreak of

epidemic catarrhal jaundice in a public school of seven houses and some 400 boys in which the evidence appears strongly to suggest that transmission was usually by nasopharyngeal "droplet" infection and that it was favoured by intimate contact, especially in sleeping quarters. That some cases in the outbreak were due to infection by swimming-bath water was possible, but he concluded that in the majority of these cases the initial pyrexia was noticed after, and attributed to, swimming (*Lancet*, 1931, 1, 722).

But to resume. As there appears to be no striking difference between catarrhal jaundice occurring sporadically and cases arising during an epidemic, it has been suggested that all cases of so-called catarrhal jaundice are in reality cases of primary liver damage; that is to say, that damage to the liver cell is the fundamental lesion, though it may vary as to severity and extent within wide limits. It is only on rare occasions that help in deciding this difficulty can be had from post-mortem findings. Schrumph in 1932 obtained a portion of the liver at an operation on the eighth day of what was considered to be a case of catarrhal jaundice, and described the changes found as resembling "acute yellow atrophy in miniature." Gaskell in 1933 had an opportunity of examining a portion of liver from a case of catarrhal jaundice which ended in death from another cause on the third day, and found an acute hepatitis with degeneration of liver cells, and, more recently, I understand that Dr. Hugh Barber of Derby has recorded his findings in another case. In Gaskell's case the bile ducts showed their epithelial lining to be intact and appeared not to be involved in the inflammatory process.

On the other hand, Eppinger (quoted by Hurst), although having previously come to the conclusion that catarrhal jaundice was the result of hepatic disease and was not obstructive, was disillusioned to find the mouth of the common bile duct completely obstructed as the result of inflammatory swelling of its wall in the case of a girl suffering from a typical attack of catarrhal jaundice who had died from a fractured skull. On microscopical examination the liver and pancreas in this case were found to be normal. Moreover, we have to recognize that even severe damage to the liver can occur without giving rise to jaundice. Dr. Hugh Barber has reported the post-mortem findings in five cases of dioxan (diethylene dioxide) poisoning in factory workers. After a fatal illness lasting from five to eight days in no case was there jaundice to indicate liver damage, though, microscopically, complete necrosis of the inner half or often two-thirds of each lobule was revealed.

The Possibility of Two Forms of Catarrhal Jaundice

When we come to clinical considerations evidence is not wanting of the close association of catarrhal jaundice and acute necrosis of the liver. Every general physician of experience encounters from time to time cases of what appears to be ordinary catarrhal jaundice in which, after a shorter or longer period, the patient becomes profoundly ill, exhibiting restlessness and then increasing drowsiness, subsultus tendinum, and what used to be called the "typhoid state," with perhaps purpura or bleeding from the nose, stomach, or kidney. Examination shows a greatly reduced area of liver dullness with albumin and casts in the urine, and perhaps leucine and tyrosine in addition. In other words, the clinical picture of acute yellow atrophy or necrosis of the liver is revealed. Sir William Willcox estimates that about 0.4 per cent. of cases of catarrhal jaundice end in this way. This being

so, must every case of catarrhal jaundice be regarded as a potential case of acute yellow atrophy? Possibly the pendulum has swung too far. Hurst meets the difficulty by suggesting that there are really two forms of catarrhal jaundice: (1) catarrhal jaundice proper, in which blocking of the common bile duct occurs secondary to an acute gastro-duodenitis; (2) mild forms of subacute hepatic necrosis. In distinguishing between these two forms stress is laid on the mode of onset. In the obstructive form the initial symptoms are those of an acute gastritis—epigastric discomfort, complete anorexia, nausea, vomiting if the patient eats, and sometimes diarrhoea. He feels ill, and the temperature is raised. In two or three days improvement sets in, and just when he thinks he has almost recovered the urine becomes dark, the stools pale, and the conjunctivae and skin jaundiced. The temperature now falls, and by the time jaundice has fully developed he feels perfectly well, except that he is nauseated and vomits if he partakes of fatty food. At this stage epigastric tenderness has disappeared, though the liver may be slightly enlarged and tender and the gall-bladder and spleen may be palpable. The jaundice generally begins to fade within a week, and by the end of a fortnight all symptoms and signs have disappeared. Occasionally the jaundice lasts longer, and in rare instances may persist for two or three months.

In the second type—mild subacute hepatic necrosis—Hurst states that no pre-icteric symptoms of any kind are found in most cases, but the patient notices that his urine is becoming dark and subsequently that the stools are pale, and jaundice then appears. The onset of jaundice is accompanied by symptoms of general toxæmia, headache, weakness, anorexia with occasional vomiting, and diarrhoea. The temperature is generally slightly raised. There is no epigastric tenderness, though the liver may be tender and slightly enlarged, and the spleen is always palpable. The jaundice is generally less marked than in the first variety, and some bile is always present in the stools. The jaundice may last between a week and two or three months. In rare cases the disease is not arrested, and death results from subacute hepatic necrosis or, at a much later date, from cirrhosis of the liver.

Personally I find a little difficulty in agreeing to the statement that no pre-icteric symptoms of any kind are found in most cases of this type. I admit that my experience is of necessity limited, for a physician rarely has an opportunity of seeing cases at the initial onset of the disease, but in cases that I have seen of epidemic catarrhal jaundice the attack has been ushered in with fever four or five days before the jaundice appeared, while nausea, vomiting, anorexia, headache, and discomfort in the upper part of the abdomen have shown themselves in the pre-icteric period. How these manifestations are to be distinguished from the symptoms of acute gastritis which Hurst emphasizes as preceding the other variety—the obstructive form of catarrhal gastritis—I find it hard to determine. I am not convinced that the two forms of the disease do not exist, but I find it difficult, from a consideration of the mode of onset, to get much help in distinguishing between these two types of so-called catarrhal jaundice. If I were pressed to try to distinguish between them I should stress the greater depth of jaundice and the paler colour of the stools as favouring a blocked duct, and the enlargement of the spleen as being more constant in mild subacute hepatitis. On theoretical grounds one would expect in the early stages of a blocked duct a prompt direct van den Bergh reaction, and a biphasic reaction in the case of the mild subacute hepatitis, but I doubt if the test is reliable enough to be trusted to cut the Gordian knot. Perhaps more may be claimed for the laevulose-tolerance

test, more especially the new test as described by Stewart, Scarborough, and Davidson in the April (1938) number of the *Quarterly Journal of Medicine* (p. 229); but only four cases out of eight of catarrhal jaundice investigated gave abnormal curves, and it is interesting that in the case giving the highest icteric index—164—normal curves were obtained for both laevulose and total sugar.

Speculations concerning a Progressive Lesion

Before concluding there is one other point I should like to touch upon. Addis in his studies of Bright's disease has clearly shown the existence of long latent periods following an initial damage to the kidney (as by acute nephritis) when for years the affected person apparently remains in perfect health. In spite of this, careful tests of renal function have demonstrated the presence of a relentlessly progressive lesion which finally terminates in renal insufficiency and uræmia. Bloomfield, in the April number of the *American Journal of Medical Sciences* (p. 429), raises the interesting speculation whether something of the same sort may not hold in cases of hepatitis, supporting his contention by the fact that many people who have suffered from an attack of catarrhal jaundice show evidence of impaired hepatic function in the form of a high bilirubin content. Certainly one comes across cases of relapsing subacute hepatitis in which, after perhaps three or four attacks of jaundice spread over a couple of years, the final attack is attended by signs of portal congestion, ascites developing as in cases of multilobular cirrhosis before the final exitus. The speculation raised by Bloomfield makes one wonder whether a progressive though silent change of this sort may possibly explain the varying effect that alcohol exerts on different people. While some can partake of large quantities without apparent harmful effect, others gradually show indications of liver damage. It is a subject worthy of investigation.

Finally, may I say what a real contribution to clinical medicine would be made by anyone who would place on record the details of even a few cases of catarrhal jaundice followed from its onset to its termination.

I have only had time to put before you general conceptions of jaundice and to consider in any detail one form, and that the most common, of toxic jaundice, but many other aspects and varieties of toxic jaundice will be dealt with by succeeding speakers.

The Executive Committee and the Council of the International Union against Tuberculosis, whose secretary-general is Professor Fernand Bezançon, President of the Academy of Medicine, met in Paris at the headquarters of the Union, 66, Boulevard Saint-Michel, last month, under the chairmanship of Professor Lopo de Carvalho (Portugal). Delegates from sixteen countries attended this meeting. The administrative meeting of the Council was devoted to the preparation of the programme of the conference to be held in Berlin in September, 1939. The agenda of this conference is now definitely settled, and will include the following three subjects: the problem of the virulence of the tubercle bacillus, the value of systematic examinations for the diagnosis of pulmonary tuberculosis in subjects over 15 years of age, and the rehabilitation of the tuberculous. At the scientific meeting of the Council Professor Frølich (Norway) occupied the chair; Drs. Maingot, Cottenot, and Etienne Bernard submitted a report on radiological sections of the thorax and their value in the diagnosis of pulmonary tuberculosis, with diagrams and radiographs illustrating this subject. Before these sessions a meeting of the After-Care Committee of the International Union against Tuberculosis (secretary, Dr. Bachmann, Switzerland) had been held under the chairmanship of Sir Pendrill Varrier-Jones.