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XANTHOMATOSIS: SOME ASPECTS OF ITS BLOOD CHEMISTRY AND PATHOLOGY.

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Blood Chemistry and Metabolism.

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THE following summarises a series of observations during the past few months on some aspects of the metabolism of fats in four cases of xanthomatosis.*

CASE I.—**Xanthoma Multiplex.**—Mrs H., aged 57. For at least ten years the patient had been noticeably jaundiced but xanthomatous nodules had only developed during the last twelve months of the condition. In this case, the nodules did not stand out dark in contrast with the surrounding skin, but were, as a rule, paler in colour, owing to the darkening of the skin by the jaundiced condition. Especially on the face, the palms of the hands, and the soles of the feet, the nodules were so aggregated as to form distinct plaques. Nodules were also present on both the flexor and extensor aspects of the elbow joints. The liver and spleen were both markedly enlarged. The urine and stools were both bile stained. Her previous medical history was not satisfactory, oöphoritis, rheumatism, six miscarriages in twelve pregnancies, and chronic constipation. After 7/4/24 the patient was put on a mixture containing sodium sulphate to test the claim put forward by the French school[1] of its decholesterinising

* By xanthomatosis is meant any condition in which xanthomatous nodules or plaques appear on the skin in any area accompanied by a disturbed fat metabolism, as contrasted with the localised xanthelasmic nodules appearing in the face and neck where no such disturbance has been noted.

powers. The figures of Table I. obtained in this case, while not those of fasting blood, are given for what they are worth: the blood being drawn at times when normally no excess of fat would be expected to be present in the blood.

TABLE I.

Date.	Time of Previous Meal.	Time of Blood Sample.	Blood.*		
			Sugar.	Total Fat.	Cholesterol.
31.3.24	10.30 A.M.	12 noon	111	2184	721
7.4.24	1.30 P.M.	3.0 P.M.	118	1921	817
26.4.24	10.30 A.M.	12.45 „	129	1953	552
5.5.24	10.30 „	11.0 A.M.	125	1602	491
12.5.24	10.30 „	12 noon	...	1783	507

The fat content of the stool showed no abnormality.

* The figures under this heading represent mgrms. per 100 c.c. of blood. The methods used for the blood lipoids were these of Bloor cholesterol being estimated by his second method. The term "total fat," includes the total fatty acids and cholesterol, total fatty acids consisting of these contained in combination in lecithin, cholesterol esters, and fat of the blood, cholesterol including both that present in the free and combined forms in the blood: the normal being taken as 290 to 420 mgrms. per cent. total fatty acid, 190 to 250 mgrms. per cent. cholesterol, or 480 to 670 mgrms. per cent. total fat (Bloor (2)).

The first case presents some features of considerable interest, and its pathology is perhaps a little more obvious than that of the succeeding cases. The very high figures obtained for cholesterol in this case are quite in accordance with these obtained by others (M'Nee[3]) in obstructive jaundice. While here the obstruction was not complete, it was sufficient to interfere with the normal excretion of cholesterol in the bile, but in addition the numerous pregnancies and chronic ovarian disturbance may have had some causative influence on the hypercholesterinæmia. The xanthomatous deposits probably consisting largely of cholesterol fat combinations, of high melting-point as compared with the ordinary body fat were in all probability secondary to the excess of cholesterin circulating in the blood. By assuming a high melting-point, the hardness of the lesions at body temperature and the softening that she observed resulting from their immersion in hot water is readily explained. In experimental hypercholesterinæmia one can trace the deposition of the excess of cholesterol from one organ to another according to the severity of the condition (M'Means[4]), so that the extensive cutaneous deposits found in this case are up to a point an index of the extent and chronicity of the underlying

condition. The lesions were all too widespread to allow of trauma having been a predisposing factor in all cases. Similar high findings are reported for total fats (Widal, Weill and Laudat[5]) in obstructive jaundice due to gall-stones or cancer of the pancreas, so that the figures obtained are not unique in this respect. Allen[6] reports a case of hepatic cirrhosis with a total fat of 3.07 per cent., another instance of disturbed fat metabolism in liver disease. With regard to the effect of sodium sulphate on the blood cholesterol, even although there was a considerable fall in the fat values and more especially the cholesterol, too much stress must not be laid on this, in spite of the lower and more nearly constant lower level of the last three cholesterol readings, the control observations not being too adequate.

CASE II.—**Xanthoma Diabeticorum.**—L. N., watchmaker, aged 30. Diabetes had been present for three years. Thirst, polyuria and emaciation first noted in December 1920. Improved under the Allen regime, and kept fairly well till August 1922, when he had to stop work for three months. Under diet and rest he again improved. In October 1923 the fasting blood sugar was 190 mgrms. per cent. and the urine sugar free. His diet, previously low, was increased, and he was given insulin 5 units per diem. Re-admitted to the Royal Infirmary, Edinburgh, for further treatment 11.11.23. There was no history of boils, peripheral neuritis, or pruritus. His previous illnesses were unimportant, his general surroundings, habits, and family history satisfactory. General systemic examination was negative. Xanthoma nodules were first observed two years ago, beginning at the inner canthus of the left eye as a solitary plaque and later appearing as a similar plaque in the right eye and on the palmar surfaces of both hands.

His blood sugar curve on admission was definitely diabetic and glycosuria was present. Table II. gives the response to the ingestion of 25 grams of glucose along with other metabolic data.

TABLE II.

Hours after Injection of Glucose	0.	1.	2.	3.	4.	5.
Total blood fat . .	2346	2415	3004	...	...	2838
Blood sugar . . .	235	307	307	285	207	160
Respiratory quotient .	0·79	0·71	0·74	0·72	0·72	0·77

The basal sample of urine contained 9 grams glucose, and 8.1 grams glucose were passed during the test.

The patient's tolerance to a meal containing 20 grams carbohydrate, 6.5 grams protein and 30.5 grams fat is recorded in Table III.

TABLE III.

Hours after Ingestion of Meal .	0.	1.	2.	3.	4·5.
Total blood fat . . .	2965	2604	3117	2744	2802
Blood cholesterol . .	297	376	350	333	...
Blood sugar . . .	200	235	266	211	182
Respiratory quotient . .	0·89	0·75	0·81	0·79	0·77

Urine sugar- and acetone-free. The blood on standing did not show any marked lipæmia. The patient was discharged on 14.12.23 on a diet of 1900 calories and 30 units of insulin per diem.

In this second case, one of true xanthoma diabeticorum, we find a different picture. This case showed only 2 to 3 per cent. total fat in contrast to the numerous high figures obtained by other workers, but the figures are high enough to be typical. His blood did not show any lipæmia noticeable by the naked eye; the lipæmia was "masked." This masking of the presence of excess of lipoid is a not uncommon phenomenon more especially in the minor grades of increase in the blood lipoids. Generally, if the oxalated blood be allowed to stand for twenty-four hours, the excess fat becomes visible, a fact which has been considered to be the result of the breaking up of the lipoid portein or other combination which is apparently not very stable and the appearance of the fat in a free state. The blood cholesterol was also above the normal level but not so high as in Cases I. and III. During the ingestion of fat the cholesterin showed a very marked rise (Table III.). The ingestion of fat in a normal individual has no effect on the total cholesterol at least, not until very late. It is of interest to note, however, that the ingestion of carbohydrates *per se* usually causes a fall in total cholesterol. The total fats show a descent from the fasting (blood fat) level followed by a rapid rise to a maximum a little earlier than normal. Under the conditions of our experiments the rise in the blood fat after the ingestion of 250 c.c. of cream containing 40 per cent. fat reached its maximum in three and a half to four hours.[7] From this one may conclude that the ultimate utilisation was probably delayed since in all cases the blood fat level is not an absolute index of the available fat of the body but rather represents a balance between that which is being carried to the depots for storage and that which is to be metabolised. Thus the meaning of the level of the blood fats in relation to fat metabolism is analogous to the meaning

of the blood sugar level in relation to carbohydrate metabolism. The respiratory quotient throughout the experiment seemed to indicate that more than fat was being utilised by the patient's tissues. This type of case usually clears up on adequate diet restriction as illustrated by the very severe case of xanthoma diabeticorum previously reported in this *Journal* (Murray Lyon[8]), which has now completely cleared up. Whether there are variations in the level of the blood lipoids in diabetes or not is as yet unsettled, but it is probable that even under adequate dietary regime there are variations (Gray[9]), a fact which seems to be confirmed by data (as yet unpublished) on the blood lipoids in patients under treatment both with and without insulin. The nodules in this case, as also in Case III., were widely distributed over the areas where there was great opportunity of damage from the exterior. The distribution was that of the usual diabetic type (Major[10]). That trauma might quite well be a predisposing factor in the production of xanthomatous lesions is well shown by the case of the appearance of such a lesion on the site of a mosquito bite in a diabetic boy.[10] But this is certainly not the only predisposing factor in addition to the hypercholesterinæmia, there are probably other factors of which we are not at present cognisant.

Case III.—**Xanthoma Tuberosum.**—P. D., aged 25 (Indian). The condition was of some five years' duration, first appearing in the distal creases of the phalanges in 1918 and over the bend of the elbow in 1922. On coming to this country it became more prominent. The nodules were always softer when immersed in hot water; a similar effect of increased temperature on the nodules was also observed in the first case. Previous illnesses—chronic malaria 1916-1920, influenza 1919, right orchidectomy for tuberculous disease in 1921.

The blood serum was definitely lipæmic. The response to the ingestion of 100 grams of glucose was normal (Table IV.).

TABLE IV.

Hours after Ingestion of 100 grams Glucose	0.	1.	1·5.	2·1.	3·3.
Blood sugar . . .	114	142	138	121	108
Respiratory quotient . .	0·83	0·81	0·79	0·83	0·80

The bicarbonate reserve showed the normal post-absorptive rise.[11] The blood was very resistant to hæmolysis by saponin, a fact which pointed to a possible hypercholesterinæmia. The response of this

case to the ingestion of 250 c.c. of cream containing 40 per cent. of fat is given in Table V.

TABLE V.

Hours after Ingestion of 250 c.c. Cream	0.	1.	2·5.	4·5.
Total blood fat . . .	1,311	1,485	1,402	1,195
Blood cholesterol . .	417	368	308	317
Respiratory quotient . .	0·75	0·80	0·73	0·76

The rise in values for total fats here is earlier and more sustained than usual. The metabolic rate in these experiments showed no very significant change and is not recorded. At no time did the urine show any abnormal constituents whatever. An attempt was made to clear up the condition on a fat-free diet, but this proved abortive, and the patient was lost sight of.

This case belongs to that type of xanthoma classed as xanthoma tuberosum. The glucose tolerance curve showed no evidence of pancreatic damage that might lead to a clinical diabetes, carbohydrate assimilation and storage being apparently normal. The response to the ingestion of fat, however, is striking in that the maximum value for total fat in the blood occurs in the first hour, and also because of the large fall in the blood cholesterol values during the period of observation. These results were not due to the type of fat given; the rise in a normal with the same type of cream occurred between the third and fourth hours, while the cholesterol remained steady within the limits of error of the method. The respiratory quotient during this period indicated a considerable combustion of fat falling back to its original low level after a preliminary rise to 0.80. Case IV. under similar conditions showed a more normal fat absorption, but there was still a considerable fall in cholesterol, a fall of 86 mgrms. per cent. Data are too scanty to postulate that this is a constant feature in such cases, but it certainly seems to point to an excessive mobility of cholesterol at certain stages of fat absorption, a fact which is suggestive. According to Bloor[12] cholesterol plays an important part in the absorption of fats and their ultimate utilisation. The high cholesterol figures obtained in this Case (III.) are in accordance with the findings of other workers (Burns[13]).* Observations were not carried on long enough to decide whether this high cholesterin

* For a general summary of the various findings in this condition up to 1923, see Harrison and Whitfield, *Brit. Journ. Dermatol.*, 1923, xxxv., p. 185.

content was a constant feature. The findings in Case IV. seem to indicate that it is not necessarily constant. This is also very strikingly demonstrated in a case of hæmochromatosis in a female who suddenly developed xanthomata on the eyelids and various parts of the face where, during the acute stage, the blood cholesterol was 800 mgrms. per cent., and three weeks later after the subsidence of the acute stage it was 250 mgrms. per cent.[14] The previous medical history gave no indication of a possible cause for this lipæmia. There were some indications that the patient had been previously on a diet high in fat, but it cannot be definitely stated that this was the sole factor in bringing about the lipæmia. In diabetic conditions at least, Waller and Marsh,[15] supporting the previous findings of Blatherwick,[16] have shown that the blood fat level seems to bear no relationship to the amount of fat ingested and apparently metabolised. It is of interest to remember that Grigaut[17] found that in animals increased cholesterin feeding did not necessarily raise the fasting level of the blood cholesterol. Thus while the dietetic factor may be of importance there are other unknown factors of equal or greater importance. The ingestion of a substance rich in cholesterol as, for example, bran, certainly will temporarily raise the cholesterin content of the blood, but only temporarily. Despite the high figures for blood fat there were never any signs of acidosis so that apparently the oxidation of the final products of fats catabolism was practically normal. The high total fats in this case serve as a warning not to be too ready in diagnosing diabetes mellitus from such results in that clinically this condition is not diabetes although it may be as Harrison and Whitfield have suggested a pre-diabetic condition.

Case IV.—**Xanthoma Tuberosum and Diabetes Insipidus.**—D. S., aged 22, admitted to Royal Infirmary, Edinburgh, 21.2.24. *Complaint*—Rash, three and a half years' duration, thirst and polyuria three years, shortness of breath and palpitation six months, constriction of the throat five months, and huskiness of the voice four months. The rash consisted of raised, round, and in most cases of discrete papules 1 to 4 mm. in diameter, varying in colour from golden yellow to chocolate brown. It first appeared round the neck and then spread down the arms. Two and a half years ago similar papules appeared round the eyes, while one year ago spots appeared on the abdomen in the epigastrium and also on the lateral aspect of the thighs and buttocks. Nine months ago the voice became impaired and during the four months previous to admission it had become continuously husky. During these latter months the spots began to appear around the mouth. In the lateral areas of the neck the spots were very closely aggregated, while the

infraclavicular fossæ were relatively clear. The upper extremity was involved with scattered papules down to the middle of the forearm in both flexor and extensor aspects, but principally on the flexor aspects. They were also scattered over the trapezii and deltoids on both sides extending down to the anterior fold of the axilla (Fig. 1) and into the axillæ.

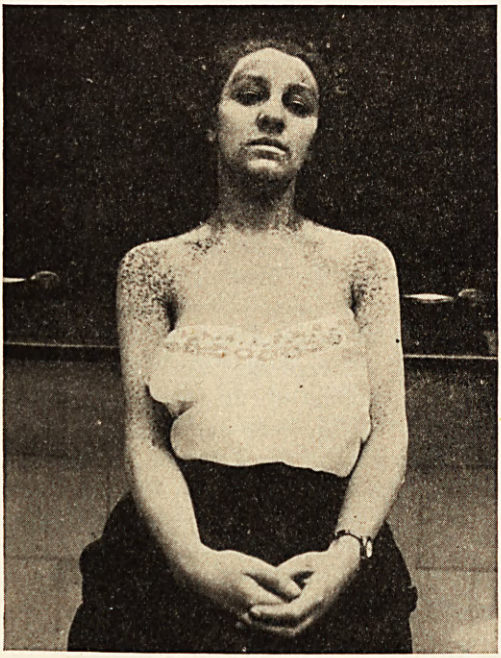


FIG. 1.—Note distribution of the lesions on forehead, eyelids, chin, neck, and arms.

A portion of skin bearing the xanthoma nodules was excised during life and examined microscopically. A large proportion of the fat from the nodules was doubly refracting, and Nile blue showed the purple of neutral fat and fatty acid. The findings were essentially similar to these described in the post-mortem report, to which the reader is referred for full details. The melting-points of these fats were considerably above body temperature as determined with the hot-stage microscope.

Examination of the other systems revealed nothing except the involvement of the mucosæ of the mouth, pharynx, glottis and epiglottis with xanthoma nodules (see separate description) and the presence of a diabetes insipidus.

The patient was put on pituitrin 1 c.c. on wool to nasal mucosa and ten units of insulin + 30 grams of glucose t.i.d.

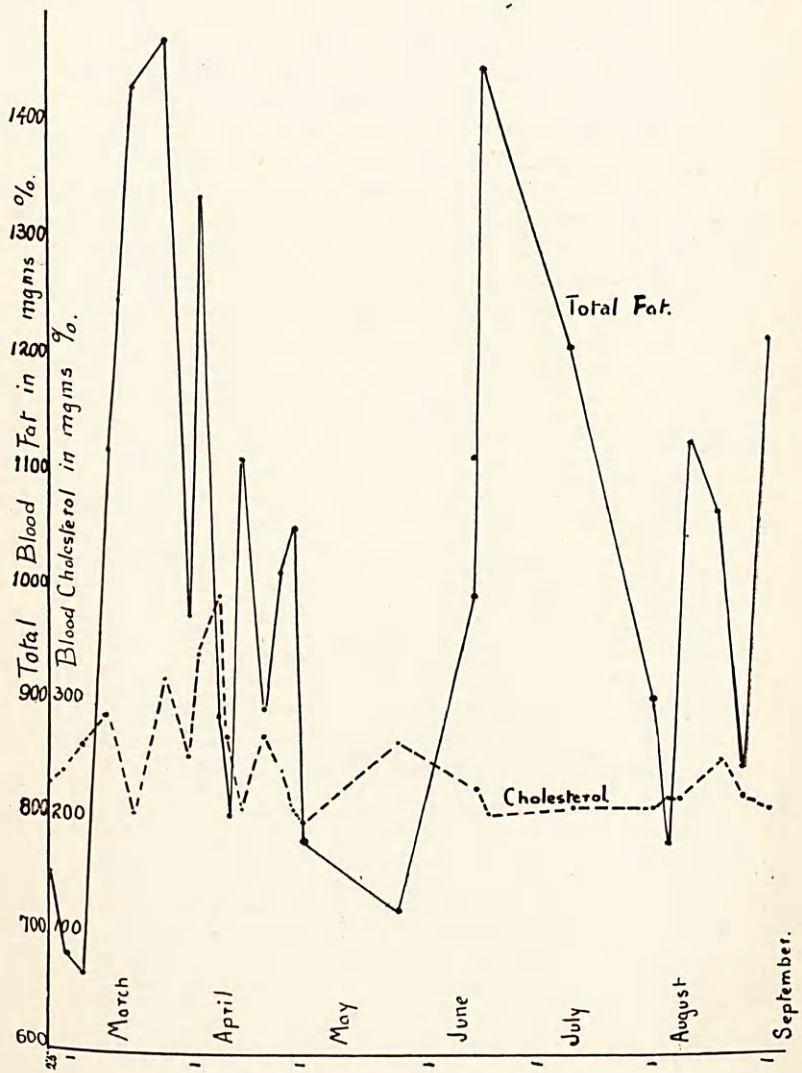


FIG. 2.—Fasting blood lipoids of D.S.

14.6.24.—Re-admitted for observation. The rash was slightly redder and paler yellow in places, and there were no fresh involvements, but dyspnœa was more marked on exertion.

The patient was put on thyroid grs. II and 10 units of insulin without additional glucose, but the thyroid had later to be stopped and treatment with insulin and glucose resumed.

31.7.24.—Re-admitted. The dyspnœa had increased during the previous four weeks, confining her to bed, becoming more marked after a cold three weeks previous. The patient had further noticed a fresh appearance of the eruption around the lips and extending down to the chin on both sides. The eruption was now darker, and there was a marked inspiratory wheeze followed by a less marked expiratory wheeze. There was no change reported in the laryngeal eruption, but one of the vocal cords had become more fixed. Later, tracheotomy was advised to relieve the dyspnœa. Tracheotomy performed 9.9.24 by Mr Gardiner. Ever after this the patient had several attacks of severe dyspnœa necessitating the use of oxygen to relieve them. The passage of a catheter down to the bifurcation of the trachea did not relieve the dyspnœa. Such occurrences indicated that the respiratory obstruction extended below the level of the vocal cords, probably an xanthomatous involvement of at least some of the larger bronchi, a fact substantiated by the post-mortem findings. On the evening of the 30th September the patient died during an attack of sudden, severe spasmodic dyspnœa.

In Fig. 2 the findings of the values for total fat, and cholesterol of the fasting blood are given *in extenso* in view of the wide variations in total fat that were found.

In addition the response to the ingestion of 250 c.c. of 40 per cent. cream was observed (3.3.24). The rise in blood fat was normal if a little late, while the cholesterol fell considerably, see Table VI.

TABLE VI.

Hours after Ingestion of 250 c.c. of Cream	0.	2·5.	3·5.	5·0.	6·5.
Total blood fat . . .	668	698	672	770	727
Blood cholesterol . .	267	202	217	211	181
Blood sugar . . .	150	160	142	152	...
Respiratory quotient . .	0·73	0·74	0·69	0·72	0·75

On two occasions the tolerance to 50 grams of glucose was observed and both times it showed a diabetic type of reaction, rising well above the normal threshold figure, but on both occasions the cholesterol was 40 mgrms. per cent. lower than at the commencement, the total fat also having dropped about 100 mgrms. per cent. by the end of two hours. The figures for the later observation (6.6.24) are given in Table VII.

TABLE VII.

Hours after Ingestion of 50 grams. Glucose	0.	1·25.	2·0.	2·5.
Total blood fat . . .	995	946	944	882
Blood cholesterol . .	229	201	197	189
Blood sugar . . .	148	322	222	220
Respiratory quotient . .	0·65	0·80	0·72	0·80

The glucose tolerance curve of a pure diabetic showed a similar change in blood lipoid figures. This result is in agreement with the findings of the French workers[1] namely, that glucose reduces the blood cholesterol. During her last stay in hospital it was found, under treatment with 30 units of insulin and 90 grams of glucose, and pituitrin 3 c.c. per diem, on a diet of 69.9 grams of carbohydrate, 67.65 grams protein, and 74 grams fat, 42.78 grams of fat per diem were lost in the fæces (46.2 per cent. of which was unsplit fat). The total quantity of urine per 24 hours was 3,300 c.c. containing 1.05 grams P_2O_5 and 3.3 grams N_2.

Laryngological Findings.

A. Logan Turner.

Nasal and Naso-pharyngeal Cavities.—No changes were observed in the mucous membranes of these cavities.

The Tongue (Plate I.).—The upper surface of the tongue presented a smooth, faintly yellow discoloration distributed in the form of a narrow band lying close to and parallel with each lateral margin of the organ. A similar band lay across the dorsum of the tongue immediately anterior to the circumvallate papillæ. The area then outlined somewhat resembled the shape of a heart.

The circumvallate papillæ were prominent as firm, raised, rounded, yellowish-brown eminences. At the anterior extremity of each limb of the reversed V formed by the papillæ and situated on the edge of the tongue, there was a large pale yellow tube, marked on the surface by a shallow groove, and measuring 1 cm. in diameter. Several small yellow nodules were seen in the region of the lingual tonsil.

Soft Palate and Fauces.—A number of raised yellow patches were scattered over the mucous membrane of the soft palate and tonsils. Some circular, some oval and others slightly irregular in shape, they varied in size from 1 to 10 mm. in diameter. While some presented a light yellow appearance, others had a browner tint. One moderately large nodule was a conspicuous object on the surface of the right tonsil.

The Pharynx.—A few scattered nodules were observed on the mucous membrane of the oral and laryngeal pharynx.

The Larynx.—The laryngoscopic appearances are seen in Plate I. The laryngeal surface of the epiglottis was studded with a number of minute, smooth, yellow elevations. The mucous membrane over both arytenoid cartilages and in the interarytenoid fold was swollen and yellow stained. It was impossible to obtain a satisfactory view of the interior of the larynx, and only a very limited portion of the right vocal cord was visible.

The stenosis of the two main bronchi explained the slowly increasing dyspnœa which terminated in an attack of fatal asphyxia.

Pathological Findings.

J. DAVIDSON.

At the post-mortem examination made on 2.10.24, the body was found to be that of a well-developed but somewhat poorly nourished female. No œdema was present. There were areas of a raised, brownish, firm eruption (xanthomatosis) on the forehead, in the vicinity of the orbits, mouth, round the neck, and at both sides of the thorax, spreading into both axillæ and round to the back. The skin over both iliac crests was also covered by this rash. There were no deposits in the skin of the lower limbs.

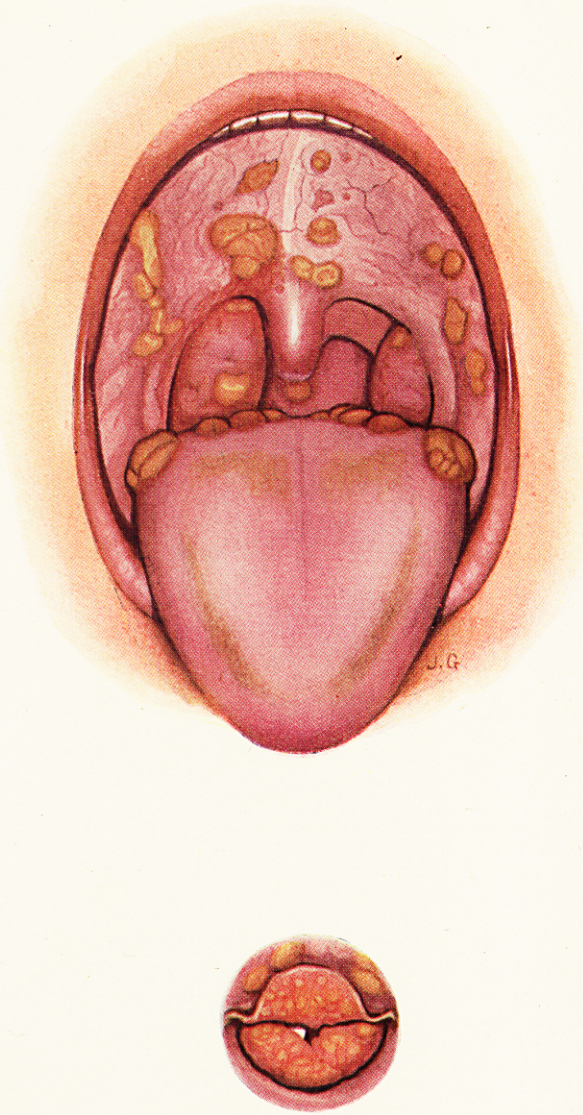
Serous Cavities. — The right pleural cavity was almost entirely obliterated by chronic adhesions. The apex of the upper lobe of the right lung was firmly adherent to the thoracic wall.

Circulatory System.—The heart was of average size and there was nothing abnormal to note regarding the chambers or the valves. There were no signs of xanthomatous change in any of the blood vessels.

Respiratory System.—The laryngeal surface of the epiglottis was covered with xanthomatous nodules, as were also the arytenoids. The upper laryngeal aperture was very much stenosed by the presence of xanthomata, the aperture being reduced to 0.5 cm. or less in diameter.

The mucous membrane of the trachea and bronchi was studded with raised yellow xanthomatous nodules. These xanthomatous masses infiltrated the wall of the trachea and bronchi and caused a considerable amount of thickening and diffuse yellow staining of the tissue composing the wall. This was well marked at the bifurcation of the bronchi and in the two bronchi, causing the lumena to be very definitely narrowed. In some parts the walls of the bronchi and trachea were 1 cm. in thickness (Plate II.).

Right Lung.—The pleural surface of all three lobes was covered by chronic adhesions. In the upper lobe infiltrating into the apex for a



distance of 4 cm. was a firm pale mass of fibrous tissue. It was almost cartilaginous in consistence, and infiltrated the lung tissue in a manner similar to that of neoplastic growth, and was quite distinctive from old tuberculous scarring. This mass of fibrous tissue in the lung was in relation to a hard cartilaginous mass of tissue (4 × 1.5 × 2 cm.), similar in consistence and appearance to a hard fibroma which lay in relation to the usual situation of the thymus gland, and may have replaced it.

Left Lung.—There was a fibrinous exudate present towards the posterior border of the lower lobe. Both lobes were firm in consistence, congested, and there was a commencing broncho-pneumonia in the lower lobe.

Alimentary System.—Tongue, xanthomatous nodules were present in some of the circumvallate papillæ. Both tonsils were affected, also the mucosa of the soft palate and pharynx. The nodules varied in shape and size from about 1 to 10 mm.

The distribution of the nodules stopped sharply, and was well defined at the commencement of the œsophagus, the mucous membrane of which did not contain any.

The stomach was larger than usual. The mucous membrane of the lower half of the organ to the pyloric valve showed a great hyperplasia; this ended abruptly at the proximal side of the pyloric valve. There was nothing to note in the duodenum or remainder of the alimentary tract. No xanthomatous patches were present on the serous surface of the bowel.

Liver.—Of normal size and appearance; pale reddish-brown in colour.

Gall-bladder.—Small; wall thickened by increase of fibrous tissue; filled with pale pus-like fluid. No gall-stones were present.

Pancreas.—Of average size and naked-eye appearance; pale red in colour.

Spleen.—Enlarged, being about half as large again; malpighian bodies enlarged.

Genito-Urinary System.—There was nothing to note regarding the naked-eye appearance of both kidneys, urinary bladder, uterus or ovaries, which were of normal size and naked-eye appearance.

Cranium and Contents.—The pituitary gland was slightly larger than usual, and here and there could be seen pale yellowish areas scattered through the anterior and posterior lobes of the gland. There was nothing to note in the cerebrum or cerebellum.

Thyroid Gland.—Both lobes were smaller than usual and hard in consistence.

Microscopic Appearances—*Xanthomatous Nodule.*—The formation of a xanthomatous nodule was characterised by the appearance

of numbers of mononucleated cells, endothelial in type. Their nuclei were either rounded, oval, or elongated in shape, and there was a considerable quantity of cytoplasm. These cells gradually increased in size, and their number of nuclei increased until finally there was produced a cell which was similar in appearance to the typical multinucleated foreign-body giant cell. In paraffin sections the cytoplasm of this type of cell was seen to become vacuolated. First of all a few vacuoles appeared and then the whole of the cytoplasm was replaced by small vacuoles, all of which were about the same size. The nuclei did not show any degenerative change in the earlier stages, but in the end a cell was produced, the cytoplasm of which was entirely replaced by vacuoles and there might or might not be the remains of a nucleus. This was the typical "foamy" cell of xanthomatosis. This vacuolation could also be seen commencing in the mononucleated cells, which had not yet changed into multinucleated giant cells.

On staining these sections with sudan III the contents of the vacuoles were observed to be fatty in character and with polarised light a certain number of typical myelin bodies or liquid crystals could be distinguished. In the well-formed xanthomatous nodules there were numbers of thin-walled capillaries, the whole being extremely vacular.

Pituitary Gland.—In sections stained for fat this tissue showed a great quantity of fatty material, lying in both the anterior and posterior lobes. The remains of multinucleated giant cells were found in sections stained with eosin and hæmatoxylin.

Stomach.—There was an increase in the glandular elements which were also much dilated. The intervening tissue was increased and was almost entirely composed of plasma cells and large mononucleated cells which could be seen forming multinucleated foreign-body giant cells; in fact all the typical cells of an xanthomatous nodule were present. Little vacuolation was present, however, and only some cells showed a commencing "foamy" appearance. The condition was an early diffuse xanthomatosis of the mucosa of the stomach wall accompanied by a hyperplasia of the glandular elements.

Lung.—In sections taken from the apex of the upper lobe of the right lung a large mass of well-formed avascular fibrous tissue was seen to be infiltrating the lung tissue and gradually replacing the alveoli and bronchioles. At the advancing margin of this fibrous tissue were areas, the cells of which contained fatty material. Fat staining material was present in the cells in the collapsing alveoli. The cartilage in the bronchi and trachea contained fat. Sections from the mass in the mediastinum also showed well-formed avascular fibrous tissue. Areas of small round mononucleated lymphoid cells

were numerous. No Hassall's corpuscles were seen. Scattered through were groups of fat globules presumably in cells.

Suprarenals.—There was nothing abnormal noted in the section stained with eosin and hæmatoxylin. It was difficult to come to any conclusion as to whether or not there was an increase in the quantity of fatty substances present.

Pancreas.—The pancreatic tissue showed atrophy and in some cases replacement fibrosis, intralobular in type. There was a moderate sprinkling of fat cells. Islet tissue showed a rather frequent hypertrophy of islets as a whole. Few of the islets had the usual proportion of the three types of cells. Most contained almost exclusively the very dark nucleated type with pink cytoplasm, whereas the granular nucleated type was absent except in a few instances. There was very marked congestion of the islet tissue.

Thyroid Gland.—A distinct replacement fibrosis was present with numerous areas of small round mononucleated cells and plasma cells, but no endothelial cells or multinucleated giant cells could be seen. The acini were smaller and in places were of a fœtal adenomatous type.

An interesting feature in this case is the widespread distribution of the xanthomatous nodules which showed a definite cellular reaction accompanying a deposit of lipoids. These were present in such varied situations as the skin (but only in certain areas), the mucous membranes lining the tongue, fauces, tonsils, epiglottis, arytenoids, trachea and bronchi (fatty material being also found in the cartilages of the trachea), and a very rare situation, namely, the mucosa lining the stomach. Deposits were also found in the pituitary gland and this might account for the symptoms of diabetes insipidus. Fatty material was present in the apex of the right lung and in the fibromatous-like mass in the mediastinum.

The limitations of these xanthomatous nodules are also of interest. For example only the mucous membrane of the lower half of the stomach was affected, while there was no change in the œsophagus, upper half of the stomach, or the remainder of the alimentary canal. Again, the rash was only present in certain parts of the skin and not throughout the whole surface of the body. There was also no evidence of any deposition of lipoids in the walls of the vessels—a common situation in arteriosclerosis.

In cases of xanthomatosis the skin is the most usual site

for the occurrence of the lesions, *e.g.* xanthoma diabeticorum. It might therefore be suggested that under certain circumstances there was some relationship between this condition and the sebaceous glands. There we find cells which are loaded with fatty substances and which in appearance resemble very closely the so-called "foamy" cells found in xanthomatous nodules.

As regards the more widespread distribution of the lesions it is difficult to arrive at any explanation why this should occur. Cholesterin fat deposits are found in such varied conditions as the case under consideration, namely, in cases where the wall of the gall-bladder has a marked lypoid deposit giving rise to the condition known as strawberry gall-bladder. Again, in choleasteatoma of the choroid plexus we find a great localised deposit of cholesterin. Arterial atheroma is perhaps the commonest manifestation of this widespread deposition of cholesterin fat. These conditions are considered by Stewart in a recent paper[18] to be manifestations of a hypercholesterinæmia. To be compared with these there are the localised deposits of lipoid which are due to local tissue changes. Examples of this condition are found in the myelin kidney, the myeloid tumour of tendon sheaths, certain subacute and chronic inflammatory conditions, dermoid cysts, omental cysts, and tumours.

There is no evidence in the case just described that xanthomatous reaction is primarily an irritative hyperplasia of fibrous tissue followed by a fatty or lipoidal infiltration of the connective tissue cells. The change may certainly be due to the presence in the tissues of cholesterol fatty-acid esters deposited from the blood, but the first reaction noted in these areas is the appearance of numbers of mononucleated cells resembling endothelial cells. These cells gradually change into larger cells which are multinucleated, and finally, these multinucleated giant cells correspond morphologically to the multinucleated foreign-body giant cell. They were found in the vicinity of blood vessels, the xanthomatous nodules being very vascular. Lipoidal and fatty substances are taken up by both the large mononucleated and multinucleated cells which gradually become vacuolated, until finally the typical "foamy" cell is produced.

The question arises as to whether the presence of fat and lipoids in these cells is to be regarded either as a simple

ingestion of infiltration, or that of a degeneration of the cytoplasm due to a metabolic disturbance. There are various factors which point to its being more of an infiltration or ingestion than a degeneration. Thus, the nucleus during the process of vacuolation of the cytoplasm does not show degenerative changes; even after the whole of the cytoplasm has become replaced by fat the nucleus remains more or less intact for some considerable time. The presence of plasma cells also indicates some reaction to an extra-cellular disturbance. However, it is conceivable that after a certain amount of fatty and lipoidal infiltration has occurred, degeneration of the cellular cytoplasm will follow, but it would appear that primarily the lipoids and fats are present simply as ingested material.

The generalised increase of fibrous tissue in certain of the organs is frequently present in cases of xanthomatosis and at first sight has no obvious relationship to the xanthomatous lesions. For example, in the present case, a large mass of fibrous tissue was found in the mediastinum and infiltrating the upper lobe of the right lung, while histologically in the xanthomatous nodules, especially the early ones, there was no evidence of an increase of connective tissue. As far as can be seen, the fibrosis is a secondary irritative process following the appearance and development of the endothelial and "foamy" cells. Amongst the areas of fibrosis, numbers of fat-containing cells, the remains of "foamy" cells were found. These cells were also seen along the advancing margin of the infiltrating fibrous tissue in the lung. These observations tend to indicate that the fibrosis is a secondary irritative lesion secondary to the appearance of the fat- and lipoid-laden cells.

The distribution of the lesions in this case gives no indication as to the site of the primary disturbance of metabolism.

Chemical Findings.

A. C. WHITE.

In view of the prolonged observations in this case and the pathological findings it must be considered in greater detail. The first fact that emerges is the apparently cyclical type of change in the fasting values for the total blood fats. It must further be observed that this change involves more the total fatty acids than it does the cholesterol which does not show

variations of as great magnitude or frequency as the former. During the six months or so that the case was followed the total fats rose to a maximum between 1400 and 1500 mgrms. per cent. on two occasions, the changes occurring over six to eight week periods. These facts offer a plausible explanation of the varying results obtained by different observers. It will be noted also that in this case, even more than in the three previous cases, there is a marked deviation from the normal at times at least in the relative proportions of cholesterol and total fatty acids in the blood. This is also borne out in the patient's response to the ingestion of fat where there is an early and marked lowering of the blood cholesterol. It would almost appear as if the cholesterol were being utilised too quickly or that there was a relative shortage of this substance. Normally, fat absorption proceeds as follows. There is first of all a steady but variable increase in fatty acid accompanied by an increase in lecithin, which does not run absolutely parallel with the increase in fatty acid, while at a later stage there may be an increase in cholesterol. In persistent lipæmia cholesterol may become more abundant than lecithin. Therefore in this case, and similarly the previous two cases, we have a definite abnormality in the lipoid metabolism, Cases III. and IV. showing a fall and Case II. a rise in cholesterol during the absorption of fat. A normal person under the same condition showed the rise in the total fat but no change in the cholesterol figures during the time of observation. Whether these findings will prove to be constant in the various types of xanthomatosis must await future investigation. In view however of the abnormality of the cholesterol fatty acid ratios in the blood one may also suspect a probable abnormality in regard to lecithin also. Whatever the defect, it seems to result in the deposition of fat in certain areas in such an altered physio-chemical relationship that the re-transport and ultimate utilisation is hindered by the fact that the melting-points of the cholesterol fatty acid deposits in the skin are considerably higher than that of the normal temperature of the body, and as a result would be less subject to the agents which normally affect the transport of fats at body temperature. Histological evidence further supports the hypothesis that the disturbance of fat metabolism was the primary error, in the transition types observed in the xanthoma nodules between the foreign-body giant cell and the typical vacuolated foamy cell of the xanthoma

nodule within the skin, and in the mucous membrane of the stomach and elsewhere, and in the marked deposition of fat in the pituitary body, where normally no fat cells of the type found exist. The findings in the very hard fibrous mass found in the right lung and the mediastinum tell a similar story. Here, however, it is continued further, the irritation apparently caused by the presence of this foreign fat led to a very marked irritative fibrosis wherein the major portion of the fat was ultimately absorbed, a little only remaining in the region of the blood vessels. With regard to the sites of the various lesions, the reason for the selection of the areas described is not very clear. In this skin at least the process seems to start where cholesterol fatty acid components are present normally in the region of the sebaceous glands and spread wider, but this does not hold elsewhere. In the intima of the blood vessels where there is usually cholesterol we do not find xanthomatous deposits, and in the stomach and lung where there is normally no cholesterol fatty acid we find considerable deposits; similarly with the findings in the bronchi. It may be that the widespread involvement is an index that the severity and chronicity of the condition was such that these various areas were ultimately involved. The skin manifestation appeared six months before the evidence of pituitary involvement in the shape of diabetes insipidus, therefore we may conclude the diabetes insipidus was a secondary phenomena. The diabetes insipidus presented, as far as urinary examination went, the ordinary features characteristic of this disease and the condition was kept under control by means of the pituitrin. The beneficial effect of pituitrin applied to the nasal mucosa in this case is not unique. Motzfeldt[19] and others have also obtained similar results. The role of the pituitary in controlling the metabolism of carbohydrates and fats is not sufficiently clear for any profitable discussion and will not be dealt with in this case. Weidman and Freeman[20] have recorded a case of xanthomatosis of almost as general wide involvement in which diabetes insipidus was also present. This fact along with clinical findings in this case led to a clinical diagnosis of xanthomatous involvement of the pituitary, which was confirmed post-mortem. The question of the relationship of this xanthomatous condition to diabetes mellitus is of some importance in view of the diabetic type of glucose tolerance curve obtained. If Table VII. be considered along with the clinical absence of any other

symptoms of diabetes and the disturbed fat metabolism, it would appear as if we have here a transition stage between a disturbance purely of fat metabolism and one of carbohydrate metabolism. Indeed it would appear that during the period under which the case was under observation, at least as far as one might judge from the glucose tolerance tests done, the first immediately on admission to hospital when the blood sugar rose to 200 mgrms. per cent. and recovered in an hour, and the second some months later, that an increased difficulty and in carbohydrate metabolism was gradually developing. Such a development is not surprising in view of the intimate inter-relation of fat and carbohydrate metabolism. Neither Case III. nor Case IV. ever showed any signs of acidosis, so that the term used by Harrison and Whitfield "pre-diabetic" may be fairly appropriately applied to them.

In such a case then is insulin of any value in ameliorating the condition? It is well known, that insulin and carbohydrate are specific in relieving the symptoms of diabetic acidosis, experimental and clinical, which is due to a disordered fat metabolism whereby the end products of the long fatty acid molecules are not completely broken down. Insulin 30 units administered in 10-unit doses through the day were given this case, and in addition to avoid any tendency to hypoglycæmia glucose in 30-gram doses three times a day sixty to ninety minutes after each injection. It was considered that if carbohydrate metabolism were so increased that the oxidation of the fats might be facilitated. The figures for fasting blood fats show, however, that the end desired was not attained, nor was there clinically any definite signs of improvement, so that the disturbance was not of the same nature as that involved in diabetic ketosis. In normal individuals the effect of insulin on the blood sugar is very definite but the effect on blood fats is not so marked, at any rate during the time of fall and recovery of the blood sugar, nor is the effect on the blood cholesterol. With the exception of the days when the glucose tolerance tests were made there was at no time evidence either of hyper- or hypoglycæmia, the blood sugar remaining within normal limits so that the large carbohydrate element of the diet was being utilised to some extent at least. The respiratory quotient during the absorption of carbohydrate never rose to the height it normally should, the highest figure being eighty, but in view of the abnormal condition of the air passages a possible

retention of CO_2 and consequent mechanical lowering of the respiratory quotient has to be borne in mind. Marked cases of diabetic lipæmia are slow in reacting to treatment even with insulin.[21] Therefore the absence of response in this case where there was no ketosis is perhaps not so surprising.

Recently,[22] it has been suggested in view of the improvement occurring in xanthoma diabeticorum under insulin that it may prove of value in the treatment of xanthoma of hepatic origin. While xanthomatosis results from a deranged fat metabolism the results in the present case tend to throw some doubt on the utility of insulin in cases of disturbed fat metabolism other than that of diabetic origin. The changes observed in the pancreas cannot be accurately correlated with the chemical findings, but are sufficient evidence that pancreatic function both internal and external was somewhat damaged.

Speculation as to the exact cause or the site of the damage is not at this stage justifiable, but there seems no doubt that in more detailed study of the fats in the blood, the factors influencing them and their relative proportions and their types may shed considerable light in this field.

Summary and Conclusions.—1. Four cases of xanthomatosis are described, all of which showed disturbed fat metabolism.

2. In the first case the cause seemed related to definite liver damage.

3. The xanthomatosis of the second case was related to a disturbed fat metabolism in diabetes.

4. The third case showed a primary disturbance of fat metabolism which might have been pre-diabetic.

5. In the fourth case we have a type apparently intermediate between that in the second and third, starting as primarily a disturbed fat metabolism the carbohydrate metabolism apparently being involved secondarily.

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DESCRIPTION OF PLATE III.

FIG. 1.—Section of skin showing xanthomatous nodule, with multinucleated giant cells and "foamy" cells. Hæm. and eosin. × 50 diam.

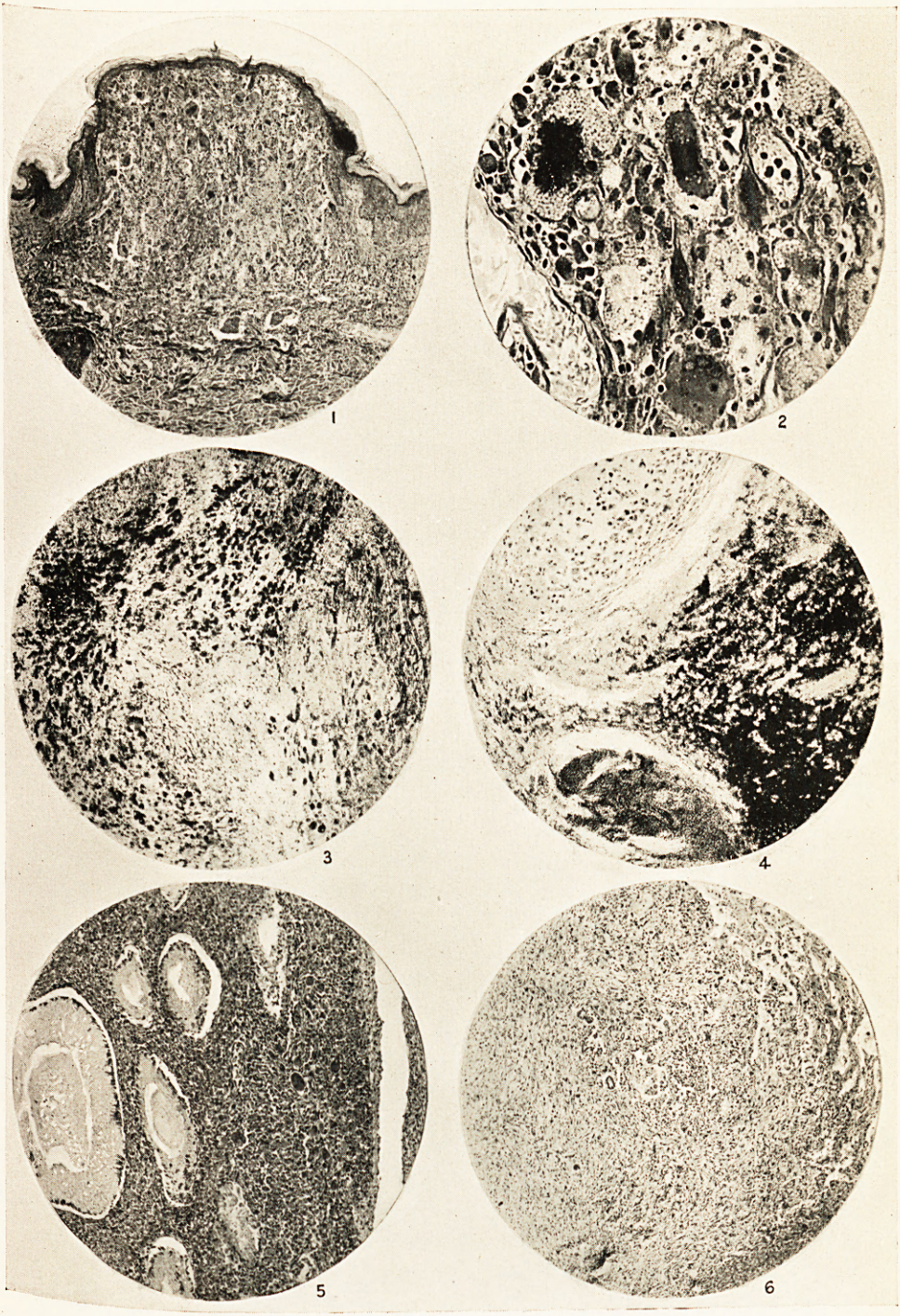
FIG. 2.—Xanthomatous nodule showing multinucleated giant cells and vacuolated or "foamy" cells. Hæm. and eosin. × 300 diam.

FIG. 3.—Section of pituitary gland showing deposition of fats in anterior and posterior lobes. Sudan III. × 45 diam.

FIG. 4.—Section of trachea with fatty deposit in xanthomatous nodule lying in relation to cartilage which also contains fat. Sudan III. × 45 diameter.

FIG. 5.—Mucosa of stomach with hyperplasia of glandular elements and increase in numbers of cells; numerous multinucleated giant cells are present. Hæm. and eosin. × 75 diameter.

FIG. 6.—Section showing fibrosis of lung. Hæm. and eosin. × 60 diameter.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