CLINICAL SECTION
CLINICO-PATHOLOGICAL CONFERENCE—No. 9*

A Case of Obstructive Jaundice

Clinical History (Dr. Sheila Sherlock)

The patient, a housewife aged 65, was first admitted to Hammersmith Hospital on September 1, 1947. She had enjoyed a healthy life, her only complaint being that at the age of 42 vitiliginous skin pigmentation developed, which was aggravated during the summer of 1946. However, in October, 1946, there was a fairly acute onset of upper abdominal pain with vomiting and occasional chills, and this was rapidly followed by jaundice which persisted with but little fluctuation. The stools continued pale with dark urine. The skin itched continuously and she had lost 2½ stone in weight, though her appetite was fair.

In January, 1947, an operation was undertaken at another hospital, and the gall bladder, bile ducts and pancreas were reported to be normal. A biopsy was taken from the liver which showed the features of obstructive jaundice.

On examination in September, 1947, she was seen to be a thin, jaundiced woman. There were

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* Held at the Postgraduate Medical School of London (Hammersmith Hospital), October 11, 1950. The report was assembled by Dr. Bernard Lennox, to whom the Editor is most grateful. Histological sections by Mr. J. Griffin and photomicrographs by Mr. E. V. Willmott.
scratch marks on the skin; the forearms, neck and trunk showed alternating patches of light and dark skin and this was interpreted as vitiligo. The blood pressure was 126/78. The liver was enlarged to the umbilicus, the edge was firm and the surface smooth. The spleen was just palpable. Ascites could not be clinically detected. Rectal examination demonstrated piles. Urine showed persistent absence of urobilin; bile pigments were present. The faeces were always acholic. Biochemical investigations during the course of the illness are shown in the table.

Haematological examination showed haemoglobin 13.4 g. per cent., red blood corpuscles were 4,000,000 per c.mm., white blood count 8,000 per c.mm., prothrombin time 85 per cent. of normal, and the erythrocyte sedimentation rate was 105 mm. in an hour. Radiologically the wrist bones were normally calcified. A biopsy of the skin showed some excess pigment in the deeper layers but was otherwise normal. An aspiration liver biopsy was performed and during this a little ascitic fluid was aspirated. Hepatic sections showed considerable biliary cirrhosis.

Clinical and biochemical findings and the hepatic histology all suggested obstructive jaundice, and a further laparotomy was considered necessary. This operation was performed by Professor Ian Aird on October 7, 1947. The liver was considerably enlarged and the portal venous radicles were congested. A firm mass was felt high up in the portal fissures in the region of the left hepatic duct. The gall bladder was empty; there was no apparent biliary obstruction and the common bile duct was not opened.

The post-operative course was complicated by a biliary fistula which drained for seven weeks but which did not influence the depth of the jaundice. On December 4, 1947, the patient was well enough to go to a convalescent home.

In April, 1948, there was a further short admission for the drainage of an abscess in the laparotomy scar. The pus in this abscess was bacteriologically sterile. The jaundice continued unchanged. From September, 1948, to June, 1950, the patient was under the care of her general practitioner, Dr. Dudley-Dunn of Highgate, and also attended fairly regularly at the hospital outpatient department. In September, 1948, she was still tired and weak and complained of itching. She also had pain in the epigastrium two hours after meals which was relieved by alkalis. A new development was pain in the chest and shoulders. On examination a fresh clinical sign was the presence of xanthomas under the eyelids. A barium meal at this time was non-contributory. In December, 1949, she was still very weak with epigastric pain and backache. The itching, however, had considerably abated. Over the past six months she had had occasional epistaxes. A vascular spider had developed on the right hand and ascites could now be detected clinically. She was treated with vitamin K by mouth and with a low fat, high protein diet.

The patient was admitted to hospital for the third time on June 16, 1950. She complained of generalized body pains, repeated epistaxes, swelling of the ankles of one month's duration and, very recently, had had some diarrhoea. Her eyesight was blurred and she complained of seeing yellow; her appetite remained good. Examination showed that she was dyspnoeic at rest; there were spider angiomata over the face, arms and neck, and a haematoma over one finger; kyphoscoliosis had developed. The pulse rate was 90 and the blood pressure was 105/55. A systolic murmur could be heard maximally over the fourth left interspace. The liver was still greatly enlarged and firm. The spleen could be felt 4 cm. below the left costal margin. There was gross ascites. The rectal piles had prolapsed. There was oedema of sacrum and ankles. Urine showed, as before, excess bile pigments and absence of urobilin. X-rays now showed generalized osteoporosis with multiple fractures of the ribs and also probably of the pubic ramus. The serum calcium was 9.2 mg. per 100

Biochemical Investigations

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ml. and the serum phosphate was 1.8 mg. per 100 ml. An electrocardiogram showed the QTc at the upper limit of normal. It was thought that the generalized pains were related to the skeletal lesions. The patient was treated with a high protein, low fat diet, and it was now possible to give the vitamin K intramuscularly. In spite of this, on June 26 the patient had a haematemesis and became unconscious. A further small haematemesis occurred on June 27 and the circulatory findings of severe anaemia and liver failure were shown, viz. jugular venous pressure +2 cm. above the sternal angle, blood pressure 115/60, an apical murmur with presystolic rhythm, the hands were warm. The haemoglobin was 9.3 g. per cent. and the blood urea concentration 28 mg. per 100 ml. On June 28 there was a further haematemesis with melaena. Blood pressure fell to 95/50 and the patient went into deep coma. In spite of the liver failure the fasting blood glucose was 129 mg. per 100 ml. On June 29 the blood urea concentration was 28 mg. per 100 ml. and the non-protein nitrogen 64 mg. per 100 ml., indicating that aminoacids were probably increased in the blood, presumably as a result of liver failure. On June 30 the haemoglobin was 7.3 g. per cent. On the next day the patient was much more conscious, and on July 2 two pints of blood were given slowly. This raised the haemoglobin to 9.9 g. per cent. On July 7, however, the patient passed bright red
blood per rectum and in spite of the transfusion of a further two pints of blood, died on July 9.

The clinical diagnosis was obstructive jaundice, probably of primary intrahepatic type, with terminal liver failure and gastrointestinal haemorrhage. Osteomalacia and multiple fractures were associated.

**Autopsy Findings (Prof. Dible)**

At post-mortem the body was that of an old woman with deep greenish jaundice. The legs were oedematous and the abdomen distended. There were effusions in the abdominal and both pleural cavities and the pericardial sac. The heart was rather atrophic. The lungs were somewhat collapsed, but otherwise apparently normal.

The chief lesion was found in the liver, which was of approximately normal weight, but finely granular, deep-green in colour and tough when cut. The main bile ducts within the liver were markedly distended with thin watery light-coloured fluid. At the junction of the two hepatic ducts there was a mass of cicatrical tissue which occluded both ducts. Below this the common bile duct was of normal diameter and was not bile stained. There was no obvious obstruction to the pancreatic duct. The gall-bladder was normal in appearance and contained brown, thick mucin. The cystic duct was lost in cicatrical tissue and its opening could not be identified.

Histologically the obstruction to the hepatic ducts was due to a scirrhous adeno-carcinoma arising in this situation (Fig. 1). The various biopsies of the liver which had been taken at the fourth and tenth month of the disease and the final picture of the liver at post-mortem gave a good illustration of the progress of a biliary cirrhosis due to obstruction. The earliest biopsy (Fig. 2) showed a fibrosis of the portal tracts which was essentially monolobular with pigmentation of the parenchymatous cells of the liver. The second biopsy showed a more advanced fibrosis (Fig. 3) which now extended from portal tract to portal tract and was associated with the presence of very many bile canaliculi of new formation. There was also well marked evidence of degenerative changes in certain groups of liver cells in this material (Fig. 5).

The final picture at post-mortem was one of a gross cirrhosis (Fig. 4) with considerable nodular hyperplasia of the liver and a more mature condition of the fibrous tissue, associated with the disappearance of the bile canaliculi so prominent in the earlier biopsy.

The liver had been partially fixed by the intraperitoneal injection of formalin immediately after death and a noteworthy feature was the extreme autolysis of the central part of the organ and the good fixation of the outer rind which had been exposed to the action of the formalin. Nevertheless, evidences of liver cell necrosis in parts of the liver which had been fixed were not wanting. It was thought that this was a terminal event.

The other organs of the body did not call for much comment except for the haemopoietic system. Here the femoral marrow showed marked activity throughout the whole length of the bone, the cortex of which was stained deep green. Histologically there was general activity of all the marrow elements.

The spleen weighed 575 g. and showed a markedly active condition of the pulp, and the sinuses were packed with haemopoietic cells which were also seen in the Malphigian corpuscles. The
liver capillaries were stuffed with polymorphs (Fig. 6) and leucocytic thrombi were present in many of the smaller pulmonary veins. The appearance almost suggested a leukaemoid state, but a blood film made four days before death showed only marked polymorphonuclear leukocytosis.

An incidental finding was very extensive calcification of almost all the mesenteric lymph glands. A single gland which was not affected showed an extreme degree of dilatation of the lymph sinuses which were, as elsewhere, filled with pigment-containing phagocytes.

The kidneys, which to the naked eye were heavily bile-stained, showed only moderate autolysis of the epithelium of the proximal convoluted tubule and surprisingly little bile staining.

There were fractures of several ribs, the bones cut more readily than is usual, but their structure appeared normal to the naked eye.

Summary. Intra-hepatic carcinoma of the main bile ducts, producing advanced biliary cirrhosis.

Discussion

Dr. Sherlock: This patient showed all the features of obstructive jaundice; she had persistent jaundice over a long period, pruritis and dark urine with yellow or pale stools. The difficulty lay in making up one's mind whether the obstruction was intra- or extra-hepatic, and in this particular instance we had nothing to help us. The clinical findings would have passed for either condition: The biochemistry was, as you see, quite unhelpful, and it is useless to do liver biopsies in these patients because they will only tell you what is happening inside the liver and give no clue as to the state of the bile ducts. So we must rely on the surgeons. This patient had two laparotomies and the surgeons, understandably, failed to find the obstruction which was high up in the portal fissure, probably arising at the junction of the three main ducts. We were also prevented from making a correct diagnosis by the persistence and duration of her illness. It is most unusual for patients with carcinomatous jaundice to survive as long as four years with a good appetite and weight fairly well maintained.

The pathology of the tumour is, of course, interesting. This is not a common tumour; only 45 cases have been recorded of primary tumour in this site and they are not usually as scirrhoues, they are usually more cellular. Well, what are the effects of long continued obstructive jaundice of this kind? The first things to be guarded against are deficiencies in the fat soluble vitamins. This patient demonstrated defects in vitamin K and vitamin D. Vitamin K deficiency was demonstrated by her bleedings, but I should mention that vitamin K was not the complete answer because she continued to bleed after being given vitamin K. Vitamin D deficiency was shown by her osteoporosis, multiple fractures and bone pains. Well, then, the other thing one must expect (but can

Fig. 8.—Showing clinical and biochemical landmarks.
do nothing about) is progressive liver cell failure. This was shown very well in this patient by the development of ascites, spider naevi and oedema, and by the changes in the biochemical tests, the fall in serum cholesterol and albumen, and the flocculation test. One can only treat the deficiencies by giving the fat soluble vitamins parenterally, and as for the liver cell failure there is very little one can do apart from a reasonable diet. The difficulty in diagnosing intra- from extra-hepatic causes of obstructive jaundice is beautifully shown in this case.

Dr. Doniach: It is not clear from the clinical notes whether she had vitamin K parenterally or whether she had it with her food.

Dr. Sherlock: She had it orally as an outpatient but it was given her intramuscularly in large amounts on her last admission from 16th to 26th.

Dr. Cope: Would you expect the vitamin K to act in that time on a person with a liver as damaged as hers presumably was?

Dr. Sherlock: I think that is a very reasonable point. I think that is why it did not act, though recent work on bleeding in jaundice shows that there are other accessory coagulation factors working besides vitamin K.

Dr. Bull: Had she been in bed for a long time before death to account for the decalcification?

Dr. Sherlock: No, Dr. Bull, she had not. She took to her bed just before her last admission on June 15.

Dr. Lennox: I do not think Prof. Dible demonstrated any bone sections. I did not take many sections, but my own impression was that she did not show any evidence of vitamin D deficiency.

Prof. Dible: No, I did not show the bones.

Dr. Fraser: I do not think it is clear whether she had osteoporosis or osteomalacia. She might have had osteomalacia because of her difficulty in absorbing vitamin D; but the fall in blood calcium and phosphorus is not very extreme in view of all the X-ray abnormalities, and furthermore you cannot see any Milkman’s pseudo-fractures, though the X-rays are not very clear on this point. So I think it must have been mainly osteoporosis rather than vitamin D deficiency, due to deficient protein absorption and general malnutrition plus age, though of course vitamin D may have been involved to a small extent. The histology of the bone should settle the matter; if there was no histological evidence of osteomalacia she did not have osteomalacia.

Dr. Lennox: That was certainly my opinion.

Dr. Sherlock: We rather thought that the low serum phosphate with the relatively normal serum calcium supported osteomalacia. Of course, in the presence of obstructive jaundice phosphatase is of no value in the diagnosis of bone pathology. I wonder whether the parathyroids were looked at—they are often hypertrophied in osteomalacia and not in osteoporosis.

Prof. Dible: The parathyroids were normal.

Dr. Fraser: I rather think severe osteomalacia due to vitamin D deficiency nearly always has a low blood calcium rather than merely a low blood phosphorus. The blood biochemistry in this case was more suggestive of slight osteomalacia or of osteomalacia due to a renal leak.

Professor King: Yes, but calcium in osteomalacia is not very low, and this is certainly on the low side. The very high phosphatase might very well be due to bone disease as well as the liver condition.

Prof. McMichael: Is not the ramus of the pubis—which was said to show fractures—one of the sites of Milkman’s fracture?

Dr. Fraser: We have just examined the X-ray of the axillary border of the scapula and the pubic rami. It is hard to be sure whether they are really pseudo-fractures or not; and it is very rare not to see them in cases where there is sufficient osteomalacia to produce multiple fractures of the ribs.

Prof. Dible: I am not quite clear how the histological examination should help us to differentiate between osteomalacia and osteoporosis. Perhaps you will tell us.

Dr. Fraser: In osteoporosis I imagine the primary deficiency is in nitrogen and in the growing capacity of the osteoblasts, so that you get thin bone seams laid down. In osteomalacia you get lack of calcium to lay down in calcification, so you have thick osteoid seams with a small amount of calcium.

Prof. Dible: Yes, but in both you get thinner bones.

Dr. Fraser: Yes, not histologically thinner, they are only thinner in grammes of calcium per unit area. Thicker seams of osteoid tissue is a characteristic feature of osteomalacia and if they are not thick I do not see how you can call it osteomalacia.

Prof. McMichael: I think that Dr. Russell Fraser should see the sections with Professor Dible and they should issue a combined report.*

Dr. Bearn: Would a cholangiogram taken at the time of operation have shown the site of obstruction?

Dr. Sherlock: I should think it might have

* It was agreed in later discussion that the sections showed no osteoid seams, but that in view of the limited material sectioned and the patient’s age that this did not entirely exclude vitamin D deficiency.
done so. We should have seen a block distally. It is an important point.

Dr. Harrison: Did Dr. Sherlock say that only 45 cases of intra-hepatic carcinoma of the bile ducts have been reported?

Dr. Sherlock: I thought so. I have not searched the literature very extensively however.

Dr. Harrison: I can show her two cases from records in this hospital.

Dr. Fraser: On that same point, may I ask if any of these recorded cases were diagnosed or treated ante-mortem, or had surgical treatment?

Dr. Sherlock: I do not think so. They are all autopsy reports.

Prof. McMichael: Could we have a surgical opinion on this?

Mr. Shackman: I think we have tried to treat such conditions surgically. I have, for instance, helped Professor Aird to anastomose an intra-hepatic bile duct to the intestinal tract, and it was temporarily successful.

Dr. Sherlock: I think perhaps I have been misunderstood about the rarity of the condition. I mean the rarity of carcinoma of the junction of the two hepatic ducts and the common bile duct, not of those lower down, which are relatively common. It is the high ones which are rare.

Mr. Shackman: I was referring to high obstructions. Those which are lower down are, of course, more amenable to surgical resection. The higher they are the harder it is to get at them.

Dr. Lennox: I suppose your point is, Dr. Sherlock, that if they are lower down they are easier to recognize, and if they are higher up they do not cause obstructive jaundice because one lobe or the other would continue to secrete; it is the ones at the level which produce the precise picture seen in this case which are rare.

Dr. Sherlock: Yes, just so.

Prof. Dible: Why is it that the bilirubin reaches a certain level and stays there? Why doesn't it go on rising all the time in complete obstruction?

Prof. King: I think it has gone up to 36 in this hospital, hasn’t it, Dr. Sherlock? In most cases of obstructive jaundice it spills out into the urine after it has reached a certain high level in the blood.

Dr. Sherlock: Yes, but this is a very good example of one which did not ever reach a high level. We have records for over three years and her serum bilirubin remained at a moderate level. It is a matter of the attainment of a state in which formation balances excretion. There is a decreased formation of bilirubin which is almost balanced by the output in the urine.

Dr. Lennox: Could I ask another rather theoretical question? What makes the liver in a case like this ‘hyperplase,’ if I might coin a word? If you take out three-quarters of the thyroid you get production of thyrotropic hormone and that makes the remaining thyroid grow. Here you have got continuous destruction of liver tissue for years and it is continuously being replaced. Has anyone any idea what makes it do this?

Dr. Harrison: G R. Cameron did some work on that in the 'thirties with Karunaratne.

Dr. Fraser: It is often said to be the result of direct stimulation by necrotic liver tissue.

Dr. Doniach: I suppose that the regeneration of the liver might be regarded as a response to the resultant additional load of work caused by the lessened total volume of liver tissue—a ‘work’ hypertrophy, comparable with that seen in the kidney submitted to an extra load.

Dr. Homer Smith: I want to say that I open my mouth in this conference just as a student. But there are three questions that I would like to ask. The first that I would like to ask Dr. Sherlock is about seeing yellow. This patient was said to be seeing yellow. Now I would like to know if she was asked any leading questions about that?

Dr. Sherlock: Yes, Dr. Homer Smith, it was in answer to a leading question. I always ask that question and it was the first time I have heard that answer.

Dr. Homer Smith: I thought so. The second question I want to ask is if you have any ideas about the origin of these vascular spiders. My third question—but before I ask that and get thrown out, I would like to comment on the preservation of the tissue in the superficial layer of the liver. Recent physiological studies indicate that all cells are constantly engaged in doing metabolic work in order to maintain their integrity, which requires oxygen consumption. I wonder if the injection of oxygen into tissues, the abdominal cavity or into any space where it would be retained temporarily has ever been tried as a means of preserving tissues against autolysis.

Now I come to my other question. I would hesitate to disagree with the diagnosis because I would be overruled here by at least 100 to 1, but may I ask if the diagnosis of carcinoma can be accepted with certainty? Is there a possibility of ascending infection, perhaps from the alleged mesenteric tuberculosis? Might it have been the primary factor in the obstruction and the carcinoma entirely accidental or coincidental, or perhaps even secondary to the cell changes?

Dr. Sherlock: Shall I deal with the spiders first? The vascular spider is said to be due to oestrogen effects. The liver cells fail to detoxicate oestrogen and you get an oestrogen effect on the skin vessels. Now that is by no means certain,
because studies of patients with cirrhosis have shown that the urinary excretion of oestrogen may not be particularly abnormal. Of course, that does not mean that the blood oestrogen is not raised. Anyhow that is the accepted explanation at the moment, though not a very good one.

Prof. Dible: The last question is a little complex and I am not sure that I remember all the implications. First of all it was a carcinoma, there is no doubt about that. They were carcinoma cells, although the glands looked very well developed, there was plenty of penetration and invasion of the perivascular and lymphatic channels. Secondly, could there be any relation between the carcinoma and the abdominal tuberculosis? I would say directly no, because abdominal tuberculosis is an extremely common condition and one that is met with often in the post-mortem room, perhaps not so often now as previously, but it is still a common enough condition and I do not think such a correlation has ever been demonstrated all this time. At the same time the presence of abdominal tuberculosis does raise certain points in the case which have been running through my mind, and one of them is that presumably in the mechanism of the absorption of fat the lacteals must have been obstructed by these necrotic glands. One knows that the lymphatic network is so extensive that there must have been plenty of by-paths; at the same time it is possible that the absorption of neutral fat may have been interfered with and that the alternative mechanism may have been over-active. So that although I cannot see all the way along the route I am trying to travel, it is possible that the participation of the liver in fatty acid absorption may have been over-active and that that may have led to some pathological condition in the liver a long way back which may have expressed itself as a carcinoma of the ducts.

Dr. Sherlock: If that is so it is queer that we do not have some fatty change in the liver. Most of the steatorrhoeas and chronic diarrhoeas which we have seen showed fatty change in the liver and we have related that to an increased portal vein absorption of fat.

A student: Is it not possible that the obstruction was primary and that led to cirrhosis of the liver and then to carcinoma?

Prof. McMichael: I think this is not the type of carcinoma which complicates cirrhosis of the liver. This cancer must have been primary and the cause of the obstruction, that is the obvious interpretation.

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