

## RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS \*

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In 1921, I had the opportunity to study a patient with a pathologic condition to me entirely unique. At that time, I did not succeed in finding similar cases reported in the literature. I was at a loss to give a satisfactory name to the condition or disease, and so did not place it on file in the literature. Recently, in a report of a meeting of the Association of Physicians of Great Britain and Ireland, held May 29, 1925, I saw a brief notice of an entirely similar case, reported by F. Parkes Weber, and subsequently read his report in the *British Journal of Dermatology and Syphilis*.<sup>1</sup> The name he used intrigued me; now, with a title for my report, it seemed appropriate to present my observations before the Association of American Physicians, which furnished a model for the society before which Weber made his report.

The name used by me, febrile relapsing nodular nonsuppurative panniculitis, is descriptive of the process. I have added "febrile" to the terminology that Weber used to emphasize a feature which is striking and the one most likely to arouse the interest of the internist. There is fever in recurring attacks or relapses; there is inflammation of the pannicle, or panniculus adiposus, nodular in distribution and nonsuppurative; the panniculitis results in localized atrophy of the panniculus adiposus, subsequently causing a depression in the contour of the skin and giving a marked appearance of scarring. The patient is seriously sick. The cause of the inflammation remains unknown. In my study, blood cultures and cultures from the nodules were sterile. Organisms could not be found in excised tissue. In my patient, leukocytosis did not accompany the febrile periods. Histologically, in a healing lesion excised in 1920, I found in places edema and necrosis of the fat tissue, edema of the connective tissue between fat lobules, and a focal infiltration between the fat cells and in the connective tissue septums of lymphoid cells, plasma cells, young connective tissue cells, endothelial cells phagocytic for fat droplets, a few polymorphonuclear leukocytes and a rare foreign body giant cell, so that much of the subcutaneous adipose tissue thus was infiltrated. Fatty acid crystals were not present. Blood vessels, as a rule, were normal. A few showed periarteritis; rarely one showed endarteritis with proliferation of the endothelial cells.

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\* Reported at a meeting of the Association of American Physicians, Washington, D. C., May 3, 1928.

1. Weber, F. Parkes: *Brit. J. Dermat.* **37**:301, 1925.

The inflammatory process did not extend to the dermis, and so the skin itself was not scarred. No organisms were seen. The process is well shown in the accompanying photomicrographs (figs. 1 to 7), which will serve in place of a more detailed verbal description.

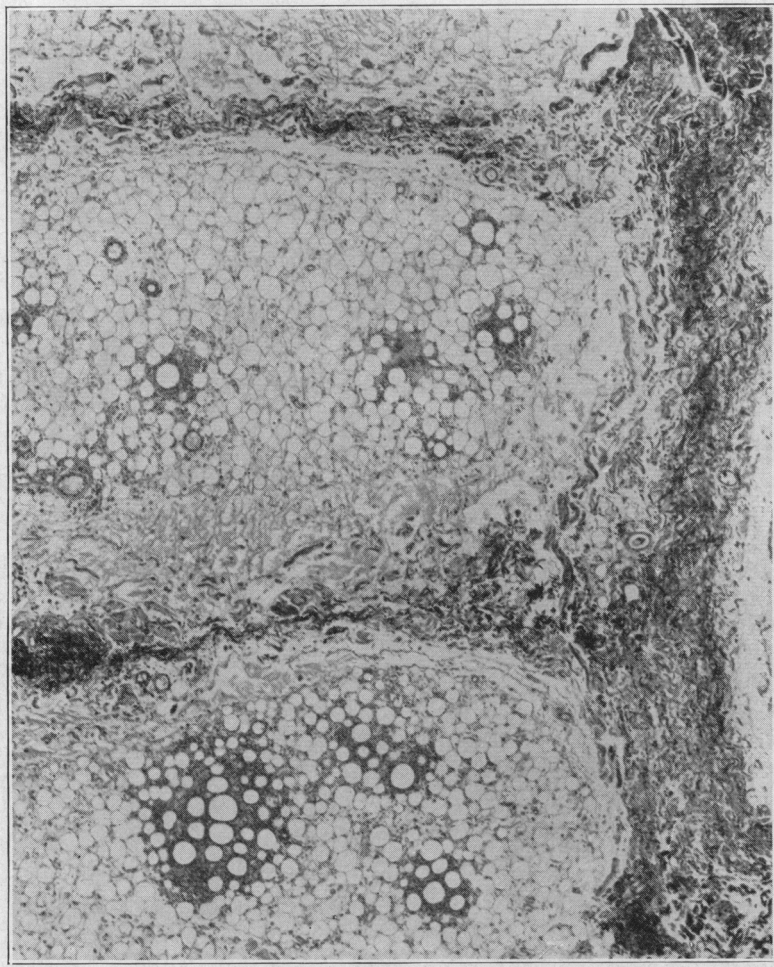


Fig. 1.—Low power magnification of area of panniculus adiposus in a case of “relapsing febrile nodular nonsuppurative panniculitis.”

#### REPORT OF A CASE

*History.*—A single woman, aged 25, was admitted to the Peter Bent Brigham Hospital on Feb. 5, 1921, for observation. She was of native American stock, intelligent, a college graduate and a chemist. She had never been in the tropics. The family history was negative. She had had mumps and whooping cough in

childhood, and scarlet fever at the age of 12, followed by otitis media. Her disease first appeared in 1918 with a lump under the skin of the right upper arm, followed in six months by a similar lump over the left scapula. In 1919, many lumps, described as of pea to lemon size, appeared over both lower legs. They developed in a short time. At first they were reddened, and the patient believed they were associated with some diffuse swelling from the middle of the tibia to the

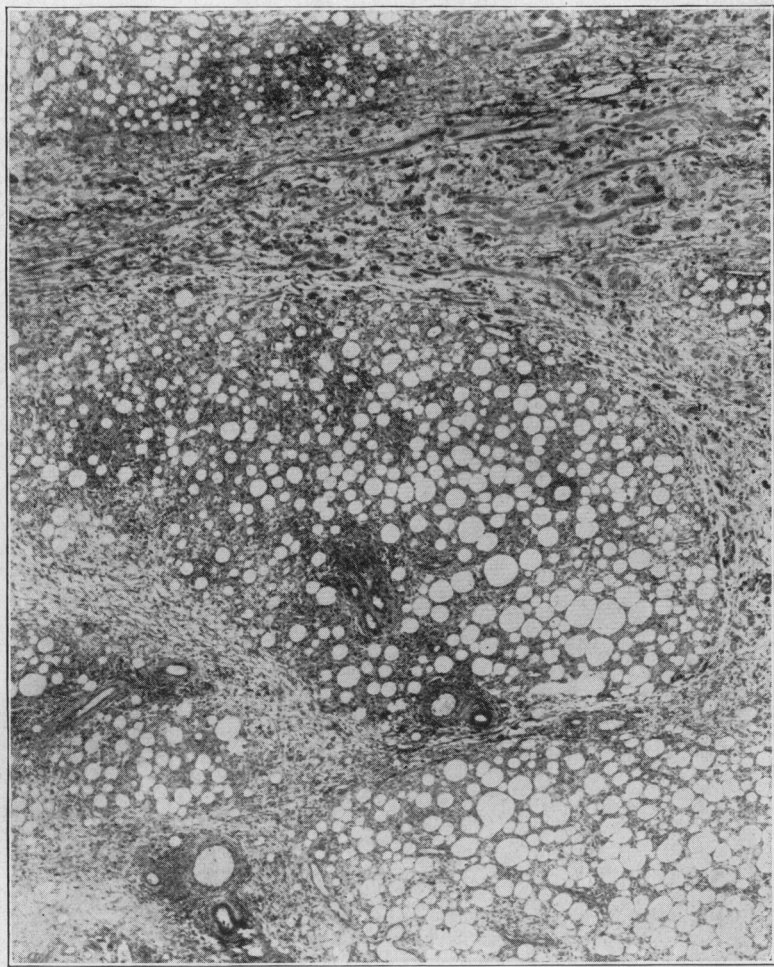


Fig. 2.—Low power magnification of area of panniculus adiposus showing marked inflammatory infiltration.

ankle. A month after the appearance of the nodules on the legs, she began to have fever associated with headache, nausea, vomiting and muscle pain. The fever fluctuated daily, but the time of highest temperature was not constant each day. For a time these variations of temperature reached a daily higher level, and then lessened each day until the normal again was reached. Defer-

vescence lasted longer than the rise. During the course of fever, other lumps might appear. The lumps would gradually flatten out, seem to attach themselves to the skin and finally leave a depression. After the temperature returned to normal, the patient felt well for four months. Then in the course of two to three weeks at least fifty new lumps appeared, with fever, chilly sensations, nausea and vomiting lasting about one month. In this attack only the

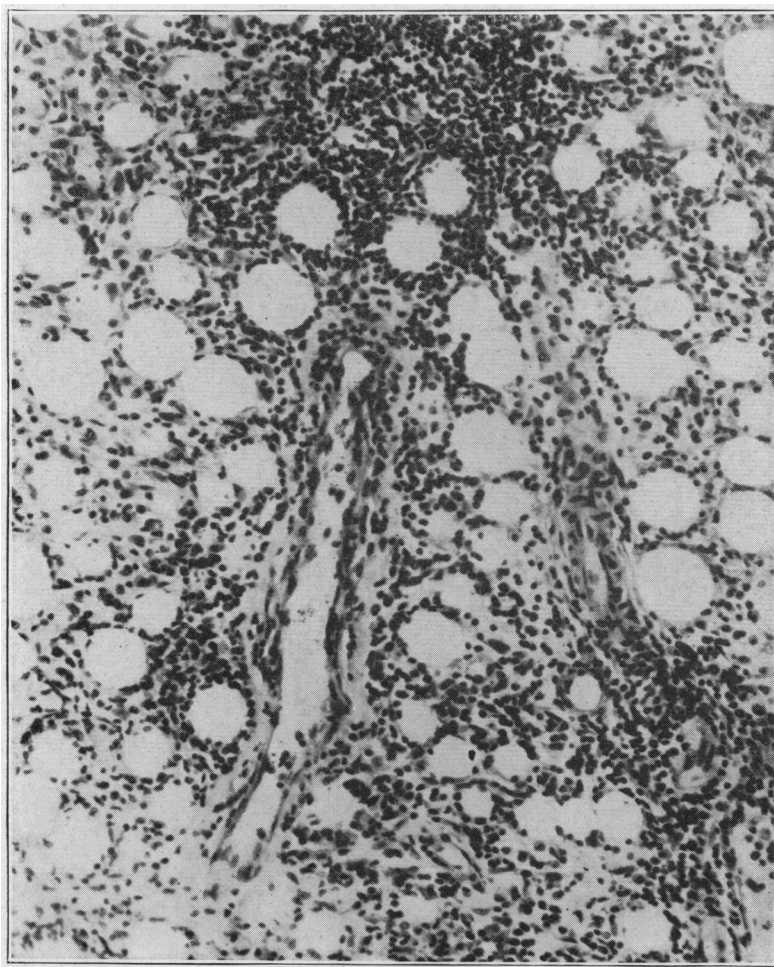


Fig. 3.—High power magnification, showing cellular infiltration of fat and connective tissue. There is evidence in places of replacement of fat by young connective tissue.

face, right forearm, palms of the hands and soles of the feet were spared. There was an interval of one month; then the third attack began and lasted for five weeks. A fourth attack occurred nine months later, in June, 1920, and lasted for a month (fig. 9 shows the fever curve in the latter part of this attack). After an interval of two months, a fifth attack developed. This was the most severe one



to date (fig. 10 shows the fever curve) and, in addition to previous symptoms, was accompanied by a slight dry cough with a "catch" over the lower sternum and slight jaundice for one day. Fever persisted for over five weeks. Between the fourth and fifth attacks the patient felt continuously tired. The sixth attack began on Jan. 24, 1921 with chills, fever and a dry cough. In this attack, she entered the Peter Bent Brigham Hospital on Feb. 5, 1921.

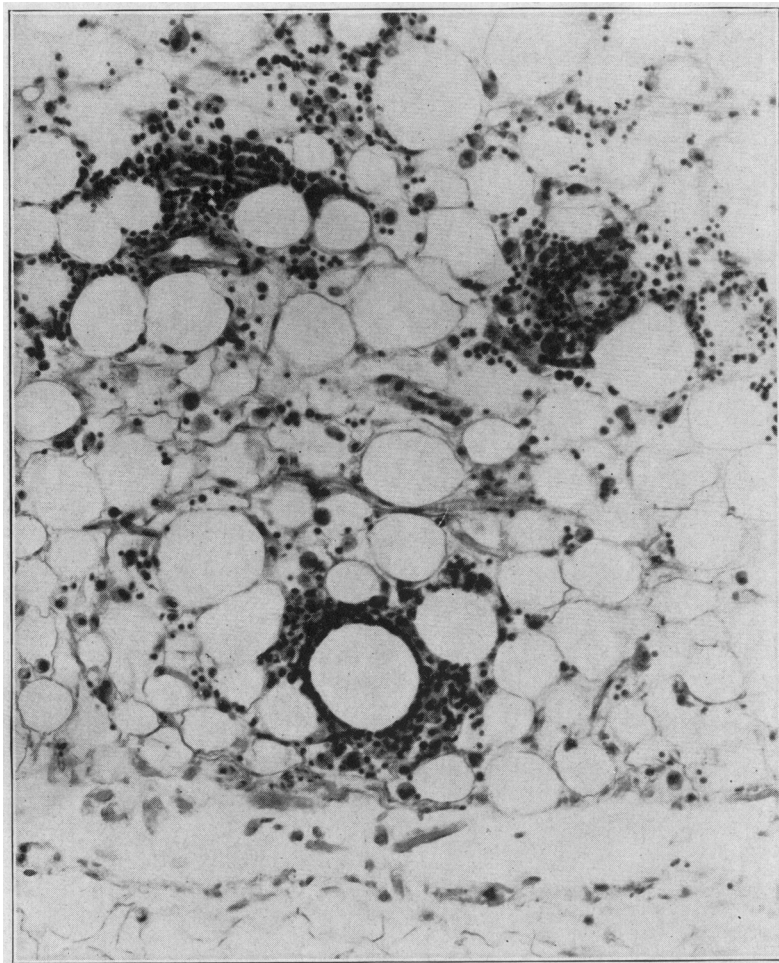


Fig. 4.—High power magnification, showing cellular infiltration of fatty tissue and a few macrophages.

*Examination.*—With the exception of the observations made on the subcutaneous tissue, the results of the physical examination were negative. Laboratory examination revealed: urine normal; hemoglobin, 85 per cent; red blood cells, 4,929,000; white blood cells, 3,000. The differential count showed: polymorphonuclears, 55 per cent; lymphocytes, 45 per cent. Five days later, there were 4,200 white cells; 50 per cent polymorphonuclears, 47.5 per cent lymphocytes

and 2.5 per cent large mononuclears. Six days later, the white cell count was 6,100. The Wassermann reaction was negative. The blood culture on Feb. 6, 1921, did not show any growth (on June 15, 1920, and on Nov. 11, 1923, blood cultures did not show growth). The basal metabolic rate was —12 per cent. Figure 11 shows the fever curve of this, the sixth, attack. Cultures made from the nodules on Nov. 11, 1923, were negative.

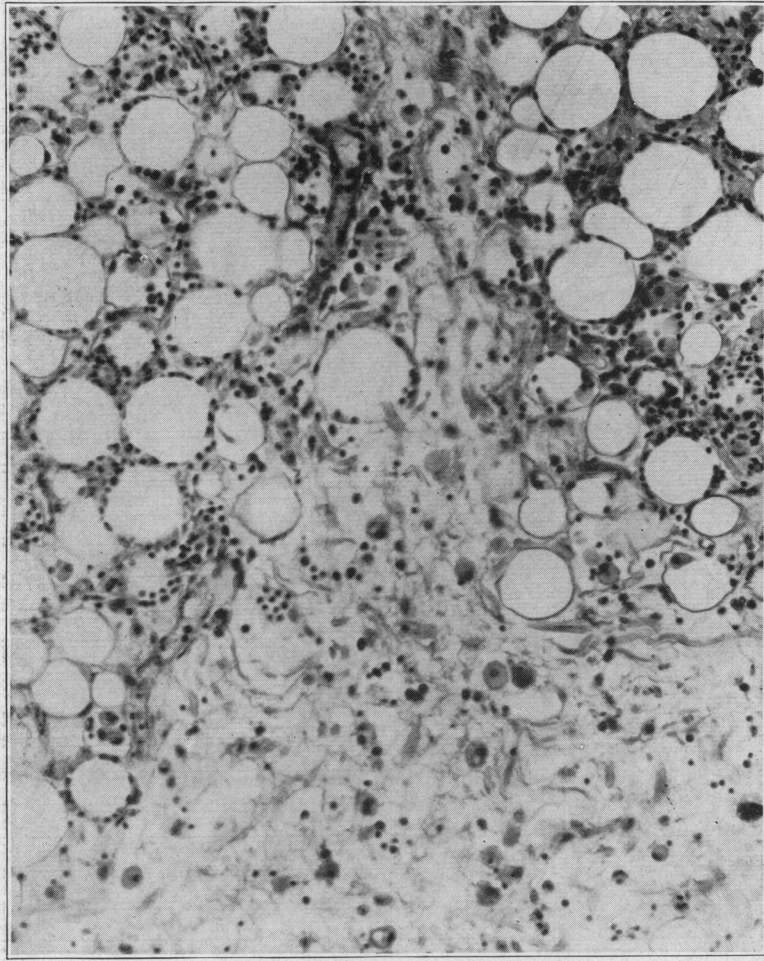


Fig. 5.—High power magnification, showing more macrophages and an area of edematous connective tissue.

*Clinical Observations.*—The skin condition (sixth attack) was described at the time by me as follows: "The striking thing, seen at first glance, are deep, irregular depressions in the cutaneous surfaces, distributed as will be described, not symmetrical in distribution and usually without color change in the skin (fig. 8). There is no local heat. The left lower leg shows, as the most striking phenomenon, an unsymmetrical contour due to irregular depressions with intervening slight

elevations, more marked between the middle of the tibia and the knee than below, and rather more marked on the external than on the internal surface. Over the region covered by the anterior surface of the tibia, just above the mid-point, there is a definite swelling with ill defined margins, measuring 5 by 7 cm., the middle slightly reddened, being a dull, pale red, that almost disappears under pressure, leaving a slightly pale brownish background. This area does not pit on pressure.

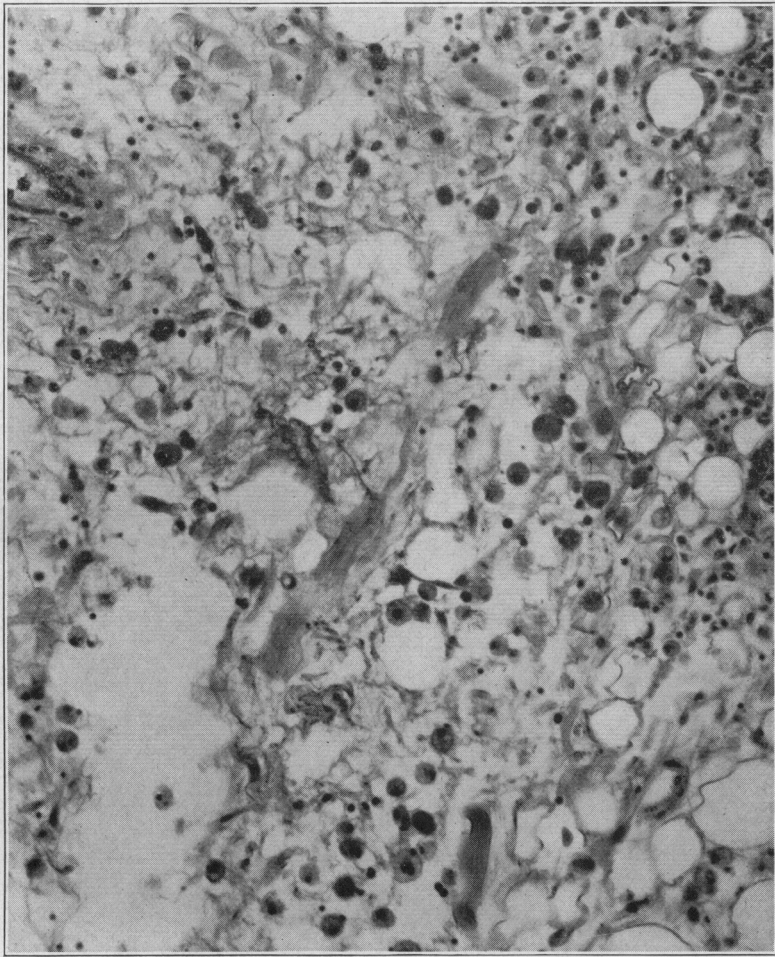


Fig. 6.—Similar to figure 5, with small area of necrotic fatty tissue at one margin.

On palpation this nodule of swelling is not of uniform consistency, but has slightly firmer portions with intervening softer portions, giving a vague sense of fluctuation. At the outer surface of this is a depression about 3 cm. in length by 2 cm. in width with indistinct margins, apparently the result of a loss of subcutaneous tissue. Just above the outer side of this depression is another slightly elevated

area about 2 cm. in diameter, rather firmer than the elevation first described. Like the first one, this is vaguely outlined, apparently shading off into surrounding normal tissue. Over these elevations the skin can not be picked up in folds as well as over the unaffected part, and much less well than over the depressed areas. The texture of the skin over all of these places seems normal, and there is no

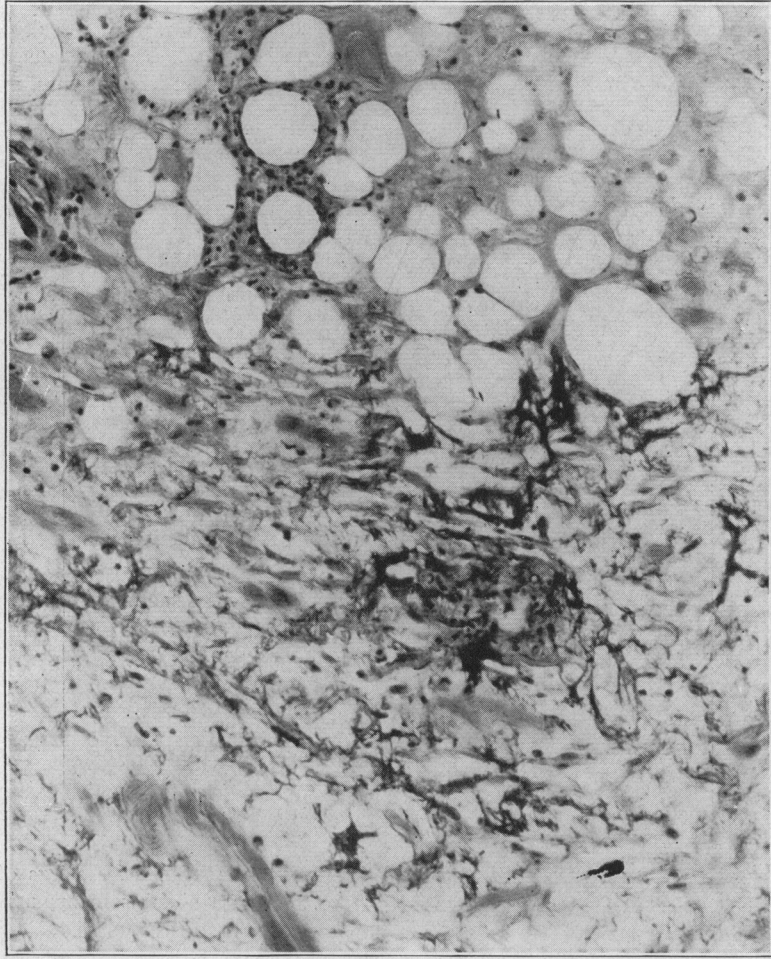


Fig. 7.—High power magnification, showing necrotic fatty tissue and an area with fibrin threads.

firm induration to be made out of either the swellings or the elevations. Over the lower half and outer surface of the leg, there seems to be considerable diffuse atrophy of the subcutaneous tissue, which leaves the surface depressed; the skin feels a trifle thickened, but may be picked up easily in folds. The skin here has a slightly brownish discoloration. This is one of the older lesions and represented at one time a diffuse uniform swelling.

"Just between these two areas, but more posteriorly on the leg, is the only lesion that has developed during this period of fever. It appeared on February 12, noticed at that time by the patient as a slight local discomfort, feeling somewhat tender and like a little nodule under the skin. This was very indistinct, and I was uncertain as to whether at this time I could make it out definitely. Two days later, there was a definite, though not very firm nodule at this point, apparently in the subcutaneous tissue, not more than 0.5 cm. in diameter. It subsequently has not increased in size. About the middle of the calf of this leg, there is a depression. Along the inner surface of the leg, there are irregularities of subcutaneous tissue, not visible swellings but areas which are felt as distinct irregularities, more

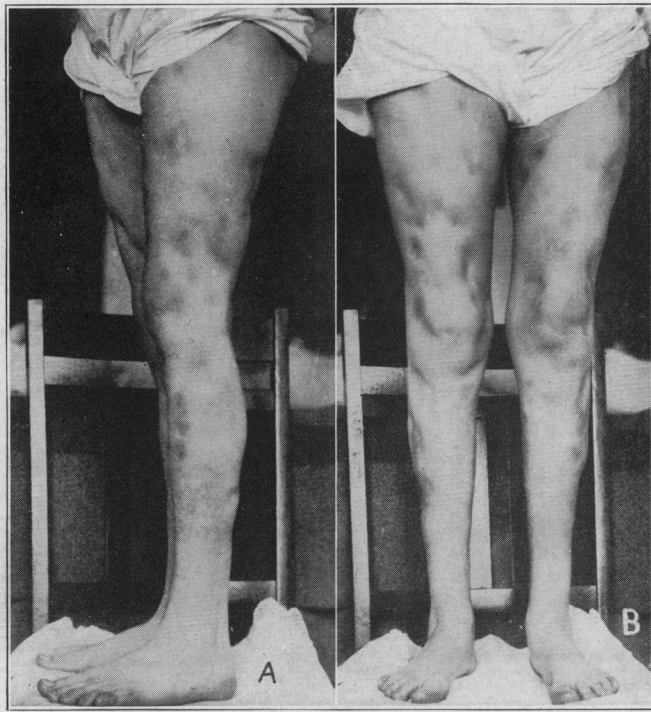


Fig. 8.—Deep irregular depressions in the cutaneous surface of the legs of a patient suffering from an attack of relapsing febrile nodular nonsuppurative panniculitis.

flattened than those already described, and feeling a bit as if the skin were attached slightly to them. To one's fingers, moving up and down the leg, they give the sensation of irregular, beaded or button-like masses not entirely separated from each other and extending in a linear arrangement. There are none of these on the dorsum or sole of the foot.

"The right leg shows a similar irregularity of contour, with depressions from 3 to 5 cm. in diameter, and intervening moderately elevated areas, as described for the other leg. Just as on the left leg, so on the posterior surface of the right leg there is a band or string of irregular nodules extending from a little below the

knee nearly to the ankle. None of these areas looks as red as those on the left leg, but the skin in places shows a slight redness and quite definite brownish discoloration. None of these masses seems attached to the deep fascia over the muscles, and they apparently are not attached to the muscles or tendons.

"On the upper right leg there are larger, similar depressions with intervening indefinite elevations. Just over the thigh region, a little anterior to the head of the femur, there are rather deep depressions. In between these are no definite nodules, but the subcutaneous tissue in places feels firmer than normal. The upper leg on the other side shows much the same picture.

"The right hand and forearm do not show any lesions. The left arm shows a depression on the forearm on the outer surface a little below the elbow. The upper right arm shows a scar slightly above the elbow where a nodule had been excised for examination, and just back of the deltoid muscle there is a very definite depression. Over the insertion of the deltoid there are vague swellings, but nowhere on the upper arm are these swellings definite or firm. The upper left arm is quite similar in general to the right. Just beneath the outer border of the left clavicle there is a deep depression, in which the subcutaneous tissue has entirely disappeared. Here the skin is not indurated, and no irregularity or thickening is felt. There have been no lesions on the neck, face or scalp. There are a scar and a depression from one of the early lesions over the middle of the left scapula. In the lower right axillary region there is a moderate depression. In the lumbar region, just over the lower right half, there is a depression 3 to 4 cm. in diameter, and at its lower border is a small, irregular nodule in the skin. On the abdomen are scattered irregular, smaller depressions with, in places, irregularities to be felt in the deeper subcutaneous tissue."

For two years the patient remained well, but in February, 1923, a seventh attack began with typical lumps developing on her legs. She kept at her work as a chemist until May 10, 1923, though during the latter part of the period she had a daily afternoon temperature of 100 F. On that date, her temperature rose to 103 F., and many new lumps appeared, chiefly on the legs, but also on the arms and back; nausea developed and she felt worn out. By June 1, this attack was over. On August 3, an eighth attack began, with many lumps and a rise of temperature to 102 F. This attack lasted two months, but thereafter the patient continued to feel bad and to ache as if she were going to have grip; her ankles felt tense, and at night were slightly swollen. I saw her again on November 7. The lesions on the skin were much as previously described; they felt firm and seemed to be in the subcutaneous tissue; they were not tender; the depressed areas were rather darkly pigmented. The ankles were red and tender, and the right felt brawny to the touch. The results of the general physical examination were negative. The blood showed: hemoglobin, 96 per cent; white cells, 3,800, and red cells, 4,992,000. The urine was normal. The patient gradually improved and was well until about the middle of July, 1924; then a ninth attack began, of the usual character and length.

After recovering from the ninth attack, the patient remained well until the latter part of November, 1927; then a tenth attack began. The character of this attack was much like that of the others and it lasted into January, 1928. Late in February, 1928, when well along in convalescence from her tenth attack, the patient developed acute appendicitis; she was operated on, and complications did not follow.

Weber's case, also that of a woman, aged 50, was observed in three attacks accompanied by fever. His description and the photomicrographs

in his report show that the conditions he observed were very similar to those observed in my case, except that the bit of tissue from his patient showed more multinuclear giant cells than that from mine. I find no other essential difference between his case and mine. Weber seems to have considered his case as possibly unique, though he believed that it should be regarded as allied to Whitfield's<sup>2</sup> type of erythema induratum.

In 1916, Gilchrist and Ketron,<sup>3</sup> under the title, "A Unique Case of Atrophy of the Fatty Layer of the Skin Preceded by the Ingestion of the Fat by Large Phagocytic Cells, Macrophages," described a girl aged 8 in Baltimore whose mother stated, in giving the child's history, that "she had had feverish attacks and loss of appetite on several occasions," and who showed changes in the legs (illustrated in the article by photographs) strikingly similar to those observed in Weber's patient and in mine. The 8 year old patient had slight fever while in the hospital. The changes were confined to the legs. Excised bits showed, on microscopic examination, appearances similar to those described by Weber and by me, changes confined to the subcutaneous fat. Looking at the illustrations and reading the descriptions of Gilchrist and Ketron, one can but feel that the condition is the same as that described by Weber and me. Weber used, too, in his title the words, "showing phagocytosis of fat cells by macrophages."

Warfield<sup>4</sup> has made a report of a condition under the descriptive title of "Multiple Symmetrical Gangrene of the Fat of the Abdominal Wall in a Case of Alcoholic Neuritis," which may be closely related to the disease here being described. Unfortunately, excised tissue was lost before histologic examination could be made. In Warfield's case, the subcutaneous tissue became gangrenous and the skin ulcerated; it did not in the three cases just reviewed, but there was the feature of indurated lesions in the panniculus, developing in succession.

In 1922, Lee and Adair<sup>5</sup> described a condition, unique in their opinion, under the title "Traumatic Fat Necrosis of the Breast," in which the tissue has some similarity in histology to the tissue from the cases under discussion here. They believed that in their patients trauma had been a causative factor, leading to necrosis of the fat tissue of the breast with subsequent cellular infiltration. Perhaps this condition bears some relation to the more generalized distribution of focal areas of inflammation of the subcutaneous fat described here.

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2. Whitfield: *Am. J. M. Sc.* **122**:828, 1901.

3. Gilchrist and Ketron: *Bull. Johns Hopkins Hosp.* **27**:291, 1916.

4. Warfield: *Ann. Clin. Med.* **5**:884, 1927.

5. Lee and Adair: *Surg. Gynec. Obst.* **34**:521, 1922.



The term panniculitis is used, too, in a somewhat different relationship, expressive of a form of chronic rheumatic disease. Stockman,<sup>6</sup> for example, has just published a paper under the title "Chronic Muscular Rheumatism and Panniculitis," in which he says:

Panniculitis is a fibrositis of the panniculus adiposus, and has the same etiology and pathology as fibrositis generally. Its anatomical distribution, however, confers on it certain clinical characteristics which merit some special description. The new fibrotic tissue assumes two forms, according to its situation. Over the deltoids, shoulders, back, flank, upper abdomen, hips, and outer sides of the thighs it is dense and evenly spread, giving the skin a hard brawny feel, while on the inner surfaces of the upper arms and thighs, abdomen, and pectoral regions it is in numerous pea-like masses lying in the subcutaneous fat and often forming veritable fibro-fatty pads at the inner sides of the knees and elsewhere. The little masses can be easily felt, and are exceedingly tender on pressure, as is likewise the whole subcutaneous overgrowth. Sometimes distinct encapsulated

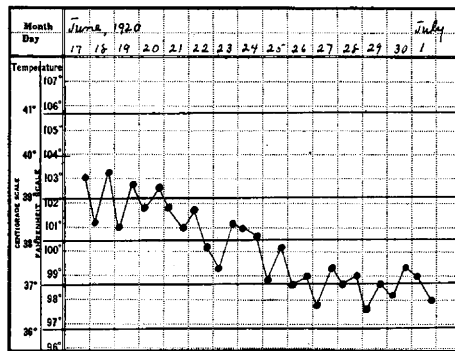


Fig. 9.—Temperature curve of the patient during the fourth attack of relapsing febrile nodular nonsuppurative panniculitis.

lipomata are found, and these have a core of inflamed fibrous tissue, as if the local irritation had determined their growth.

He regards this as an extremely common condition. The nodular form, as described by him, has some resemblance to the condition described in the present paper and conceivably might be a mild form of it. The exact relationship of Stockman's panniculitis to acute rheumatic fever is not very clear from his paper, though he seems to think that there is some relationship.

There is another condition that may be closely related to relapsing febrile nodular nonsuppurative panniculitis, which I have seen through the courtesy of colleagues at the New England Children's Hospital.<sup>7</sup>

6. Stockman: Brit. M. J. **1**:293, 1928.

7. Wilens, Gustav, and Derby, Joseph: Calcification of Subcutaneous Tissue in a Child (Calcinosis Universalis), Am. J. Dis. Child. **31**:34 (Jan.) 1926.

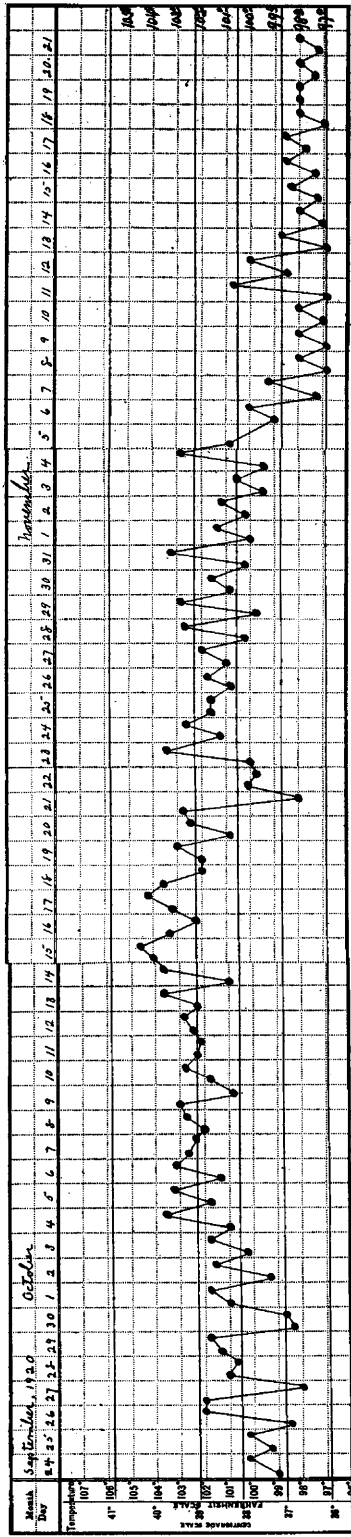


Fig. 10.—Temperature curve during the fifth attack.

In this condition areas of calcification occur in the subcutaneous fat, presumably following inflammation and necrosis. It is a question whether cases of this kind should be included. In certain respects, they seem unlike enough to be regarded, for the present at least, as of a different clinical entity. In some of the reported cases, in addition to calcification, there are changes in the tissue suggestive of those described in this paper.

The fever and relapses suggest that the condition here being reported may be a manifestation of undulant fever (infection with organisms of the mellitensis abortus group. But cultures in my case were negative, and there was no opportunity at the time of observation to test the serum for immunity reactions to fit such a hypothesis.

Possibly a more diligent search of the literature would reveal the fact that other patients have suffered from the disease represented by

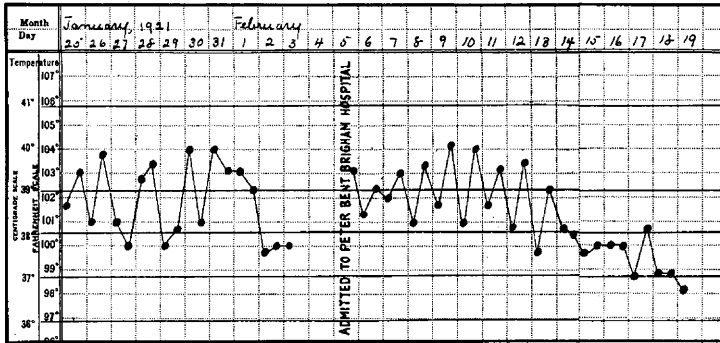


Fig. 11.—Temperature curve during the sixth attack.

the three cases of Gilchrist and Ketron, Weber, and myself. It seems to be a reasonably definite clinical entity, possibly a syndrome, rather than a disease. The severity of symptoms with fever during attacks and their repetition again and again are most notable.

#### SUMMARY

There is a disease characterized by recurring attacks of fever, associated with a peculiar nodular inflammation of the subcutaneous tissue. Some of the fatty tissue necroses, and much of it becomes infiltrated with lymphoid and plasma cells. Macrophages take up fat in fine droplets. A few foreign body giant cells form. There results in time atrophy of the inflammatory nodule causing a depression in the contour of the skin. Suppuration does not occur, and the continuity of the skin is unbroken. The cause of the disease is unknown. The term "relapsing febrile nodular nonsuppurative panniculitis" is descriptive of the condition.