the amount of the sugar present must be taken into account. The fluid obtained from the organ must be titrated before and after hydration with sulphuric acid. In making such an estimation the organ was extracted with alcohol, and the extract divided into two parts: the sugar in one half was estimated at once with the ammonio-cupric test; the other half was treated with sulphuric acid, and titrated again. If the second estimation gave a higher figure, it was a proof that the sugar in the organ was a sugar differing from glucose, and approaching nearer to maltose. Experiments with cold blooded animals, in whom *post-mortem* changes were slow, gave, as might be seen from the tables, exactly similar results, that is to say, the amount of sugar in the liver and other structures was practically the same.

At the conclusion of his lectures, Dr. Pavy demonstrated lantern slides of ozazones from various sources, among others from certain organs, from beef tea, and from peptonised meat.

REMARKS ON CIRRHOSIS OF THE LIVER, WITH ESPECIAL REFERENCE TO ITS OCCURRENCE IN CHILDREN, AND TO THE MODE OF DEATH IN CIRRHOSIS WITH JAUNDICE.

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I PROPOSE in this paper to narrate certain cases of cirrhosis of the liver in children, in which careful microscopical examinations were made, and to describe and discuss the pathological changes observed.

CASE I.—F. H., aged 7 months, was brought to the hospital as an outpatient in August, suffering from jaundice. The mother said the jaundice had first appeared about two weeks previously, and, except for this, the child seemed in good health. The child was deeply and universally jaundiced, but otherwise was fat and well nourished, looked lively, and was easily induced to crow and laugh. There was no sign of rachitis; the thoracic and abdominal viscera were normal; the pulse, respiration-rate, temperature, also normal. For the last few days there had been slight diarrhœa, with the passage of green, watery stools. There was no vomiting. The child had always been fed at the breast. A few days later the condition was about the same, except that the diarrhœa had ceased; the urine was found to contain much bile pigment and a little albumen. For the next two or three weeks the symptoms were unaltered, but towards the end of that time the child became rapidly worse. When brought up to the hospital, on September 3rd, an alarming change had taken place. The pulse was hardly to be felt, rate 140; respiration rate 40. There was great œdema of the legs, and marked general anasarca. No ascites. There were purpuric spots in various situations, the largest the size of a threepenny piece on the left anterior axillary fold, and others on the right thigh, on the abdomen, and left foot. The infant lay in a listless state, uttering a feeble cry from time to time; the anterior fontanelle was depressed; there had been almost entire suppression of urine during the previous 24 hours, and a little blood had been passed *per anum*. The mother now consented for the child to be admitted. When lying in bed the little patient became very restless, often cried as if in pain, and drew the legs up on the abdomen; when the mother came to her she took the breast eagerly. The edge of the liver could be felt to be rounded and to come a little way below the ribs. She passed into a semi-conscious state, in which she remained till death, on the following morning, September 4th, at 6 A.M. The respiration and pulse rates became quicker and quicker, the former being 60 to 80, and the latter 160 when last counted. The temperature began to rise at 6 P.M., and steadily rose till it reached 101.2° at death; previous to this there had been no elevation of temperature. A little urine was passed during the night, which contained albumen, bile pigment, and reacted readily to Pettenkofer's test for the bile acids. Careful questioning elicited no history of syphilis in the child's parents; there were no signs of it in either the mother or child, and the latter had never suffered from any symptoms of congenital syphilis. See had never had measles or scarlet fever. The home was a healthy one, and the parents were temperate.

At the necropsy the body was well nourished; there was extreme anasarca, with rather a waxy appearance of the skin; the conjunctivæ were deeply jaundiced, the skin less so except over the thorax; *rigor mortis* absent; lungs very bloodless but otherwise healthy; heart muscle substance very pale, but the valves were normal. On opening the abdomen it was found to contain a considerable quantity of dark fluid blood, which was also contained between the layers of the great omentum. In the hilum of the left kidney and in the perirenal connective tissue was a large extravasation of blood; that in the hilum had clotted, a dark clot closely surrounding the renal vein; at one spot the lining membrane of this vessel was dark and blood-stained, and looked softened. As far as I could ascertain this had been the seat of hæmorrhage around the kidneys; the blood did not come from the kidney itself. The aorta, the inferior vena cava, and their large branches were found to be healthy. The portal vessels were large, but I could not discover any other seat of origin for the hæmorrhage, which might, however, easily have been overlooked. The liver weighed 4½ ozs. and came about to lower border of ribs. Capsule appeared normal, surface smooth and pale. On section it was studded with granules or nodules, the granules being dirty yellow in colour, raised, consisting of the liver lobules, massed together in groups, and separated from each other by pale fibrous tissue which surrounded them. The portal vessels were dilated; the gall bladder was contracted and empty, the bile ducts not obstructed; there was no lardaceous change in the liver. The spleen (1 oz.) was congested and enlarged, and Malpighian bodies somewhat large and translucent; no iodine reaction was obtained. Each kidney weighed 2½ ozs. Capsules stripped easily, leaving a smooth, pale surface. On section the surface was smooth, the cortex was broad (1-3) in relation to medulla, pale yellow in colour, with a streaky appearance. Vasa recta rather full; pyramids pale. The boundary zone was deeply congested, contrasting with pallor of other parts of kidney. The kidneys showed a beautiful example of a more or less general cloudy swelling of the epithelium of the convoluted tubes; otherwise they were normal (Fig. 6). Except that the other organs were rather bloodless, the brain soft, and the dura mater adherent to the cranial bones, no other morbid changes were noted.

To return to the liver. The central parts and the right lobe contained less connective tissue, were softer and more brilliantly coloured; the peripheral parts, and the left lobe were paler and firmer, with more connective tissue. Sections were taken from all parts, and stained in eosin and logwood, methylene blue, picro-carmine, and osmic acid, fuchsine, and methylene blue. In all parts the ordinary structure of the liver and its arrangement into lobules could no longer be distinguished. In the softer parts the field of the microscope is occupied by a finely granular, almost homogeneous material, arranged in a more or less reticular fashion, amongst which lie the remains of the degenerated liver cells, containing pigment granules, minute oil droplets, and often vacuolated. In some fields there are very many, in others very few of these liver cells. In very thin sections the liver cells have almost entirely disappeared, probably partly dropped out in preparing the section, and the character of the intracellular connective tissue appears as a fine soft granular reticulated stroma (Fig. 2). In most parts there is scanty round-celled infiltration, and in a few minute hæmorrhages. In the firmer parts (left lobe and for a depth of about ¼-inch under the capsule) the liver substance was composed of much more fully formed and firmly set connective tissue, with greater infiltration of round cells. In this tissue the remains of the hepatic cells were embedded. The capsule itself was quite thin and of healthy appearance. In the firmer connective tissue close to the older vessels can be seen a few newly formed blood capillaries. In most sections the connective tissue is richly nucleated; these nuclei are irregular in shape but mostly small, as if they had recently divided, and the discovery of a spot under the liver capsule, in which were a number of liver cells whose nuclei were actively dividing, suggests this source for the origin of some at least of the nuclei. Throughout the liver there is an overgrowth of firm connective tissue in the portal areas, and in parts trabeculæ extend from them into the liver. There are no newly formed bile canaliculi, the arteries, large and small, everywhere show signs of endarteritis; their lumen being choked by a structureless material containing very numerous large elongated nuclei with prominent nucleoli, evidently arising from proliferation of the endothelial cells. The internal coat appeared to be more or less disorganised, and the elastic membrane of Henle often broken up or unrecognisable. The muscular coat was thickened and its nuclei very abundant, the external coat normal. (See Figs. 3 and 5.) Similar changes were found in the bile ducts, medium sized and small, their lumen being in most cases choked by the products of the disintegrated and proliferated epithelium and their coats thickened. (Fig. 4.) The portal veins were dilated. There were neither micrococci nor crystals of leucin or tyrosin present.

The condition in the liver seemed to consist of an inflammatory exudation of the vessels, with a rapid formation of fine connective tissue throughout the organ, attended with atrophy of the liver cells; the process being more advanced and the connective tissue more completely developed in some parts than in others. The connective tissue appeared to take its origin from the connective tissue of the portal areas and to spread throughout the lobules between the rows of cells from the periphery to the centre; the process being, in short, an acute diffuse cirrhosis accompanied by a very rapid destruction of liver cells. A powerful agent in accomplishing the latter change would be the proliferation of the endothelium in the arteries, which by choking their lumen would

quickly and seriously diminish the supply of blood to the organ, and thus induce necrosis of the liver cells. No doubt the pressure of the newly formed connective tissue would also aid in the destruction of the cells. I do not think it likely that endarteritis was the primary change in the organ and the sole cause of the growth of connective tissue and of the cellular atrophy. Rather is it probable that the endarteritis and inflammation of the duct epithelium accompanied the acute cirrhotic process, and that both endarteritis and cirrhosis were due to a common cause, namely, to the intense irritative changes taking place in the liver during the rapid formation of connective tissue and destruction of cells. At the same time, the endarteritis must have secondarily helped to bring about the destruction of liver cells. Knowing the frequency with which endarteritis occurs in syphilitic new formations, have we to do here with syphilitic interstitial hepatitis? Almost the only argument in favour of syphilis being the cause of the condition lies in the presence of endarteritis. But the changes in the vessels in this case do not correspond with those of syphilitic endarteritis. In this disease there is a round-celled infiltration and growth of connective tissue in the internal coat of the arteries, while in my case there was no such change, but an active proliferation of the endothelium only.

If the figures are compared with the drawings of syphilitic endarteritis in Cornil and Ranvier,[1] or with those of Dr. Sharkey[2] in the *Pathological Transactions*, the difference between the two is at once apparent. The changes in the liver do not correspond to those described in published cases of congenital syphilis of the liver. Stress is always laid on the presence of miliary gummata, which are visible to the naked eye, and the growth in syphilitic disease shows no relation to the portal canals.[3] There were no syphilitic changes in the other viscera; no symptoms during life, though the child was aged 7 months; no history of syphilis in the parents; and I gather from records of such cases that where interstitial hepatitis forms one of the lesions of congenital syphilis the child generally dies in the first few weeks of life. Further, the epithelium of the biliary ducts showed precisely the same changes as the arterial endothelium, and was presumably due to the same cause. I cannot find, however, that such a lesion of the ducts has ever been described in congenital or acquired syphilis. Endarteritis is, finally, sometimes found in interstitial inflammations of organs.

On these grounds, then, I conclude that the morbid process in the liver was not due to syphilis, and that it was an acute diffused cirrhosis, accompanied by a rapid destruction of the liver cells, the latter being, at any rate in part, due to a widely-spread endarteritis.

The distinction from acute yellow atrophy lies in the presence of the connective tissue, in the changes in the vessels and ducts, and in the almost complete destruction of the liver cells, whereas in acute yellow atrophy some healthy lobules can generally be found. It is, perhaps, worth while incidentally to point out the relations of the change in this case with the conditions found in the parts of the liver affected with so-called "red atrophy" in those who die of acute yellow atrophy.

Wilks and Moxon say that here "an inflammatory condition is proved to exist not only by these pus-like cells in certain cases, but also by the thickening of the vascular stroma, which resembles the thickening of it in cirrhosis, differing from this chiefly in two points, (1) that it extends more uniformly throughout the lobules, instead of being limited to the tracks of the portal vein, as in cirrhosis; (2) in the destruction of the liver cells being greatly beyond what the pressure of this thickening will explain."[4] The morbid changes in this infant's liver seem to form a connecting link between acute atrophy on the one hand and an acute cirrhosis on the other. I have been able to find two similar cases, both in young children. Dr. Ormerod[5] reports on the liver of a child aged 6 months: "The hepatic cells appeared as scattered irregularly-shaped bodies, embedded in finely fibrillated connective tissue, the latter uniformly distributed, and not limited to area of portal veins. The liver was pale, firm, and smooth, and on section of a uniform lemon-yellow colour, with no trace of proper structure; it was enlarged, reaching half way between umbilicus and pubes. There was no history of syphilis or struma in parents. The child was suckled, and died of progressive asthenia, with enlargement of abdomen of two months' duration." The difference from my case appears to lie in the larger size of the liver and absence of arterial changes.

The other case described by Dr. Goodhart corresponds more closely.[6] A female child, aged 23 months, suffered from jaundice for one week; after a few days fever and vomiting came on, and she died in convulsions with a temperature of 102° F. on the thirteenth day from the onset of the jaundice. The child was well nourished, the liver extended half way to the umbilicus. There was no syphilis. The liver weighed 14 ozs., was large, hard, dirty yellow, or purple; liver cells fatty, cystic duct obliterated, others pervious. Microscopically the "liver sections were crowded with nuclei which studded a small-meshed connective tissue. The hepatic cells were clamped in masses between this new growth, and were greatly diminished in number; many of them contained fat globules, but their nuclei were for the most part distinct, though they often appeared increased in number; no connection could be traced between them and the nucleated tissues outside them. The lobules were affected throughout with remarkable uniformity from periphery to centre, although in some parts there was some slight excess of growth in the portal area, but the smaller hepatic ducts .....were conspicuously absent." This case differs from that of F. H., chiefly in the greater destruction of the liver cells in the latter; otherwise they closely correspond.

Dr. Goodhart thinks that the changes must be regarded as cirrhotic rather then atrophic. Both these cases are distinguished from mine by the absence of lesions of the lining membranes of the arteries and ducts, but the general changes throughout the liver and the clinical course and symptoms of Dr. Goodhart's case show a close resemblance.

I should be inclined to consider the early occurrence of jaundice in the above case partly to the obliteration of the minute biliary canaliculi by the newly-formed connective tissue, partly to the proliferation of the epithelium of the ducts.

The character of the extensive destructive changes in the liver in my case suggests the action of some intense poison, either organised or chemical. In the sections stained with methyl blue, fuchsin, etc., no micrococci or other organisms were observed.

CASE II.—A. J. C., aged 12, was admitted into the Bristol General Hospital on June 8th. The history given by his mother was that, twelve days before, the boy had had some febrile symptoms, with pain in the head and sore throat, and on this account he stayed in bed for two days; after this he got up and went about his ordinary work. He soon noticed, however, that his abdomen, feet, and legs were beginning to swell; the swelling was most marked in the abdomen and never affected the thighs. There was no rash with the sore throat. He had always enjoyed good health until about a month before admission, since which time he had suffered from pains in the abdomen, with occasional attacks of nausea and retching. He had always been a teetotaller. His parents were healthy and temperate; there was no syphilitic history. The abdominal swelling rapidly increased and he came to the hospital. The only symptoms complained of on admission besides the swelling of the legs and abdomen were a little pain in the head and some abdominal tenderness.

On admission, the heart and lungs were normal; the abdomen was tense, the umbilicus protruded, but the surface veins were not prominent. There was shifting dulness in the flanks and a wave of fluctuation. There was some tenderness in the right hypochondriac region, and on "dipping for the liver," its edge could be felt to come below the ribs. The legs, feet, and ankles were œdematous, but there was no œdema in any part of the body above the knees. There was no jaundice at this time. The urine was acid, and contained a good deal of bile pigment but no albumen. At first it was very scanty, and for twenty hours he passed none at all.

Two days after admission it was seen that his skin was beginning to peel about the chest, face, neck, arms, and thighs, and he was consequently placed in an isolated ward. The desquamation was of a fine branny character, and not like that following scarlet fever. There he went on very well at first, except that on June 11th there was a slight rise of temperature; it came down at once, however, and did not rise subsequently. The bowels were freely acted on by saline aperients; the quantity of urine became normal and was non-albuminous, and the swelling of the abdomen decreased. After a few days' rest in bed the œdema of the lower extremities entirely disappeared. After the slight rise of temperature on June 11th jaundice was first noticed. The boy grew steadily worse after the first few days. The ascites again increased, but not sufficiently to form an indication for paracentesis of the abdomen until a few days before his death, when he was obviously too ill for it to be done. The jaundice steadily and gradually increased in intensity. The œdema of the legs remained slight or absent.

For the last five days he was practically unconscious and was delirious; he seemed in a great deal of pain over the abdomen, and shouted "Nurse" from time to time. There was diarrhœa during this time, and

he passed all his water into the bed. The last two days of his life he was completely unconscious and silent. The urine contained a little albumen before the onset of coma; it was scanty and contained much bile pigment. During the latter part of his life none could be obtained for examination.

Necropsy 22½ hours after death. The body was deeply jaundiced, all the thoracic and abdominal organs being bile-stained. The epidermis peeled off very easily. With the exception of some congestion of posterior borders and bases the lungs were normal. At the root of the lungs there were a few enlarged bronchial glands, one or two being caseous and one or two converted into hard white calcareous matter. Each pleura contained about 6 ounces of bile-stained serum. The cavities of the heart were dilated and contained much white and dark clot; its walls were flabby, but otherwise it was healthy.

The abdomen was prominent, especially at the umbilicus. On opening the abdominal cavity it contained about 8 pints of bile-stained serum. The liver did not come into view, but lay concealed beneath the ribs; it was small, weighing 26 ounces. The shape was normal, borders sharp, not prolonged into a thin edge or rim. Its surface was studded over with numerous rounded, raised, firm nodules of a dull yellowish green colour. On section it was finely nodular or granular; the granules were of varying size, round, raised, formed of larger or smaller aggregations of liver cells. For the most part they were of a bright ochre colour, but some were green, and these were especially numerous in the left lobe. Between these granules was a smooth, firm, pale, somewhat translucent-looking tissue in places of a delicate pink colour. General consistence of liver tough. The portal veins were distended. The gall-bladder was full of light-coloured bile. The bile ducts were normal and patent. The spleen weighed 11 ounces, and was large, dark, and soft. Kidneys, right, 3⅔ ounces, left, 4½ ounces; smooth on surface and on section; cortex was deeply congested in places, but as a whole the kidneys were pale; the cortex bore the normal relation to the medulla, and there were no other naked-eye changes. The mucous membrane of the stomach showed two or three large ecchymosed patches. No varices of œsophageal veins. Other organs all normal, and there was no evidence of tubercle or syphilis.

Under the microscope the liver showed much newly-formed connective tissue in wide tracts which surrounded and enclosed lobules of greater or smaller size, and invaded the lobules themselves from within outwards. Speaking generally, the connective tissue was of loose texture, richly enucleated, and made up of fine fibres and branching cells. It contained numerous thin-walled vessels, but no newly-formed biliary canaliculi were observed. In parts the connective tissue was firmer and more closely fibrillated; this was especially the case in the portal areas; the branches of the portal vein were as a rule flattened as if compressed by the growth.

Where the process was least advanced the liver lobules were large and the cells fairly healthy, but even these lobules were invaded by fine connective tissue running from the periphery to the centre between the cells, which latter contained a little fat. Other lobules showed more infiltrating connective tissue and greater changes in the cells, most marked at the periphery. In parts more altered the lobules were almost entirely replaced by connective tissue, consisting of fine fibrils and branching cells; in this small, shapeless, granular, or pigmented liver cells, destroyed by pressure, were still recognisable.

Where the changes were most advanced the proper liver structure was replaced by connective tissue containing a few isolated, degenerated, hepatic cells. No conversion of liver into connective tissue cells was traced. In parts of the liver where the morbid change was greatest, when the remains of the cells were removed, a fine reticular connective tissue stroma was seen to run through it. Bile ducts normal. No leucin or tyrosin crystals. In kidneys the glomeruli were opaque, and in a few cases some increase of nuclei of pavement epithelium. The cells of the convoluted, straight, and spiral tubes of cortex were swollen, finely granular, and encroached on the lumen. This change, though widely spread, was not universal.

The pathological changes in this liver, as in the first case, consisted of a new formation of connective tissue, most marked along the course of the portal vessels, but also extending through the lobules themselves throughout the organ, and accompanied by more or less degeneration of the hepatic cells. The chief points of difference from the first case are (1) that the liver cells were not so extensively nor so completely destroyed, there being lobules which presented a fairly healthy appearance, briefly a less degree of destruction of hepatic cells; (2) that the newly-formed connective tissue was firmer and more distinctly fibrous, and that there was a greater development of it in the portal areas; and (3) absence of endarteritis and proliferation of epithelium of bile ducts.

The development of the new tissue in this case might be considered to be more chronic, that is, more gradually produced, and the cell degeneration also more gradual and more partial in distribution. The more chronic development of the disease than in the first case would entail a greater formation of connective tissue, and less destruction of the hepatic cells. In the first patient death, probably arising from the rapid destruction of the liver cells, brought about as suggested above by the presence of endarteritis, occurred early. Consequently there was not sufficient time for the formation of connective tissue to the extent found in the second case. The minute changes in the liver of this boy differ then from the first case and from cases of acute atrophy of liver in the large amount of connective tissue formed, and from the so-called "biliary" or hypertrophic cirrhosis in the greater destruction of liver cells and in the absence of the new formation of biliary canaliculi. Too much stress must not be laid on this last point, however, as it has been shown that it is not typical of any form of cirrhosis."[7]

The presence of ascites, a rare symptom in such cases, in the later stages of this patient's illness can be explained by the slow course of the disease allowing the newly-formed connective tissue time to contract.

Undoubtedly ordinary atrophic cirrhosis occurs occasionally in children just as in adults from the abuse of alcohol. In addition a diffused form of cirrhosis or interstitial hepatitis with miliary gummata is found as a consequence of congenital syphilis, and a form of cirrhosis, generally of partial distribution, is sometimes found in connection with tubercle. Putting aside altogether cases of this kind, there is evidence that cirrhosis may occur in infancy and childhood independently of the above causes or of any well-defined etiological factor. On this question Henoch[8] says: "I have, however, often observed in children interstitial hepatitis with increase in size and a granular surface of the organ, the so-called hypertrophic cirrhosis.....Much more common are the cases in which clinical symptoms are either quite or nearly quite absent during life, and it is not till after death that we discover hypertrophy of the interstitial connective tissue along with fatty degeneration of the liver cells." He also states that most frequently interstitial hepatitis is due to hereditary syphilis, and in some to tuberculosis, but that in a few cases the cause of the interstitial hepatitis remains unknown, and he regards the opinion expressed by Barthélemy, that these cases are due to syphilis tarda, as quite unproved.

In my second case the desquamation of the skin noted was rather like that following measles than scarlet fever; the mother emphatically denied the existence of a rash during the preceding slight attack of fever. Whatever the illness was, it could not have acted as the cause of the liver changes, for these were obviously of very much longer standing. It may, however, have hastened the fatal termination by interfering with the renal functions. In both cases the influence of syphilis and alcohol could be excluded, nor was there any sign of tubercle in any organ, with the exception of the old caseated glands at the root of the lung in the boy's case. We must, I think, conclude that cirrhosis of the liver may occur in children from causes at present unknown. On the analogy of alcoholic cirrhosis it would seem most likely that some poison—of the nature, perhaps, of a ptomaine—is formed by the occurrence of abnormal changes during the process of intestinal digestion, is carried to the liver, acts as a direct irritant to it, inducing interstitial hepatitis with destruction of liver cells. In connection with this it may be stated that the infant's mother had not been taking any medicine, so that the infant could not have been affected through the milk by any means of this kind.

More observations are required to show what is the clinical course and what are the most frequent morbid changes in these cases of cirrhosis in children. Possibly their course is more acute than in the adult, and the cirrhotic process is more widely diffused through the liver and accompanied earlier by degeneration of the hepatic cells.

With the above cases I will narrate the following case of atrophic cirrhosis, which ran a very unusual course:

CASE III.—A. J., aged 46, a labourer, had never had syphilis nor any bad illness until the present one began, but up to this time had been in the habit of drinking 10 to 12 pints of beer daily. He first began to feel weak and to have a yellow tinge about the conjunctivæ in September, 1886. Three months later marked jaundice came on rather suddenly, and he left off work. He was admitted into the Bristol General Hospital, under

Dr. Markham Skerritt, in February, 1887. The notes state that there was at this time marked jaundice; no ascites; liver enlarged, dulness in nipple line beginning at fifth rib above and extending to about 2 inches above the umbilicus, where its lower edge could be felt to be rounded, hard, and smooth. No albumen, but bile pigment, in urine. Spleen not stated to be enlarged. He had severe attacks of epistaxis; they ceased, however, and he remained well except for persistent jaundice until August, 1889, when he was again admitted, and I first saw him. He was a well-nourished deeply-jaundiced man. Temperature normal; pulse rate 66; skin moist; a moderate degree of pulmonary emphysema and a blowing murmur at the apex, conducted into axilla; no ascites. Liver dulness began above at sixth rib, and its edge could be felt a little more than half an inch below the ribs; the surface was rough. Spleen considerably enlarged. Urine acid, 1015, no albumen, much bile pigment. He had suffered from frequent attacks of epistaxis, and a few times from hæmatemesis. He had had a mild febrile attack, with pains in left side of abdomen, after which the jaundice deepened. Besides jaundice and hæmorrhage, he suffered from heavy sweats, nausea, and constant disagreeable bitter taste. He went out slightly improved. During the next twelve months he remained at home, growing steadily weaker, and occasionally taking to bed for two or three days; jaundice persisted.

He was admitted on September 16th, 1890, with violent pains in the abdomen, diarrhœa, and vomiting. He had now lost flesh, looked much worse than the year before, and the jaundice had deepened in tint. The attacks of epistaxis had continued, and he had gradually become deaf. No ascites. Liver dulness in nipple line began at the sixth rib above and extended downwards only 2¾ inches. Spleen enlarged. Urine 1020, no albumen, acid; quantity in twenty-four hours 58 ounces; urea 1½ per cent. Pulse rate 78 to 84. Temperature normal. He continually expectorated small quantities of blood-stained sputum, and there was occasional epistaxis. On September 22nd he passed a large quantity of blood from the bowels. On September 26th the quantity of urine diminished to 35 to 40 ounces daily; it contained no albumen nor deposit. In the beginning of October he had a severe attack of diarrhœa and vomiting, with melæna. The quantity of urine diminished to 30 ounces. He grew rapidly worse, and died on October 9th. He was dull and heavy, being roused with difficulty, and was occasionally delirious for three or four days before his death, which took place in coma, the coma gradually deepening and the pulse and respiration failing. The temperature was 100° just before death. There were no convulsions.

At the necropsy, on October 10th, the body was deeply jaundiced; no cutaneous hæmorrhages; the diaphragm lay at the level of the fifth rib on the right, of the eighth on the left side. The upper lobes of the lungs were emphysematous, the lower œdematous and congested. The segments of the mitral valve were thickened and its aperture dilated. The liver weighed 40 ounces, and came nearly to lower border of ribs; its surface was granular. On section it was very tough, hard and nodular, the nodules being raised, varying in size, the larger a bright orange, the smaller a dull yellow in colour. These nodules evidently corresponded to groups of liver cells, and were separated from each other by pale connective tissue. The section was also thickly studded with hæmorrhagic points, the size of a pin's head or larger. The branches of the portal and hepatic veins in the liver were about the normal size. Those of the portal vein traced from its fissure were also of natural size. The gall bladder contained a little dark bile; bile ducts patent. The spleen weighed 19⅓ ounces, was dark in colour, and soft. The right kidney weighed 8 ounces, the left 8½ ounces. They were smooth on surface and on section; the capsule stripped easily; the cortex bore the normal relation to the medulla; the cortical epithelium had an opaque appearance and was of a deep red colour. The mucous membrane of the stomach was thin and atrophic, and showed numerous small hæmorrhagic areas, and in one situation small pale spots, probably due to degeneration of epithelium. Intestines and other organs normal.

Microscopical examination showed that the liver presented the ordinary changes of atrophic cirrhosis. The connective tissue formed was firm, fibrillated, with but few cellular or nuclear elements; it was interlobular, and did not penetrate within the lobules. These latter showed much diversity in degree of morbid change; some were almost healthy, except that the peripheral cells contained a little fat; in others the cells were highly granular, fatty, or actively proliferating, and in still others there was complete atrophy, apparently from pressure. There was in some places formation of minute bile ducts in the interlobular connective tissue, but they were not at all numerous, not approaching the number very commonly seen in cirrhotic livers. In a few places there was proliferation of the epithelium of the medium-sized bile ducts. The small hæmorrhagic points noted above corresponded to minute extravasations of blood corpuscles in the interlobular connective tissue. In the kidneys the cortical vessels were intensely injected, the epithelium of the convoluted tubes swollen and granular, and their nuclei obscured; in some tubes there were epithelial casts. Glomeruli injected and opaque. No crystals of leucin or tyrosin were found in the liver.

The persistence of jaundice for such a long time, the frequency of hæmorrhages from the mucous membranes, the absence of ascites, the enlargement of the liver in the early stages of the illness, and its contraction in the later led me to the diagnosis of hypertrophic or biliary cirrhosis running a protracted course with progressive decrease in the size of the liver. It is said that cases of hypertrophic cirrhosis which have lasted a long time have presented a contracted liver, and Strümpell states that in such cases the characteristic appearances in the liver disappear, and it cannot be distinguished from the liver of alcoholic cirrhosis. But in these cases the much more general distribution of the connective tissue growth in "biliary" cirrhosis, extending as it does right through the lobules from the periphery to the centre will still afford a ground of distinction from alcoholic cirrhosis, as in a case of contracted cirrhotic liver which I have previously described.[9] Both the naked-eye and the microscopical appearances, however, were those of an ordinary alcoholic or atrophic cirrhosis, and afforded no explanation of the unusual clinical course, and in particular of the absence of ascites. The hæmorrhages may be attributed to alterations in the composition of the blood consequent upon the long continued jaundice. The long duration of symptoms is also unusual, as cirrhosis, with jaundice, generally runs a more rapid course than cirrhosis without this complication. The absence of new formation of biliary canaliculi does not explain the occurrence of jaundice, for this has been a prominent symptom in cases where they have occurred abundantly.

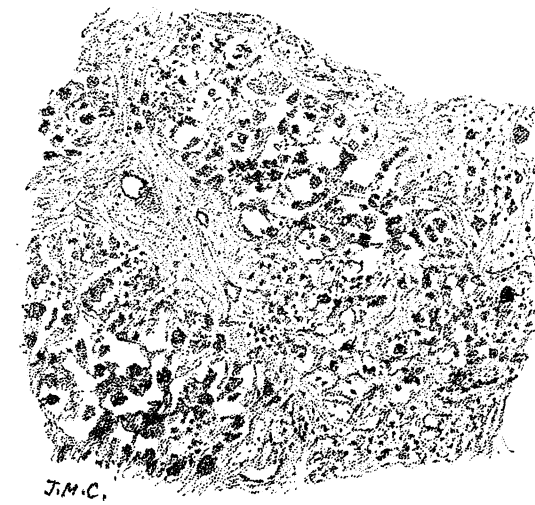

Fig. 1.—To show the general appearance of the liver in Case I; increase of connective tissue in portal area; invasion of lobules by intracellular new connective tissue; atrophy of liver cells. × A Zeiss, oc. 3.

In all three cases the mode of death presents considerable resemblance. This termination with delirium, coma, or convulsions has long been known to occur in cirrhosis, particularly in those cases which are attended with jaundice. Frerichs's view of the cause of these symptoms seems to be the most satisfactory one, namely, that they are due to the injurious influence of those substances which, under ordinary circumstances, are converted by the liver into bile, but which in such cases accumulate in the blood and in the tissues. Further, the liver fails to perform its due share in the work of disassimilation, in the manufacture of the nitrogenous waste material into a form suited for renal elimination, and its "protective" action in destroying poisonous material absorbed from the intestines, is also probably in abeyance.

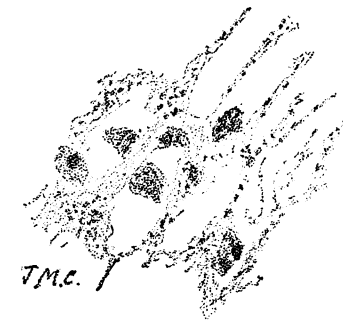

Fig. 2.—Under high power to show fine connective tissue, stroma of lobules, the cells being mostly removed. × D Zeiss, oc. 3.

In the above three cases, with symptoms in some respects dissimilar, there is common to all a diseased condition of the renal cortex. In the first case the morbid change consists in cloudy swelling of the epithelium of the convoluted

tubes; an acute change probably excited by the rapidity with which the disorganisation of the liver was taking place. In the second a similar change, but of more advanced type, had occurred, and it is at least very likely that the slight attack of fever of doubtful nature from which this patient suffered three weeks before his death caused rapid changes in a kidney already irritated by abnormal excrementitious products reaching it on account of the cirrhosis of the liver, and may thus have directly induced the final phenomena of the disease, which ended in speedy death. In the third patient acute congestion of the cortex supervened as the culminating change on older inflammatory changes produced by the irritation of the long-continued jaundice.

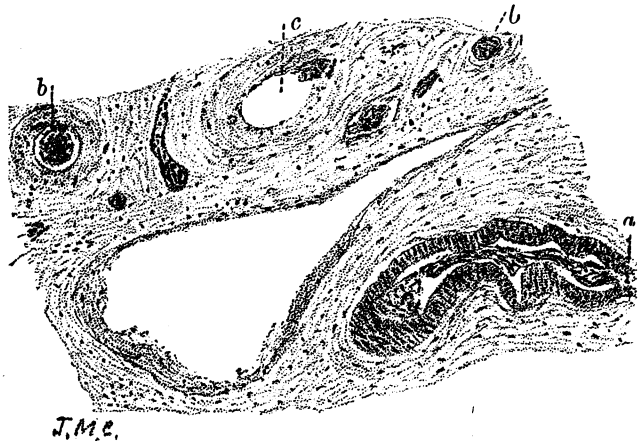

Fig. 3.—Case 1; a portal area; increase of connective tissue; endarteritis; *a*, artery cut obliquely, its lumen choked and muscular coat thickened; *b*, *b*, other arteries; *c*, hepatic duct. × A Zeiss, oc. 3.

In each case the pathological change in the kidneys must, I think, be regarded as the precursor of the fatal termination, and probably the direct cause of it. The grave prognostic import of renal disease in cases of jaundice has for a long time been recognised; provided the kidneys act well, the symptom of jaundice is *per se* not a very serious one. If we take catarrhal jaundice as the best example because the cause producing it is one easily capable of removal, it is not a very grave affection, but if there is at the same time renal disease, this slight ailment may at any time take on the threatening symptoms of the so-called pernicious jaundice or icterus gravis.

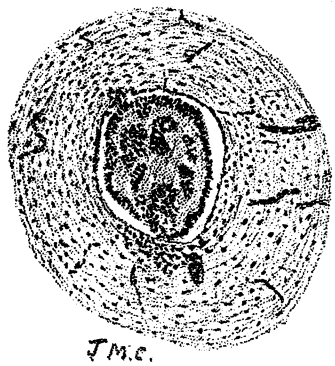

Fig. 4.—Case 1; section of bile duct, its lumen is occupied by a mass of desquamated epithelial cells the nuclei of which have enormously increased in number. × D Zeiss, oc. 3.

Professor Bouchard[10] has some interesting observations on this head. He shows that the most toxic components of the bile are the colouring matters—corresponding to one-third of its total toxicity—and the bile salts. He regards the symptoms of jaundice resulting from the staining of the connective tissue as an effort on the part of Nature to shield the higher tissues of the organism from damage by the retained bile. This is accomplished by the fixing of the poisonous colouring matters by the indifferent connective tissues. He further shows that the maintenance of the renal function is all-important. So long as the kidneys act well they are able, in jaundice, constantly to excrete a portion of the biliary salts and of the colouring matters, and so remove them from the body. If the kidneys fail, then there is the gravest danger, for the noxious material is retained in the blood.

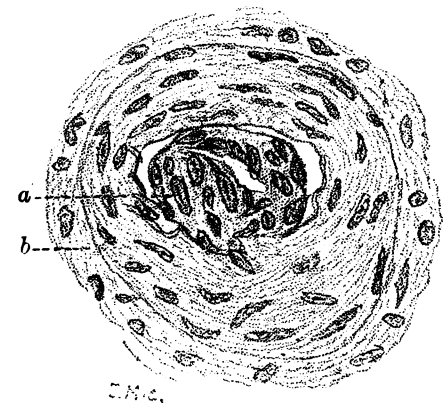

Fig. 5.—Case 1; Endarteritis; *a*, lumen of small artery obstructed by inflammatory products from internal coat; *b*, thickening of middle coat. × $\frac{1}{12}$ oil immersion, oc. 3.

The bile salts have a tendency to irritate both the hepatic cells and the epithelium of the renal cortex. In persistent jaundice the renal cells may remain unaffected, and discharge their functions for a long time. The liver cells are first involved; their functions, other than bile-forming, are after a time interfered with, that is to say, they no longer efficiently convert the nitrogenous and other waste matters reaching the liver from the tissues into the final forms that are suited for elimination by the kidneys. The products of dissimilation, imperfectly elaborated, will accumulate in the circulation, and cause irritation of the renal epithelium in attempts at elimination of them. These morbid changes once started continually increase, and lead to the retention within the body of a constantly increasing amount of effete and hurtful matter.

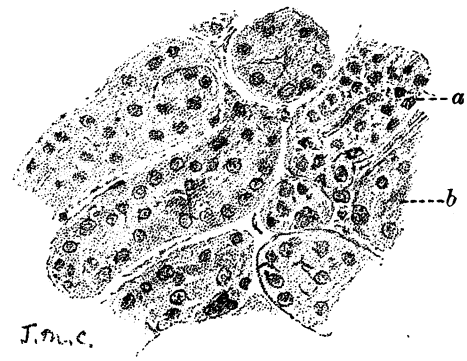

Fig. 6.—Case 1; cloudy swelling of epithelium of convoluted tubes of the kidney, lumen absent in most; outlines of cells and nuclei obscured; *a*, protoplasm of cells highly granular in this tube, nuclei proliferated. × D Zeiss, oc. 3.

As a further factor tending to add still more to the quantity of retained excrementitious material, the retained bile salts will gradually injure the renal cells. In those cases where—as in the first two which form the subject of this paper—there is, besides jaundice, a rapid and extensive destruction of the hepatic cells, these processes will take place all the more rapidly. Finally, we reach the stage in which the kidneys can no longer meet the excessive labour thrown upon them; they become the seat of inflammatory changes, and, to the failure of the liver, failure of the kidneys and uræmia, with their consequences, are added.

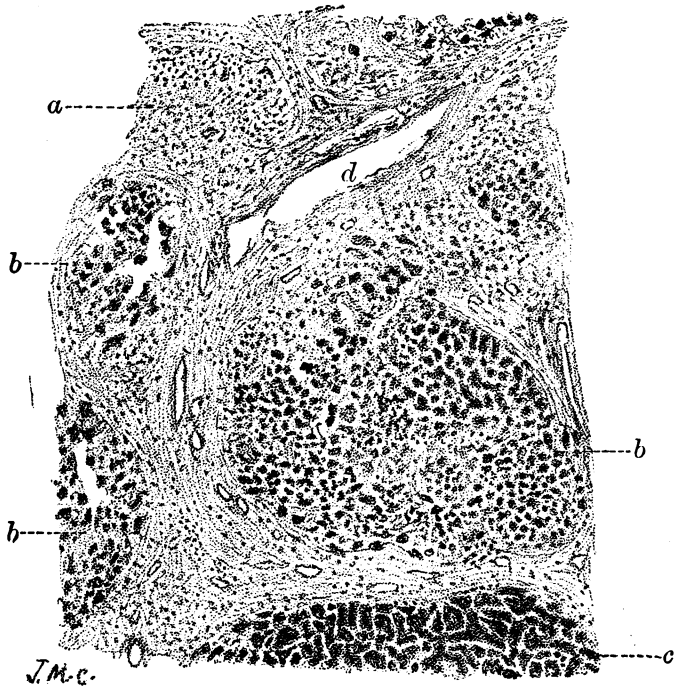

Fig. 7.—Case II; biliary cirrhosis; *a*, remains of lobule replaced by connective tissue; *b*, lobules infiltrated with fine connective tissue and cells becoming atrophied; *c*, more healthy lobule, but even in this one there is fine connective tissue between the cells; *d*, vessel compressed by contracting new growth. A Zeiss oc. 3.

REFERENCES.

[1] American Edition. [2] Vol. xxxviii, p. 124. [3] See again Cornil and Ranvier, p. 515; and cases by Dr. Symonds (*Path. Soc. Trans.*, vol. xxxvii), and Dr. Penrose, *ibid*, vol. xxxix. [4] Wilks and Moxon, *Lectures on Pathological Anatomy*, Third Edition. [5] *Transactions of Pathological Society*, vol. xl, p 137. [6] *Atlas of Pathology*, New Syd. Soc., Fasc. iv, pp. 18, 19. [7] Saundby, *Path Soc. Trans.*, vol. xxx. [8] *Lectures on Children's Diseases*, New Syd. Soc. Trans, vol. ii, p. 114. [9] BRITISH MEDICAL JOURNAL, 1890, vol. i, p. 1090. [10] *Leçons sur les auto-intoxications dans les maladies.*

HAGAR'S WELL AT MECCA.

By E. H. HANKIN,

Fellow of St. John's College, Cambridge; Chemical Examiner to the North-West Provinces and Oude, India.

[From the Government Laboratory, Agra.]

IN view of the widespread attention that has been conferred on Mr. Ernest Hart's recent articles on waterborne cholera, and the great importance of the Meccan infection as a source of the extension of cholera, I think the following analysis of water from the holy well at Mecca may be of interest to the readers of the BRITISH MEDICAL JOURNAL.

I was enabled to make this analysis by the kindness of Dr. George Ranking, the well-known Arabic scholar, who placed a sample of this water at my disposal. It had been given him by a "hadji" of repute and position, who brought it himself from Mecca. The water was contained in a vessel made of tin known as a "dibia," and was hermetically soldered up. The vessel was shaped like a watch, and held about 200 c.c. of water. Owing to the small quantity of the water at my disposal, the analysis was only carried out with difficulty, and the results are no doubt somewhat inaccurate. They are as follows:—

Total solids in grains per gallon	259
Chlorine grains per gallon	51.24
Free ammonia parts per million	0.93
Albuminoid ammonia parts per million	0.45

The figures for ammonia are no doubt without value owing to the very good reason that at least eight months elapsed between the collection of the sample and its coming into my possession. The amount of chlorides is not necessarily an indication of pollution, as it would generally be regarded in England. In India, at all events, chlorides in well water are I believe more often an indication of the presence of saline matter in the soil than of contamination with organic matter. The quantity of total solids is, however, far greater than I have ever found in any well water reputed to be fit for potable purposes.

I learn that it is a universal custom for the pilgrims to bring away with them these tin vessels, or dibias, of Zem-Zem water. Rich pilgrims may bring away one or two hundred of these dibias to distribute to their friends on their return to their native country. Poor pilgrims are, however, content with one or two. The Zem-Zem water is put into the dibias by the Mecca traders during the time of the year when no, or few, pilgrims are present; and it is very probable that the Zem-Zem water is often diluted. as this does not diminish its sanctity, and the supply of water in the well is by no means equal to the demand.

RESEARCHES ON VACCINIA AND VARIOLA.

By M. ARMAND RUFFER, M.D.,

AND

H. G. PLIMMER, M.R.C.S.

THE literature of research which has appeared during the last ten years contains numerous references to the etiology of vaccinia and variola. Many observers have thought that the two diseases were caused by a micro-organism belonging to the vegetable kingdom, whilst others—Renault, Pfeiffer, Van der Loeff, Guarnieri, Monti, Ruffer and Plimmer—have described protozoa in vaccinia and variola pustules. It is not to be denied, however, that many of these so-called protozoa were nothing but anatomical elements more and less altered, and Renault was the first to show that the epithelium cells covering the vaccinia and variola pustules, often contained a peculiar body which he regarded as parasitic, whilst Guarnieri demonstrated the fact that, when vaccinia was inoculated, this body again appeared in the fresh pustules. Thus, on inoculating vaccinia on the cornea, these protozoa appeared in the epithelium cells covering the cornea. Monti, as well as Ruffer and Plimmer, confirmed some of Guarnieri's results, and at the International Medical Congress at Rome one of us compared some of our specimens with some kindly exhibited by Professors Guarnieri and Monti, and established the identity of the bodies described as protozoa by Guarnieri, Monti, and ourselves.

During the last year we have studied a fair number of vaccinia pustules taken from man, the cow, monkey, and rabbit; and in all, provided the disease was not too far advanced, we found this peculiar parasitic structure. The fresh tissue was placed in a saturated solution of sublimate and then hardened in 30 per cent., 60 per cent., 90 per cent., and absolute alcohol. After embedding in paraffin, the sections were passed through tincture of iodine, in order to remove the excess of sublimate, and stained with hæmatoxylin or with carmine and lichtgrün, or with the Biondi-Ehrlich mixture, or with some other staining reagents.

The parasite in question is a small round body, which sometimes appears to have a more darkly-staining centre. It is about four times the size of an ordinary staphylococcus and generally lies in a clear vacuole in the protoplasm of the epithelial cell. It occasionally indents the nucleus, though we have never seen it enclosed in the latter structure. It appears to multiply by simple division into two or multiples of two, but we have not yet satisfied ourselves as to the formation of spores.

When examined fresh it shows slight amœboid movements, and may be observed in tissues which have been kept for several days or weeks, even though no antiseptic precautions have been taken.

It stains easily with both nuclear and protoplasmic dyes, but it appears to have a preference for the latter class, as it retains them after the nuclei of the cells of the body have yielded them to alcohol or other reagents. With Biondi's reagent, for instance, it stains red with the acid fuchsine, often exhibiting a central green part. Carmine stains it intensely, but if lichtgrün or indulin be used as a counter stain it retains these stains after all traces of them have left the