JAUNDICE PRESENTING UNUSUAL FEATURES

BY

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Four cases of jaundice coming under observation at a Naval hospital within a very few months presented unusual features. The pathological reports upon material removed at operation from the liver of two patients with "subacute hepatitis" constitute a valuable addition to the case records; the following is the story of "four instructive mistakes."

Case I. Jaundice due to Subacute Hepatitis: Exploratory Laparotomy: Recovery

An officer aged 24 was suddenly seized with acute abdominal pain at the end of Jan., 1942; it was fairly generalized, but the maximal intensity was in the epigastrium. The pain was colicky, and came on in spasms, which "doubled him up" and were followed by intervals of comparative freedom, although a dull ache persisted between the "spasms." This first attack lasted about 12 hours, but was not associated with vomiting; the pain gradually wore off. For nearly two months after this attack the patient had little appetite, felt "out of sorts," and experienced occasional pain of moderate severity in the upper abdomen. During early April a second stage may be said to have begun with frequent severe attacks of abdominal pain at night; there was no radiation of pain to the back or lumbar region. His urine was dark in colour and his skin and conjunctivae looked slightly yellow; there was no pruritus.

His general condition deteriorated, and on admission to a Naval hospital for further investigation the jaundice was marked and of a deep yellow colour; all pain had now disappeared. He was considerably emaciated, but cheerful and optimistic in outlook. Severe persistent headache and dimness of vision were other symptoms; at no time was there any vomiting, although nausea was complained of occasionally after meals. The liver was slightly enlarged and tender; the gall-bladder could not be felt: the spleen was not palpable. The tongue was furred; the teeth were good, but there was considerable sponginess of the gums, which bled on the slightest pressure. No enlargement of glands in axillae, neck, or groin was found. The urine was dark and contained bile pigments and bile salts.

A direct van den Bergh gave an immediate positive reaction. Quantitative indirect gave 7.2 mg. (14.4 van den Bergh units). Paul-Bunnell test was negative. Blood picture: R.B.C., 4,550,000; Hb, 86% (Haldane); C.I., 0.95; leucocytes, 5,200—polymorphs 45%, lymphocytes 45%, large mononuclears 5%, eosinophils 2%, mast cells 0, basophils 0; B.S.R. (Westergren), 11 mm. in 1 hour, 22 mm. in 2 hours; Wassermann, negative. Radiographs revealed no opaque calculi. The pulse was regular about 80; temperature showed a slight evening rise. The past history disclosed nothing of significance. He had never served outside British waters.

The clinical picture was not characteristic of any of the more frequent types of jaundice, but the most probable diagnosis appeared to be an obstructive jaundice due to cholelithiasis. The prolonged jaundice was considered to necessitate an exploratory laparotomy. After the liberal administration of glucose and vitamin K, operation was performed on April 21. The liver was moderately enlarged, but its surface smooth and its outline even; nothing abnormal was seen in the appearance or texture of the gall-bladder. No gall-stones could be felt in gall-bladder or ducts. An enlarged lymph gland was found near the cystic duct, and two more were easily palpable along the common bile duct, but it was obvious that these two glands were not obstructing the flow of bile; the lesion was evidently intrahepatic. Two of the lymph glands were removed for microscopical purposes and a small portion of liver was also resected. Bleeding at the operation was minimal.

Pathological Report (Dr. W. W. Woods).—"Subacute hepatitis: There is severe albuminous and vacuolar degeneration of the liver cells, their cytoplasm being swollen, coarsely granular, and vacuolated, and their nuclei showing karyolysis. In frozen sections sudanophil fat can be found in only a few scattered cells. Disappearance of a few liver cells as the result of necrosis has occurred in the centres of the lobules, where there is conspicuous dilatation of the sinusoids. There is bile pigmentation of the liver cells, but there are only a very few bile thrombi in the canaliculi. Regeneration of parenchyma is indicated by many cells with two nuclei, some of them having

deeply eosinophilous cytoplasm; only one mitotic figure can be found. Inflammatory infiltration is almost confined to the portal systems, extending thence only slightly between liver cells. It is more severe in the smaller than in the larger portal systems. It consists of numerous lymphocytes, a few eosinophil leucocytes, and very few neutrophil leucocytes. There has been slight proliferation of fibroblasts, but there is no fibrosis. The bile ducts are normal and empty. In the lymphatic glands from the region of the cystic and common bile ducts there is a pronounced degree of hyperplasia of the endothelial cells of the lymph sinuses (sinus catarrh)."

Post-operative progress was uneventful. Glucose was given freely, and occasionally small doses of calomel and magnesium sulphate. The jaundice began to diminish as the general condition improved, and six weeks after operation had entirely disappeared. The officer was ultimately sent on sick-leave.

Case II. Jaundice due to Subacute Hepatitis: Exploratory Laparotomy: Death Two Months after Operation

An officer aged 34 complained in Aug., 1940, of a sensation of fullness in the abdomen, flatulence, loss of appetite, and general debility, present for some weeks; no previous history of any similar illness. He was jaundiced, the icterus being of moderate intensity. The abdomen was somewhat distended, the distension being uniform; the liver could be palpated beneath the right costal margin.

After several weeks, during which the jaundice increased somewhat in intensity, he was admitted to a Naval hospital. By this time jaundice was marked, and the patient listless and disinterested; he had lost much weight, and his appetite was poor. The abdomen was distended, tumidity being most pronounced in the right hypochondrium, the musculature of which showed some rigidity. The liver was enlarged, and its lower border was felt three finger-breadths below the costal margin; the outline appeared fairly regular, and there was tenderness on pressure over it. The gall-bladder was not palpable: no enlargement of spleen or kidney could be detected. The glands in the groin, axillae, and neck were not involved. Rectal examination yielded no positive information of value. The urine contained bile salts and bile pigments.

Faeces were slate-grey in colour; total fats 64.48 g.%—neutral fats 2.8%, soaps 36.68%, free fatty acids 25%; no pathogenic bacteria, cysts, or ova. A blood count showed: R.B.C., 4,110,000; Hb, 88% (Haldane); C.I., 1.08; leucocytes, 6,800—polymorphs 51%, lymphocytes 43%, large mononuclears 4%, eosinophils 2%. Slight anisocytosis and achromia were noted. Fragility of red cells, bleeding time, and coagulation time were within normal limits. The van den Bergh gave an immediate direct reaction. The laevulose-tolerance test showed no impairment of hepatic efficiency. The Wassermann reaction was negative on several occasions. A straight radiograph showed no opaque gall-stones. The gall-bladder was not seen by opacol radiograph. No calculus or other abnormality seen. The patient stated that during the previous 6 or 8 months while serving in small ships he had frequently been exposed for two or three hours daily to acetylene fumes in his cabin. However, no others exposed to similar fumes had reported sick.

The hope still lingered that the case might be one of "catarrhal jaundice," and initially in hospital the patient was treated expectantly by glucose, fat-free diet, and an occasional dose of calomel and magnesium sulphate. His condition, however, steadily declined; his appetite and weight decreased, and his jaundice became more intense. The possibility of a neoplasm involving the main bile channel now obtruded itself more and more menacingly: exploratory laparotomy was considered necessary. At operation the liver was found to be much enlarged and of firmer texture than normal; here and there the organ showed definite scarring, and a definite thickening could be felt in the portal fissure. The gall-bladder was of small size, whitish, and quite empty. The common hepatic and bile ducts were not dilated, and the obstruction was obviously above the junction of the hepatic and cystic ducts; the thickening in the portal fissure seemed to localize the obstruction to the very commencement of the extrahepatic canals. The spleen was not enlarged. A wedge of liver tissue was removed for microscopical examination. The findings at operation suggested either a malignant growth in the portal fissure or a syphilitic hepatitis despite the negative Wassermann reaction. Further serological tests also proved negative.

Pathological Report (Dr. W. W. Woods).—"Subacute hepatitis with portal fibrosis: The portal fibrosis is of a subacute, active, recent type. Thus the portal systems in every lobule are uniformly enlarged by a rarefied oedematous network of thin and thick collagen fibres and moderately numerous, rather slender fibroblasts. They are infiltrated with numerous lymphocytes, remarkably numerous neutrophil

leucocytes, a few round and spindle macrophages full of bile pigment, and a few plasma cells. There is considerably less inflammatory infiltration in the large portal systems than in the small. This infiltration has spread between the liver cells of the periphery of the lobules. These inflamed fibrotic portal systems contain numerous regenerated pseudo-bile canaliculi, which seem to have budded out from the liver cells; they contain much bile pigment, mostly in their lumina, some in the cytoplasm of their cells. The fibrosis is unilobular. There has been no nodular regeneration of liver cells to disturb the normal lobular pattern. Regeneration of single cells is indicated by the presence of two nuclei in some cells. There is albuminous degeneration and vacuolation of liver cells, and the nuclei of many show karyolysis. In one group of liver cells vacuolation is conspicuous. In the absence of frozen sections the presence of fat cannot be determined. In the centres of the lobules there is slight inflammatory infiltration. There is much bile pigment in the liver cells, and large bile thrombi are numerous in the bile capillaries. The bile ducts in the small and large portal systems are not dilated and are empty except for a very little coagulum in one of the larger ducts. All arteries and veins are normal."

The patient recovered from the immediate effects of the operation, and some two weeks later was able to get up and walk about. However, he subsequently relapsed, and increasing debility and progressive emaciation necessitated his return to bed. Jaundice steadily increased, and ascites developed so that regular paracentesis had to be employed to relieve the abdominal distension. Death occurred about 2 months after the laparotomy.

Comment on Cases I and II

Clinical jaundice readily suggests the three most frequent groups of cases characterized by this arresting symptom, and attempts were made to assign the patients to their particular category: (a) catarrhal jaundice; (b) the effects of cholelithiasis; and (c) malignant obstruction of the extrahepatic biliary channel. In both of the above cases an erroneous pre-operative diagnosis was made, but material removed at laparotomy led to the diagnosis of subacute hepatitis from the pathological laboratory. The term "hepatitis" suggests vagueness of diagnosis, since it may include all the results of damage to the liver, chemical or physical, or due to the action of micro-organisms and their toxic products. It might also include the various processes of reaction and repair which follow the injury. Unfortunately, in these two cases the precise cause of the hepatitis is still wanting.

It must be most exceptional in a case of hepatitis to have the onset of the disease heralded by symptoms of such severity as to suggest gall-stone colic. The persistence of the jaundice which followed the last attack of severe pain in Case I seemed to demand surgical investigation and some operative effort to relieve the obstruction. The absence of any gross obstruction along the course of the extrahepatic ducts occasioned the greatest surprise.

The pathological diagnosis of a hepatitis suggests some relationship to so-called "catarrhal jaundice," in which severe pain certainly never occurs. Doubtless both conditions are due to an infective agent, and recent investigation into the cause of catarrhal jaundice tends to demonstrate the infectivity of the disease and its possible spread by droplet infection (Newman, *British Medical Journal*, 1942, 1, 61): many cases have been found in a locality among individuals living together or spending their lives in fairly close contact, but in our case the officer was certain there had been no similar cases among his colleagues. He gave no history suggestive of gastro-duodenal catarrh as the early pathology of the condition. The pathological findings are of unusual interest because of the rare occurrence of a biopsy of liver tissue in this disease and because of the severe degeneration of the liver cells seen in section, amounting in some areas to a complete atrophy.

In Case II the absence of pain, the increasing jaundice, and the emaciation suggested the possibility of a neoplasm, and an exploratory laparotomy seemed to be indicated. The fibrotic changes and scarring in the liver seen at operation raised the question of a syphilitic infection, but serological tests negated this suggestion. The spleen was only slightly enlarged, and detached blood examination excluded any of those blood dyscrasias associated with gross splenic and hepatic enlargement with cirrhosis. The whole pathological process was intrahepatic; and the hepatitis was considered to be toxic in origin, the

identity of the actual toxin remaining obscure. The patient had volunteered the information of his exposure to acetylene fumes while asleep in his cabin, adding how listless and unrefreshed he felt in the morning. However, no reference in the literature could be discovered relating to acetylene as producing hepatitis with jaundice; but whatever the toxin was, its virulence was demonstrated by the unfavourable course of the illness and its fatal termination.

Case III. Jaundice due to a Mass of Lymphadenomatous Glands compressing Main Bile Channel. A Case of Hodgkin's Disease, Rapidly Fatal

An officer aged 27 was admitted to hospital in March, 1942, with a history of increasing jaundice of about 10 weeks' duration. He complained of loss of appetite, constipation, and general debility; about 7 days later jaundice appeared, and he was treated by a light fat-free diet, glucose, and abundant fluids. No improvement took place, and 6 weeks later an indefinite swelling, thought to be a distended gall-bladder, was felt in the right hypochondrium. A straight radiograph showed a vague opaque shadow which suggested a gall-stone. Further facts were now elicited. At no time had he any pain—only a feeling of intermittent discomfort in the abdomen; there was no history of digestive trouble, and no similar cases had occurred among his colleagues. He was losing weight rapidly. Early in 1940 he had suffered from pleurisy, but his recovery was apparently complete, and full investigation had suggested no possibility of persistent tuberculous infection.

When admitted to hospital he was deeply jaundiced and emaciated. The liver was slightly enlarged and could be felt beneath the costal margin, but a movable swelling was now easily felt in the right hypochondrium, extending down to the right iliac fossa, and not continuous with the liver margin; this appeared to be a distended gall-bladder. Neither the kidneys nor spleen were palpable. One rather large discrete solitary gland was felt in the right supraclavicular fossa; this was not tender, and was not attached to the skin or deeper structures. No glands were palpable in the axillae; and those in the groin were within normal limits. No abnormality was detected per rectum. Almost the whole of the body was covered by a diffuse rash, produced by constant scratching due to the intractable itchiness of the skin. The urine showed no abnormality except bile salts and pigment and a faint trace of albumin. R.B.C., 4,050,000; Hb, 80% (Haldane); C.I., 0.9; leucocytes 7,000—polymorphs 65%, lymphocytes 20%, large mononuclears 4%, eosinophils 1%, mast cells 0. Wassermann reaction negative. A direct van den Bergh gave an immediate positive reaction; quantitative indirect, 20 mg. (40 van den Bergh units) per 100 c.cm.

A second straight radiograph a week after admission showed a shadow to the right of the ascending aorta in an antero-posterior view of the chest. The cervical gland enlargement was considered to be either secondary to some intra-abdominal neoplasm or, alternatively, of lymphadenomatous nature. The biopsy pathological report was provided by Dr. I. Doniach, pathologist to Mount Vernon Hospital, who reported: "The architecture of the gland is destroyed by a reticulum-cell hyperplasia. Scattered throughout are numerous giant cells of the Dorothy Reed type, together with a good number of lymphocytes, eosinophils, and plasma cells. The cells have laid down only a moderate amount of collagen. Fairly numerous mitotic figures were observed. The picture is typical of Hodgkin's disease." Within a month the patient's condition was miserable in the extreme. The pruritus had become much worse, and sleep was impossible without large doses of sedative, morphine frequently being necessary. Although the prognosis appeared hopeless, and further blood counts showed a progressive anaemia, it was considered desirable to perform a cholecyst-gastrostomy in an attempt to relieve the pruritus.

At operation, on April 4, the gall-bladder was greatly distended, and rather more than half a pint of fluid was aspirated before the anastomosis was done. Examination of the fluid revealed no bile pigment and only a trace of bile salts; cholesterol was found in the merest trace. A large mass of glands was felt in the portal fissure and along the common bile duct. The spleen was enlarged to about twice normal. The anastomosis was rapidly completed and the abdomen closed. The patient failed to rally from the operation and died the following day.

At the time of the patient's admission to hospital the diagnosis was fraught with less difficulty than that which obtained at the onset of the illness. The progressive painless jaundice associated with an enlarged liver, the considerable distension of the gall-bladder, the enlarged gland in the right supraclavicular fossa, and the gradual emaciation strongly

suggested a sinister cause of bile-duct obstruction. The biopsy proved the cervical gland to be lymphadenomatous, and the laparotomy deemed necessary by the severe pruritus gave evidence of the rare nature of the obstruction to the main bile channel.

There are certain unusual features about this case. Death indirectly due to cholaemia from obstruction to the main extra-hepatic bile channel by a mass of lymphadenomatous glands is exceptional, although Rolleston and McNee do make reference to the possibility of compression of the chief bile channel by such a mechanism. These authors note that jaundice is infrequent in lymphadenoma, but allude to possible glandular compression of the common duct; they also mention two cases of periodic jaundice in Hodgkin's disease, the jaundice coinciding with fever and enlargement of superficial lymphatic glands. In Hodgkin's disease it is most exceptional for the clinical picture to be dominated by obstructive jaundice and its consequences; the rapidity with which these hastened the fatal ending of the case contrasts with the natural history of the malady: in 15 weeks from the first symptom the disease had proved fatal. The case presented other atypical features: the lymphatic glandular involvement was far less widespread than usual; one discrete enlarged lymphatic gland palpable on the right side of the neck, and the existence of a possible second in the posterior mediastinum demonstrated by radiograph, constituted the only evidence of the disease. The operation performed to relieve the pruritus enabled us to discover a glandular mass in the portal fissure which had produced the jaundice; further, the lymphatic involvement was more or less confined to those glands. It will be recalled that this patient was investigated after pleurisy some 18 months previously, and although no evidence of active tuberculous disease was found, the theory of the possibility of a coexistence of the two maladies or even of their causal relationship is revived.

Case IV. Calcified Mass embedded in Head of Pancreas compressing Lower End of Common Bile Duct: Removal: Recovery

A stoker aged 49 was admitted to a Naval hospital with 4 months' painless jaundice. An enlarged liver and a distended gall-bladder suggested a growth obstruction of the choledochus. A two-stage operation was done after taking pre-operative measures. At the preliminary cholecyst-gastrostomy a firm lump could be felt near the lower end of the common bile duct, and the pre-operative diagnosis of an "ampullary carcinoma" seemed to be confirmed. At the second operation the mass was found embedded in the head of the pancreas, and was removed with some adjacent pancreatic tissue by a retro-duodenal approach. The choledochus was seen to be compressed but not infiltrated, and was not injured during removal of the "tumour."

The pathological material proved to be a mass of agminated calcified tuberculous glands. Surgeon Rear-Admiral Gordon-Taylor, who operated on the case and recently reported it, remarks: "There was perhaps some justification for the mistake in diagnosis, but at least the patient is to be congratulated on the pathological nature of the compressing mechanism, which before this experience I might have seriously doubted."

Summary

Four cases of jaundice have been described in which a diagnosis based on careful clinical examination, reinforced by laboratory and other investigations, was proved by operation to be inaccurate. The experience and knowledge to be gained from them appear to act as a deterrent, and to justify restraint on the practitioner who feels confident in his capacity to assign correctly to a particular category any case of jaundice on clinical grounds alone. The descriptions given above demonstrate that although the cases had not a few features in common, nevertheless the exact pathological detail obtained as the result of operation proved that the morbid process varied greatly. Specific infectivity, toxicity, granulomatous disease, could all be considered in the course of diagnosis. It is also worthy of note that despite our surprise in being able to exclude malignant neoplasm on three occasions (Cases II, III, and IV), yet in two of these (Cases II and III) the disease ran a fatal course in a comparatively short period. Case IV claims special mention in being apparently illustrative of its author's hope that palliative treatment for neoplasms in the region of the pancreatic head may sometimes be replaced by radical surgery, offering a reasonable prospect of cure.

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DEFICIENCY DISEASE AND ACADEMIC EVIDENCES OF SUBNORMAL VITAMIN METABOLISM

BY

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The present war with its food restrictions and black-out conditions inevitably focused attention on vitamins throughout Great Britain. Interest in the essential food factors, which was extensive before the war, flared up in both academic and trade circles. Eventually, through the media of the medical and general press and official and unofficial propaganda by circular, screen, and air, the public and the profession became almost hysterically vitamin-minded.

In certain directions there was a complete loss of perspective, incompatible with an emergency which demands a realistic view of the practical issues at the fighting fronts over-seas, and conservation of academic energy at home for more essential problems. In fact, the cult of vitamin deficiency both here and in the U.S.A. has become in part a racket. This state of affairs is largely due to the premature booming of experimental observations, and the attempt to fit them into the jigsaw of human physiology, psychology, or pathology as the case may be. The clinician is not blameless. He lends support to the situation by the empirical use of proprietary vitamin products in all manner of affections and in acclaiming their value by *post hoc* argument. However important the study of vitamin deficiency, the application of academic findings to the maintenance of fighting efficiency should be discussed at a level compatible with total war. Such discussions can hardly be conducted in perspective by those who have no first-hand experience of the clinical aspects of the vitamin deficiency disease syndromes as they exist in man and of the conditions appertaining at the various fronts. Yet just now probably more attention is given to theoretical considerations in this connexion, both here and in the U.S.A., where the clinical picture of frank vitamin deficiency disease as it appears in man is familiar to few, than in parts of the world—such as China, Russia, India, Africa, and Japan—where the human manifestations constitute a familiar everyday problem, the practical economic importance of which is great but subordinate to more urgent issues.

General statements such as these demand at least some support. Let us take the case of night-blindness in vitamin A deficiency.

Vitamin A Deficiency and Night-blindness

Night-blindness, better referred to for psychological reasons as "hemeralopia," is a prominent symptom of A-deficiency disease. It is the only subjective symptom until the later stages of the disease syndrome. This syndrome constitutes an important ever-present economic health problem in large population groups in various parts of the world, such as in the above-mentioned countries.

Frank predominant vitamin A deficiency disease is common in the Madras Presidency, which has a population bigger than that of England and Wales. Its manifestations differ in children and adults or, as Frazier and Hu (1934) have suggested, in the pre- and post-puberty periods. I have for years urged that it is the greatest cause of preventable blindness in children in South India on account of the associated corneal metaplasia or keratomalacia (Wright, 1931, 1937). The latter term is commonly used for convenience throughout the Far East for the whole syndrome, which emphasizes the importance of this complication. The most common sign, and possibly the earliest clinical evidence, of this syndrome is smokiness of the conjunctiva. This is my own view, and might possibly be disputed by such experienced clinical observers as Frazier or Pillat. I formerly held that night-blindness was the earliest evidence of keratomalacia (Wright, 1934). This conjunctival sign is unrecognized or not considered worthy of mention by those who discuss the effects of vitamin A deficiency in this country, probably because few of them have ever seen the disease as it exists in man. Kirkpatrick (1936) mentions it. It is well recognized in China (Mu *et al.*, 1937). It is not referred to by Nicholls (1938) of Ceylon: this is hardly because he does