29TH MARCH, 1899.

The President, DR. ALEX. MILLER, *in the Chair.*

I.—CASE OF ACUTE YELLOW ATROPHY OF THE LIVER OCCURRING DURING THE EIGHTH MONTH OF PREGNANCY, WITH SOME REMARKS ON THE ETIOLOGY OF THE DISEASE.

BY DR. CARSTAIRS DOUGLAS.

Acute yellow atrophy of the liver in genuine form is a disease so uncommon that every case ought to be put on record. Not only is it one of the complications of pregnancy most seldom met with, but it is, under any circumstances, a disease of which one may see an example only once in a dozen years. Some idea of its rarity may be gained when I state that Murchison[1] saw only 1 case out of 25,700 admissions to the London Hospital during a period of nine years, while Osler,[2] of Baltimore, says that in a somewhat varied *post-mortem* and clinical experience no instance has fallen under his observation.

[1] Murchison, *Diseases of the Liver*, 1885, second edition, p. 293.
[2] Osler, *Principles and Practice of Medicine*, 1898, third edition, p. 551.

The case of which I am going to give you a short account occurred some years ago, but has never been reported in any journal, and I am indebted to your late honorary president, Professor A. R. Simpson, for permission to bring it before you, as it came under my notice when I was his house physician.

The patient, R. B., æt. 35, and a v-para, appeared to take seriously ill first on 16th December, but for ten days previous to that (from about 5th or 6th December) her health had not been good; she was troubled with vomiting, and noticed that her urine was the colour of porter. To the appearance of her motions she did not pay any special regard, and had not observed whether they were blood- or bile-stained, clay-coloured, or otherwise altered, though she did notice that they had an offensive odour.

She was at this time nearly eight months advanced in pregnancy.

About 8th December the skin was observed to show a yellow tinge, but the patient had always had a tendency to biliousness, and apparently paid little heed to this. On the night of Sunday, 14th December, she was very restless in bed, constantly starting up and having to be pushed back again. Next morning, 15th December, her husband had to leave home and go out of town by an early train; his wife spoke to him before his departure, but did not get up. She remained all day in bed in a kind of stupor, which continued through the night and into the following day (16th December). On the afternoon of that day a neighbour, on turning down the bed-clothes, found in the bed a dead child, newly born. Her friends now came to hospital to the ward, and on hearing of the case I visited and examined the woman in her own home. Her condition was so grave that I ordered her to be brought up to the infirmary in the ambulance waggon, which was duly accomplished on the afternoon of 17th December.

On admission the patient was comatose and deeply jaundiced; she could not be made to speak, or to give any answer even when spoken to in a loud voice. When subjected to much manipulation she groaned and moved uneasily. There were no signs of paralysis or of convulsions, and the pupils were equal and moderately dilated. The pulse was good, regular, and reasonable in rate, while the temperature was 97° F. The cardiac sounds were somewhat impure, the breathing apparently normal. Scattered here and there over the legs were purplish spots like ecchymoses, the evidence of subcutaneous hæmorrhages. Examination of the liver revealed a distinct diminu-

tion of the usual hepatic area of dulness. Liver dulness (relative) could only be made out between the fourth and sixth ribs, and there was no absolute dulness at all. The urine was drawn off; it was the colour of pale porter, and contained neither albumen nor sugar. Chloroform having been administered, I dilated the cervix and thoroughly explored the uterine cavity, which was found to be empty and healthy, placenta and membranes having come away completely. A carbolic intra-uterine douche was given, and a hypodermic injection of ergotine. A sharp purge was ordered, but the bowels did not move till 3 minims of croton oil had been given by the mouth, aided by two glycerine suppositories and a soap and water enema.

The patient lay quiet during the night, save when the bowels were moving; she passed water herself. On the 18th the coma was deeper, and the icterus, seen by day, was intense. The temperature was still 97° F. Examination of the urine obtained this day showed it to be a reddish-yellow fluid, containing neither albumen, sugar, nor blood; it reacted fairly well to Graclin's test for bile. Microscopically, it contained many epithelial cells, chiefly polygonal, and deeply pigmented to a bright brown colour, also a few pus cells and some bacteria. Somewhat imperfect crystals of leucin were obtained, but none of tyrosin. On the afternoon of this day (18th December) it was clear that the patient was worse. At 3·30 P.M. the breathing was rapid (40 per minute), rough, and tubular; the radial pulse was imperceptible, though the apex beat could still be felt. A hypodermic injection of strychnine and ether caused a temporary rally, but the patient continued deeply comatose with rapid breathing and a feeble cardiac beat, and expired at 4·30 P.M., 18th December, on the fourth day after the onset of serious symptoms.

The *post-mortem* examination was performed two days after death; the following is a summary of the leading features of it:—

There was general intense icterus of the skin, the pupils were moderately dilated, and the veins of the legs somewhat enlarged. Striæ gravidarum were present, and the nipples were deeply pigmented. On opening the abdomen the stomach was seen to extend 4½ inches below the ensiform cartilage. The tip of the liver was just visible below the seventh costal cartilage, 1½ inch to the right of the middle line. The liver weighed only 27½ oz. (barely 700 grms.), and was small, tough, and extremely flabby to feel. On section, it was tougher than normal. The atrophy seemed to be rather in thickness than

in general surface area. The right lobe showed slight chronic perihepatitis, while the inferior surface of both lobes was light yellow in colour, the superior and posterior aspects showing a darker brown-red colour with a slight yellow mottling. On section, the lobules were small in size, and presented a semi-diffluent appearance, especially in the upper and posterior parts. The liver was markedly non-vascular, and the anterior part was of a canary-yellow colour both in the right and left lobes. Where it was possible to see the peripheral part of the lobules, the centre seemed to be disintegrated and of a dirty red colour. The left kidney weighed 7 oz., and the right 6; both showed marked yellowness (fatty change) in the cortical parenchyma, and engorgement of the vessels. The spleen weighed 4½ oz., and showed numerous pale areas on section; the Malpighian bodies were enlarged. The heart showed no special features except that there was slight thickening of the cusps of the mitral valve. The endocardium was bile-stained, the myocardium pale and somewhat yellow (? fatty). The lungs showed small hæmorrhagic points on the pleura, and the bronchial glands were pigmented and enlarged. Hæmorrhages were also found into the mucous membrane of the stomach. The intestines appeared normal.

This, then, completes my short account of this interesting case, and it will be noted that it presents practically all the features of a typical case of acute yellow atrophy of the liver. It occurred in a pregnant woman, and I need not remind you that fully 60 per cent of the cases of this disease occur in women, and that among these women 40 per cent are pregnant. Even in pregnancy, however, it is rare, and Braun gives 1 to 28,000 as the ratio among pregnant women. The illness began, as it often does, with the symptoms of an ordinary catarrhal jaundice; vomiting followed, with increase of the icterus, and presently the disease entered on its serious and rapidly fatal stage, the patient falling into a coma which never lightened, and showing hæmorrhages under the skin. The urine contained some bile, but it is not necessary that this element be present. The reddish-brown colour was probably due, in part, to urobilin, following perhaps upon marked blood disintegration; I was able to demonstrate a considerable amount of this substance lately in the urine of a patient who presented a very similar clinical history. Leucin and tyrosin in the urine are generally regarded as important points in the diagnosis of acute yellow atrophy. In my case

only leucin was found, but genuine cases of the disease may occur where neither of these bodies is present. Hunter,[1] out of 23 recently collected cases, found both absent in 9 (about 40 per cent), and both present only in 10 (43 per cent). On the other hand, they may occur in cirrhosis of the liver, in leukæmia, and in phosphorus poisoning. Röhmann[2] reports a case where neither was present, but where there was great abundance of aromatic oxy-acids, such as hydro-paracumaric acid. Some writers have held that emptying the uterus is a means of cure. P. Müller,[3] however, says that delivery seems to have little effect on the course of the disease, and that the obstetrical treatment is a purely expectant one. In this case the natural emptying of the uterus produced no beneficial effect, and Thomson,[4] of Odessa, in a case recently reported and very similar to this, had a like experience.

Post-mortem, the most striking points are the enormous diminution in size of the liver (from the normal 1,500 grammes to barely 700), and the alteration in its colour and consistency. Part of it was a canary-yellow colour and part of it a dull red. The lobules showed distinct signs of breaking down, as is usually the case. Hæmorrhages into various organs (stomach and pleura) were present, and there were indications of fatty changes in the kidneys and the muscular fibre of the heart.

The etiology of this disease is still obscure. The impression which it makes upon the clinical observer is that we are dealing with a profound toxæmia of a very lethal character. The actual source of this poisoning probably lies in the body itself, that is to say, we are dealing here with an auto-intoxication. The poison which causes the fatal coma, whatever it be, is neither leucin nor tyrosin, for in the first place, as I have pointed out, they may be absent from the urine even in fatal cases, and in the second place, Bouchard[5] has shown that they produce no poisonous effect when administered by the mouth. As Halliburton says,[6] they appear in the urine in but small quantity, and simply indicate the small

[1] Hunter, Clifford Allbutt's *System of Medicine*, 1897, vol. iv, p. 111.

[2] Röhmann, "Chemische Untersuchung von Harn und Leber bei einem Fall von acuter Leberatrophie," *Berl. klin. Woch.*, 1888, S. 861.

[3] P. Müller, *Handbuch der Geburtshülfe*, 1889, Bd. ii, S. 917.

[4] Thomson, *Centralb. f. Gynæk.*, 1898, No. 45, S. 1229.

[5] Bouchard, *Lectures on Auto-Intoxication*, 1892, p. 119.

[6] Halliburton, *Essentials of Chemical Physiology*, 1899, third edition, p. 108.

amount of these bodies which are usually present in the intestine, and which appear in the urine in virtue of having escaped destruction by the disorganised liver. The poisoning is to be referred, in all probability, to a group of substances, some of them possibly deleterious bodies absorbed from the gastro-intestinal canal, some of them the results of ordinary tissue metabolism, and some of them, perhaps, the broken-down and disintegrated liver cells themselves.

I need not, at this time of day, emphasise the important position which the liver holds as a poison-destroying and poison-transforming organ. Interposed between the alimentary canal and the heart, it acts, in virtue of its relation to the portal system, as a filter of a very important kind. That it possesses a "schutzcraft," as the Germans term it, or protective power for the organism, there is abundant evidence to prove. For example, Pick,[1] of Prague, by the injection of dilute sulphuric acid into the bile-ducts of an animal, caused destruction of the liver parenchyma, and the development of a central necrosis which, after the advent of convulsions, terminated in death. Nencki,[2] Pawlow, and others working in St. Petersburg, threw the liver out of the circulation, as it were, by establishing a communication (Eck's fistula) between the vena porta and the inferior vena cava. The results of their investigations showed (to quote their own words, s. 174) that "dogs in which the blood of the alimentary canal goes, as a result of an Eck's fistula, direct into the inferior vena cava without passing through the liver, cannot stand a meat diet without suffering severe disturbances of the nervous system, which often end in death." Roger[3] made a large number of experiments on this subject, and concluded that the liver played an important *rôle* as a protective agent to the organism. He argued that it fulfilled its function in a threefold way:—

1. By accumulating toxic principles, and eventually handing them over, little by little, to the general circulation, or eliminating them in the bile.

2. By transforming various poisons introduced from without or developed within the organism.

3. By diminishing the intensity of intestinal fermentation through the action of the bile.

[1] Pick, "Versuche über functionelle Ausschaltung der Leber bei Säugethiere," *Arch. f. exper. Path. u. Pharmak.*, 1893, Bd. xxxii, S. 382.

[2] Nencki, &c., "Die Eck'sche Fistel zwischen der unteren Hohlvene und der Pfortader, und ihre Folgen für den Organismus," *Arch. f. exper. Path. u. Pharmak.*, 1893, Bd. xxxii, S. 161.

[3] Roger, *Action du Foie sur les Poisons*, Paris, 1887.

He experimented with nicotine, atropine, strychnine, veratrine, and other powerful alkaloids, in some cases comparing the effects of injection into an intestinal vein with those produced by introduction into the general circulation, in other cases studying the effect on the lethal dose of removal of the liver, and in others still, injecting the poison at one time alone and at another after maceration with fresh liver-tissue. In general terms, he found that the influence of the liver as a neutraliser and transformer of poisons was very great, and that it could arrest 50 per cent of an alkaloid that had to traverse it.

Surmont[1] approached the matter from another point of view by studying the toxicity of the urine in liver disease. He found that it was increased in certain affections of the organ, such as atrophic alcoholic cirrhosis, chronic malaria, tubercle, retention icterus, and cancer.

In phosphorus poisoning, again, we have a toxic body of well-known chemical nature producing a lesion in the liver simulating that of acute yellow atrophy (though the liver is not diminished in size), and leading, like it, to the development of jaundice, hæmorrhages, and coma ending in death.

Lastly, in eclampsia puerperalis, we deal with a disease the outcome apparently of self-poisoning, in the pathology of which insufficient attention is often paid, in my opinion, to the liver changes. The investigations of Schmœl,[2] Klebs, and others have established the fact that the liver is often the seat of pathological changes sufficiently marked to suggest that they have a bearing on the genesis of the disease. In the face of these and other arguments that might be adduced it is easy to understand that, if the functions of the liver be abrogated by such a disease as acute yellow atrophy, the organism runs a grave risk of suffering from self-poisoning of a serious kind. I may sum up this point by quoting from Albu,[3] that "the cause of the coma and other grave symptoms lies in the destruction of the liver cells, with consequent loss of their function, whereby the metabolic processes are all disturbed, while at the same time the products of the destroyed cells enter the blood." The poison, as already mentioned, is probably a complex one, composed, it may be, of such elements as potash salts, amido acids, ammonia compounds, albumoses,

[1] Surmont, "Recherches sur la toxicité urinaire dans les maladies du foie," *Arch. gén. de Médecine*, 1892, vol. i, pp. 162 301.

[2] Schmœl, *Pathologisch-anatomische Untersuchungen über Puerperal-eklampsie*, Leipzig, 1893.

[3] Albu, *Ueber die Auto-intoxicationen des Intestinaltractus*, Berlin, 1895.

peptones, and various more or less complex azotised derivatives of tissue-change. But when we come to ask what is the primary virulent poison which acts as a first cause, and leads to this rapid wasting and disintegration of the liver, we must admit frankly that we do not know.

It does not appear to be, so far as we know yet, of microbic origin: in a few cases micro-organisms have been sought for, but usually with negative results. M'Phedran and Macallum,[1] in a carefully investigated case, found no trace of bacteria or micrococci, and Thomson,[2] of Odessa, in his case carefully searched for organisms both in the liver and uterus, but found none. The first mentioned writers incline to the view that the poison is a chemical one, probably an abnormal albumen absorbed from the intestinal canal, and conveyed to the liver by the radicles of the portal vein; while Hunter[3] says we have to do here with a virulent organic poison, probably formed within the intestine, and acting on the liver, kidneys, and blood after absorption.

This is as far as our present knowledge of the subject permits us to go. We may surmise that, under circumstances that are very exceptional (otherwise the disease would be more common), a potent chemical poison is generated in the bowel, is absorbed, and attacks the liver, leading to a rapid wasting and degeneration of that organ; and that, as a result of this, the organism is quickly poisoned by the products of its own metabolism. Or it may possibly happen, though it does not seem so probable, that the primary intestinal poison is itself the cause both of the liver changes and of the central narcosis.

As we note the occurrence of this disease among women, and especially among pregnant women, we are once more reminded of the paramount importance of attending to the action of the kidneys, liver, and bowels in our female patients; and above all things, during the time of utero-gestation, simple as this point is, it cannot be insisted on too emphatically or supervised with too great care, for if auto-intoxication is a veritable cause of disease, neither internal medication nor intestinal antisepsis will combat it half so effectually as will a free and regular action of the ordinary emunctories with which Nature has provided us.

[1] M'Phedran and Macallum, "Acute Yellow Atrophy of the Liver," *British Medical Journal*, 1894, vol. i, p. 293.
[2] Thomson, *Centralb. f. Gynæk.*, 1898, No. 45, S. 1229.
[3] Hunter, Clifford Allbutt's *System of Medicine*, 1897, vol. iv, p. 116.