Lettsonian Lectures

ON

JAUNDICE: WITH SPECIAL REFERENCE
TO TYPES OCCURRING DURING
THE WAR.*

By WILLIAM HENRY WILLCOX, C.B., C.M.G.,

M.D. LOND., F.R.C.P. LOND., COLONEL A.M.S.,

PHYSICIAN TO OUT-PATIENTS, ST. MARY'S HOSPITAL, LONDON.

LECTURE I.—PATHOLOGY, DIAGNOSIS, AND
TREATMENT.

THE subject of these lectures—"Jaundice: with special reference to types occurring during the war"—was chosen because it has aroused during the period of the war a great deal of interest, owing to the many new types studied and brought to notice, and because during the last four and a half years a great deal of original work has been carried out on this important subject.

I have personally had the privilege of studying closely some of the new types of jaundice. Thus, in November, 1914, at my out-patient department at St. Mary's Hospital, London, I examined the first case of jaundice recorded¹ as being directly due to the inhalation of the vapour of tetrachloride of ethane; an investigation of this case led on to the discovery of the cause of an outbreak of toxic jaundice occurring at that time amongst acetylene workers in this country. In this research² Dr. T. M. Legge, His Majesty's Medical Inspector of Factories, and Dr. B. H. Spillbury, pathologist of St. Mary's Hospital, London, collaborated.

In 1914 and previously the toxicology of the arseno-benzol compounds had been a subject of great interest to me, especially in its relation to toxic jaundice, and in 1916, in conjunction with Mr. John Webster, F.I.C., a record of this work was published.³

In 1915 and 1916, while serving with the Mediterranean Expeditionary Force as consulting physician, I saw a very large number of cases of epidemic jaundice, both in Egypt and in the Dardanelles.

From 1916 to 1919, whilst serving with the Mesopotamian Expeditionary Force as consulting physician, I have had the opportunity of seeing a very large number of cases of jaundice of epidemic type similar to those occurring in the Dardanelles, and also a large number of cases due to such infections as paratyphoid, enteric, and relapsing fever, malaria, etc.

HISTORY.

The word "jaundice" is derived from the French *jaune* (yellow). Wickham Legg gives⁴ several possible derivations for icterus in his work on *Bile, Jaundice, and Bilious Diseases*—namely, "*ictis*, the yellow-breasted marten; *iktēpos*, the golden oriole, the sight of which was supposed to cure jaundice, whereas the bird died (Pliny); and *iktivos*, a kite, from the colour of its eyes."

DEFINITION.

Osler gives the following brief but excellent definition: "Jaundice or icterus is a condition characterized by coloration of the skin, mucous membranes, and fluids of the body by the bile pigment." It must be remembered that jaundice, like albuminuria, is a symptom, and not a disease, and may be met with in a variety of conditions, the common and essential factor being obstruction at some point to the passage of bile along the bile capillaries or ducts.

HISTORICAL.

Jaundice has attracted a great deal of attention in medical literature from the earliest times. There are frequent references to it in the writings of Hippocrates, Galen, and Celsus. Dr. Redman Coxe of Philadelphia, in his work⁵ on the writings of Hippocrates and Galen, gives the following extracts from Hippocrates on the subject:

When jaundice occurs in ardent fever on or after the seventh day, with difficult yet abundant expectoration and the fever does not decline, it denotes that instead of terminating as above an abscess will form in some great tumour with severe pains, or a colligation from the great heat of the humours.

This is quite a good description of the jaundice of septicaemia or pyaemia. Again from Hippocrates we have:

But in whatever manner ardent fever ends, if jaundice succeeds, sweats and abscesses rarely follow but recovery ensues.

And also from the same author:

If in violent fevers jaundice appears on the seventh, ninth, or fourteenth day, it is favourable provided a hardness does not occur in the right hypochondrium. If so, it is of doubtful character.

Hippocrates gives a guarded prognosis, evidently being familiar with the dangers of suppurative cholecystitis.

Bile was used as a remedy for internal use from the earliest times. *Fel bovinum* of the *Pharmacopoeia* is a preparation consisting mainly of salts of the bile acids. Modern research, resulting in the discovery of the bile acids, has led to the use of these constituents of bile as valuable remedies in certain abdominal conditions—for example, cholelithiasis, hepatic conditions, constipation, etc.

In more recent times the exact causation of the various forms of jaundice has led to most interesting discussions, of which full accounts are to be found in the writings of Murchison, Wickham Legg, Budd, Frerichs, Moxon, George Harley, and later of Hunter and Rolleston. Reference to the work done during the war will be made later.

CAUSES.

We shall do well to regard jaundice as being due to a variety of causes. When the great number of chemical poisons which may produce toxic jaundice of similar type is considered we are forced to admit that there must be at least as many bacterial poisons, probably more, which are also capable of producing jaundice of a like type.

There has recently been rather a tendency to narrowness of vision with regard to the causation of infective jaundice of microbic origin. Thus, because a most interesting form of jaundice has been recently proved to be due to an infection by *Spirochaeta icterohaemorrhagiae*, some writers have gone so far as to suggest that this organism is probably the cause of all forms of epidemic jaundice. This standpoint is obviously impossible.

PHYSIOLOGICAL CONSIDERATIONS.

An accurate knowledge of the physiology of the liver and its secretions is the basis of the pathology of jaundice, and further physiological research in this direction is bound to lead to a more accurate conception of the exact causation of the various forms of jaundice.

Bile.

The external secretion of the liver differs from the other digestive secretions in not possessing any marked ferment action on the organic foodstuffs. Only minute traces of a diastatic ferment are present in it. Bile assists in the digestion and absorption of fats, and increases, by reason of the presence of the salts of the bile acids, the rate of action of the pancreatic enzymes. The chemical composition of bile has been carefully studied, and detailed analyses of bile and fistula bile are given in the textbooks of physiology.

The salts of the bile acids are the most important constituents. In carnivora sodium taurocholate occurs and in herbivora sodium glycocholate is present. In man both these salts occur, but the glycocholate predominates in the proportion of 9 to 1.

The bile acids have been isolated in pure condition and their chemical composition accurately determined. Thus each is a compound of cholalic acid with an amino compound. *Glycocholic acid* results from the combination of glycine (amino-acetic acid) and cholalic acid, into which constituents it splits on hydrolysis. *Taurocholic acid* results from a similar combination of taurine (amino-ethyl-sulphonic acid) and cholalic acid.

The bile acids occur in bile as sodium salts, soluble in water and alcohol, but insoluble in ether.

The bile salts are secreted by the liver in the bile, but are reabsorbed in the intestine and carried back to the liver, so that a portal circulation of them occurs. This explains why fistula bile is so deficient in bile salts as compared with normal bile—for example, Copeman and

* Delivered before the Medical Society of London, April-May, 1919.

Winston found in fistula bile from a healthy woman the amount of bile salts to be 0.628 per cent., while Frerichs found normal human bile to contain 9.14 per cent.

The bile salts have most important functions. They markedly accelerate the action of pancreatic enzymes on the organic foodstuffs; they precipitate native proteins, and thus aid in their further hydrolyzation and absorption. In addition they act as solvents of the alkaline earth soaps—namely, those of calcium and magnesium in the intestines—and they are solvents also of cholesterol. No doubt the presence of bile salts in the bile is the chief factor from the chemical point of view in the prevention of the formation of gall stones.

Bile salts taken by the mouth cause an increased flow of bile, and Schafer⁶ regards them as the only true cholagogues. Consideration of their physiological properties points to a more extensive use of bile salts therapeutically. Thus in the treatment of cholelithiasis, since gall stones are composed commonly of cholesterol and calcium bilirubinate, probably the most potent solvent would be a mixture of sodium glycocholate and sodium oleate. The former would dissolve the cholesterol, and the latter would tend to convert the calcium bilirubinate into soluble sodium bilirubinate and calcium oleate, the latter being soluble in the sodium glycocholate.

Bile salts cause a slowing of the pulse, and it is due to their presence in the blood stream in obstructive jaundice that this symptom occurs; they probably also account for some of the other symptoms of this condition.

Bile pigments are important constituents of the bile; by their presence in the blood stream they give rise to the characteristic colour of jaundice.

Bilirubin and its oxidized form biliverdin have the character of weak acids. Their alkali salts—for example, those of sodium, potassium, and lithium—are readily soluble in water, while the alkaline earth salts (those of calcium and magnesium) are insoluble. Free bilirubin is insoluble in water, alcohol, ether, benzene, and glacial acetic acid, but soluble in chloroform. Virchow showed that haematoidin crystals in old blood clots were closely allied to bilirubin, and Schafer⁷ states that they are usually identical.

Hydrobilirubin (reduced bilirubin) has been shown to be identical with urobilin and stercobilin.

Haematoporphyrin, the iron-free derivative of haemoglobin, is isomeric with bilirubin, and on reduction yields hydrobilirubin. The bile pigments are undoubtedly derived from haemoglobin. Nenki and Sieber have shown⁸ that in the liver haemoglobin splits up into haematin and protein, and that haematin loses iron and undergoes hydrolysis, yielding bilirubin. Animals having no haemoglobin in the blood have no bile pigments. Increased destruction of red blood corpuscles or the intravenous injection of haemoglobin, or of distilled water, which has the same effect, result in the formation of bile pigments in increased amount.

It is thus seen that the bile pigments are derived from haemoglobin and are formed almost entirely in the liver where the decomposition of haemoglobin occurs.

Bile pigments, if injected into a vein, are poisonous, they are not normally absorbed from the bile in the intestine, but are converted into stercobilin and evacuated with the faeces.

There is no doubt that further physiological chemical investigations with regard to bile pigments and bile salts, especially with a view to the quantitative estimation by simple clinical methods in the blood and urine, will throw a great deal of light on the pathology of the conditions causing jaundice.

Blankenhorn⁹ has done some good pioneer work in this respect. He examined a large number of cases due to jaundice and conditions associated with it and found that bile pigments may be present in the blood without jaundice. He represents the cholaemia, which he determined by colorimetric methods, quantitatively in figures ranging from 15 to 375. When the degree of cholaemia reaches the figure 40 then jaundice will appear clinically. He finds that bile pigments may be present in the blood, and jaundice result without bile pigments being in the urine. In cases of obstructive jaundice, catarrhal jaundice, secondary anaemia, passive congestion of the liver, and pneumonia, he has shown the quantitative relation of bilirubin in the blood and urine, and he has made similar determinations for urobilin.

He states that the estimation of bile salts in the blood is attended at present with great difficulty.

Blankenhorn's work is undoubtedly most valuable, and its further development should enable important diagnostic tests to be made in diseases like relapsing fever, spirochaetosis icterohaemorrhagica, etc., where jaundice is usually a prominent symptom, though it may be absent. Also in the early stages of conditions, such as T.N.T. poisoning, which will ultimately develop jaundice, an early diagnosis might be made, and this would be of great value from the point of view of prevention and treatment.

Cholesterol may be present in bile in amount ranging from 0.5 to 5 per cent. It is excreted by the bowel, not being reabsorbed. As is well known, it is an important constituent of gall stones, and its solubility in bile salts has been alluded to as an important factor in the prevention of the formation of gall stones.

Lecithin is a lipid compound of choline, oleic acid, glycerin, and phosphoric acid. It is a product, like cholesterol, of nervous metabolism, and is an important constituent of bile which is not reabsorbed by the bowel; like cholesterol, it is kept in solution by the bile salts.

FUNCTION OF LIVER IN RELATION TO FAT METABOLISM.

Major Alexander G. R. Foulerton¹⁰ has, in a most interesting paper, brought out the relation of this function of the liver to certain forms of toxic jaundice. Normally available organic fat is stored up in the liver, and has a high iodine value, being composed of a large proportion of unsaturated fatty acids. Leathers has shown that in chloroform and phosphorus poisoning the liver becomes engorged with fat which has a low iodine value, being composed of a large proportion of saturated fatty acids.

Foulerton has shown that in poisoning by trinitrotoluene, dinitro benzene, phosphorus, chloroform, ether, and tetra-chlorethane, impaired fat metabolism occurs as a consequence of impaired action of the liver cells due to toxic chemical influences.

Thus the liver in these conditions becomes engorged with fat of low iodine value. The engorgement of the liver with fat is a concomitant of the occurrence of jaundice in the early stages of many forms of toxic jaundice, and it is perhaps to some extent a contributory factor.

GLYCOGENIC FUNCTION OF THE LIVER.

This has been fully studied by physiologists. It is interesting to note that the occurrence of glycosuria has sometimes been observed in cases of jaundice. For example, Garrod¹¹ records a case of glycosuria in catarrhal jaundice. Glycosuria has been also observed in biliary colic, phosphorus poisoning, etc. I have on several occasions found glycosuria of a transient nature in jaundice cases.

FUNCTION OF LIVER IN PROTEIN METABOLISM.

The most important function of the liver is the part it plays in breaking down the complex products of protein metabolism into simple nitrogenous compounds—for example, urea, uric acid, hippuric acid, etc.—which are excreted by the kidney. If this function of the liver fails, then intermediate products of protein metabolism occur in the blood, and speedily symptoms of the gravest kind, usually fatal, result—as, for example, in icterus gravis.

The symptoms of icterus gravis, or acute yellow atrophy of the liver, are undoubtedly due to an auto-intoxication, but what the exact chemical compounds of protein metabolism are which cause this condition we do not know. A great field of research is here open to physiological and pathological chemists.

CLASSIFICATION.

All cases of jaundice may be classed in the two great divisions: (1) Simple obstructive jaundice; (2) haemo-hepatogenous or toxæmic jaundice.

SIMPLE OBSTRUCTIVE JAUNDICE.

This type results from obvious mechanical obstruction independent of changes in the blood or bile. Its causes are:

1. Obstruction by foreign bodies within the ducts—for example, biliary sand or calculi, mucus, worms, etc.
2. By inflammatory swelling of the duodenum or the mucous membrane of the duct, as in ordinary catarrhal jaundice.
3. By stricture or congenital deficiency of the duct.
4. Tumours closing the orifice of the duct or growing in its interior.

5. By pressure on the duct from without from various causes—for example, enlarged glands in the portal fissure, tumours of the liver, stomach, pancreas, kidney, omentum, faecal accumulation, abdominal aneurysm, etc.; movable kidney, pregnant uterus, also inflammatory processes adjacent to the bile ducts—for example, perihepatitis, cirrhosis of liver, periduodenitis, etc.

Symptoms of Simple Obstructive Jaundice.

In this condition a relatively undamaged and functioning liver exists with simple obstruction of the flow of bile, so that, apart from the symptoms due to absorption of the bile into the circulation, the condition of the patient remains good. It is remarkable how few toxic symptoms occur in cases where the most pronounced simple obstructive jaundice may have existed for weeks or months. In this condition the "cholaemia" reaches a high degree both as regards bile pigments and bile acids, and both exist in relatively high amount in the urine. The sweat contains bile, but the saliva, tears, and milk are rarely stained. The cerebro-spinal fluid and central nervous system remain unstained.

The icterus or tinting of the skin and conjunctivae ranges from a lemon yellow in the early stages to a deep yellow, olive green, or greenish-black colour in cases of long duration. Skin affections, such as pruritus, which may be of a distressing type, sweating, lichen, urticaria, and boils, may occur. Xanthoma and telangiectases may be observed in advanced cases. It is important to remember that skin affections due to the cholaemia of jaundice are almost invariably absent in haemo-hepatogenous jaundice.

The urine has a marked brownish-yellow colour, but may be tinted greenish or be blackish-green if the bilirubin present has undergone oxidation to biliverdin. The froth caused by the shaking of a urine containing bile is unusually permanent and is markedly stained; this is a good rough test.

Bile pigments are detected by Gmelin's test, or better by Trouseau's iodine test, in which a very dilute alcoholic solution of iodine is poured carefully into a test tube so that the iodine solution floats above the urine; a greenish zone gradually develops between the two layers. These tests should be made in good daylight.

Bile acids may be tested for by Hay's sulphur test, or the more delicate peptone test of Oliver.

In the urine albumin and bile-stained casts may be present in long-standing cases.

The stools are of a pale drab or slate-grey colour; they are usually very fetid and pasty. Daily inspections should be made, since, when the obstruction is complete, yellow colour is absent continuously; while with a partial or intermittent obstruction some altered bile pigments may give a yellowish appearance to some of the stools. With complete obstruction the percentage of fat in the stools is usually from three to six times the normal. Also the fluorescence test for stercobilin with zinc chloride and ammonia becomes only slightly marked or absent.

The pulse is markedly slowed in the early stages, due to bile acids in the blood. It may fall to 30 or 40. In the later stages the pulse increases in frequency, because the production of bile acids by the liver has diminished, and the kidney has gradually got rid of the excess in the blood. Further, the cause of the obstructive jaundice in a prolonged case probably has, *per se*, an accelerating effect on the pulse-rate.

Haemorrhages and a tendency to bleeding are characteristic of a chronic case. The blood coagulation time has been shown to be much prolonged.

Cerebral symptoms, irritability, depression, and even melancholia, may occur. A special terminal phase, sometimes known as "cholaemia" or "cholesteraeemia" (which rapidly proves fatal), may terminate long-standing cases. This condition is probably identical with the symptom-complex of icterus gravis or acute yellow atrophy, and is due to an auto-intoxication caused by the impairment of function of the liver cells in dealing with the products of protein metabolism. The symptoms are not due to the action of bile or cholesteria in the blood, so that the terms "cholaemia" or "cholesteraeemia," as applied to this condition, should be abolished.

Diagnosis.—In this type of jaundice a careful physical examination and the usual methods of clinical investigation will reveal usually the cause of the simple obstructive jaundice.

HAEMO-HEPATOGENOUS OR TOXAEMIC JAUNDICE.

This form of jaundice is caused by the circulation in the blood of toxic substances of chemical or microbic origin, as a result of which occur destruction of red blood corpuscles, an obstructive catarrh of the small intrahepatic bile ducts, an increased viscosity of the bile, and in severe cases a degeneration of the liver cells, resulting in auto-intoxication (icterus gravis).

The following varieties occur:

1. *Toxic.* Jaundice, sometimes known as "toxic jaundice," due to the action of chemical poisons, such as tetrachlorethane, trinitrotoluene, chloroform, phosphorus, toluylene-diamine, nitrobenzenes, nitrophenols, arsenobenzol derivatives, arsenifuretted hydrogen, mushrooms, snake venom, etc.

2. *Microbic.* Jaundice due to the microbic toxins formed in various specific fevers and infections, such as relapsing fever, malaria, the enteric group of disease, typhus, pneumonia, influenza, syphilis, yellow fever, pyaemia, septicaemia, etc. In this group should be included infective jaundice due to *Spirochaeta ictero-haemorrhagiae*, and probably epidemic catarrhal jaundice and Weil's disease.

3. *Blood Diseases.* Jaundice associated with splenic anaemia, pernicious anaemia, acholuric jaundice, haemoglobinuria, etc.

In haemo-hepatogenous jaundice the obstruction caused by inflammatory catarrh of the smaller intrahepatic ducts is not usually complete, so that many of the symptoms due to the direct action of bile in the circulation as described under simple obstructive jaundice are absent. Thus the skin complications and the slowing of the pulse are not present in toxæmic jaundice. In it the yellow coloration of the skin is usually much less pronounced, and in cases in which it becomes deep the complete intrahepatic obstruction is only temporary, and does not last long enough to cause symptoms of bile toxæmia. The stools may be pale for a day or two during the stage of temporary complete obstruction, but usually are well coloured with faecal pigment.

The urine in cases of marked jaundice will contain bile pigment, which in milder cases is often absent. Bile salts are generally absent, since their rate of production is diminished owing to defective liver function in consequence of the toxic agent causing the jaundice.

The blood contains bilirubin, and when this reaches a certain degree jaundice will occur. At about this stage bilirubinuria will be recognized; exceptionally it may appear before the jaundice, but usually occurs afterwards.

In haemo-hepatogenous jaundice the symptoms due to the jaundice *per se* are unimportant as compared with those due to the primary intoxication. Thus with chemical poisons the action of the substance on the body generally, and especially on the liver cells, in causing auto-intoxication is much more profound than the mere effect on the bile capillaries, causing jaundice.

In the case of microbic poisons the action of their toxins in causing the specific symptoms of the disease—for example, malaria, relapsing fever, enteric, influenza, etc.—is much more important than the symptoms resulting from the mere production of jaundice, the latter being quite overshadowed by the former. In toxæmic jaundice the blood shows a great liability to haemolysis, the red corpuscles are smaller and have increased fragility. In simple obstructive jaundice the red corpuscles are larger and show increased resistance to haemolysis (Chauffard).¹²

Severe constitutional symptoms are much more marked generally in toxæmic jaundice, and in this condition the grave and fatal symptoms of icterus gravis are much commoner and likely to occur very much earlier in the disease.

PATHOLOGY OF JAUNDICE.

In simple obstructive jaundice due to mechanical obstruction of the common or larger bile ducts the causation is clear. Bile cannot pass *per vias naturales*, and it thus becomes dammed back and is absorbed by the lymphatics, and, in severe cases, probably also by the blood capillaries of the liver. Adams¹³ quotes the following experimental proof of the probability of direct passage of bile into the hepatic blood capillaries as well as lymphatics in obstructive jaundice. If in a dog the common bile duct be tied jaundice results quickly. If at the time of tying the bile duct the thoracic duct be also tied, jaundice will still

occur, but its onset is usually delayed. Bile is thus conveyed into the blood stream, jaundice resulting, and the blood and urine containing both bile pigments and bile acids.

In *haemo-hepatogenous* or *toxaemic jaundice* the causation is different. Toxic substances, whether of bacterial or chemical origin, circulate in the blood; they cause a certain amount of destruction of red blood cells, the products of which are conveyed to the liver, in company with the circulating poison. The poison or its products have a direct action on the liver cells, causing a degeneration. They also act on the bile capillaries, causing inflammatory catarrh, as a result of which the secretion of the bile capillaries becomes very viscid and the lumen of the fine ducts narrowed. In this manner an intrahepatic obstruction to the flow occurs in the fine bile ducts, and bile pigments find their way into the blood stream via the lymphatics, and probably also by the blood capillaries. The absorbed bile in *toxaemic jaundice* is usually rich in bile pigments, which arise from the increased destruction of haemoglobin; it is deficient in bile salts, owing to the impaired function of the liver cells.

When the bilirubinaemia reaches a certain degree jaundice occurs, and at a still higher percentage bilirubinuria. Bile salts are not usually passed in the urine, since their percentage in the blood is too low, but in some cases they occur in small amount.

The above expression of the pathology of *toxaemic jaundice* is the result of the work of Stadelmann¹⁴ and his co-workers in 1881 on the action of toluylene-diamine, phosphorus, arseniuretted hydrogen, etc., in causing jaundice. Later Hunter, in 1885 and 1886, by a fine piece of research,¹⁵ placed the causation of jaundice on a still more accurate basis, and his work and conclusions hold good to-day.

The injection of toluylene-diamine into a dog with a biliary fistula was, Stadelmann showed, followed by jaundice, thus proving that the obstruction occurred in the finer ducts. He found that the injection of toluylene-diamine into the blood stream of a dog caused a marked increased destruction of red blood corpuscles. From the second to the twelfth hour after the injection the bile secretion was increased and rich in pigments, then the secretion changed to a viscid colourless one, and from the fourteenth to the sixtieth or seventieth hour this condition remained. Jaundice was marked during the whole of this stage; afterwards the bile became normal and the jaundice cleared up. Bilirubinuria occurred soon after the onset of the jaundice—that is, about the fourteenth hour—but bile salts did not appear in the urine until the thirtieth hour, and they only remained for a few hours.

With phosphorus Stadelmann found a similar condition except that the stages were slower in production; thus the colourless viscid conditions of the bile commenced after twenty-four hours and lasted for five to eight days during which jaundice was present.

With *arseniuretted hydrogen* he found similar stages to occur, but noticed that the bile pigments were increased much more than with the two previous poisons, though the jaundice was much less marked.

In the above experiments neither haemoglobinaemia or bilirubinaemia occurred in the first stage following the administration of the poison, so that the red cell destruction and conversion of the haemoglobin into bile pigment did not occur in the blood stream but in the liver itself. The production of bile pigments was shown to be quite independent of the formation of bile acids, which latter are produced by the liver cells and have no relation to haemoglobin destruction.

Hunter confirmed Stadelmann's work, and, by careful *post-mortem* and pathological examinations of animals after the administration of toluylene-diamine, showed that a marked inflammatory catarrh occurred of the fine bile ducts. He also found degeneration of the liver cells, and engorgement of them with fat; the intralobular bile capillaries were also filled with the remains of haemoglobin and broken down red blood cells.

The duodenum, after a few days' action of the drug, showed a markedly swollen and reddened condition of its mucous membrane with small haemorrhages in places. This inflammatory condition extended for a distance of 12 in. or more below the opening of the bile duct and was obviously due to a catarrh set up by irritating products in the bile. Hunter pointed out that only minute traces of toluylene-diamine were present in the bile, and that the drug, if given by the mouth, did not cause this marked duodenitis. He therefore attributed it to irritant bodies in the bile set up by the action of the toluylene-diamine on the liver.

Hunter pointed out that the catarrh set up in the intrahepatic bile ducts by toluylene-diamine began high up and descended to the duodenum. He considers it likely that in ordinary catarrhal jaundice the catarrh may be of a similar descending

nature. The French school have long held this view, but Murchison taught that the catarrh started in the duodenum and spread up the common bile duct, blocking it or its larger branches.¹⁶

The above experiments showed that the production of jaundice is not directly proportional to the amount of red blood cell destruction. Thus in dogs arseniuretted hydrogen causes great blood destruction and slight jaundice, while toluylene-diamine causes slight blood destruction and deep jaundice.

The same conclusion was arrived at by experiments with toluylene-diamine on the cat, rabbit, and dog. In all the drug caused red cell destruction. In dogs marked jaundice occurred, but no haemoglobinuria. In cats no jaundice resulted, but haemoglobinuria followed. In rabbits neither jaundice nor haemoglobinuria occurred.

Recent histological studies of the liver in long-standing cases of toxic jaundice from tetrachlorethane, trinitrotoluene, etc., by Spilsbury and others, have shown that considerable destruction of the liver cells occurs, and when this destruction is compatible with life the normal liver tissue becomes replaced by tissue of an inflammatory nature, resulting from the absorption of the necrosed liver cells. In this abnormal tissue leakage of bile from the small capillaries into lymphatics and blood vessels no doubt occurs, and is a factor in causing jaundice.

Summary.

The toxic substances causing haemo-hepatogenous jaundice have three important actions:

- (1) Degeneration of the liver cells with impairment of hepatic function;
- (2) Destruction of red blood cells;
- (3) The production of an obstructive catarrh of the fine intrahepatic bile ducts.

Each toxic substance differs in the relative degree of its respective action in these three respects.

Thus, if (1) predominates, only slight jaundice may occur, but the symptoms will be those of auto-intoxication (*icterus gravis*) and of the gravest character. Examples of this type of poison are arseno-benzol derivatives, chloroform, mushroom poisoning, arseniuretted hydrogen. If (2) predominates, anaemia will be marked and jaundice may be slight only (for example, metadinitrobenzene). If (3) predominates, jaundice will be very marked (for example, in tetrachlorethane, trinitrotoluene, and toluylene-diamine).

Bacterial poisons likewise possess these three actions in varying degree—for example, (1) predominates in yellow fever, (2) in malaria, and (3) in relapsing fever, epidemic catarrhal jaundice, spirochaetosis icterohaemorrhagica.

Importance of Experiments on Dogs.

Our knowledge of the pathology of *toxaemic jaundice* has been of the utmost practical value to the nation during the present war. It rendered possible the early recognition and detection of the cause of the toxic jaundice which was so common amongst aeroplane and munition workers, and it directed the preventive methods which were so successful.

Let us not forget that this knowledge has been gained almost entirely as the result of carefully conducted experiments on dogs, and that in this research other animals, as shown above, were found unsuitable.

It will be nothing short of a national calamity if this source of research is to be denied the medical profession in the future. The recent letters to *The Times* of Professor Schafer and Dr. Leonard Hill express the vital importance of carefully conducted experiments on dogs in scientific research, the knowledge gained by which will be of inestimable practical benefit to the nation. It is sincerely to be hoped that the ill-conceived bill now before Parliament for preventing experiments on dogs will be thrown out.

DIAGNOSIS OF JAUNDICE.

It is important that the examination should be made in daylight, since jaundice is invisible in ordinary artificial yellow light. Special attention should be paid to the examination of the conjunctivae, skin, palate, stools, and urine, as described above.

Care must be taken to exclude the lemon-yellow tint associated with the cachexia of malignant disease or pernicious anaemia. An examination of the conjunctivae

over the sclerotics usually differentiates these. The bronzing of sunburn and the pigmentation of Addison's disease and other conditions are likewise distinguished.

In coloured races sometimes difficulty occurs; thus in some Indians a definite yellow pigmentation of the conjunctivae occurs, giving a characteristic appearance of jaundice. In Mesopotamia I had a Madrassee servant who had markedly yellow sclerotics resembling deep jaundice; this condition was entirely due to pigmentation.

In doubtful cases an examination of the blood serum for bilirubin is of great importance. This test has been used by Dr. Castellain and others in the detection of toxic action of trinitrotoluene on the liver in munition workers before the yellow coloration of the skin has actually developed.

In a case of jaundice careful search should be made by the usual clinical methods for the primary cause of the condition.

TREATMENT OF JAUNDICE.

The important course is the treatment and removal of the primary cause of the condition.

Speaking generally, the diet should be free from fats, since, as pointed out above, there is a tendency for fat engorgement of the liver cells.

Protein constituents of the diet should be reduced, since there is a tendency, especially in toxæmic cases, to acid intoxication. Alcohol is best avoided. Saline aperients should be given, but powerful purgatives are best avoided. Calomel in small repeated doses is not advisable, since there is a risk of symptoms of mercurial stomatitis developing.¹⁷ Alkalies—for example, sodium bicarbonate—should be given by the mouth in large doses, and in toxæmic cases¹⁸ strong solutions of sodium bicarbonate may be given by the rectum as frequently as it can be retained.

Any special symptoms will require appropriate treatment as they arise.

FALSE JAUNDICE.

Attempts may be made to feign jaundice by coloration of the skin with saffron or turmeric or other yellow dye (Wickham Legg⁴). Trinitrotoluene produces a yellow staining of the skin, so that munition workers handling this substance are often named "canaries" by their comrades. Since in this condition the conjunctivae are unaffected and the urine and stools are normal, little difficulty in detection is experienced.

During the war picric acid has not uncommonly been taken by malingerers for the purpose of simulating jaundice, and some care is required lest the physician may be deceived.

Cases have been published as occurring in the French and Italian armies. Fontaine studied this condition and published¹⁹ an investigation of several cases. He laid stress on the absence of colourless stools, the less marked staining of the tissues, and the absence of pyrexia and premonitory symptoms before the occurrence of jaundice. He pointed out that the conclusive test was absence of bile pigments in the urine and the presence of the picric acid derivative—picramic acid.

Professor Masuata, in May, 1917, described²⁰ two interesting cases in Italian soldiers of jaundice artificially produced by picric acid. In these cases 1 gram of the drug had been taken every twenty-four hours. The symptoms were nausea, anorexia, coated tongue, and severe epigastric pain. In one case there was a scarlatiniform eruption and pyrexia. The skin and conjunctivae were definitely yellow, and resembled mild catarrhal jaundice. The stools were stained yellow, and the urines gave definite reactions for picramic acid and bile pigments were absent.

The presence of a rash and pyrexia in one of these cases shows the difficulty of diagnosis on clinical observations alone. The only sure test is the presence of picramic acid in the urine.

In large doses picric acid might cause true haemohepatogenous (toxæmic) jaundice, when both bile pigments and picramic acid would appear in the urine.

REFERENCES.

- ¹ A Fatal Case of Poisoning by Tetrachloride of Ethane, *Lancet*, December 26th, 1914.
- ² W. H. Willcox, B. H. Spilsbury, T. M. Legge: An Outbreak of Toxic Jaundice of a New Type amongst Aeroplane Workers, *Transactions of the Medical Society of London*, vol. xxxviii, 1915.
- ³ W. H. Willcox and J. Webster: The Toxicology of Salvarsan, *BRITISH MEDICAL JOURNAL*, April 1st, 1916.
- ⁴ J. Wickham Legg: *Bile, Jaundice, and Biliary Diseases*, 1880, p. 225.
- ⁵ Dr. J. Redman Coxe: *Writings of Hippocrates and Galen*, Philadelphia, 1846.
- ⁶ E. A. Schafer: *Textbook of Physiology*, p. 391.
- ⁷ *Ibid.*, p. 384.
- ⁸ *Arch. f. Exper. Path. u. Pharmacol.*, Leipzig, 1888, Bd. xxiv, S. 430.
- ⁹ Blankenhorn: *Transactions, Association of American Physicians*, 1917.
- ¹⁰ Major Alexander G. R. Foulerton, R.A.M.C.(T.F.): On the Pathology and Treatment of Poisoning by Trinitrotoluene, and on the Action of Certain other Poisons which affect Fat Metabolism, *R.A.M.C. Journal*, June, 1918.
- ¹¹ A. E. Garrod: Glycosuria in Catarrhal Jaundice, *Lancet*, 1912, i, 560.
- ¹² Chauffard: *Sem. méd.*, Paris, xxviii, 48, 1908.
- ¹³ Adami: *General Pathology*, vol. i.
- ¹⁴ Stadelmann: *Der Icterus und Seine Verschiedenen Formen*, Stuttgart, 1891. Also *Archiv f. Exper. Path. u. Pharmacol.*, 1882, xv, 337.
- ¹⁵ W. Hunter: Thesis Univ. of Edinburgh, 1886. The Physiology and Pathology of Blood Destruction, *Lancet*, 1892, ii, 19. The Action of Toluylene-diamine, *Journ. Path. and Bact.*, 1896, iii, 259.
- ¹⁶ Murchison: *Diseases of the Liver*, 1885.
- ¹⁷ Willcox: The Epidemic Jaundice of Campaigns, *BRITISH MEDICAL JOURNAL*, February 26th, 1916.
- ¹⁸ Willcox: The Treatment of Toxic Jaundice due to Tetrachlorethane Poisoning, *BRITISH MEDICAL JOURNAL*, February 26th, 1916.
- ¹⁹ G. Fontaine: Contributions to the Study of False Jaundice caused by Picric Acid, Université de Montpellier, May, 1915.
- ²⁰ Professor Masuata: Artificially-produced Jaundice by Picric Acid, *Lancet*, August 11th, 1917.

CONDUCTIVE ANAESTHESIA BY THE INTRA-SACRAL EXTRADURAL INJECTION OF NOVOCAIN.*

BY

SAMUEL R. MEAKER, B.A., M.D., CAPTAIN R.A.M.C.

THE method about to be described is not, so far as I have been able to discover, in use anywhere in this country. It is exceedingly practical as well as simple and safe, and, in the opinion of those who have developed it, requires only to be better known in order to be widely and usefully employed.

Anatomy.

The dural sheath ends normally at the top of the second sacral segment. From this point downward the sacral and coccygeal nerves run free in the bony canal of the sacrum, surrounded by a little loose areolar tissue, until they make their exits at their respective foramina.

Of the posterior trunks, the first and second sacral supply the integument of the inner aspect of the leg and thigh respectively. The lower sacral and coccygeal branches are distributed to the anus, buttocks, perineum, and part of the skin of the male genitalia. The individual distribution of these lower nerves is not accurately known.

The spinous process of the fifth sacral segment does not exist as a median protuberance, but as two unfused halves (the so-called cornua of the sacrum). The sacral cornua and the tip of the sacrum form an isosceles triangle, of which the apex is directed upwards—the hiatus sacralis, which is the lower termination of the bony spinal canal. This gap is filled in by a dense fibrous membrane.

Since the sacrum is a rudimentary bone many variations from the normal are met in connexion with the hiatus, of which the most important are the following: (1) It frequently replaces the spinous process of the fourth sacral segment as well as that of the fifth, and may run up as high as the second. (2) It is often found slightly to one side of the median line as marked by the anal cleft. (3) One cornu is frequently much more prominent than the other, as if the sacrum were slightly rotated on its long axis. (4) The hiatus is sometimes very narrow laterally, and (5) sometimes very shallow antero-posteriorly—that is, between the occluding membrane and the anterior aspect of the bony canal. In these last two conditions the technique of injection may present some difficulty.

Scope of the Method.

When novocain is injected extradurally into the bony canal of the sacrum, anaesthesia of the third and lower sacral and coccygeal nerves is produced. The motor roots are not affected, and retention of urine after haemorrhoid operations done with sacral injection is neither more nor less common than when a general anaesthetic is given. The regions supplied by the first and second posterior sacral nerves may undergo a paraesthesia, but are not anaesthetized. This may be because the upper nerves run free for a comparatively short distance in the sacral canal, or because they are large trunks and do not readily absorb surrounding fluid.

The proven field of usefulness for sacral anaesthesia comprises operations for haemorrhoids, fistulae, and other conditions in and about the anus. The great majority of my cases have been of this sort, and in such one may employ the method with a practical certainty of

* An address given before the Aldershot Command Medico-Chirurgical Society.