A CASE OF INTRAOCULAR LIPÆMIA ASSOCIATED WITH DIABETES (INCLUDING A FULL PATHOLOGICAL REPORT OF THE BLOOD, BONE MARROW, AND VISCERA).

By H. G. TURNEY, M.A., M.D. (Oxon.), F.R.C.P., *Senior Physician to Out-Patients, and Lecturer on Special Pathology in the Medical School, St. Thomas's Hospital, London*, and LEONARD S. DUDGEON, M.R.C.P., *Director of the Louis Jenner Clinical Laboratory and of the Pathological Laboratories, St. Thomas's Hospital; Bacteriologist to St. Thomas's Hospital and Joint Lecturer in General Pathology in the Medical School.*

(PLATES I. AND II.)

THE patient upon whom the following observations were made was a female, æt. 35, who was admitted into St. Thomas's Hospital on 10th August 1904 suffering from diabetes. Her family history showed no sign of any hereditary taint. Until the present illness patient's health had always been good. She had been troubled somewhat with constipation, but otherwise had been particularly free from bodily ailments.

The present illness, so far as definite symptoms are concerned, would seem to be of about eighteen months' duration. At that time she noticed some general failure of health, and soon afterwards began to be troubled with an eruption on her back. About the same time too she suffered with excessive thirst, and had to consult a doctor. He made an examination of the urine, and, finding that it contained sugar, advised her to restrict her diet. From that time she had done her best to cut off carbohydrates, but found her efforts much restricted by the scantiness of her means. So far as can be ascertained, fat did not constitute any large proportion of her food. She had not noticed any improvement in symptoms after the change in diet. The loss of flesh had continued, and latterly she had suffered from weakness of the legs and vague rheumatic pains in them. During the past few weeks she had found that after walking or standing for any length of time her ankles were inclined to swell.

On admission her condition was as follows :—

The patient is a medium-sized woman of slender build and much emaciated. She makes no complaint of pain, is cheerful, and though weak is still quite able to get about. The skin is dry but not scurfy, and is not the seat of any pigmentary deposit.

The chest shows great emaciation, all the rib contours being visible. Its shape is symmetrical, and respiratory movements are good and equal on the two sides. The respiratory sounds are unduly loud, but this is probably due to the extreme thinness of the parietes. Apart from some prolongation of

expiration there are no abnormal sounds over the lungs. The respiratory rate is under twenty per minute, and patient has no sense of dyspnœa.

The area of cardiac dulness is normal, and the impulse within the nipple line. At the apex a localised systolic murmur is audible; this accompanies rather than replaces the first sound, and does not suggest valvular disease. The pulse rate is normal—about 80. Arterial tension is low, and the vessel wall somewhat thickened.

The abdominal wall is retracted, the skin very dry. No signs of disease can be detected in any of the abdominal viscera.

The lower extremities are extremely wasted. There is no tenderness on pressure either of muscles or nerves. Sensation of every form remains unaffected. Co-ordination is good and the gait quite normal. The knee-jerks are absent, the plantar reflex is present, the response being of the flexor type. Muscular power is good considering the wasting.

The upper extremities are normal in every respect. The tongue is clean and red. The teeth are very bad; many are missing, while those that remain are much decayed, and many of them are mere stumps. In spite of the condition of the teeth the breath is not offensive, and there is no suspicion of a smell of acetone.

The eyes externally show no change. The pupils are equal, of medium size, and react both to light and accommodation. The lenses are clear, as also the vitreous. The condition of the fundi—they are precisely alike—is very striking. The discs are somewhat pale; the vessels are well filled, but all alike, whether arteries or veins, appear as if they were filled with milk instead of blood. The only place where anything approaching a red tint is seen is in

Grains of Urea per Diem.

Grains of Sugar per Diem.

the vessels as they come up into the centre of the disc; before they have crossed the disc this has completely gone, to be replaced by a pale cream

colour. The patient makes no complaint of her sight, but on being questioned states that it is not so good as it was. She can see to read fairly well, and, so far as rough tests go, her vision may be described as normal.

The urine is of a pale lemon colour, has a specific gravity of 1034, and contains a large quantity of sugar. The reaction is acid. The smell is not in any way characteristic. The quantity passed in the first twenty-four hours is 136 oz.

The patient weighs $89\frac{1}{2}$ lb.

For the first three days after her admission she was kept on full ordinary diet; during this period the urine contained large quantities of sugar, a trace of albumin, and gave a negative reaction to tests for aceto-acetic acid and acetone. From that time on (*i.e.* from the 15th) the diet was strictly limited.

On the 18th—*i.e.* three days after strict dieting was commenced—the urine for the first time contained aceto-acetic acid, and on the 22nd acetone made its appearance in addition. Both then persisted till the end. The appended chart shows the excretion of sugar and urea day by day. The sugar was estimated by Lohmstein's fermentation saccharometer. No fat was ever detected in the urine.

EXAMINATION OF THE BLOOD.

A complete examination of the blood was made for the first time on 18th August, with the following results:—

Red blood corpuscles.—3,900,000 per c.mm.

Hæmoglobin.—92 per cent.; *Colour Index*, 1.1.

The peculiar colour of the blood may have affected this result, and therefore the hæmoglobin estimation is possibly incorrect.

Leucocytes.—3,880 per c.mm.

Fresh blood.—Rouleaux formation perfect. The blood was of a salmon colour, and definite white streaks could be seen in the drop of blood as it oozed from the puncture.

Differential Count of the Leucocytes.

Polymorpho-nuclear neutrophiles	369 = 73.8 per cent.
Small lymphocytes	107 = 21.4 "
Large lymphocytes	9 = 1.8 "
Large hyaline cells	12 = 2.4 "
Polynuclear eosinophiles	2 = 0.4 "
Finely basophilic cells	1 = 0.2 "

A few "ghosts" were seen, otherwise nothing abnormal was noted in the stained specimen of blood.

The *Specific Gravity* of the blood was found to be 1.055. (Hammerschlag's method.)

No definite fat droplets could be seen in the fresh blood for some few minutes after the blood had been obtained from the finger.

The *Glycogenic reaction* was not present in the large majority of the leucocytes, and only present to a slight degree in some of the polymorpho-nuclear neutrophiles.

DEMONSTRATION OF FAT IN THE BLOOD.

The blood was obtained from the finger in typhoid serum tubes. One of these tubes was placed in a test tube of ice, another in an incubator at 37° C., another was left at the room temperature. In the serum tube which had been placed in the tube of ice a very rapid separation of the fat took place, and it collected in the upper part of the tube, but only separated very slowly in the tube which was placed in the hot incubator.

Film preparations of the blood were made in the usual way, fixed in formalin vapour, stained with Scharlach, and mounted in Farrant. Very large numbers of free fat droplets of all sizes were seen; some of the droplets were only the size of minute granules. We could not demonstrate any fat either in the erythrocytes or in the leucocytes.

Blood films were stained with Busch's osmic acid preparation, but only most unsatisfactory results were obtained.

No fat could be seen in either red or white blood corpuscles.

The patient did not take her food well, and on the 22nd was found to have lost 2½ lb. in weight. On the 23rd the temperature, which had hitherto been normal or subnormal, rose to 100°·2. On the 24th the patient complained of pain in the left side on breathing, and very soon developed signs of consolidation at the base of the left lung. The fever persisted, the maximum temperature being 102°·6; breathing and pulse both grew rapid, but consciousness was retained almost till death, which took place on the 27th.

The treatment consisted in strict diabetic diet with the addition of lævulose, and the administration of carbonate of soda after the appearance of acetone.

POST-MORTEM EXAMINATION.

We were only able to procure a limited examination of the body through a small incision in the abdomen, but fortunately all the important viscera were obtained except the brain and spinal cord. The body was much wasted. There was no abnormal pigmentation or discoloration of the skin anywhere in the body. The subcutaneous body fat was very much diminished in amount, but was normal in colour. When we opened the peritoneal cavity the great omentum presented a most striking appearance, as every trace of fat had disappeared, and the tissue had a gelatinous appearance. It was afterwards found that all the adipose tissue around, or in contact with, the important viscera was similar in appearance. This condition was perhaps most striking in the epicardial fat, which resembled jelly.

There was no evidence of fat necrosis in the peritoneal cavity, or elsewhere. Subperitoneal emphysema was present throughout the abdominal cavity. There was no free fluid present.

EXAMINATION OF VISCERA.—Liver.—This organ weighed 52 oz.; it was pale, and appeared to be fatty. There was nothing abnormal otherwise to be seen either on the surface or on section.

The *gall bladder* appeared to be normal.

The *pancreas* was very soft, but beyond this it did not present any naked-eye changes.

The *spleen* weighed 7 oz. The colour of this organ was exactly similar to the patient's blood during life, *i.e.* pale salmon colour. It was soft, but did not present any other abnormalities.

The *kidneys* weighed 12 oz. The capsule of each kidney stripped quite easily. The organs were pale, obviously fatty, and showed minute pale specks in the cortex.

The *adrenals* were pale, but otherwise appeared to be normal.

There were no enlarged mesenteric glands.

The *intestines* from the stomach to the lower part of the rectum appeared to be absolutely normal.

The *generative* organs and bladder were normal.

The *heart* weighed 7 oz., the muscle substance was soft and pale, and the epicardial fat presented the peculiar features to which we have already drawn attention. There was nothing abnormal to be seen either on the pericardium or endocardium.

Lungs.—The right lung weighed 25½ oz., and the left lung 23½ oz.

There were recent but firm pleural adhesions on both sides of the chest, but there was no fluid in either pleural sac. The greater portion of both lungs was solid. The bronchi were filled with long casts of fibrinous material. The cut surface of the lungs was greyish in colour, and both organs were very friable. In the upper lobe of the left lung a large abscess cavity with ragged walls, about the size of a walnut, was found. There was a small quantity of pus present in the cavity. There was no evidence of tuberculosis either in the lungs or bronchial glands to the naked eye.

POST-MORTEM EXAMINATION OF THE BLOOD.—Blood was collected in flasks from the aorta and was shaken up with ether, but no fat was obtained from the ethereal extract. Film preparations of the blood were made in the same way as during the patient's life, but we failed to obtain the slightest evidence of fat.

MICROSCOPICAL EXAMINATION.

Small pieces of each viscus which had been examined at the post-mortem were placed in various fixatives,—Orth's fluid, weak alcohol, and 10 per cent. formalin. Those pieces of tissue which had been placed in formalin for twenty-four hours were either cut in gum, or carried through Busch's fluid. The sections which were cut in gum were stained with Scharlach R. The remaining sections were cut in paraffin, and stained with hæmalum and eosin, Van Gieson's stain, Leishman's stain, and with osmic acid. Most of the viscera were examined for the presence of the iron reaction.

ABDOMINAL VISCERA.—*Liver.*—The outline of many of the hepatic cells is most indefinite. The cells are separated in most places by granular material, which is found along the line of the connective tissue. There is well-marked cloudy swelling of the hepatic cells, and in some of them the nuclei have disappeared, in others they are swollen, and in others very much shrunken. Large amount of fine golden-brown granules can be observed in most of the cells, especially around the central vessels. These granules do not give any iron reaction or glycogenic reaction. There is no increase of fibrous tissue, but a large number of round and spindle cells are present in the connective tissue, especially around the portal system. Large numbers of fat cells can be seen, chiefly in the hepatic cells, but also in the connective tissue stroma and in the walls of the blood vessels. In two blood vessels there are large masses of fat, but otherwise it is in a very fine state of subdivision in the interior of the vessels. Some of the fat droplets in the cells and in the stroma are very large, but the most characteristic feature in every viscus is the fine subdivided state of the fat globules into a kind of granular material.

Kidneys.—The flattened epithelium of Bowman's capsule is shed into the interior of the tufts. Many of the glomeruli are very much shrunken, and contain large numbers of vacuoles. There is no true increase of fibrous tissue. The epithelium of the tubules is completely shed in places, so that only a supporting framework is left. Some of the cells of the tubular epithelium are very much distorted, and the nuclei are either very much swollen or shrunken. There is no evidence of free iron. Fat is present in large amount, especially in the outer zone of the glomeruli. There is also plenty of fat to be seen in the interior of the small blood vessels, but the epithelium of the tubules only shows a very slight amount.

Adrenals.—The outline of many of the cells is most indistinct. The nuclei show all stages of degeneration. The separation of the cells into columns is most indefinite. The point of greatest interest in connection with the adrenal gland is the enormous amount of fat which is present. The fat droplets almost fill the interior of the cells, and also occupy the interior of the blood vessels, but the connective tissue which surrounds the gland

hardly contains any fat. The fat globules are most abundant in the zona glomerulosa, but in the normal gland fat is always found in large amount in this portion of the adrenal.

Spleen.—This organ contains a large quantity of blood, and also of fat in the capillaries, pulp, and stroma. The fat is chiefly present as small globules. The Malpighian bodies are much reduced in size, and the lymphoid cells in numbers. There is a well-marked endothelial cell proliferation, but no true giant cells have been seen. The iron reaction is negative.

Bone marrow (Rib).—A few cells are present in every section, which contain two or three nuclei, but the true giant cells are absent.

A Differential Count of the Cells of the Bone Marrow gave the following result :

Polymorpho-nuclear neutrophiles	0 =	0 per cent.
Small mononuclear cells	212 = 42.4	} 69.0 "
Large mononuclear cells	133 = 26.6	
" " with nucleus eccentric		
and basophilic cytoplasm	57 = 11.4	"
Large hyaline cells	10 = 2.0	"
Transitional leucocytes	4 = 0.8	"
Neutrophilic myelocytes	61 = 12.2	"
Polynuclear eosinophiles	23 < $\frac{2}{21}$	} = 4.6 "
Mononuclear eosinophiles		
Mast cells	0 =	0 "

Sixty-seven normoblasts and four megaloblasts were seen, while 500 leucocytes were counted.

Mesenteric glands.—These are found to contain a small quantity of fat, but otherwise are normal.

Pancreas.—Large areas of pancreatic tissue are quite normal, but in some places we meet with islands of the gland which are degenerated beyond recognition. In these areas the tissue stains in a uniform manner, the outlines of the cellular structure are completely lost, and there is absence of any nuclear staining. We have not observed, however, any small-celled infiltration in these degenerated areas. Some of the pancreatic cells show an indistinct outline and swelling of the cell nuclei. The pancreatic ducts appear to be normal in every detail.

There is no increase of the fibrous stroma of the gland, but this tissue is degenerated in patches, such as we have already referred to in the description of the glandular portion of the organ. We have failed to find any of the isles of Langerhans, although numerous sections have been examined from various portions of the gland. Microscopical sections which have been stained by Gram and Leishman's methods show large numbers of bacilli, which are morphologically identical with the *Bacillus aerogenes capsulatus*, and which also stain intensely by Gram's method. This bacillus, however, is found to be present in the lungs in large numbers and in many of the other viscera. The iron reaction is negative.

THORACIC VISCERA.—Heart muscle.—The transverse striation is completely lost in most of the muscle cells in every section examined. Many of the cells are vacuolated, and many contain yellowish granules scattered throughout the cells which do not react to either osmic acid or Scharlach. Most of the muscle cells are segmented, the cell outline is indistinct, and the nuclei are swollen, and in some of the cells they are absent. A small amount of fat is present in the cells and also in the capillaries, but the amount of fat is only very slight in comparison to that found in the other viscera. There is no evidence of any fibrosis. The fibrous tissue which runs between the muscle fibres contains a small amount of fat.

The adipose tissue which normally is present to some extent around the base of the heart is almost entirely converted into a kind of mucoid tissue.

The stroma of this tissue does not react to the fuchsin in Van Gieson's stain, but is stained by the picric acid.

Lungs.—The sections of the consolidated portions of the lungs consist of enormous masses of leucocytes which help to fill the alveoli. There is also a large amount of granular matter present and a few endothelial cells. The small bronchi are plugged with a similar exudate. Sections which were stained for micro-organisms show the presence of enormous numbers of bacilli which are morphologically identical with the *Bacillus aerogenes capsulatus*, and which stain intensely by Gram.

Scharlach's stain shows very large numbers of minute fat droplets, which resemble a granular deposit owing to the fine subdivision in which the fat droplets are present. The fat serves to map out the alveolar walls, as it is here that we meet with the fat in largest amount.

It is almost needless to add that there is not the slightest evidence of tuberculosis in any portions of the consolidated areas of the lungs.

We have referred throughout this paper to the disappointing results which we have obtained by staining the various viscera and the blood by means of osmic acid. Our results would have been almost valueless if we had not used other fat stains, such as Scharlach R. or Sudan III. It appears that many of the fat droplets are stained a yellowish brown colour while hardly any of the fine granular matter, which is so beautifully mapped out by the red stains, is stained with the osmic acid preparation. It is only a few of the very large fat drops which stain black with osmic acid.

Dr. Hale White obtained similar results with osmic acid in his case, and was therefore led to believe that the substance in the blood was not true fat. He, however, failed to employ either of the well known red stains to which we have referred.

Mr. Shattock, in a paper on "Fatty Infiltration of the Nucleus of Fat Cells," states that he preferred Sudan III. to osmic acid because the fat is dyed of a positive red colour, and nothing except the fat is stained red. It would appear from our investigations that the fat droplets were surrounded by a kind of albuminous envelope which hindered the action of the black stain, but had no effect on the action of the red stain.

The occurrence of lipæmia ranks as one of the oldest observations in medicine; in fact, a large proportion of the numerous records of the condition are found during the earlier period of accurate record rather than the later. As Fischer has pointed out, the commonness of such records in the medical literature of the first three quarters of the last century (and even before that) is due to the extensive opportunities for inspection of the blood which were afforded by the universal practice of venesection. When the barber's shop window was naturally adorned by a bowl of blood and its naked-eye appearances were studied with almost as much care as the augurs of old bestowed upon the entrails of the sacrifice, it is small wonder that such a condition as this attracted attention. Many of these earlier records must of course be accepted with reserve, as they were not checked by the microscope and would include such independent entities as leukæmia; but even

making these deductions, it is clear that a milky appearance of the blood, due in a large proportion of cases to an excess of fat, is no uncommon event. The present record is not, therefore, called for by the rarity of the condition, nor does it claim to throw fresh light on its pathogeny; it is hoped, however, that it presents certain features which are not unworthy of discussion.

Though not the first case in which the lipæmia was recognised during life by the condition of the intraocular blood vessels, yet it is one amongst extremely few recorded since Heyl's original observation in 1880. Hale White, in reporting a case, mentions another which had come under his observation, and expresses the opinion that the condition is not excessively rare. Still, considering the striking appearance presented by the fundus and so well illustrated in Hale White's paper, and considering too that the eyes in diabetes are examined almost as a matter of routine, it is remarkable that recorded observations should be so scarce. If it were not a rare event, ophthalmologists would certainly be familiar with it, and yet in Bernard Fischer's case so experienced an ophthalmologist as Reis attributed the appearances during life to arterio sclerosis.

It is remarkable that the presence of fat in such quantity in the retinal vessels should not bring about some failure of sight, even though the symptom complex of retinal embolism be absent, and this fact supplies an additional argument, if one were needed, against the old theory of diabetic coma being due to fat embolism. The explanation of this absence of symptoms is probably to be found in the extremely fine state of division in which the fat occurs. Whether this also accounts for the failure of osmic acid to give its usual reaction is uncertain, but as a matter of fact it is the finer granules of fat which mainly escape the stain.

The degree of fineness of division of the fat may be of importance in other ways. Schwarz has pointed out that the serum of diabetics may display a typically milky appearance without there being any increase of fat by direct estimation, and this, though he does not offer it as an explanation, would seem to be probably due to change in the mechanical condition of the fat normally present.

A further question suggests itself: Does the condition of the blood in the small vessels give any true criterion of its state in the larger arteries and veins? The visible change in the blood in the ocular fundus was much grosser than that found in blood drawn from a vein; in fact, the naked eye appearance of blood obtained in this way did not on the first occasion attract attention, while the ophthalmoscopic examination was almost startling. The abstracted blood being in greater bulk than that seen in the vessels of the fundus, might naturally be expected to show any change in a more striking fashion, whereas the reverse was the case.

One possible explanation of this anomaly is that in the small

Fig. 1.

Fig. 2.

Fig. 3.

FIG. 1.

FIG. 2.

FIG. 3.