# SYSTEMIC NODULAR PANNICULITIS *

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In 1892, Pfeifer[1] described a patient with subcutaneous nodules in the extremities and in the trunk. The nodules were freely movable, red, and were associated with fever. A similar condition was reported by Gilchrist and Ketron[2] in 1916, who noted the ingestion of fat by macrophages as an essential change in the lesion. Weber,[3] in 1925, described the third patient and gave the name of "relapsing, non-suppurative nodular panniculitis" to the disease, which was characterized by the presence of multiple subcutaneous nodules. In 1928, Christian[4] added the fourth case and also the term "febrile" to the name. Brill[8] was the first to refer to the condition as "Weber-Christian disease." Since then some 43 additional cases have been reported (Table I).[5-39]

## SUBCUTANEOUS NODULAR PANNICULITIS

The subcutaneous nodules appeared on extremities, abdomen, chest, and back. They varied from 1 to 12 cm. in diameter. They were slightly red and sometimes tender.[25] The nodules either disappeared,[34] to recur frequently, or were reduced in size and fixed by proliferating connective tissue. After disappearance of nodules, there were areas of atrophy with depression of the skin which was adherent to the subcutaneous tissue. Very infrequently, the nodules showed superficial ulceration.[23]

Histologically, the lesion was well defined, limited to the subcutaneous tissue, and showed progressive changes.[34] At first, when the nodules were barely palpable, there were edema, congestion, exudation of polymorphonuclear cells between fat cells,[38] and mononuclear phagocytes with ingested fat.[25] In the second phase, that of the mature lesion, there was an appearance of patchy necrosis of fat tissue.[9,23,25,32] The cell membrane of the fat cells ruptured, the cells collapsed, and were flattened.[23,28] Lymphocytes and phagocytes invaded the fat cells. The phagocytes became distended with ingested fat and lymphocytes. The epidermis and the dermis remained uninvolved.[32] The cellular exudate between fat cells was composed of neutrophilic polymorphonuclear leukocytes, lymphocytes, plasma cells, and macrophages.[9]

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Many of the fat cells and the vacuoles in the macrophages did not take the fat stain.[23] Disintegrated fat cells and free fat droplets were present in the tissue.[9] A rare giant cell could be found.[9] Periarteritis with intimal proliferation,[9,23,32] edema of vessel walls,[23] swelling of elastic fibers, and perifolliculitis characterized the lesion at this stage.

In the third or the atrophic phase,[23] connective tissue had replaced much of the inflammatory activity.[25,34] Giant cells were present in most of the nodules. In some lesions, inflammatory reaction persisted with the lymphocyte as the predominant cell. The vascular changes consisted of periarteritis with organization and intimal proliferation.[9] Scar tissue produced a contraction of the nodule with adhesion of the subcutaneous tissue to the epidermis and depression of the latter.

The clinical manifestations were indefinite. The condition attacked both sexes and all ages. The youngest patient was 23 months old,[24] and one of the older was 64 years of age.[11] The female appeared to be more prone to the disease. Recurrent, slightly tender, subcutaneous nodules, either freely movable or fixed to skin, occurred on arms and legs and less frequently on chest, back, abdomen, feet, and face. Malaise, and general weakness with fever were frequently associated with the first two phases of nodule formation. Fever ranged up to 104° F. Less often there were generalized aching pains, chilly sensations or frank chills, loss of weight,[9] nausea, headaches, joint pains,[5] and enlargement of the liver, spleen, and lymph nodes. The attacks lasted for periods varying from 1 month[21,22] to 15 years.[5,9] Occasionally, anemia was encountered. The number of red blood cells varied from 1.5 to 3.5 millions with the hemoglobin from slightly over 5 to 8.5 gm. The sedimentation rate, when done, was increased slightly to moderately. The white blood cell picture varied from leukopenia of 1,800[23] to marked leukocytosis[2] with an increase in the number of granulocytes. Death occurred seldom. Two of 27 patients died, one of them from intercurrent tuberculosis. Other conditions which may simulate panniculitis are Dercum's disease, erythema nodosum, erythema induratum,[24] subcutaneous sarcoidosis,[11] and post-traumatic fat necrosis.[28]

## ETIOLOGY

The cause of nodular panniculitis has not been established. In one compilation of 28 patients, 8 had received either bromides or iodides.[24] In some patients bacterial infection appeared to precede the development of panniculitis.[5,13] As it is true with other conditions of unknown cause, many factors have been implicated. They include:

Injuries of chemical, thermal, and mechanical nature

Drug sensitivity, especially to iodides and bromides
Bacterial allergy
Avitaminosis
Injection of various substances such as insulin and hypertonic dextrose
Infectious diseases, including virus infection

If one or more stimuli such as drugs and infections can produce the lesion of panniculitis, it must be assumed on the basis of the rarity of the condition that unusual susceptibility of the adipose tissue exists in certain predisposed individuals. Very few of the patients had a personal or family history suggestive of allergic manifestations. However, a specific hypersensitivity may be assumed without evidence of the usually accepted evidences of allergy.

## NECROPSY REPORTS

There are 6 recorded necropsies on patients with panniculitis.

Miller and Kritzler,[28] in 1943, reported the first necropsy on a 34-year-old woman with multiple recurrent nodules who was ill for 18 months prior to death. Histologic examination of a subcutaneous nodule showed changes consistent with nodular panniculitis. There was splenomegaly (360 gm.), and moderate hepatomegaly (2,440 gm.). The spleen and liver showed areas of focal necrosis, centrolobular in the latter organ, with fatty metamorphosis. The reticulo-endothelial cells of the spleen and the Kupffer cells of the liver were engorged with red blood cells. The lipid of the adrenal cortex was reduced.

The second necropsy was performed by Spain and Foley,[25] in 1944, on a 51-year-old male who was ill for 10 days prior to death. The patient was in an acute alcoholic state and in the end stage of chronic glomerulonephritis. A subcutaneous nodule showed histologic changes consistent with nodular panniculitis. Similar nodules were found in mesenteric, omental, and pretracheal fat.

Friedman[27] reported the third necropsy in 1945. The patient was a 23-year-old white girl who had had recurrent crops of subcutaneous nodules for 5 years and died of staphylococcic bacteremia. There was splenomegaly (350 gm.) and hepatomegaly (2,200 gm.) with many fat droplets in the liver. The spleen contained many phagocytes filled with red blood cells.

The fourth necropsy was presented by Ungar[31] in 1946. The patient was a 37-year-old woman with recurrent subcutaneous nodules, who died of peritonitis. She had nodules in the adipose tissue surrounding the abdominal organs and of the omentum and mesentery.

TABLE I
*Reported Cases of Nodular Panniculitis*

| Authors | Year | No. of cases | Pertinent remarks |
|---|---|---|---|
| Pfeifer[1] | 1892 | 1 | |
| Gilchrist and Ketron[2] | 1916 | 1 | |
| Weber[3] | 1925 | 1 | Introduced the present name |
| Christian[4] | 1928 | 1 | Added the term "febrile" |
| Alderson and Way[5] | 1933 | 1 | |
| Netherton[6] | 1933 | 1 | |
| Weber[7] | 1935 | 1 | No biopsy |
| Brill[8] | 1936 | 1 | Introduced "Weber-Christian disease" |
| Bailey[9] | 1937 | 5 | Review |
| Reed and Anderson[10] | 1937 | 1 | |
| Cummins and Lever[11] | 1938 | 1 | |
| Shaffer[12] | 1938 | 1 | |
| Puente[13] | 1938 | 1 | |
| Binkley[14] | 1939 | 1 | |
| Hartwell, Thannhauser[15] | 1940 | 1 | |
| Tilden *et al.*[16] | 1940 | 2 | Summary of 9 previous cases |
| Hazel and Lamb[17] | 1940 | 2 | No tissue examined |
| Skiöld[18] | 1940 | 1 | |
| Ziegert[19] | 1940 | 1 | |
| Hanson and Fowler[20] | 1941 | 1 | |
| Larson and Ootkin[21] | 1941 | 1 | |
| Rosenberg and Cohen[22] | 1942 | 1 | |
| Miller and Kritzler[23] | 1943 | 1 | Review of 26 cases and first reported necropsy, visceral changes without involvement of perivisceral fat |
| Larkin *et al.*[24] | 1944 | 1 | Review of 27 previous cases |
| Spain and Foley[25] | 1944 | 1 | Second necropsy, lesions in mesenteric, omental, and pretracheal fat |
| Arnold[26] | 1945 | 1 | |
| Friedman[27] | 1945 | 1 | Third necropsy, splenohepatomegaly |
| Ives[28] | 1945 | 1 | |
| Pierini *et al.*[29] | 1946 | 1 | |
| Zee[30] | 1946 | 1 | |
| Ungar[31] | 1946 | 1 | Fourth necropsy, widespread panniculitis and intra-abdominal lesions |
| Mostofi and Engleman[32] | 1947 | 1 | Fifth necropsy, perivisceral lesions |
| Bunnell and Levy[33] | 1948 | 1 | |
| Johnson and Plice[34] | 1949 | 1 | Reviewed 35 cases; three stages |
| Kennedy and Murphy[35] | 1949 | 1 | Review |
| Rubin and Bland[36] | 1949 | 1 | |
| Bendel[37] | 1949 | 1 | Review |
| Brudno[38] | 1950 | 1 | |
| Hanrahan *et al.*[39] | 1951 | 1 | Sixth necropsy, splenohepatomegaly |
| Eisaman and Schneider[40] | 1951 | 1 | |

The fifth necropsy was performed by Mostofi and Engleman,[32] in 1947, on a 38-year-old man who was ill for 7 months. Subcutaneous nodules appeared 6 months after the onset of illness and presented histologic changes consistent with nodular panniculitis. There was moderate hepatomegaly (2,275 gm.) with extensive fatty changes and focal necrosis in midzonal and central areas. Changes like those of nodular panniculitis were found in the epicardial, peripancreatic, intralobar, perirenal, periadrenal, and mesenteric fat. There was reticuloendothelial hyperplasia of the spleen and lymph nodes with decrease of lymphoid tissue.

Hanrahan, Ippolito, and Dilworth[39] presented the sixth necropsy in 1951. The patient was a 20-year-old woman who was ill for 3 months before death. She had subcutaneous nodules in the extremities and face, with histologic changes of nodular panniculitis. Hepatomegaly (3,400 gm.) and splenomegaly (500 gm.) were found. The liver contained much fat. No other significant changes were found.

Of the 6 reported necropsies on patients with nodular panniculitis, 4 may be distributed into three categories. The necropsies of Friedman[27] and of Hanrahan, Ippolito, and Dilworth,[39] which showed no pertinent abnormal visceral changes except for splenomegaly and hepatomegaly, are excluded. If nodular panniculitis in some way contributed to these two deaths, the subcutaneous lesions may be assumed to be responsible. Since no pertinent visceral changes were identified in these two necropsies, they can be considered to represent a local, subcutaneous phase of nodular panniculitis. The necropsies of Spain and Foley[25] and of Ungar[31] showed nodular lesions of the perivisceral adipose tissue and of the mesentery and omentum. The similarity of the lesions justifies the inclusion of these two patients in the first category of systemic nodular panniculitis. The necropsy of Miller and Kritzler[23] disclosed areas of focal necrosis of the liver and the spleen without perivisceral nodular lesions. This case may be considered as the second type of systemic nodular panniculitis. The necropsy of Mostofi and Engleman[32] revealed both types of visceral lesions, the perivisceral nodules and focal necrosis. The findings in this patient suggest that both types of lesions represent the manifestations of systemic nodular panniculitis and that this case falls into the third category.

## REPORT OF CASES

### *Case 1*

The patient was a white woman, 61 years of age, who was followed from April, 1941, to her death in October, 1949. Her first entry to the hospital in April, 1941, was

for right hemiplegia and aphasia. Her red blood count was 3.5 millions; hemoglobin, 6.2 gm.; white blood count from 8,800 to 13,650 with 62 segmented forms, 21 staff cells, 15 lymphocytes, and 2 eosinophils per 100 cells. Several platelet counts varied from 1,750,000 to 2,780,000, the normal for the method being 240,000.

She was readmitted in June, 1948, 7 years later, because of a Colles's fracture produced by a fall. The patient stated that she was allergic to tomatoes and chocolate. The liver was enlarged 2 fingerbreadths downward, and the spleen was enlarged considerably. Her blood pressure was 100/80 mm. of Hg. The red blood cell count was 4 millions; hemoglobin, 12.5 gm.; white blood cell count, 13,400, with 42 segmented forms, 27 staff cells, 6 juveniles, 2 myelocytes, 14 lymphocytes, 5 monocytes, 2 eosinophils, and 2 basophils per 100 cells. Platelets were 250,000.

On her third entry in April, 1949, she complained of malaise, cough, a fever of 102° F., and substernal chest pain. Blood pressure was 118/60. There was slight ankle edema. The patient was dyspneic and had a productive cough. There was a non-tender, freely movable, subcutaneous nodule in the left supraclavicular region. Red blood cell count was 2.81 millions; hemoglobin, 9.3 gm.; white blood cell count, 12,100, with 81 segmented forms, 8 staff cells, and 11 lymphocytes per 100 cells; platelets were 496,000.

Her last entry was in October, 1949, with an additional complaint of weakness. Blood pressure was 130/76. Both lung bases were dull to percussion and had moist râles. The abdomen was distended and showed a fluid wave. Liver and spleen were enlarged. Red blood cell count was 3.04 millions; hemoglobin, 10.9 gm.; white blood cell count 18,400, with 70 segmented cells, 14 staff cells, 12 lymphocytes, and 4 monocytes per 100 cells; platelets, 470,000; serum protein, 4 gm. per cent; albumin, 2.2 gm. per cent; globulin, 1.8; icterus index, 8; cephalin flocculation, 1 plus. Straw-colored fluid (3600 cc.) was removed from the peritoneal cavity. The patient became weaker and complained of generalized pain before her death.

Necropsy was performed 5 hours after death. The body was emaciated but well developed. It weighed 110 lbs. The abdomen was distended. There was edema of the labia and lower extremities. Several subcutaneous nodules were present in the left supraclavicular region, right breast, chest, back, and arms. The nodules varied from 2.5 to 6 cm. in diameter. They were firm, adherent to the skin, and on section were dirty gray and irregular in outline. The adipose tissue of the peritracheal region, mesentery, omentum, peripancreatic, perinodal, perirenal, and periadrenal regions was light yellow-gray studded with minute, irregular, white-gray areas. The pericardial fat presented a similar picture. The left internal jugular vein was thrombosed. The spleen weighed 725 gm. The cut surface was deep red with multiple hemorrhagic areas. The follicles were not apparent. The pulp was fairly firm. The liver weighed 1,850 gm. The capsule was thick, measuring 0.5 to 0.7 cm. and was light to dirty gray. The portal triads and the blood vessels were surrounded by yellow-white areas 2 to 7 mm. thick. The central veins were dilated and red. The submucosa of the small and large bowel was thick and of a dirty gray-white color and studded with minute yellow-white areas. The tibial marrow was yel-

low-white with areas of gray and deep red. The rib and sternal marrow presented a similar picture.

*Microscopic Examination.* Tissues were fixed in 10 per cent formaldehyde and in Zenker's solution and stained with hematoxylin and eosin, Sudan III for fat, van Gieson's mixture, and with Masson's trichrome stain. The subcutaneous nodules showed extensive fibrosis of the adipose tissue with areas of necrosis involving fat cells. There were areas of inflammation composed of lymphocytes, neutrophilic polymorphonuclear leukocytes, macrophages with cytoplasmic vacuoles, and infrequent multinucleated giant cells. The cell membranes of some fat cells were collapsed and in others the nuclei were centrally placed. Some of the fat cells accepted the fat stain only partly, as was true, also, of many of the cytoplasmic vacuoles within the macrophages. A similar picture was found in the adipose tissue of the peritracheal region, pericardium, omentum, mesentery, intestinal submucosa, and perirenal and periadrenal tissue. The liver capsule and the perivascular and the portal areas of the liver showed a greater degree of fibrosis and hyalinization. The myocardium showed patchy fibrosis. There were emphysema, edema, and passive congestion of the lungs, and marked passive congestion and fatty metamorphosis of the liver. Liver sinusoids contained many macrophages filled with vacuoles. The follicles of the spleen and lymph nodes were markedly decreased or absent. The splenic pulp and the lymph node sinuses contained many macrophages with cytoplasmic vacuoles and there was considerable reticulum cell hyperplasia. The bone marrow of the tibia, sternum, and ribs contained areas of fibrosis, lymphocytic infiltration, macrophages with vacuoles, and fat necrosis with alternating areas of myeloid hyperplasia. The brain showed patchy gliosis and senile arteriosclerosis.

*Final Diagnoses.* Systemic nodular panniculitis involving subcutaneous tissue, peritracheal, pericardial, perihepatic, perirenal, and periadrenal tissue, submucosa of the gastro-intestinal tract, active and inactive bone marrow, mesentery, and omentum; splenomegaly, follicular hypoplasia and reticulum cell hyperplasia of spleen and lymph nodes, myocardial fibrosis without significant coronary arteriosclerosis, pulmonary emphysema and passive congestion, passive congestion of liver, thrombosis of internal jugular vein, senile arteriosclerosis, and patchy gliosis of the brain.

*Case 2*

The patient was a white woman, 66 years old, who was followed from 1925 to her death in 1943. In 1925, at the age of 48, she complained of fatigue and "skin trouble"

with questionable subcutaneous nodules. In that year, she had an appendectomy and tonsillectomy. In 1926 her symptoms were fatigue, general malaise, and "colitis." Red blood cell count was 3.68 millions with hemoglobin of 78 per cent and platelets of 323,000 (normal for the method: 240,000).

In 1930 she had a definite, tender, erythematous nodule in the right thigh with crops of more nodules appearing on both legs, back, and abdomen. During the year, some of the nodules became adherent to the skin. She had a fever not in excess of 101° F. Liver and spleen were enlarged. Red blood cell count was 4.22 millions; hemoglobin, 92 per cent; white blood cell count, 8,300. One of the nodules and a lymph node were excised. The tissues were sent to the registry of lymphoid tumors of the Army Medical Museum, as a result of which it was reviewed by eight of the well known pathologists of that period. The diagnoses offered included tuberculosis, syphilis, reticulum cell sarcoma, Hodgkin's disease, infectious hyperplasia, and foreign body reaction. From the descriptive side, the subcutaneous tissue showed necrosis of fat cells, accumulation of lymphocytes, neutrophilic polymorphonuclear leukocytes, plasma cells, macrophages with ingested vacuoles, periarteritis with organization, endothelial proliferation, and edema of vessel walls. The picture was that previously[1-4] and subsequently described as nodular panniculitis, but neither the consultants nor I was aware of this condition in 1930–1931.

The lymph node showed reticular hyperplasia and the presence of many macrophages laden with fat globules and red blood cells as described in necropsies later. The perinodal tissue contained a part of a subcutaneous nodule with the changes of nodular panniculitis.

In 1931 the patient was seen by a Chicago physician who found absence of knee jerks and ankle clonus, fatigue, achylia, a red blood count of 4.6 millions with hemoglobin of 100 per cent, white blood cell count of 6,100, and numerous subcutaneous nodules. A diagnosis of pernicious anemia was made and liver was given.

In 1940 the patient slipped on ice and fractured the neck of the left femur. Her temperature was 98.4° F.; red blood cell count, 3.8 millions; hemoglobin, 70 per cent; white blood cell count, 4,450 to 7,750, with 80 segmented forms, 8 staff cells, 1 juvenile, and 11 lymphocytes per 100 cells; reticulocytes, 0.8 per cent.

She was seen in 1942 and 1943 when she complained of fatigue and tiredness. The radiologist observed an asthmatic contour on a flat film of the chest. Temperature was 99° to 102° F.; pulse, 100 to 130; respirations, 20 to 40. Red blood cell count was 4.21 millions with 72 per cent hemoglobin. White blood cell count varied from 1,200 to 2,800 with 25 per cent segmented polymorphonuclear leukocytes, 44 per cent staff cells, 19 per cent monocytes; platelets were 100,000; hematocrit, 24 per cent. The patient became listless, mentally confused, and died.

## Necropsy

The post-mortem examination was performed 9 hours after death. The body was well developed and fairly well nourished. There were multiple irregular subcutaneous nodules on the chest, back, abdomen, and extremities. Some were fixed to the skin and the surrounding tissue, others were slightly movable. They varied in size from 0.4 to 1.8 cm. in diameter. The feet and ankles were slightly edematous. The subcutaneous fat was a dirty yellow with streaks of gray-white. There was fatty infiltration in the right ventricular musculature. The fat was gray-yellow. The lungs were emphysematous and there were some sub-

pleural petechiae. The spleen weighed 1,100 gm.; the follicles were not apparent and the pulp was deep red with regular yellow flecks. The liver weighed 1,950 gm. The cut surface showed dilated central veins and flecks of gray. The periadrenal tissue was a dirty yellow with light red streaks. The bone marrow of the tibia, sternum, and ribs was deep red with patches of gray-white and deep yellow.

*Microscopic Examination.* The subcutaneous nodules showed abnormal changes confined to the subcutaneous tissue. The abnormalities consisted of:

Irregular fibrosis

Necrosis of fat cells, collapse of walls of fat cells, infiltration of the cells by lymphocytes, macrophages, and multinucleated giant cells

Intimal proliferation of blood vessels, perivascular hyalinization (organization of perivascular inflammatory reaction)

Exudation of inflammatory cells, largely lymphocytes and some plasma cells and monocytes

Presence of a large number of multinucleated giant cells.

The picture was that of the third or atrophic stage of nodular panniculitis. The periadrenal adipose tissue, the perirenal and pelvic fat, the interlobular pancreatic fat, and parts of the bone marrow showed changes of variable degree, which included necrosis of fat cells; collapse of walls of fat cells; presence of inflammatory cells, largely lymphocytes, within fat cells and between the cells; and slight fibrosis. The abdominal lymph nodes were enlarged.

The splenic follicles were either markedly decreased in size or absent. The pulp was filled with macrophages laden with vacuoles, some of which stained for fat. There was considerable hyperplasia of reticulum cells. The liver showed dilated sinusoids filled with vacuolated cells, lymphocytes, and monocytes. There were also areas of necrosis in the central and midcentral zones. The liver cells contained many vacuoles which stained for fat. The lymph nodes showed an extensive reduction of lymphocytes and replacement by macrophages filled with vacuoles and red blood cells.

The heart showed patchy myocardial fibrosis and arteriosclerosis of intramural coronaries. The kidneys showed arteriolar sclerosis with patches of cortical interstitial fibrosis, tubular atrophy, and glomerular hyalinization.

*Final Diagnoses.* Nodular panniculitis of subcutaneous tissue of trunk and extremities; splenomegaly and hepatomegaly; nodular panniculitis of periadrenal, perirenal, renal pelvic, myocardial, marrow, and pancreatic adipose tissue; extensive hypoplasia of lymphatic tissue

of spleen and lymph nodes; extensive invasion of fat-laden macrophages of splenic pulp, lymph nodes, and liver sinuses; focal necrosis of liver; passive congestion and fatty metamorphosis of liver; myocardial fibrosis; intramural coronary arteriosclerosis; arteriolar nephrosclerosis.

## Discussion

The necropsies recorded in the medical literature and those presented here make it possible to follow the progressive changes in the pathogenesis of nodular panniculitis. The primary process consists in

Table II
*Pathologic Changes in Systemic Nodular Panniculitis*

| Pathologic changes | Organs and tissues involved |
|---|---|
| Panniculitis: Formation of irregular nodules with the following changes: | Subcutaneous tissue, bone marrow, omentum, mesentery, perivisceral adipose tissue of heart, liver, pancreas, adrenal glands, and kidneys |
| Stage 1, Onset: Inflammation of adipose tissue with neutrophilic polymorphonuclear leukocytes, lymphocytes, and macrophages; phagocytosis of fat | |
| Stage 2, Maturity: Fat necrosis; collapse of cell membrane, invasion of fat cells by phagocytes and other inflammatory cells; periarteritis and intimal proliferation | Intravisceral:<br>Pancreas<br>Liver<br>Intestinal submucosa |
| Stage 3, Regression: Fibrosis of fat; inflammation, multinucleated giant cells, many fat-laden macrophages, periarterial fibrosis | |
| Enlargement of the organ, focal necrosis, Kupffer cell hyperplasia, fatty metamorphosis, fat-laden macrophages in sinusoids | Liver |
| Enlargement of the organ, reduction in size or absence of follicles, reticulum hyperplasia, variable number of fat-laden macrophages, decrease in the number of lymphocytes | Spleen and lymph nodes |

the destruction of adipose tissue. It is not unlikely that disintegration and phagocytosis of fat cells observed in the lesions are preceded by a chemical transformation of the fat which is rendered inimical and foreign to the body. The failure of some of the fat to accept specific stains and the inflammatory reaction which precedes observable fat disintegration suggest this possibility.

The abnormal changes of the adipose tissue in nodular panniculitis are variable in extent and in degree. The condition may be limited to the subcutaneous tissues. Some 40 cases in the literature demonstrate this limitation. The necropsies of Friedman[27] and of Hanrahan, Ippo-

lito, and Dilworth[39] indicate that the subcutaneous disease is associated also with splenomegaly and hepatomegaly. It is probable that enlargement of the two organs is due to the presence of fat-laden macrophages and hyperplasia of the reticulo-endothelial elements. The term for the disease as it is known now is unnecessarily cumbersome. The name may be simplified to subcutaneous nodular panniculitis in the case of involvement of the subcutaneous tissue only.

That nodular panniculitis varies in severity is apparent from the variable number of subcutaneous nodules and the number of "crops" of lesions. Another factor is the duration of the disease. It may extend for a few weeks, months, or over a period of years.

In addition to the subcutaneous tissue, the disease may involve the perivisceral and even the intravisceral fat of several organs, as well as the omentum and the mesentery. It may also produce focal necrosis of the liver. It may attack the bone marrow with consequent abnormalities of the hematopoietic system. Although the difference between localization to the subcutaneous tissue and systemic involvement is probably a matter of degree, it is suggested that the generalized condition be labeled systemic nodular panniculitis.* Since the disease is usually limited to the subcutaneous tissue and systemic involvement implies the corollary reactions of several organs, the two phases may well be differentiated.

Extension of the disease to perivisceral and intravisceral adipose tissue creates an increased demand for phagocytes and a resultant hyperplasia of the involved organs. This greater and persistent requirement for macrophages may result in a decreased production of other cell types. The marked reduction of lymphocytes in lymph nodes and in the spleen may be due to this process. A second reaction to the increased number of phagocytes is the excessive filling of the spleen, liver, and lymph nodes with fat-laden macrophages, with whatever functional disturbances this type of blockage may imply. Another effect of perivisceral panniculitis is the resultant thickening and fibrosis of organ capsules with loss of elasticity and tendency to constriction. Intravisceral panniculitis may interfere further with the functions of the organ. Focal necrosis of the liver compromises its functions as indicated by the abnormal responses to liver function tests.

Panniculitis with resultant patchy fibrosis of the bone marrow was associated with abnormalities in response on the part of the hemato-

* The inappropriateness of the term panniculitis for a process in regions where there is no panniculus is recognized. However, it is employed in default of a better term and in accordance with established usage.

poietic system. Anemia, leukopenia, appearance of abnormal and immature cells in the blood, and disturbances of platelet production as seen in the two cases presented in this report and by other observers, demonstrate the effects of nodular panniculitis upon the bone marrow.

The pathogenesis of nodular panniculitis gives me little or no help in determining the cause of the disease. Sensitivity to foods in one patient in this report and the radiologic suggestion of an "asthmatic contour" in the other suggest an allergic background. Administration of bromides, iodides, and penicillin in many of the patients reported in the literature throws further suspicion on this mechanism. On the basis of the available evidence, any further interpretation is still more speculative. Adipose tissue may be considered as one of the shock organs in allergy. Antigen-antibody reaction in the adipose tissue of predisposed individuals may be assumed to alter the chemical nature of the fat. Subsequent pathologic changes may result from this alteration. Since the liver is a shock organ, it is not unlikely that in severe instances of the disease, the liver becomes involved. Focal necrosis develops as seen by Mostofi and Engleman[32] and in one necropsy in this report.

The indefinite clinical manifestations of subcutaneous nodular panniculitis include: malaise, fatigability, cough, generalized aching, generalized abdominal pain, chills or chilly sensations, night sweats, occasionally nausea and vomiting; fever of 99° to 104° F.; rapid pulse of 100 to 130; hepatomegaly; splenomegaly; normocytic and normochromic anemia; normal number of white blood cells or leukocytosis or leukopenia with an increase in staff forms and monocytes; normal, increased, or decreased platelets; positive cephalin flocculation test.

In systemic nodular panniculitis more of these symptoms and signs are present and they are more pronounced. Involvement of the bone marrow is followed by leukopenia, thrombocytopenia, and anemia. Extensive panniculitis appears to be associated with an increase in circulatory monocytes. In liver involvement the cephalin flocculation test becomes positive and there is a disturbance in the prothrombin time.

In the patients studied so far, the systemic form has been associated with subcutaneous nodules. Histologic examination of a subcutaneous nodule remains the best diagnostic test for the disease.

## Summary

A systemic disorder, hitherto unrecognized, is presented. The condition known as relapsing non-suppurative nodular panniculitis, or

Weber-Christian's disease, had been thought to be confined to the panniculus. Data in this presentation indicate the existence of a systemic disease in which there is involvement of the thoracic, abdominal, perivisceral, and intravisceral adipose tissue. The abnormal changes in the fatty tissue are similar to those observed in the panniculus. Focal necrosis of the liver and the spleen has been found in some of the patients. Involvement of fatty bone marrow results in the interference with the hematopoietic activity and consequent confusion in the diagnosis of blood dyscrasias. Invasion of the lymph nodes, the spleen, and the liver with fat-laden histiocytes produces an enlargement of these organs. The large number of histiocytes, especially in the lymph nodes, has been confused with neoplasia and systemic panniculitis should be considered in the differential diagnosis of lymphomas.

It is suggested that the term for the localized lesion of the panniculus be simplified to subcutaneous nodular panniculitis. Since the condition is known now in the literature as panniculitis, it would be well to retain the name for the systemic disorder. Although panniculitis refers to the subcutaneous adipose tissue, it is suggested that because of previous usage the term systemic panniculitis be used.

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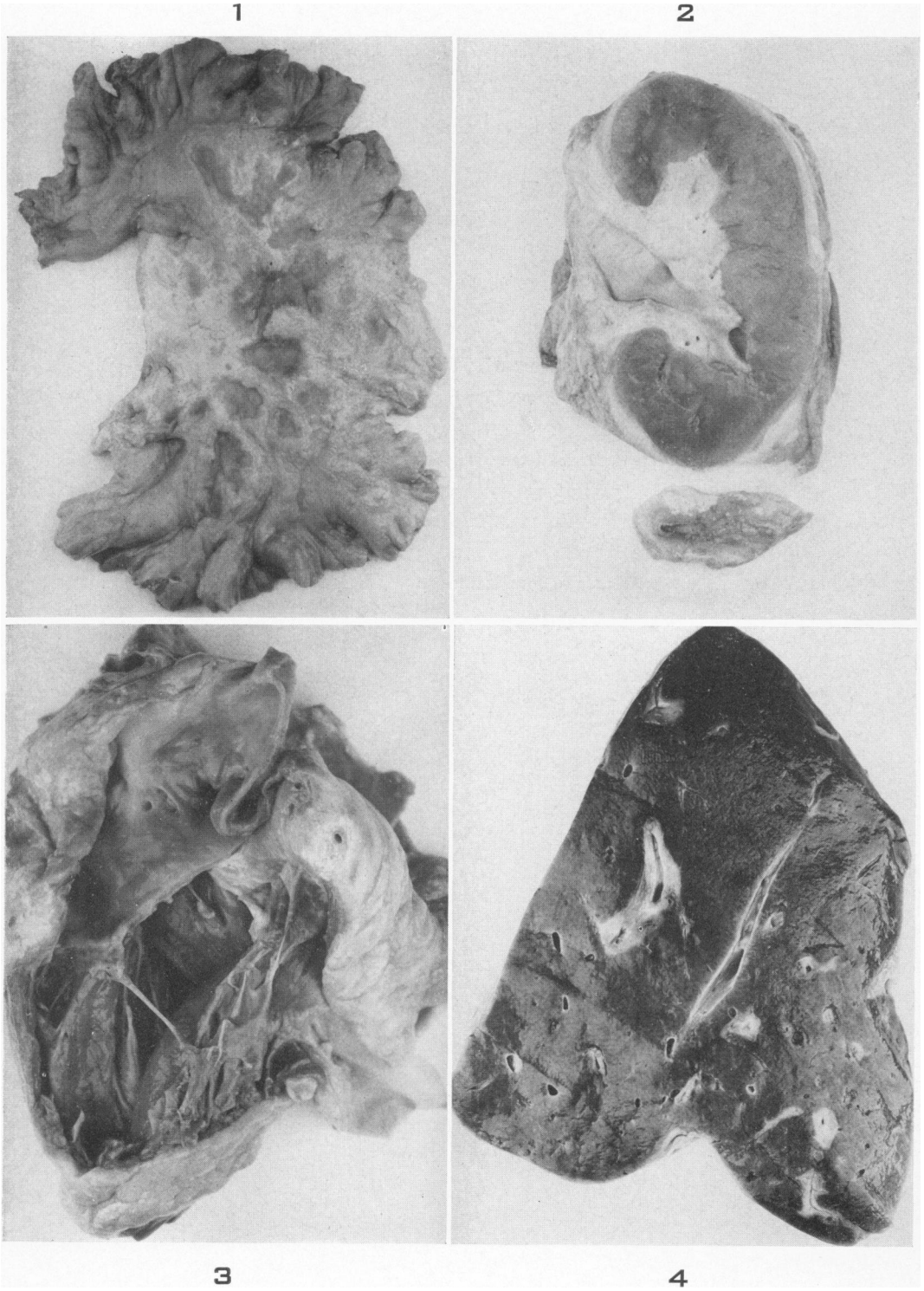
[ *Illustrations follow* ]

## LEGENDS FOR FIGURES

FIGS. 1 to 4. Gross photographs of (*Fig. 1*) omentum, (*Fig. 2*) kidney and adrenal gland, (*Fig. 3*) heart, and (*Fig. 4*) liver of case 2. The omental fat is nodular and shows change in color. The perirenal and pelvic fat of the kidney is thickened and nodular. The periadrenal fatty tissue shows a change in color which is also apparent in the subepicardial fat of the heart and in the perivascular areas of the liver.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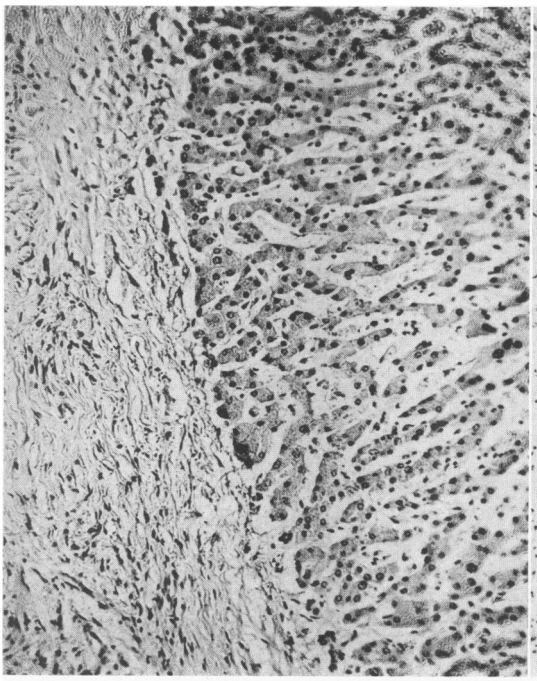
FIGS. 5 to 8. Case 1.

FIG. 5. Liver with perihepatic tissue showing fibrosis, lymphocytic infiltration, and replacement of fat cells.

FIG. 6. Adrenal and periadrenal tissue showing replacement of much of the fatty tissue by fibroblasts and lymphocytic infiltration.

FIG. 7. Bone marrow shows fibrosis, lymphocytes, and only a few fat cells. No myeloid tissue is present.

FIG. 8. Liver showing an area of focal necrosis.



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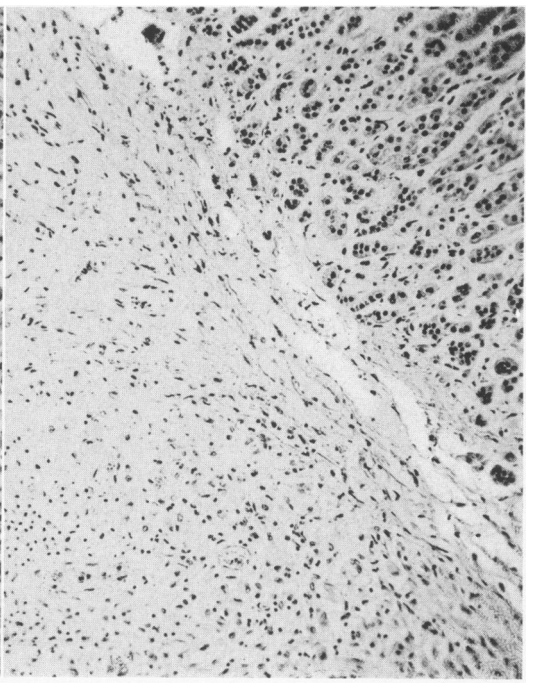

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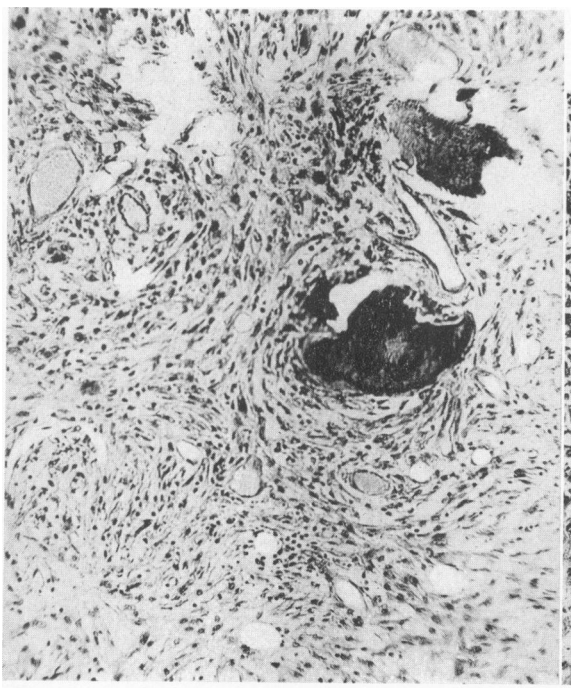

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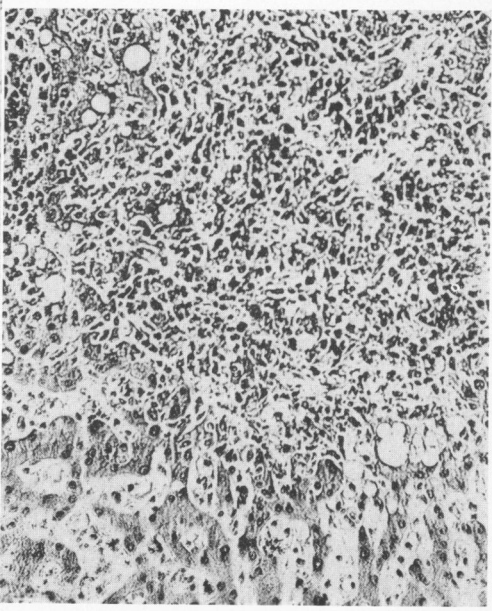

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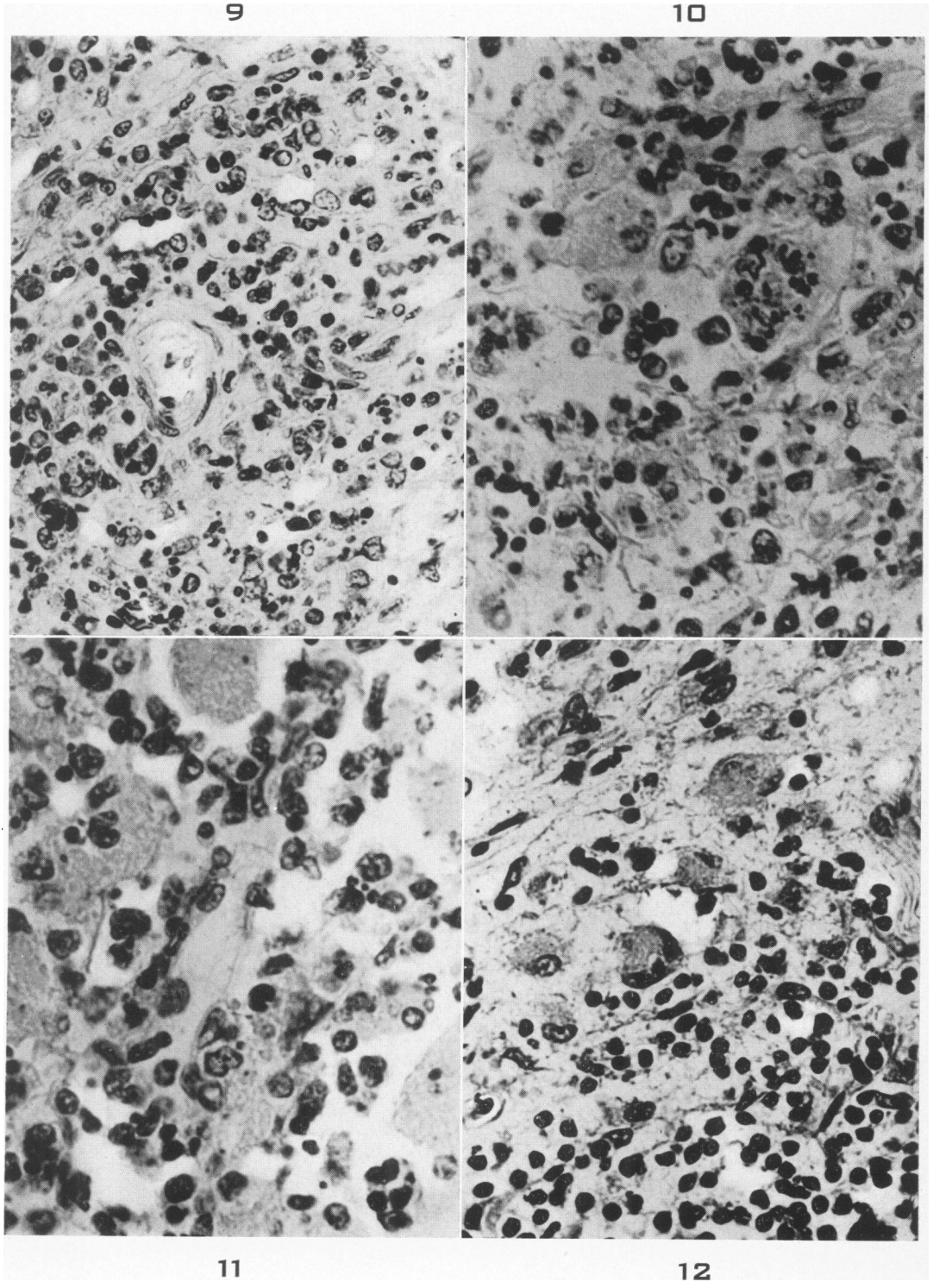
FIGS. 9 to 12. Case 2.

FIG. 9. Spleen shows considerable hypoplasia of a follicle with very few lymphocytes remaining in the follicle.

FIG. 10. Splenic pulp with many macrophages filled with minute vacuoles, presumably fat. A similar picture is present throughout the pulp.

FIG. 11. Lymph node shows relatively few lymphocytes. The sinuses contain macrophages with ingested vacuoles, some of which take the fat stain. The entire lymph node shows a similar picture.

FIG. 12. Periadrenal tissue shows the second stage of panniculitis with fat cell necrosis, inflammation, and macrophages containing vacuoles, some of which stain for fat.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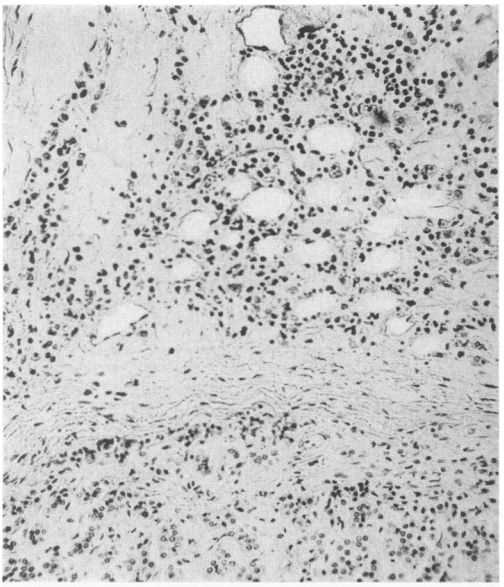
FIGS. 13 to 16. Case 1.

FIG. 13. Panniculitis. First stage shows inflammation of adipose tissue with some inflammatory cells invading fat cells, rupture of walls, and collapse of some of the fat cells.

FIG. 14. Case 1. Panniculitis. Third stage (Fig. 3 may be seen for second stage). There is extensive fibrosis, lymphocytic infiltration, and partial destruction of many fat cells.

FIG. 15. Case 2. Panniculitis. Third stage. Multinucleated giant cells filled with vacuoles, some of which take the stain for fat.

FIG. 16. Case 2. Panniculitis. Third stage. Endothelial proliferation of artery, edema of wall, and organization of adventitia and perivascular area.



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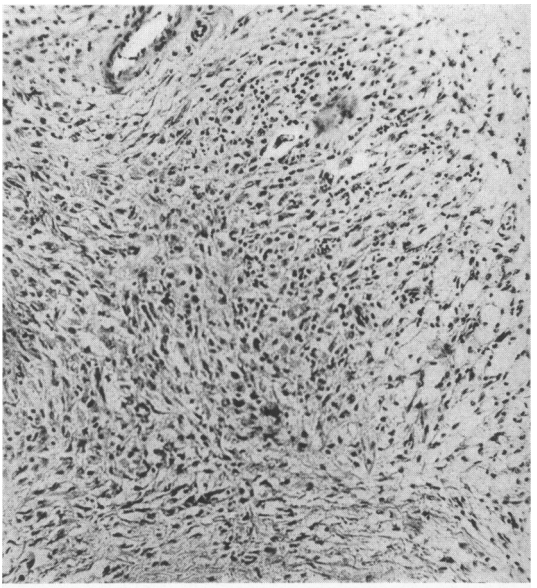

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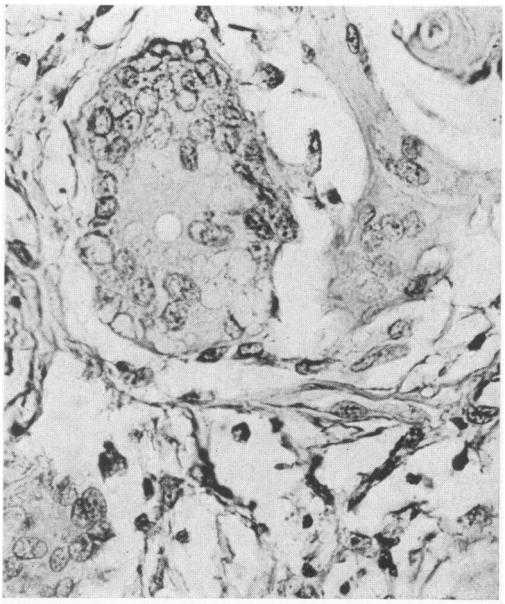

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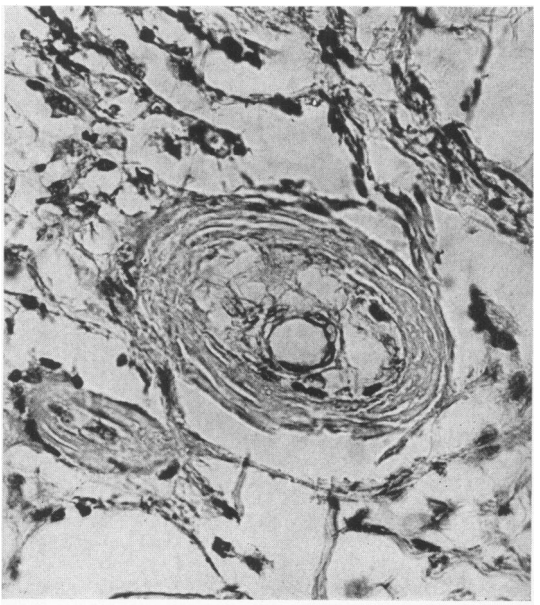

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