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**WHIPPLE, George Hoyt. - A hitherto
undescribed disease characterized
anatomically by deposits of fat and
fatty acids in the intestinal and
mesenteric lymphatic tissues**

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which show scattered tubercles in the viscera, and tuberculous mesenteric glands.

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A HITHERTO UNDESCRIBED DISEASE CHARACTERIZED ANATOMICALLY BY DEPOSITS OF FAT AND FATTY ACIDS IN THE INTESTINAL AND MESENTERIC LYMPHATIC TISSUES.

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The following case was characterized clinically by a gradual loss of weight and strength, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs, and a peculiar multiple arthritis. The diagnosis lay between neoplasm and tuberculosis of the mesenteric structures. Pathologically the lesions of interest were found in the intestines and the lymphatic tissue draining this region. The intestinal mucosa showed enlarged villi due to deposits of large masses of neutral fats and fatty acids in the lymph spaces and an infiltration of the interglandular tissue by large mononuclear and polynuclear giant cells. The submucosa in many places shows similar deposit in the enlarged lymph spaces and invasion by large mononuclear cells. The mesenteric glands in gross showed the most striking changes, but under the microscope the picture closely resembled that seen in the intestine. The glands showed the same deposits in even greater amounts, and a chronic inflammatory reaction with replacement of much of the gland tissue by fibrous scar tissue, masses of large mononuclear cells or polynuclear giant cells of the foreign-body type. The lymphatic tissue of the bronchial glands, bonemarrow, and lungs showed no abnormalities of importance. The other organs are described below, but no changes were found which seemed related to the intestinal lesions.

CLINICAL HISTORY.

(53,803), X, physician, *et. 36*, single, was admitted to the Johns Hopkins Hospital on April 12, 1907, complaining of "loss of weight and strength; rheumatism; bronchitis; shortness of breath; dilated (*sic*) abdomen; tumor of abdomen."

Family history.—Unimportant. No history of tuberculosis in any branch of family.

Previous history.—Up to five years before the entry the patient had been a remarkably healthy man. Measles and whooping-cough as a child. Chills and fever at 10. Slight attack of pleurisy at 14—in bed only a day or so. In 1899, mild attack of influenza.

Has had some trouble with his nose for which a small portion of each inferior turbinate bone has been removed without benefit. Tonsils were excised when he was a child.

As long as he can remember he has had a slight hacking cough and a desire to "clear his throat." For four and a half years the patient has, he says, had a "bronchitis" with chronic cough, which has always been worse in cold and damp weather.

The patient has been working as a medical missionary in the East, mainly in Constantinople, whither he went in 1899. In his work he has frequently been thrown with tuberculous patients.

The present illness began insidiously, five and a half years ago, immediately on his arrival in Turkey. The first symptoms were attacks of arthritis coming on in various joints. They were transient, the first lasting but six or eight hours. These recurred again and again three or four times a week in damp weather, once a week perhaps, in dry weather, lasting from six to twenty-four hours; rarely severe enough to keep him from work. Nearly every joint has been affected. Sometimes the joints were hot, swollen, and tender; at other times, only painful. Again the pain might seem to be in the muscles; or with pains in the joints there were also pains along the course of both sciatic nerves. The attacks were never associated with fever and on but one occasion were they of sufficient severity to confine him to bed and for but two days. These attacks were associated with a gradual loss of weight and strength. In the course of a year he developed a cough which has continued ever since, varying, however, greatly in severity according to weather and climate—better in dry seasons and climates, worse in damp. This was associated with an expectoration of moderate quantity, of a yellowish color, tenacious and raised with difficulty—more abundant in the morning.

Although gradually losing weight and strength he kept at work, with occasional vacations, until September, 1906, when he came back to America, spending a month in the Adirondacks, where he gained five or six pounds. Thence he proceeded to Atlanta where, in the course of five or six weeks, his cough became much worse, the expectoration increased, and a slight evening fever developed, the temperature rising to about 100°. There were occasional "night sweats" and notable loss of strength and weight. Physical examination showed nothing definite.

Examination of the sputa for tubercle bacilli was negative.

In December, 1906, the patient, fearing tuberculosis, went to New Mexico, where his bronchitis improved. The loss of weight, however, continued, and a diarrhea set in which has persisted ever since, the stools, from three to four a day on an average, of fluid or semi-solid character. Examination by the patient himself, revealed a deficiency in bile and an excess of fat.

Shortly after reaching New Mexico, three and a half months ago, the patient observed a swelling of the abdomen, which gradu-

ally increased until the circumference amounted to thirty-three inches, since when it has remained stationary. Soon after this a mass became palpable below and to the right of the umbilicus, while there was a still larger indefinite area of dulness and resistance in the same region. There has been some tenderness on pressure in this region.

About four weeks ago both ankles, especially the left, became hot, swollen, red, and tender and attempts to walk were painful. This condition, although somewhat improved, still persists.

For the last four or five weeks he has noticed dyspnea on exertion. The appetite has always been good. No history of jaundice.

BLOOD EXAMINATIONS.

April 14. Fresh blood—red cells are pale and irregular in size, there being many microcytes. No nucleated red blood cells. No myelocytes. No marked poikilocytosis.

R. B. C., 4,468,000; W. B. C., 8180; hæmoglobin, 52%.

Differential count:

Polymorphonuclears	410—80.4%
Small mononuclear lymphocytes.....	16—3.1%
Large mononuclear lymphocytes.....	32—6.2%
Eosinophiles	47—9.2%
Large mononuclear cells.....	2—0.4%
Mastzellen	3—0.6%

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April 21. R. B. C., 4,464,000; W. B. C., 8420; Hæmoglobin, 54%.

April 29. R. B. C., 3,932,000; W. B. C., 6780; Hæmoglobin, 53%.

April 30. Coagulation time, 5 minutes 30 seconds.

May 1. Differential count:

Polymorphonuclears	491—89.3%
Small mononuclear lymphocytes.....	19—3.5%
Large mononuclear lymphocytes.....	19—3.5%
Eosinophiles	17—3.1%
Mastzellen	1—0.2%

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EXAMINATION OF STOOLS.

April 14. Stool is almost white, or creamy and has a smooth silky appearance. Under the microscope one sees enormous numbers of fatty acid crystals. They appear as small needle-like crystals arranged in tufts or rosettes which do not stain with Sudan III. This stain shows an abundance of neutral fat in fine globules. Vegetable cells are present and a few pieces of striped muscle. No parasites nor eggs are seen after long search.

Several examinations for tubercle bacilli negative.

April 24. Stool is clay-colored. Microscopically it resembles the ones previously examined with perhaps some increase in neutral fat.

April 28. Stool darker colored. No bile was demonstrable. Fatty acids and neutral fat present in large amounts.

Dr. Boggs. April 20. Stool almost completely composed of split fats and soaps in crystalline form indicating interference with fat absorption. Neutral fat small in amount. Some undigested starch present. Reaction of stool is acid.

Dr. Voegtlin. April 30.

Dried stool, 20 gms.	{	Neutral fat, 10 gms.
		Fatty acids, 6 gms.
		Organic salts, etc., 4 gms.

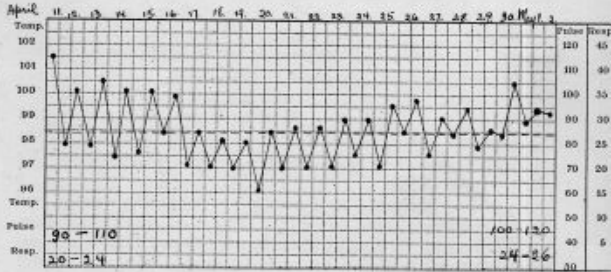
Diet.—While in the medical ward the patient was on a full diet with four raw eggs daily and eight ounces of milk every two hours. In spite of this forced feeding the patient lost weight every week, weighing 145 pounds two weeks before his death. Normal weight, 175 pounds.

URINE EXAMINATIONS.

April 12. Clear, yellow color. Specific gravity, 1029; acid reaction; no sugar; no albumin; red finely-granular sediment; no casts; many uric acid crystals; diazo negative. Later examinations showed the same general picture.

April 29. Calcium oxalate crystals were present. No bile. Urine obtained shortly before death showed the presence of a considerable amount of acetone but no diacetic acid.

May 3. .001 gr. of tuberculin was given. No reaction followed. No sputum was obtained except a small amount of clear mucus showing no tubercle bacilli.



CLINICAL NOTES.

Dr. Thayer. April 15, 1907. The patient was thin, and though sunburned was evidently pale. There remained still a good deal of tonsillar tissue with well-marked crypts.

The thorax was unsymmetrical, the cartilages of the fifth and sixth ribs of the left side being evidently prominent. The movements of the right upper front were rather freer than those of the left side, and on percussion there was a slight dulness with a trace of tympany in this area. On quiet respiration the inspiration was here a little wavy but no adventitious sounds were heard. Elsewhere, the respiration was clear.

Heart.—Sounds best audible in the fourth space, inside of the mammillary line, about 7.7 cm. from mid-sternal line, at which point dulness begins. Sounds, clear throughout; second pulmonary a little louder than second aortic.

The abdomen was rather full. Just to the left of the median line in the epigastrium there was a slight prominence which suggested a small properitoneal hernia. The abdomen was more resistant on the right than on the left, and especially in the right lower quadrant where the fulness seemed more marked; there was a "rather elastic resistance," especially below and to the right of the navel. Tympany on percussion; somewhat duller in the middle of the abdomen and in the left flank. No movable dulness.

The liver was not palpable, extending by percussion to a point a little above the costal margin in the mammillary line, and in the median line to a point midway between the umbilicus and xyphoid cartilage. The splenic dulness reached the costal margin but the border could not be distinctly felt.

A few small glands were palpable in the axillæ and the epitrochlears were both palpable.

The left ankle was swollen, the skin tense and shiny. On the outer side of the foot and on the dorsum there was a diffuse discoloration suggesting old cutaneous hæmorrhage. A greenish-yellow coloration extended from the toes to above the malleoli, while at points there were deeper bluish areas gradually fading into the yellow-green. The ankle was quite hot. On the legs and thighs were a few faded, brown purpuric spots no larger than a pin-head.

In the middle of the left leg, just to the left of the tibial crest,

there was a discolored, greenish, slightly indurated spot having the appearance of a fading patch of erythema nodosum. On the right leg and calf were several similar areas.

Dr. Baetjer. April 17. Radiograph of ankles does not show any bone changes. There is, however, a slight thickening of the peritubercular tissues around joints. This does not seem to be tuberculous. No exostosis nor erosion of any bones.

Dr. Barker. April 19. There is a little general pigmentation. Glands in right posterior portion of neck are palpable. Chest shows expansion a trifle better on the right side. There are pigmented moles on chest. Vocal fremitus is normal. Percussion clear. A slight friction heard in left lower back and a few fine crackles in right supraspinous region. Heart sounds clear. Abdomen full, slightly more marked on right side. Slight tenderness to right of navel. Dullness in right flank; none in left. Slight swelling of left, but more of right ankle.

Dr. Thayer. April 20. Abdomen is a little generally distended and everywhere tympanitic. Less tenderness to-day than last time. There is a muscular resistance to deep palpation in the right upper quadrant just above and to right of umbilicus. No definite mass is felt.

Dr. Baer. April 18. Both ankles are markedly swollen and pit on pressure. There is a slight amount of local temperature, no decided pain on pressure over bones. Dorsal flexion is somewhat limited. Abdomen is much distended with a decided movable mass just below umbilicus.

Dr. Thayer. April 25. Left ankle is not so swollen and looks better. Abdomen is not so swollen—a doughy resistance. Just below navel is felt a nodule the size of a walnut. Palpation here causes a little pain in left side of abdomen. Some suggestion of a lesion at left apex but nothing definite. On deep inspiration in left lower axilla in sixth and seventh interspaces there is an exceedingly soft friction rub—definite in forced inspiration and expiration. This is present also over left lower back, rather more audible than in front. An occasional fine crackle at extreme base of right lung.

Dr. Thayer. April 29. Auscultation of left apex shows a very interrupted inspiration but no adventitious sounds. Percussion note a little higher pitched than on right. In the left lower axilla and back a soft friction is audible, reaching to within three finger's breadths of angle of scapula. Over a small area below angle of scapula in right lower back a very rough scratchy friction is heard. Percussion note at both bases is impaired. Heart, no enlargement; sounds clear; pulmonic second sound is accentuated. Abdomen is very full with limitation of respiratory movements, walls not so resistant as before. A rather indefinite tumor felt to right of umbilicus, it is slightly tender. At times to right and above navel a tumor is felt, very movable and rather sausage-shaped.

May 5. Patient transferred to surgical wards for exploration. Operation May 6. No fluid in abdominal cavity. Mesenteric glands very much enlarged and hard. Abdomen was closed. Diagnosis, tuberculosis of mesenteric glands. Patient did well for 48 hours after the operation. He perspired quite freely at times and was troubled with joint pains but slept a good deal. He was on a liquid diet and had frequent enemata, which were not very effectual. Dyspnea was noticed two hours before death and respirations then numbered 40 per minute; pulse 120.

Dr. Cole. May 8, 1907. The patient was seen by me at 9.30 p. m., at which time he was perfectly conscious, propped up in bed and suffering from extreme polypnea. The distress seemed to be both with inspiration and expiration. There was only moderate cyanosis, though the skin was cold and clammy. There was no striking odor to the breath. A few râles were heard over both lower lobes, but no areas of consolidation were made out and the condition in the lungs did not seem to be sufficient to account

for the extreme grade of dyspnea. Pulse was rapid, but regular, and of fair quality. He did not seem to be in immediate danger. An attempt was made to have him void as a condition of acidosis was at once suspected and it seemed advisable to obtain some urine for examination. He was unable to void and preparations were being made to catheterize him when he suddenly died.

CLINICAL DISCUSSION.—*Dr. W. S. Thayer.*

The clinical pictures of this case were in many ways remarkable. The cough, the fever, the progressive emaciation, the abdominal swelling and tenderness, the remarkable character of the stools, indicative of defective fat absorption, were decidedly suggestive of a pulmonary and mesenteric tuberculosis.

On the other hand, the physical signs did not justify a diagnosis of pulmonary tuberculosis and the sputa were negative. The signs at the left apex were interpreted clinically as evidence of an old retraction and not of an active process. Again the blood picture was distinctly not that of a tuberculosis. The anemia was more marked than common and the eosinophilia present on entry was peculiar. In addition to this were the condition of the ankles with the remarkable history, together with the purpuric manifestations and the areas suggestive of erythema nodosum—symptoms which raised the question as to whether the case might belong to that ill-defined group which has been roughly brought together through the common manifestations of erythema multiforme exudativum and arthritis.

Further examination of the stools confirmed the existence of permanent interference with fat absorption without deficiency in fat splitting or azotorrhoea, while the absence of reaction to .001 tuberculin was strong evidence against the presence of an active tuberculous process.

These observations, together with the result of the exploratory laparotomy led to a final diagnosis of sarcoma or Hodgkins' disease of the mesenteric glands.

It is a matter of great regret to me that I was unable to see the patient after the operation. The remarkable manner of death was as Dr. Cole observed, suggestive of an acid intoxication.

As one looks back upon the history of this case in connection with the remarkable observations at autopsy, it is difficult to resist the conclusion that we are here dealing with a definite and hitherto unrecognized clinical picture with which we shall meet again.

Autopsy Protocol.

Dr. X. Aet. 36 years. Ward C, 2. Autopsy No. 2883. Died 10.40 p. m. May 8, 1907. Autopsy 2 p. m. May 9, 1907. *Dr. Whipple.*

Anatomical Diagnosis.—Neutral fat and fatty acid deposits in intestinal mucosa, mesenteric and retroperitoneal glands and thoracic duct; chronic lymphadenitis; anemia; emaciation; organizing peritonitis, pleuritis, pericarditis, and aortic endocarditis; cardiac dilatation and hypertrophy with fatty degeneration; chronic passive congestion of viscera; splenic tumor; hyperplasia of bonemarrow; cloudy swelling

of viscera; laparotomy wound; bronchopneumonia and œdema of lungs; caseous apical scar and tuberculous bronchial lymphadenitis.

Body is that of a well-developed, large-framed, white male, 180 cm. in length. Rigor mortis well marked. The skin of the face and hands shows a deep brownish pigmentation (sunburn). The skin over the trunk and limbs shows no excess of pigment. Over the dorsum and lateral aspect of the left ankle and instep are several diffuse purple spots and the joints show a boggy swelling. The abdomen is slightly distended, shows a recent surgical incision about 10 cm. in length closed by silver sutures just to the right of the umbilicus. The abdomen on incision shows a slight excess of slightly turbid yellow fluid. The intestinal coils are moderately distended with fluid and gas. The loops of ileum and the cœcum are adherent by rather elastic, but easily torn adhesions to the under surface of the scar described above. The peritoneal lining everywhere has lost its gloss and is covered by grains and shreds of moist thready tissue. This exudate is quite well marked in the pelvis where the threads are quite conspicuous and cannot be separated from the intestinal coat without considerable force. The same milky adhesions are present over the spleen and liver. The appendix is clear.

Thorax shows both pleural cavities to be invaded by this same type of inflammation. The cavities contain a little excess of fluid and the serous surfaces are frosted over by these rather elastic moss-like gray adhesions which are most conspicuous over the diaphragmatic surfaces and the posterior portion of the lower lobes. The fat in the region of the mediastinum shows numerous ecchymoses. The pericardial cavity is everywhere obliterated by elastic gelatinous-looking adhesions, in which new-formed blood-vessels can be seen with great distinctness. No fresh fibrin is found anywhere. The two layers can be separated with some difficulty, showing ecchymoses here and there.

Heart, together with the pericardium, weighs 680 gms. It is dilated and hypertrophied. The right auricle shows some dilatation with firm pale gray clots. The tip of the auricle is clear. The tricuspid valve measures 15 cm. in circumference. The valve leaflets are delicate. The pulmonary valve is normal. The intima of the right heart is thin and smooth, through which one sees well-marked mottling of the muscle columns with yellow flecks. The left auricle is moderately dilated, its intima smooth. The mitral valve measures 12 cm. in circumference, and is delicate. The aortic ring measures 8 cm. in circumference. Two of the cusps are normal. The third cusp situated posteriorly and just above the anterior curtain of the mitral valve shows a small sessile vegetation 6 mm. in long diameter, situated on the line of closure close to the *Corpus Arantii*. It is of an opaque yellow color on its upper portions, but its base shows invasions by delicate capillaries growing up from the base of the valve. The intima of the left heart is smooth and the muscle shows through it, of a brownish color, mottled with yellowish flecks. The coronary vessels show a few patches of sclerosis. The heart muscle is pale and flabby and of a mottled yellowish-brown color on tangential section. The wall of the left ventricle averages 13 to 15 mm. in thickness.

Lungs.—The left lung is voluminous. The vessels and bronchi at the hilum are clear. The pleural surface shows the adhesions described above, some of which are invaded by delicate capillaries. On section the lung tissue is everywhere very moist and exudes a frothy serous material. It is of a yellowish-red tint in the upper lobe, becoming deeper red in the lower lobe. Here and there one sees a few slightly raised purplish areas of irregular size and extent, which are rather dryer than the surrounding tissue and just palpable. At the bifurcation of the main bronchus one finds a calcified lymph-gland, measuring 2 cm. in long diameter. In the apex of the upper lobe is found a small calcified

nodule 3 to 4 mm. in diameter, above which the pleura shows fibrous tags. Further examination of this scarred apical portion shows two or three other small foci of cheesy material, none of them exceeding 5 mm. in diameter. The right lung shows a condition in general resembling the left. There are numerous subserous hæmorrhages over the lower lobe. Cut section resembles the other lung. It is very moist. The right lung is even more voluminous than the left.

Spleen weighs 375 gms., measures 18 by 9 by 4 cm. It is adherent by old adhesions to the diaphragm. Its capsule shows numerous irregular milky areas of thickening. On section the Malpighian bodies appear very conspicuously as large indefinite milky dots, 1 to 1½ mm. in diameter. The spleen pulp is of a brick-red color, and scrapes off with ease on the knife. The trabeculae are easily seen. The organ is flabby and flattens out on the table.

Stomach is greatly distended with sour-smelling clotted material. Its mucosa shows considerable postmortem digestion and occasional ecchymoses. The duodenum shows a velvety mucosa, stained with bile. The bile papilla is normal. The bile and pancreatic ducts open side by side, they are delicate and normal everywhere.

Pancreas is rather large and pale. Consistency is about normal. Cut section shows a pale watery-gray parenchyma, on which one sees distinctly minute opacities of pin-point size. The stroma does not seem to be increased in amount, but is quite loose and œdematous.

Liver weighs 2570 gms., measures 29 by 24 by 9 cm. Its upper surface is covered over by moss-like elastic adhesions, some of which show invasion with blood-vessels. The lower surface shows a similar, but less extensive peritonitis. Cut section is everywhere quite uniform and pale. The lobulation is distinct, the lobules being rather swollen, with a pale-red center and a more opaque-gray periphery. Here and there are seen a few minute areas of yellowish opacity, one of which looks like a small tubercle. Consistency is about normal.

Kidneys weigh 420 gms. The left kidney measures 13 by 6 by 3½ cm. The capsule comes off easily, leaving a pale smooth surface, showing occasional retention cysts. Cut section shows a pale-gray cortex, averaging 6 to 7 mm. in thickness. The striations are perfectly regular. The majority of the glomeruli appear as minute red dots. The tubular portion of the cortex is swollen and gray. The pyramids are normal. The pelvis is normal. The right kidney resembles the left.

Adrenals are of normal size. On section show an opaque-yellow cortex, 1 mm. in diameter, and a thin brown medulla.

Thyroid appears normal; the neck organs could not be removed.

Aorta shows a few small patches of yellowish thickening. It retains its elasticity well.

Bladder shows a pale smooth mucosa.

Rectum normal.

Prostate, seminal vesicles, and testicles normal.

Marrow of femur is of a mottled yellowish-pink color and rather firm.

Intestine.—The jejunum is dilated, shows a pink or red velvety swollen mucosa, which is flecked over thickly with little pin-point yellowish grains, which seem to be intimately connected with the mucosa, even in some cases beneath it. No ulcerations are seen. The lower portion of the jejunum shows a rather paler mucosa of the same description, and everywhere thickly dotted over with these little yellowish-white grains. The Peyer's patches in the ileum are not conspicuous. The large intestine shows a pale smooth mucosa.

Mesenteric glands present a most remarkable appearance. They are greatly enlarged, some of them measuring 3 to 4 cm. in long diameter. They are rather elastic to the touch. There are many small glands close to the mesenteric attachment, about ½

cm. in diameter. On section the smaller glands are found to be of an opaque pale-yellowish color, with almost complete disappearance of the gland tissue. There is an indefinite translucent reticulum, through which one sees minute grains of opaque yellow color. These are thickly sown throughout all the glands, and in some instances seem to be located in cyst-like pockets, from which these little grains can be scraped out on the edge of the knife. Some of the larger glands present considerable injection and show some small hemorrhages into this translucent stroma, which everywhere is dotted over with these little grains of yellowish color. The glands on section bulge beyond the capsules. A similar condition is seen in the glands at the root of the mesentery in the neighborhood of the pancreas. Some of the glands here measure 2 cm. in long diameter. Some of them are quite opaque and yellow. They seem to be full of little cystic areas, some of which contain a viscid fluid, others little yellow grains. The retroperitoneal lymph-glands about the celiac axis show exactly the same picture.

Thoracic duct is dissected out. Smears made from its content and stained show no bacteria but many mononuclear leucocytes and large mastzellen. The fluid from the thoracic duct shows numerous small highly refractile droplets and small rosettes of pale greenish acicular crystals often attached to the side of a fat droplet.

Scrapings from the cut section of the mesenteric glands under the microscope show typical tufts and balls of delicate spindle-shaped crystals. These crystals dissolve with a slight amount of heat and are reformed on cooling. They come down in little star-like masses of needle crystals, which are much smaller than the original crystals. The crystals dissolve easily in alcohol and ether, and are evidently fatty acid. Similar crystals are found in the scrapings from the intestinal mucosa. Fresh cut section of the glands shows a neutral reaction to litmus. No bacteria are made out in smears. One of the small mesenteric lymph-glands is inoculated subcutaneously into a rabbit; animal died in seven weeks; negative for tuberculosis.

MICROSCOPICAL PREPARATIONS.

Tissues hardened in Zenkers fluid, formalin, or alcohol. The routine stain was hæmatoxylin and eosin.

Heart.—The pericardial cavity is almost entirely replaced by a loose oedematous granulation tissue of connective tissue and wandering cells in which blood-vessels are quite conspicuous. There are numerous clinks in this granulation tissue which are lined by cubical epithelium derived evidently from that of the pericardial cavity. In some small areas there is an exudate of polymorphonuclear leucocytes, red blood-cells, and fibrin. The heart muscle-cells are of about normal size but show a moderate grade of fragmentation. The aortic valve shows a dense hyaline mass of old fibrin which is being invaded by fibroblasts, wandering cells, and blood-vessels.

Lungs.—The pleura is thickened and infiltrated with many wandering cells and new-formed blood-vessels. There are numerous adhesions consisting of scar tissue or organizing granulation tissue. Beneath the pleura many of the alveoli show an exudate of red blood-cells and heart-failure cells mixed in with a fine pink granular coagulum. Other alveoli show a hyaline-like exudate of fibrin which is being invaded by wandering cells, fibroblasts, and capillaries. In such areas the alveolar walls are greatly thickened, consisting mainly of a thick mass of young fibroblasts and blood-vessels. The alveolar epithelium here is cubical and beneath it are many phagocytes full of coarsely granular yellow pigment. In all sections of lung tissue the alveoli show some coagulated serous material and numerous heart-failure cells. In some areas the alveoli show a fresh exudate of fibrin, red blood-cells, and leucocytes. The bronchi in some instances show a similar exudate and the epithelium is well

preserved. The capillaries are congested and the larger blood-vessels are normal. The lymphatic tissue of the lung is normal in amount and character. Coal pigment is present in moderate amount.

Spleen.—The capsule is thickened and shows signs of a chronic inflammatory process. The trabeculae are thickened but widely separated from each other by an increase in spleen pulp. The blood-vessels show some thickening of their walls and in some instances a hyaline degeneration of the subintimal tissue. The Malpighian bodies are enlarged, but as a rule show no abnormalities. Some of them show an increase of stroma with disappearance of lymphoid-cells in the immediate neighborhood of the central arteriole and others show many polymorphonuclear leucocytes in their peripheral zone. The venules of the spleen pulp are full of blood and their walls are somewhat thickened, showing evidences of some chronic passive congestion. The pulp-cells are increased in number, between which are seen numerous cells of polyblastic type (Maximow), red blood-cells, and leucocytes. The stroma of the pulp is definitely thickened and easily made out. Numerous accumulations of coarsely granular yellow pigment are found in the pulp, often some of the smaller grains being included in large phagocytes.

Marrow of femur.—There is considerable increase in the cellular elements, but the fat-cells are quite in evidence making up more than half of any section and appear quite normal. The giant cells and myelocytes occur in normal proportion. The eosinophile cells are not increased in number. Red blood-cells are not conspicuous, but the nucleated reds are quite numerous and definitely increased in number. They occur in clumps of 3 to 20, which are scattered thickly throughout the sections. The same yellow pigment as described in the spleen is present in all parts of the cellular marrow and is often included in large phagocytes. The lymphatic tissue of the spleen and marrow shows none of the remarkable changes found in that of the mesentery and intestine, but the changes here are dependent on a secondary anaemia.

Blood-clots. Sections show no change of importance.

Liver.—The capsule is thickened and shows many adhesions made up of scar tissue and blood-vessels. The stroma at the margins of the lobules is increased in amount and invaded by many polymorphonuclear leucocytes which are present as well in the capillaries of the lobules. This change is most marked just beneath the capsule and seems to have a direct relation to the extensive perihepatitis. The capillaries in the central portion of the lobules are dilated with a corresponding atrophy of the liver cells which here contain fine yellow pigment. The liver cells at the margin of lobules are swollen and granular, some of them showing small fat vacuoles. The bile-ducts are perfectly normal.

Adrenals.—Its cortical cells are regularly arranged and of the usual appearance. Many of them show fat vacuoles. The medulla is inconspicuous. The perirenal fat is quite normal in appearance.

Kidneys.—The cortex shows a regular architecture, but there is a slight diffuse increase in connective tissue between the tubules. The glomeruli are of normal size, but many show some thickening of their capsules. The convoluted tubules show a swollen pink-staining granular epithelium which shows the "brush border" quite well and whose nuclei stain sharply. Their lumina are slightly dilated and contain foamy or granular-looking debris but no casts and no exudate of cells. The pyramids show normal tubules which contain no casts, but the interstitial stroma is quite oedematous. Blood-vessels are normal and the capillaries contain little blood.

Pancreas.—Sections from various parts of the organ show no changes of importance. The islands of Langerhans are rather large, sharply outlined by a thin capsule, and made up of normal-

looking cells, a few of which show mitotic figures. The acini in many places show postmortem changes, but elsewhere are normal, as are the pancreatic ducts. The interlobular stroma is loose, its meshes being separated by a pink granular coagulum in which can be made out a few mononuclear wandering cells. The fat-cells in this stroma are normal. The interacinar stroma is very delicate.

Skin and subcutaneous tissue from abdomen is quite normal. The fat-cells are sharply contoured.

Thyroid.—Its acini are regularly arranged and contain normal colloid. The interacinar stroma is loose and oedematous, showing as well some pale-staining colloid material.

Jejunum and ileum.—Sections made from various levels in the small intestine all show the same general picture.

Frozen sections stained lightly with osmic acid and Soudan III, show deposits of fat in the villi and submucosa. Fatty acid crystals are not stained and show up very clearly as rosettes of needles which are intimately associated with the neutral fat (compare Fig. 1) and make a beautiful contrast. Tissue hardened in formalin and stained by the Marchi method (1) shows the presence of large masses which reduce the osmic acid and are called fat droplets for the sake of brevity. The fat in the tissue at the mesenteric attachment stains as usual, appearing as large oval or circular, sharply and evenly contoured masses of a uniform jet black. Large black masses are seen in the interglandular tissue of the mucosa and in the submucosa (Fig. 2). These are not evenly contoured, but show nodular or even serrated margins and all manner of shapes. They do not stain uniformly and one may see the center or any portion of a large mass which has a feathery or fern-like appearance, due evidently, to the presence of the crystals of fatty acid. In some instances the outlines of typical rosettes are preserved in the Marchi preparations of the intestine, but this finding is common in the gland tissue. The crystals reduce the osmic acid, but they are not as black and opaque as the fat droplets. The majority of the black masses fill the spaces in which they lie but some only partly do so, the rest of the space being filled with a fine reticulum of coagulum suggesting lymph. Some of these spaces in the villi contain a fine spider-web-like reticulum of coagulated material in which may be embedded a few mononuclear cells or a small droplet of fat (Fig. 3). A lining endothelium can often be made out in such cases, suggesting that these are dilated lymph radicles perhaps occluded by a fat embolus located proximally. One may see droplets of varying size, many of which do not exceed twice the diameter of a lymphocyte, and they may be so closely packed that it seems sure that there is a deposit of this fatty substance *outside* of the lymphatics as well as in their lumina. The epithelial cells lining the crypts of Lieberkühn show no fat droplets, but there are many goblet cells with accumulations of mucus. They are quite normal in appearance. The interglandular stroma shows but few very fine grains of fat such as one finds in its venules in the circulating white corpuscles. A few of the large mononuclear cells of the plasma-cell type show these fine black grains, but the peculiar cells which are distinctly abnormal in this location do not show any fat grains, or at the most only a few. These cells have a vesicular nucleus and a pink-staining, frothy-looking protoplasm. With ordinary stains the cells seem to be packed with fine fat vacuoles of nearly uniform size, but these do not stain with osmic acid. The polynuclear giant cells are not numerous and show only occasional fat grains. The solitary follicles show no large accumulations of fat, but they are invaded by numbers of the large mononuclear cells. Some of the plasma cells here show a few grains of fat. The muscularis mucosae is quite thickly sprinkled with fine black grains, which seem to be both intra- and extra-cellular. The capillaries and venules in this neighborhood often show some fatty grains in the endothelial cells.

Sections stained with hematoxylin and eosin show the very conspicuous vacuoles (Fig. 3), many of which contain a finely granular, pink-staining reticulum. Some of these vacuoles are lined by endothelial cells, giant polynuclear cells, numbers of the large mononuclear "foamy" cells, or a combination of any or all of them (Fig. 3). Other vacuoles are surrounded by a thin capsule of quite dense fibrous tissue in which are embedded many or few of the wandering cells. The interglandular tissue is made up of numbers of lymphocytes, plasma cells, and eosinophiles in about the normal number, plus the unusual mononuclear cells (Fig. 4). There seem to be two kinds of large mononuclear cells or very different types of the same cell. One resembles exactly the "polyblast" of Maximow (2) and is not very numerous here. Its protoplasm stains a deep pink and is finely granular, while its nucleus is vesicular, but shows well-marked strands and grains of chromatin. The majority of the giant cells appear to be formed by a fusion of such cells and show the same type of nucleus and protoplasm. The second type of cell has a pale vesicular nucleus, which is poor in chromatin, 5 to 7 μ in diameter and often eccentrically situated. Its protoplasm is abundant and has a foamy appearance, due to the presence of closely-placed vacuoles or granules which are often quite uniform in size, but may vary from 5 μ down to the size of an eosinophile granule. Some of the granules seem refractile and suggest mastzellen, but stains for these cells (1) show the same "foamy" protoplasm with non-staining vacuoles. Mastzellen are present in considerable numbers.

The "foamy" cells average 20 to 30 μ in diameter but show evidence of active motility and are of every conceivable form. Mitoses are seen in these cells very rarely. They are occasionally phagocytic to red blood-cells, old blood pigment or nuclear fragments. A few cells are seen which may be transition forms between them and the common polyblast, showing a vesicular nucleus and finely granular pink protoplasm, in which are a few of the vacuoles described in the "foamy" cells.

Maximow (2) describes cells ("eiterphagocyten") which in some points resemble these "foamy" cells, but his cells contain granules which stain by various methods. Such cells he considers to be derived from the mononuclear lymphocytes of the blood, as is true of the polyblasts. The "foamy" cells form giant cells either by fusion or nuclear division, the protoplasm retaining its peculiar appearance (Fig. 4). Some nuclei show signs of degeneration, but this is unusual, and the activity of the cells speaks against their being types of degenerating polyblasts.

They are most numerous in the tips of the villi and about the fat deposits where they often make up the entire field, with almost complete absence of the lymphocytes and plasma cells. As a result of all this invasion of foreign cells and fat deposits the villi are greatly increased (more than double) in length and diameter. Their capillaries are dilated, and the connective tissue is increased in amount. There is evidence of an occasional old or recent extravasation of red blood-cells into the villi, where one may see a few phagocytes packed with yellow granular pigment. Well-preserved red blood-cells may be seen free in the tissue round the bases of the crypts. A few polymorphonuclear leucocytes are seen in these areas. The solitary follicles are but slightly enlarged and the prevailing cell is the lymphocyte. Some are invaded by numbers of the "foamy" mononuclear cells but no very striking changes are seen.

The muscularis mucosae shows hypertrophy. The *submucosa* in some places is almost normal, but as a rule is much thickened, its vessels dilated and thickened, and the stroma filled with wandering cells. The predominant mononuclear cell is the polyblast and they often contain fine grains of fat (Marchi). Many of the "foamy" mononuclears are present, usually in the loose stroma just below the muscularis mucosae and in the neighborhood of fat deposits. The fat droplets in some places are so

closely placed as to suggest subcutaneous fat, but close inspection shows that they are of irregular size and shape. Their margins are often outlined by giant and mononuclear cells (Fig. 3) and they are separated from each other only by a delicate granulation tissue of fibroblasts, capillaries, and wandering cells. Again, the tissue will be dense and fibrous, containing only a few fat droplets and wandering cells. Numbers of extravasated red blood-cells are seen in the submucosa, often in large clumps, but usually diffusely scattered. Yellow granular blood pigment is frequently seen included in phagocytes and is most abundant in those areas where the fat deposits are most numerous. Large eosinophile mononuclears are quite numerous in all parts of the submucosa. Careful search with oil immersion lens in sections stained by various methods failed to reveal any bacteria or parasites which could have any relation to the lesion. The muscle coats and the ganglia of the plexuses are normal. The ganglion cells show some fine fat grains in their protoplasm. The serous coat shows an organizing granulation tissue of wandering cells, capillaries, etc., of the usual type.

GLANDS.

Unstained frozen sections show refractile fat globules and great numbers of long acicular fatty acid crystals arranged in sheaves and rosettes. Stained lightly with osmic acid such sections give a picture represented in Fig. 1, which shows well the large and small droplets thickly sown through the gland tissue, and a rosette of crystals. Marchi preparations show even more extensive fatty deposits (Fig. 5) than were seen in the intestine. The gland deposits are larger, even more irregular and closely packed, but in general closely resemble those described above. In places the fat is deposited in threads which are twisted, beaded, and packed together, resembling a reconstruction of the glomerular capillaries. Such deposits are often seen in a follicle and no endothelial cells can be made out in relation to them. Giant cells are numerous and closely applied to the margins of these fat deposits, often in little lacunae as though they were ingesting and eroding its substance. These cells may show a fine granular protoplasm and a few fat droplets; other giant cells in the stroma may show clumps of small fat droplets in their protoplasm which may have the "foamy" appearance. Some of the giant and mononuclear cells with the foamy protoplasm show minute comma-shaped black deposits which often outline one segment of a vacuole in the protoplasm, others are rod-shaped, again beaded like small filaments of chromatin, but always in the protoplasm. Often they are associated with definite grains of jet black fat deposits in the protoplasm and for this reason are thought to be some form of fat. The wandering mononuclear cells show varying amounts of fat deposits, some only a few minute grains, others large clumps of large and small droplets, and some are so crowded with fat droplets that the protoplasm and nucleus may be almost obscured. Cells with the foamy protoplasm seem less actively phagocytic toward the fat, and great numbers of them are entirely free from it. Just beneath the thickened capsules of some of the larger glands is seen a fine cloud of minute fat droplets (Fig. 5) which are very thickly packed all through the rather oedematous stroma. Some of these grains are intra-cellular, but many are surely extra-cellular. In such areas the large foamy mononuclears may be very numerous and yet show almost no phagocytosis of fat. It is possible that this material has recently reached the cortex of the gland from the afferent lymphatics. Some of the larger lymphatics at the hila of glands (efferent) are filled with a fine granular coagulum of albuminous material in which may be seen scattered small fat granules. The fat cells of the mesenteric tissues adjacent to the gland capsule are sharply contoured by thin cell membranes and look entirely normal except for some infiltration of the intercellular tissue by small round cells, chiefly

lymphocytes and plasma cells. Sections of various glands stained with hæmatoxylin and eosin show how extensive is the change in the larger glands. The tissue is honey-combed with the fat vacuoles and much of the cellular structure is replaced by dense fibrous tissue which is poor in cells (Fig. 6). It takes a deep blue stain with Mallory's connective-tissue stain. The capsule and trabeculae are thickened and the blood-vessels dilated and increased in number.

Some of the small glands which are slightly involved show almost normal lymphatic follicles and cords, but the peripheral lymphatic sinus may be greatly dilated by an exudate of red blood-cells, mononuclear wandering cells, a few polymorphonuclear leucocytes and lymphocytes, mixed with a finely granular pink coagulum. There are small irregular fat deposits which usually first appear in the medulla of the gland between the intact lymph-cords. They are outlined roughly by collections of giant and mononuclear cells, but endothelial cells are rarely made out. The adjacent tissue is at once invaded by numbers of large mononuclear cells, eosinophiles, young fibroblasts, and capillaries forming a loose cellular granular tissue about the deposits. It is quite possible that this cellular reaction may precede the fat deposits. This granulation tissue gradually becomes dense and fibrous causing the great distortion of the gland architecture seen in several of the photographs (Figs. 6 and 7). Free red blood-cells are present in great numbers in both large and small glands, but the ecchymoses are more striking in the older glands. Phagocytosis of red cells by polyblasts is present, but not conspicuous, and is relatively infrequent when we consider the number of both types of cells. Changed blood-pigment included in phagocytes or chunks of the stroma is hard to find except in the larger glands. In some of the small glands the eosinophile cells are very definitely increased in number, mononuclears predominating, and suggest the presence of some parasite.

A small gland which was preserved in 15 per cent formalin and stained by the Levaditi method, showed some very peculiar structures. Studied with 1/12 objective these sections show great numbers of a rod-shaped organism (?) which, with this stain, is about the diameter of the spirochete of syphilis but not of spiral shape and rarely exceeding 2 μ in length. The majority of these structures closely resemble in form the tubercle bacillus. They are very sharply contoured and appear as jet black rods, sometimes bent but more often straight or only slightly curved. Some show a slight swelling of one end and others a beaded appearance. They are most numerous in the vacuoles, which are not completely filled with fat and contain a filmy granular reticulum (Fig. 9). The structures are most numerous at the edge of the vacuoles, where the "foamy" cells are in evidence, and are contained in great numbers in these cells. When a cell contains very many of these structures they seem to clump together and lose their sharp outline as though damaged by the process of ingestion. These structures are present at the edge of the fat droplets in less numbers and become less numerous in the adjacent tissue. Careful search made in corresponding sections stained by various aniline dyes reveals no corresponding structures. If we compare them with the various spirochetes which take this stain we, perhaps, may imagine that we are dealing with some organism which resists the common stains but reduces the silver salts, effecting considerable increase in its size. Whether this is the active agent in this peculiar pathological complex cannot be determined from the study of this single case, but its distribution in the glands is very suggestive. No tissue from the intestines nor viscera was available for the Levaditi stain and all the smears from the thoracic duct and glands were used before the study of the glands by the silver method revealed these peculiar bodies.

The vacuoles do not all contain fat deposits, some of them (Fig. 8) showing only a delicate tracery of granular pink coagulum. In such spaces there may be a few degenerated cells or

small fat droplets or the coagulum may show an exact mould of a rosette of fat crystals which have been dissolved. Some of the smaller glands have a very oedematous stroma, and all the cellular elements are widely separated. Here the large mononuclear cells show many degeneration forms in which the protoplasm is full of very large irregular vacuoles and the nucleus very faint or even non-staining. In all sections many areas are found where there are large accumulations of the large foamy or granular mononuclears and here the degeneration forms are often conspicuous. Mastzellen are present in all sections, but not numerous. One large giant cell with pink granular protoplasm is seen in mitosis, the chromatin threads being very coarse and arranged as though the division was to result in three or four cells.

Briefly the microscopical findings in the intestinal and mesenteric lesions may be summarized as follows: The villi of the small intestine are enlarged, the submucosa thickened, and the mesenteric glands enormously enlarged by deposits of osmic acid reducing bodies (neutral fats and fatty acids). Such deposits are most numerous in the glands, but alike in all these situations. They are of all sizes from minute grains intra- or extra-cellular in location, up to huge irregular droplets and there is the greatest variety of forms (Fig. 2 and 5). Many of the larger masses show rosettes of fatty acid crystals (Fig. 1) and they may occupy spaces which are lined by endothelium suggesting dilated lymph channels (Figs. 6 and 7). The majority of the larger deposits are outlined by polynuclear giant cells or large mononuclear cells of polyblastic type which in some instances seem to be eroding the fatty material and are closely applied to its edge. (Fig. 8). The epithelium of the *mucosa* is normal as far as the microscope shows. The interglandular stroma contains about the usual number of lymphocytes, plasma cells, and eosinophiles, but there is an infiltration with great numbers of polyblasts—large mononuclear, ameboid cells with pink granular protoplasm. A second type of cell which is very conspicuous has an abundant foamy protoplasm, a pale vesicular nucleus and is actively ameboid; this may be a type of polyblast. Echinomoses are numerous wherever we find the fatty deposits. The *submucosa* shows invasion with great numbers of these polyblastic cells especially about the fat deposits which in some places are abundant (Fig. 2); in others absent. There may be a very definite eosinophilia in such areas. The *glands* show the most extensive changes, especially the larger ones (Fig. 6-7). In some the lymphatic nodules and cords are quite intact, the process seeming to begin in the sinuses of the glands with invasion of the characteristic cells and small irregular fat deposits. The next stage is an invasion by fibroblasts and capillaries with more or less extravasation of blood, increase in size and number of the fat deposits and distortion of the gland architecture (Fig. 8). The large mononuclear cells increase rapidly in numbers and giant cells become conspicuous. The final stage shows a very large gland packed with fat deposits of all sizes and shapes, whose stroma is made up of dense fibrous tissue full of echinomoses and great numbers of giant and mononuclear cells (Fig. 6-7). Gland tissue treated by the Levaditi method shows great numbers of a peculiar rod-shaped organ-

ism (?) which does not stain by the aniline dyes and is most numerous in the vacuoles and in the neighborhood of the peculiar "foamy" cells which often include these structures (Fig. 9). Whether this is the etiological factor in this disease can not be determined from this case.

BACTERIOLOGY.

A bacillus belonging to the colon group was isolated from the mesenteric glands. Cultures from the parenchymatous organs showed a white coccus of low virulence.

A small gland was planted subcutaneously in a large gray rabbit. The animal died of pneumonia seven weeks after the inoculation. Autopsy showed a small subcutaneous abscess full of soft yellow pus. The glands draining this area were only slightly enlarged. Microscopical sections show an abscess wall of granulation tissue containing many large mononuclear phagocytes closely resembling those described in the human tissue. The central part shows necrosis. Gland-tissue from the axilla shows merely a moderate grade of chronic inflammation and there is no evidence of tuberculosis.

CHEMISTRY.

The microscopical picture was so suggestive of an abnormal fat or a mixture of fats, fatty acids, and perhaps some toxic substance which resisted absorption by the surrounding granulation tissue that a chemical study of the glandular tissue was attempted. The small amount of available material did not permit of extended chemical investigation, but the following facts are clearly brought out. 1. The ratio of fat to fatty acid. 2. The saponification value. 3. Several negative qualitative tests.

Liver, spleen, kidney, and small intestine.—About 10 to 15 gms. of each organ were ground up in about 50 cc. of 95 per cent alcohol and allowed to stand in bottles for several days. The tissues were extracted and tested for fatty acid which was found to be present in traces in the first three tissues, and to a greater degree in the intestine. Neutral fat was present in all, apparently in normal amount.

Mesenteric glands.—About 3 gms. of material (a single large gland) preserved in 95 per cent alcohol was extracted in the Soxhlet apparatus for six hours, the alcoholic and ether extracts united and evaporated to an oily residue. Glycerine was tested for and shown to be absent. The oily residue was made alkaline and the fat removed by repeated extractions with ether. The alkaline solution showed a typical soapy appearance. This was shown to contain a soap by the following reactions: 1. One portion acidified with hydrochloric acid gave a precipitate which was soluble in alcohol. 2. A second portion treated with calcium chloride gave a typical precipitate of calcium soap which was insoluble in alcohol. The solution was made acid and the fatty acid removed with ether. The ether was evaporated and the residue weighed. The neutral fat extracted by this method weighed 0.75 gms. and the fatty acid 0.07 gms., giving a ratio of 10 to 1.

A second determination was made by another method. Four medium-sized glands weighing about 4 gms. were cut open and preserved for three weeks in about 50 cc. of 80 per cent alcohol. This alcohol was filtered off and evaporated over the water bath to a dark brown oily residue—1st fraction. The glands were then ground up thoroughly with sand and absolute alcohol and the alcohol filtered off. The residue of tissue macerated with the sand was extracted in the Soxhlet apparatus for 24 hours with ether and the ether and alcohol extracts combined. This

was evaporated on the water bath to a white waxy material—2d fraction. The glands were further extracted in the Soxhlet for a second 24 hours, but this ether extract on evaporation gave only a trace of fatty material—3d fraction.

Material from the 1st fraction (0.1116 gms.) was dissolved in neutral 80 per cent alcohol and titrated against a known solution of alcoholic potash (7.8873 gms. per liter). It required 1.05 cc. of the alcoholic potash solution to neutralize the free acid. Then 8 cc. of the alcoholic potash were added and the solution heated over a water bath with return condenser for one hour to saponify the neutral fat. At the end of this time the solution was a deep cherry red showing an excess of alkali was still present. It was found that 2.58 cc. of the alcoholic potash had been used up by the fatty acids which were set free in the saponification. This gives an approximate ratio of 5 to 2 for the fats and fatty acids in the 1st fraction. Material taken from the 2d fraction (0.198 gms.) was treated in an identical manner. This solution required but 0.35 cc. of alcoholic potash to neutralize the free fatty acid, but 3.69 cc. were used up during the saponification. This fraction showed a much higher percentage of neutral fat, the ratio to fatty acid being roughly 10 to 1. The saponification number of this material from the 2d fraction as determined by Dr. Loevenhart was 144.4. When the weights of the 1st and 2d fractions were combined the ratio of fats to fatty acids was found to be about 85 to 15 per cent—1.552 gms. fat and 0.234 gms. fatty acid extracted from all the tissue. Tests for bile pigments were negative. Tests for phosphorous were made as follows and shown to be negative. Material from the 1st and 2d fractions boiled 5 to 10 minutes with potash, then acidified with nitric acid and an equal amount of ammonium molybdate added. On boiling this solution no yellow precipitate was obtained, but the addition of one drop of an acid sodium phosphate solution gave the yellow precipitate in abundance. This test excludes the presence of lecithin in any appreciable amount. The 1st fraction showed many crystals of various types. Some of these were needles of fatty acid and others chlorides or phosphates. No crystals of cholesterol were seen. The 3d fraction showed a few tufts of beautiful slender acicular fatty acid crystals.

It is unfortunate that the tissue was not sufficiently fresh to test for enzyme action (lipase), but the following facts are suggestive. Fatty acids (0.23 gms.) were present in these abnormal mesenteric glands and presumably the majority of them were derived from high melting point fats because the well-formed crystals were present in large numbers even with a room temperature of 32 C. Neutral fats were present (1.55 gms.) and showed a low saponification number (144.4) which indicates either some abnormality of the fat or the presence of some non-saponifiable substance mixed with it. Lecithin and cholesterol were suspected but shown to be absent. In the determination of the saponification number no allowance was made for the included fatty acid (10 per cent) which would tend to raise rather than lower the number, making the contrast with normal fats somewhat less striking but would in all probability leave it abnormally low. The saponification numbers of the common fats are tripalmitin = 208.8, tristerin = 189.1, triolein = 190.4, horse fat = 199.4, hog fat = 195.6.

DISCUSSION.

Many features of this case were of great interest but it seems that in the light of our present knowledge a lengthy discussion would be of little value. The finding of acetone

in the urine shortly before death and the extreme air hunger at this time suggested some acidosis which may have been dependent on the disturbance in fat metabolism. However the acetone could be accounted for by the starvation of the tissues following the obstruction of the mesenteric lymphatics and we know that in spite of heavy feeding the patient was steadily losing weight. The large amount of unsplit fat in the stools (one-half by weight) may be explained by the incomplete action of the lipolytic ferment owing to lack of absorption of its split products. Again there may have been some lack of lipase in the pancreatic secretion, but the normal appearance of the gland is opposed to this view. The deposits of neutral fat and fatty acids in the tissues may indicate some disturbance in the synthesis of fat which Loevenhart (3) and others (4, 5) have shown to be effected by lipase. Several facts indicate that this fat is in itself in some way abnormal or that it holds in suspension some abnormal or toxic substance. 1. The saponification number is very low. 2. The fat causes a tissue reaction resembling the reaction due to an inert foreign-body. 3. The peculiar wandering and phagocytic mononuclear cells. 4. The presence of many minute ecchymoses and changed blood pigment suggests some toxin capable of effecting the solution of the capillary walls. The pathological changes are limited to the apparatus which has to do with the absorption of fats while the lymphatic tissue of the marrow, spleen, bronchial glands, etc., is relatively normal except for the changes consecutive upon a rapidly advancing secondary anæmia, resembling that seen in cancer cachexia. All this suggests very strongly that here we are dealing with some obscure disease of fat metabolism.

The disease is of some duration as evidenced by the extreme changes in some of the larger glands which show dense scar tissue and cellular reaction which must be of months' standing. From a comparison with the intestinal lesions it would seem probable that the earliest changes took place in the glands rather than in the mucosa where the dense scar tissue is much less in evidence although in general the picture is the same. Examination of the contents of the thoracic duct excludes the possibility of any occlusion of its radicles between the glands and receptaculum. The presence of fatty acid crystals in its contents must be explained by the escape of such material from the glands and the same explanation holds for the mastzellen. The presence of many eosinophile cells in the smaller glands probably accounts for the same type of cell found clinically in the blood, but no clear explanation has been found for this reaction.

The presence of peculiar structures in the Levaditi sections which do not stain by the aniline dyes, suggests a possible relation to the group of spirochaetes. It is not claimed that this is the etiological factor in this disease but its distribution in the glands is very suggestive. It is always found in the peculiar vacuoles and cellular granulation tissue which are the striking features of the microscopical picture in the glands and intestine.

There seems no sufficient reason to correlate the intestinal,

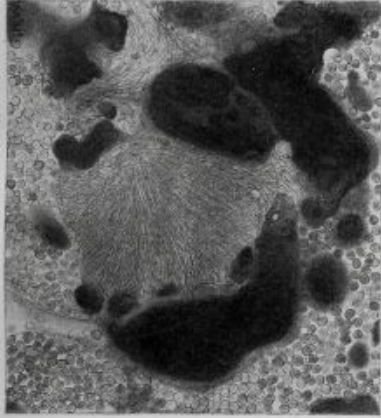


FIG. 1.—Frozen section of small mesenteric gland stained lightly with osmic acid. Rosette of fatty acid crystals and deposits of fat among lymphocytes.

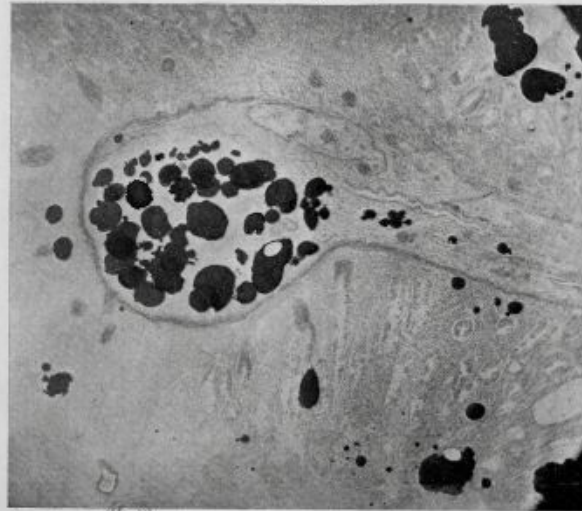


FIG. 2.—Marchi preparation. Cross section of one of the circular valves of the jejunum. Large central deposit of fat in the submucosa and on either side deposits in the mucosa. Solitary follicle (σ).

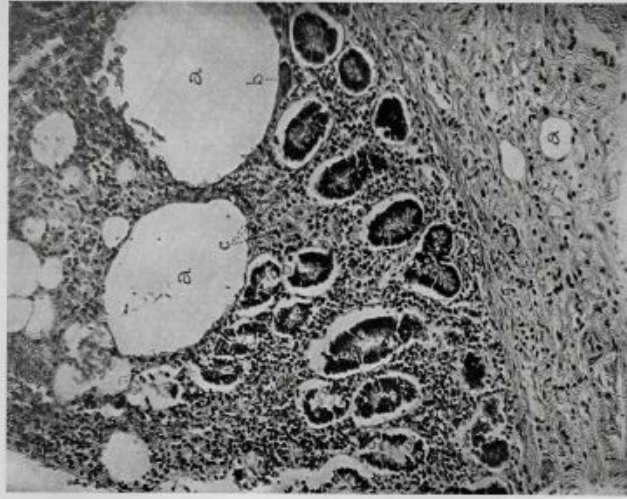


FIG. 3.—Fat vacuoles (a) in mucosa and submucosa. Giant cell (p). Large mononuclear "foamy" cells (c).

arthritic, and serous lesions but it is possible that the organizing inflammatory reaction affecting the pleura, peritoneum, and aortic valve may be closely related to the peculiar arthritis and purpura which we were unable to examine at autopsy.

In searching for a name to designate this condition great difficulties were encountered. It would seem that no suitable name can be applied to it until the etiological factor is determined. The term *Intestinal Lipodystrophy* is suggested as this seems to offer less objections and to have more points in its favor than any one word or combination of words which have been considered.

In conclusion I wish to express by most sincere thanks to Dr. Thayer for his careful clinical analysis of the case which was under his care in the private wards, to Dr. Loevenhart

for valuable assistance in the chemical study of the tissues, to Dr. Voegtlin for analyses of the stools and urine, to Dr. Ford and Mr. Harrison for the bacteriological examinations, to Dr. Welch and Dr. MacCallum for their interest and valuable suggestions, to Mr. Brödel and Mr. Ridges for assistance in preparing the illustrations.

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PANCREATITIS AND FOCAL NECROSES.

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In the following communication an attempt is made to show that the pancreas often presents minute focal necroses which at times may be related to fat necrosis and acute hæmorrhagic pancreatitis, as well as to some types of chronic diffuse pancreatitis. In the last 300 autopsies at the Johns Hopkins Hospital a careful study has been made of the pancreatic glands in 230 cases. The bile and pancreatic ducts were examined carefully. In many cases tissue was studied microscopically from the head, body and tail of the organ. When a single piece of tissue was examined it was usually removed from the tail. These cases may be grouped and classified as follows:

FOCAL NECROSES—41 CASES.

This group does not include the cases in the next three groups although many of them do show focal necroses. At times only a few very small necroses were found after long search, again many were found in a single lobule. Lobar pneumonia seemed to be the most active etiological factor, 11 cases; septicæmia, 6 cases; acute peritonitis, 6 cases; typhoid, 4 cases; bronchopneumonia (organizing), 3 cases; organizing endocarditis, 3 cases. The remaining cases were scattered (bronchiectasis, meningitis, collitis, hepatic cirrhosis).

The term "focal necrosis" is used to designate a type of focal degeneration affecting the pancreatic acini. The lesion usually appears as a granular change in the acinar epithelium with solution of the nuclei and rapid disintegration of the protoplasm. This change usually causes some increase in size of the affected acinus, and there is a very rapid invasion of polymorphonuclear leucocytes. In fact this change is recognized by the infiltration of leucocytes which may take place before the nuclei have vanished, although staining faintly (Fig. 1.). The basement membrane is quite resistant and as a rule remains intact even after all the acinar cells have undergone a granular degeneration and the membrane

may only surround a granular detritus invaded by numbers of polymorphonuclear leucocytes. This change often affects acini which are dilated by pink colloid like casts and the colloid material may persist and be invaded by leucocytes after the acinar epithelium has been destroyed. These necroses as a rule are quite diffusely scattered through the parenchyma of the pancreas and quite small, commonly affecting but a single acinus or a part of one acinus. One may see a small segment of an acinus which shows a granular degeneration of its epithelium with invasion of 2 to 10 polymorphonuclear leucocytes in this tissue and in the lumen of the acinus. Frequently the necrosis will partially destroy the epithelium of 2 to 4 acini and there will be an invasion of leucocytes into their lumina and in the oedematous stroma between them. It is remarkable what a powerful attraction the degenerated acinar epithelium seems to have for the polymorphonuclear leucocyte. These small foci are soon invaded by mononuclear wandering cells (polyblasts) and fibroblasts, but usually a few polymorphonuclear leucocytes can be seen. 3 cases of organizing bronchopneumonia showed the changes just described, which appeared to be of about the same age as the pulmonary lesion but fresh foci were present as well. These small foci of degeneration which may contain many polymorphonuclear leucocytes do *not* as a rule contain bacteria. In a few of the cases of septicæmia where the necrosis involved several acini, clumps of bacteria could be demonstrated, but in not a single case of pneumonia with focal necroses could the organisms be demonstrated as having any regular relation to the degenerated tissue.

There is no regular association of pancreatic and liver necroses. In this series liver necroses were quite common in association with acute peritonitis. 23 cases of acute or organizing peritonitis showed liver necroses in 10, and pancreatic necroses in 6. 17 cases of lobar pneumonia: 8 showed no pancreatic necroses and 2 of these showed liver necroses; 9