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SARCOIDOSIS, PSORIASIS, AND GOUT: SYNDROME OR COINCIDENCE?†

In the past year we have encountered three patients with coexistent sarcoidosis, psoriasis, and gout. Each of the patients exhibited the classical clinical features of all three diseases, and in each the diagnosis of sarcoidosis and psoriasis was confirmed histologically.

It is interesting to note that the skin lesion described by Jonathan Hutchinson in 1877,[1] and generally considered to be the first recorded instance of sarcoidosis, occurred in an elderly gentleman with gout. In a later report[2a] Hutchinson recalled this patient with the remark; "I was inclined to consider the skin-disease as essentially connected with the gout." At the same time he described a second case with the two diseases.[2b] To our knowledge no other authors have commented on the association between sarcoidosis and gout, and none has reported a case of coexistent sarcoidosis, psoriasis and gout.

Obviously the occurrence of three apparently unrelated but relatively common diseases in the same individual suggests a coincidence. However, the discovery in a one-year period of three patients with the triad prompted us to investigate the possibility of an interrelationship between these three diseases. To that end the clinical records of patients with well-documented sarcoidosis, gout or psoriasis were reviewed for evidence of any combination of those diseases. In addition, the serum uric acid levels were determined in two groups of patients with sarcoidosis and psoriasis, respectively.

The results of these studies, taken together with certain evidence culled from the literature, suggest that the coexistence of sarcoidosis, psoriasis, and gout may be indicative of some as yet obscure relationship among these diseases.

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CASE REPORTS

Case 1 (48-85-89). L. B., a 41-year-old white salesman, was admitted to the Grace-New Haven Community Hospital in April 1958 because of recurrent pain in the ankles and toes.

In 1950 there was a sudden onset of severe pain in the metatarsophalangeal joint of the right great toe, which subsequently became swollen, exquisitely tender and warm. A blood uric acid was said to be high, leading to the diagnosis of gout. The joint pain responded to colchicine, but recurred at six-month intervals initially, and then almost monthly. Benemid had been tried for one or two months on two occasions, but had had no effect on the frequency or severity of the attacks. A serum uric acid early in 1958 was 8.5 mg. per cent.

Since his early twenties the patient had been afflicted with psoriasis, which had appeared first on the scalp and legs, and had then gradually progressed to involve the arms, abdomen, sacrum, and groin. Many forms of topical therapy had proved ineffective.

Although the patient had never had any symptoms of cardio-respiratory disease, a routine roentgenogram of the chest in 1954 had shown a pulmonary lesion interpreted as silicosis.

There was no family history of arthritis or skin disease.

Physical examination revealed a moderately obese man who did not appear ill. Blood pressure was 140/100. Large, well-circumscribed, erythematous patches with silvery scales, considered typical of psoriasis, were present over the scalp, abdomen, groin, sacrum, and extensor surfaces of all four extremities. The lacrimal and parotid glands were not enlarged. The corneas and fundi were normal. There was no lymphadenopathy. Breath sounds were increased over both lung fields. The heart was normal in all respects. Neither the liver nor the spleen was palpable. Slight erythema and tenderness to compression were present over the right ankle. There were no other deformities of the bones or joints, and there were no tophi present.

Urinalysis, hematocrit, leukocyte and differential counts were normal. The NPN was 35 mg. per cent; the serum proteins totaled 7.83 gm. per cent, with 3.41 gm. per cent of albumin and 4.42 gm. per cent of globulin. The serum calcium was 10.2 mg. per cent, serum inorganic phosphorus 3.6 mg. per cent. The serum uric acid concentration on two occasions was 11.4 and 10.8 mg. per cent, respectively. Liver function studies revealed a serum bilirubin level of 1.18 mg. per cent, with a direct-reacting fraction of 0.41 mg. per cent; bromsulphalein retention at 45 minutes, 17.8 per cent; cephalin-cholesterol flocculation, 2+ in 24 and 48 hours; thymol-turbidity, 10.7 units; thymol flocculation, 4+; serum alkaline phosphatase, 14.2 units by the Shinowara-Jones-Reinhart modification of the Bodansky method; serum glutamic-oxalacetic transaminase, 32 units. Phenolsulfonphthalein excretion was normal as was the electrocardiogram.

X-ray examination of the chest revealed marked linear and nodular infiltration in both lung fields, most marked in the upper lobes, without evidence of hilar adenopathy. The bones of the hands and feet were normal, and there were no esophageal varices demonstrable radiographically. Pulmonary function tests revealed a low residual volume, hyperventilation, and an increase in the alveolar-arterial gradient to 18.8 mm. of mercury. First and second strength intracutaneous tuberculin (PPD) tests were negative.

The psoriasis responded to coal tar ointment and ultra-violet light therapy. A course of Benemid was prescribed, and the patient was discharged from the hospital.

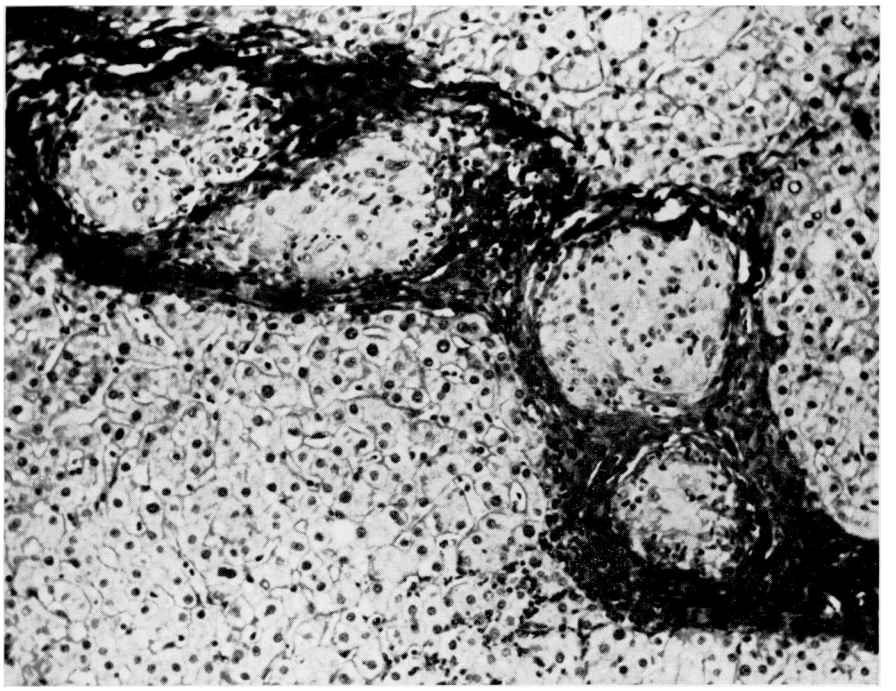

FIG. 1. Case 1. Liver biopsy specimen showing numerous noncaseating granulomata containing epithelioid and giant cells surrounded by dense collagen bundles. Masson stain, original magnification x120.

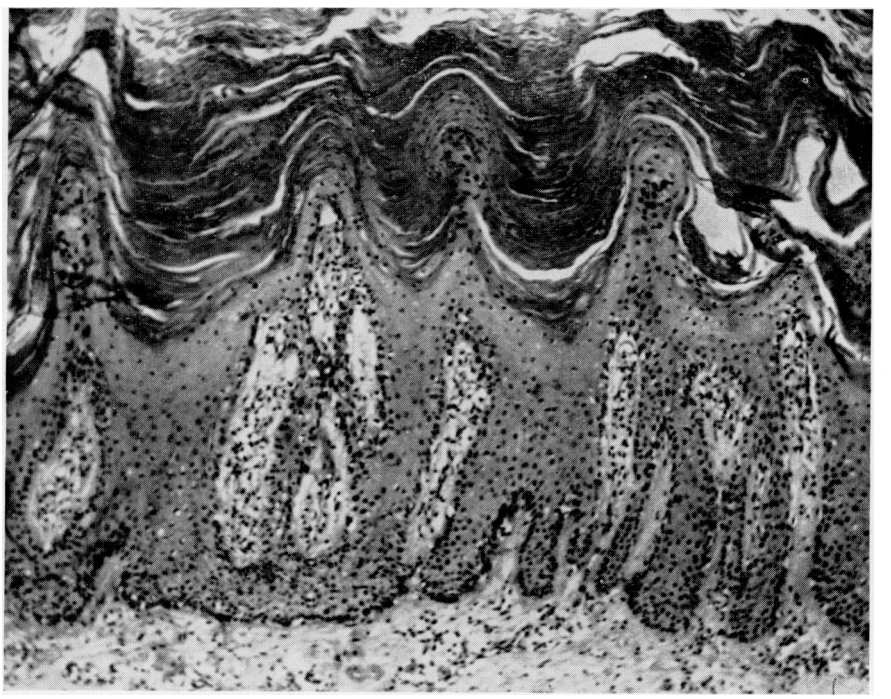

FIG. 2. Case 1. Skin biopsy specimen showing parakeratosis, elongation of the epidermal pegs with thinning of the overlying epidermis, elongation of the dermal papillae with dilatation of the capillaries, and an inflammatory reaction in the dermis, features considered typical of psoriasis. Hematoxylin and eosin stain, original magnification x60.

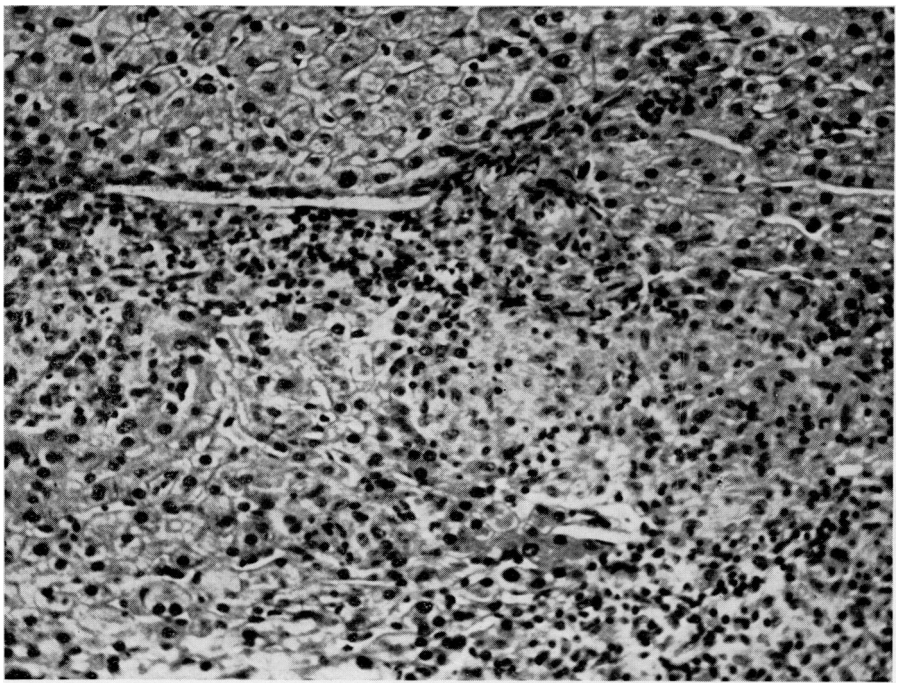

FIG. 3. Case 2. Liver biopsy specimen showing a paracentral granuloma made up of epithelioid and occasional giant cells, surrounded by a thin rim of lymphocytes. Masson stain, original magnification x120.

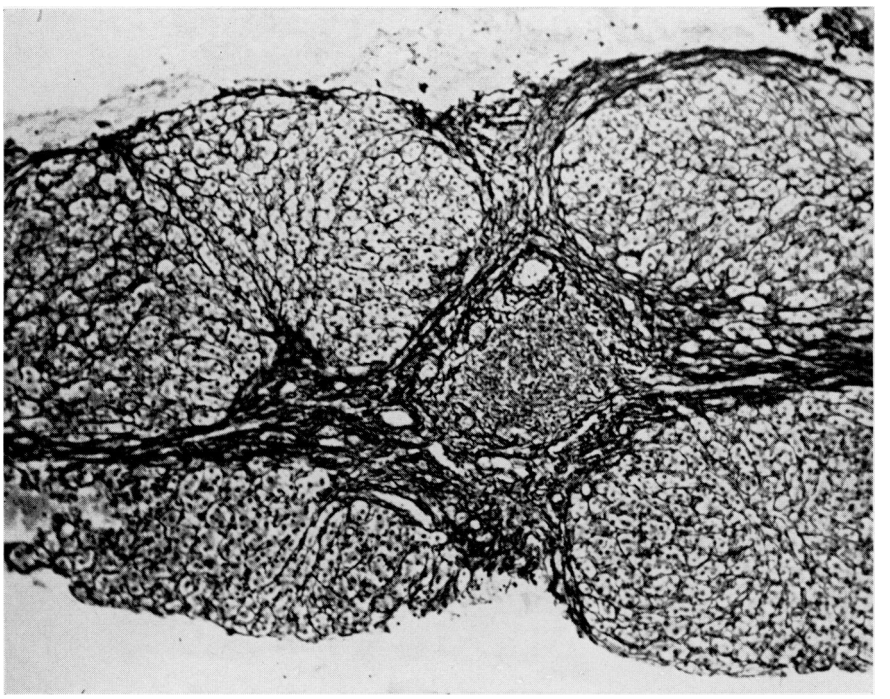

FIG. 4. Case 3. Liver biopsy specimen showing diffuse fibrosis and pseudolobule formation. In the center is a circumscribed compact mass of large monocytes, suggestive but not typical of epithelioid cells, with a paucity of reticulum fibers. Laidlaw reticulum stain, original magnification x60.

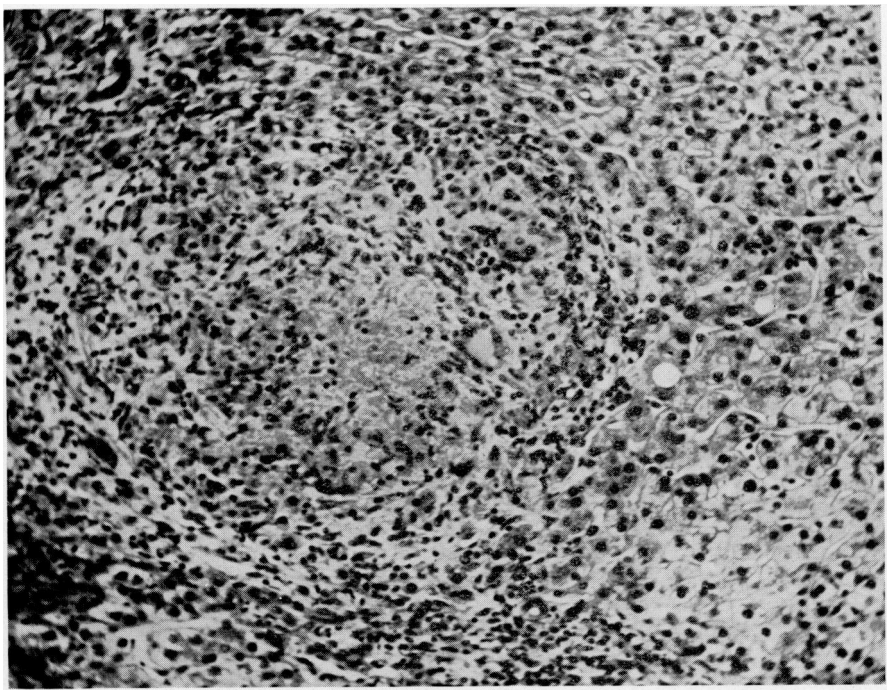

FIG. 5. Case 3. Liver biopsy specimen showing a circumscribed periportal granuloma made up of epithelioid and giant cells with a small central zone of eosinophilic necrosis and a thin rim of lymphocytes. Masson stain, original magnification x120.

One month later the patient was readmitted for a liver biopsy to establish whether or not he had sarcoidosis. He had had no joint pains since discharge, and the skin was much improved. The only new finding was parotid enlargement. The white blood cell count was 7.150 per cu. mm., with 19 per cent eosinophils. Serum calcium was 11.7 mg. per cent, while the serum inorganic phosphorus was 2.9 mg. per cent. Liver function tests and x-ray examination of the chest showed no change. A needle biopsy specimen of the liver revealed relatively normal parenchyma with numerous granulomata (Fig. 1), consisting of compact masses of epithelioid and giant cells, considered compatible with sarcoidosis. Many of the granulomata were confluent and were surrounded by collagen fibers which formed septa distorting the normal lobular architecture. In some areas the parenchyma was arranged in a nodular pattern, suggesting an early cirrhosis of granulomatous origin.

The patient was started on prednisone, 15 mg. daily, before his discharge from the hospital and was advised to continue his Benemid therapy as before.

In January 1959, eight months after starting steroid therapy, he was readmitted because of an exacerbation of his psoriasis. He had had no recurrence of gout since the institution of prednisone and Benemid therapy nine months previously. The only new finding was the presence of a palpable epitrochlear node on the right. Liver function studies showed some evidence of improvement in that bromsulphalein retention had dropped to 6.9 per cent, the cephalin-cholesterol flocculation test had become negative, and the serum alkaline phosphatase had fallen to 10.0 units. X-ray examination of the chest revealed no significant change, but pulmonary function studies showed some improvement. Again the psoriasis responded to treatment with coal tar ointment and ultra-violet light. Because of the apparent improvement in hepatic and pulmonary function, the dose of prednisone was slowly tapered.

When last seen in May 1959, the patient was taking 7.5 mg. of prednisone daily and was asymptomatic with respect to his sarcoidosis and gout; however, his psoriasis had recently flared up. Serum uric acid at this time was 4.7 per cent, and the results of liver function tests were essentially unchanged from those obtained six months previously. A biopsy specimen of the skin revealed the characteristic features of psoriasis (Fig. 2). Repeat biopsy of the liver showed essentially the same changes noted 11 months earlier, except that many of the granulomata had undergone hyalinization.

Comment. This patient had extensive psoriasis for a period of ten years, following which he developed classical, but apparently nonfamilial gout. Four years later, a routine roentgenogram of the chest disclosed the presence of asymptomatic pulmonary sarcoidosis. The possibility that the actual onset of sarcoidosis antedated the appearance of psoriasis or gout cannot be excluded, since the age of the pulmonary lesions at the time of their discovery could not be estimated. Similarly, the possibility that hyperuricemia was present before either of the other diseases had appeared cannot be discounted. Accordingly, no conclusions are warranted regarding the precise sequence in which these diseases developed.

Case 2 (C44116). C. D., a 51-year-old white university professor, was seen in February 1959, complaining of shortness of breath.

The patient had previously been admitted to the Ophthalmology Service of the Grace-New Haven Community Hospital in July 1950 because of pain in the eyes and blurring of vision bilaterally. He had had an attack of erythema nodosum one month previously. Physical examination revealed bilateral iridocyclitis. No lymphadenopathy, skin lesions, or enlargment of the salivary glands was noted. The lungs were clear, and the heart was normal except for a grade one apical systolic murmur. A soft liver edge was palpable two fingerbreadths below the right costal margin, but there was no splenomegaly. Hemogram, urinalysis, and NPN were normal. X-ray examination of the chest revealed minimal bilateral pulmonary emphysema and bilateral hilar adenopathy. A tentative diagnosis of sarcoidosis was made, following which oral cortisone was administered for a period of ten days resulting in improvement in the eye symptoms.

Two months later the patient developed bilateral secondary glaucoma, necessitating his readmission for iridectomy.

One year later, in June, 1951, he was admitted to the Medical Service because of a recurrence of his uveitis, and the appearance of a nonproductive cough associated with generalized myalgia and arthralgia. Except for the signs of bilateral uveitis and the previously described slight hepatomegaly, physical examination revealed no abnormalities. The leukocytes numbered 4,200 per cu. mm. with a normal differential count. The results of liver function tests, including serum bilirubin, bromsulphalein retention, cephalin-cholesterol flocculation, thymol-turbidity and serum alkaline phosphatase, were all normal. Serum proteins totaled 6.53 gm. per cent, with 3.38 gm. per cent of albumin and 3.15 gm. per cent of globulin. The serum concentrations of calcium and inorganic phosphorus were 10.5 and 3.9 mg. per cent, respectively. Tuberculin (PPD, first and second strengths), coccidioidin and histoplasmin skin tests, and a brucella agglutination test were all negative. Gastric aspirate inoculated into a guinea pig was negative for tubercle bacilli. X-ray examination of the chest showed bilateral hilar adenopathy without evidence of pulmonary infiltration. A needle biopsy specimen of the liver revealed numerous noncaseating granulomata composed of compact aggregates of epithelioid cells and a few giant cells (Fig. 3). Acid-fast stains for tubercle bacilli were negative. These findings were considered compatible with the clinical diagnosis of sarcoidosis. An eight-day course of intravenous ACTH resulted in a remission of the ocular symptoms, which have not recurred in eight years.

In 1955, five years after the onset of his sarcoidosis, the patient noted the insidious onset of dyspnea on exertion. Shortly thereafter, a roentgenogram of the chest revealed bilateral pulmonary infiltrates indicating extension of the sarcoidosis to the lungs. Over the succeeding three years the pulmonary lesions increased, but there was little change in the severity of the respiratory symptoms until late in 1958 when dyspnea increased rapidly and became disabling.

In June 1956 the patient was awakened one night by a severe pain in the metatarsophalangeal joint of the right great toe, which became red and hot, and swelled to twice normal size. The erythema about the base of the toe extended to the entire dorsum of the foot. Colchicine was administered by his personal physician, resulting in prompt relief. Unfortunately, the blood level of uric acid was not determined at this time, and subsequent x-ray examination of the toe revealed no abnormalities.

Two years later, in July 1958, the patient was again awakened by similar pain in the right great toe and obtained prompt relief with colchicine. Between 1957 and 1959 he experienced several episodes of pain and swelling of the knees, without associated redness or heat, of approximately two weeks' duration each. Colchicine was not tried

because the patient did not regard these as attacks of gout. However, small doses of salicylate afforded some relief.

Typical psoriatic lesions made their appearance in December 1958. Well-circumscribed, erythematous, oval patches covered with silvery scales were noted first on the flexor surface of the right forearm, and then over the elbows, calves, and scalp.

There was no family history of arthritis or skin disease.

Physical examination in February 1959 revealed a husky middle-aged man who did not appear ill. There were typical psoriatic patches over the scalp, both elbows, and both calves. Keyhole postoperative deformities of both pupils were present, but there were no signs of active uveitis or conjunctivitis. The parotid and lacrimal glands were not enlarged, and there was no evidence of lymphadenopathy. The lungs were clear. The heart was of normal size, had a normal rhythm, except for occasional runs of tachycardia, and showed a loud blowing precordial systolic murmur which radiated to the neck, axilla, and back. The liver edge was felt at the right costal margin, but the spleen was not palpable. The right knee was slightly swollen, but contained no obvious fluid, and was not tender. The toes were normal and there were no tophi.

The volume of packed red cells was normal. Leukocytes numbered 3,400 per cu. mm. with 12 per cent eosinophils. The urine contained a trace of albumin, but was otherwise normal. The NPN was 41 mg. per cent, and phenolsulfonphthalein excretion was normal. The serum uric acid concentration was 4.2 mg. per cent. The levels of serum calcium and inorganic phosphorus were 10.0 and 3.3 mg. per cent, respectively. Serum proteins totaled 7.54 gm. per cent, with 3.44 gm. per cent of albumin and 4.10 gm. per cent of globulin. Liver function tests revealed the following: serum bilirubin, direct-reacting, 0.25 mg. per cent, total, 1.2 mg. per cent; bromsulphalein retention at 45 minutes, 18 per cent; cephalin-cholesterol flocculation negative; serum alkaline phosphatase, 1.8 S—J—R units; serum glutamic-oxalacetic transaminase, 38 units; serum lipids, normal. A study of pulmonary function demonstrated a low residual volume and a high alveolar-arterial oxygen gradient. An intracutaneous tuberculin test (second strength PPD) was negative. X-ray examination of the chest revealed bilateral hilar adenopathy and marked fibrosis of both upper lobes. The histological features of a skin biopsy specimen were consistent with the diagnosis of psoriasis.

Because of the impaired pulmonary function, the patient was started on prednisone, 60 mg. daily. After one month of therapy his respiratory symptoms were mueh improved, and there was a concomitant increase in the maximum breathing capacity from 69.7 to 81.6 liters per minute.

Comment. In this case sarcoidosis was clearly the first of the triad of diseases to appear. This was intermittently active and slowly progressive over a period of six years, affecting the eyes, lungs, hilar nodes, and liver, following which attacks of acute gout developed. Two years later, coincident with a rather sudden increase in pulmonary symptoms, presumably due to rapid spread of the granulomatous process in the lung, psoriatic lesions appeared. It is noteworthy that, as in Case 1, there was no family history of gout. However, the clinical features and prompt response to colchicine were typical of the disease. The normal blood uric acid level observed during a symptom-free period was not considered sufficient evidence to exclude the diagnosis of gout, since normal values are known to

occur occasionally.[3] Whether the attacks of painful swelling of the knees were gouty in nature, or were manifestations of the nonspecific arthritis sometimes seen in sarcoidosis,[4] is uncertain.

Case 3 (36-95-75). J. M., a 59-year-old negress, was admitted to the Grace-New Haven Community Hospital in March 1959 complaining of painful calves.

In November 1954 the patient was seen in the Dermatology Clinic because of the recent development of scattered pruritic and lichenified patches on the calves, thighs, and arms. Three months later, new lesions appeared on both elbows and, over the next year, these spread to involve the entire body, except for the palms and soles. In addition to being lichenified, the lesions were covered with silvery scales suggesting psoriasis.

In February 1956 the patient had the first of many hospitalizations for treatment of her skin condition. At this time the liver was found to be palpable two fingerbreadths below the right costal margin. Liver function tests, including serum bilirubin, cephalin-cholesterol flocculation, thymol turbidity, and serum alkaline phosphatase, yielded normal results except for a bromsulphalein retention of 21 per cent at 45 minutes. The NPN and the serum proteins, calcium, and inorganic phosphorus also were normal. X-ray examination of the chest revealed no abnormalities.

The pruritus abated following a week of oral prednisone but returned when treatment was stopped. The skin lesions showed no change and were unaffected by topical therapy of several types.

In March 1957 biopsy of the skin revealed histological features considered typical of psoriasis. Serum proteins at this time totaled 7.36 gm. per cent, with 2.27 gm. per cent of albumin and 5.09 gm. per cent of globulin.

During the succeeding two years the skin showed little change except for transient improvement following a course of oral prednisone, ultraviolet radiation, and topical coal tar ointment.

In September 1958 the patient had an attack of thrombophlebitis. This recurred in March 1959, necessitating hospitalization. Because of the incidental finding of the previously noted hepatomegaly and bromsulphalein retention, which were still evident, we were asked to see the patient in consultation. Review of her history revealed additional points of interest not previously noted. For a number of years starting in childhood the patient had had recurrent attacks of left-sided renal colic and hematuria, and had been relieved of these symptoms following a nephrectomy with the removal of renal calculi. Nine years previously, at the age of 50, she had had a panhysterectomy because of recurrent spontaneous abortions. A year later, in 1951, she had had her first attack of what was almost certainly acute gout, although the diagnosis had never been suggested. Following this the attacks had recurred several times a year. Typically they began abruptly with a gnawing pain in the metatarsophalangeal joint of the right great toe, which then increased in intensity and was followed by swelling, redness, and exquisite tenderness. Usually the attack lasted for about a week during which time the patient could not wear a shoe, bear the weight of her bedclothes, or get around without crutches. Salicylates in small doses provided slight and only temporary relief. She had never tried colchicine. In addition to her attacks of acute gout, the patient had been troubled for a period of four years with a chronic migratory arthritis of the knees, elbows, wrists, and interphalangeal joints. This was characterized by dull pain, occasionally accompanied by swelling. During the past three years the patient had also had attacks of pain in both eyes accompanied by tearing bilaterally, and by blurring

of vision on the right. These episodes had occurred approximately twice yearly and had lasted up to a week.

There was no family history of arthritis or skin disease. The patient had never used alcohol to excess, and her diet had been adequate.

Physical examination revealed an obese negress who did not appear ill. Her blood pressure was 180/90. The skin lesions were as previously described. On both sides the lacrimal glands were greatly enlarged. The corneas and fundi were normal, and, on slit-lamp examination, no evidence of recent or old uveitis was noted. The parotids were not enlarged, and there was no lymphadenopathy. The lungs were clear. The heart was normal except for a rate of 102 per minute. A firm, round, slightly tender liver edge was palpable three fingerbreadths below the right costal margin in the midclavicular line. The spleen was not felt. There was tenderness to palpation, increased heat, and slight swelling over both calves. Except for bilateral Heberden's nodes, the joints appeared normal. There were no tophi.

Urinalysis, the NPN, and phenolsulfonphthalein excretion were normal. Leukocytes numbered only 3,800 per cu. mm., but the differential count was normal. The concentrations of serum calcium and inorganic phosphorus were 11.9 and 4.9 mg. per cent, respectively. Serum proteins totaled 7.61 gm. per cent, with 2.79 gm. per cent of albumin and 4.82 gm. per cent of globulin. Liver function studies showed the following: serum bilirubin, direct-reacting, 0.70 mg. per cent, total, 1.4 mg. per cent; bromsulphalein retention at 45 minutes, 2.3 per cent; cephalin-cholesterol flocculation, negative at 24 and 48 hours; thymol turbidity, 4.3 units; serum alkaline phosphatase, 7.5 S—J—R units; serum glutamic-oxalacetic transaminase, 59 units. The sensitized sheep-cell test for serum rheumatoid factor was negative. Test for brucella agglutinins was negative. An intracutaneous tuberculin test with PPD was negative in the first strength and positive in the second strength. Culture of gastric aspirate for tubercle bacilli was negative. Studies of pulmonary function revealed no abnormalities. A roentgenogram of the chest was normal except for left ventricular enlargement. X-ray studies of the knees showed minimal osteoarthritic changes bilaterally, and those of the hands and feet only early osteoporosis. A roentgenogram of the abdomen did not demonstrate calcification in the region of the remaining kidney.

Needle biopsy of the liver (Fig. 4) revealed diffuse portal fibrosis with pseudolobule formation. Some of the connective tissue septa contained numerous lymphocytes and circumscribed collections of large monocytes containing abundant cytoplasm and large nuclei. In one periportal area there was a large granuloma made up of a compact mass of epithelioid and giant cells, in the center of which there was a small zone of eosinophilic necrosis (Fig. 5). An acid-fast stain of several sections failed to demonstrate tubercle bacilli. The histological picture was considered consistent with a granulomatous cirrhosis due to sarcoidosis.

Comment. As a result of our experience with Cases 1 and 2, the association of psoriasis with joint symptoms suggested the possibility that the patient had gout and that her hepatomegaly was due to sarcoidosis, diagnoses that had not been considered previously and that were ultimately confirmed.

Both the history and the hyperuricemia were consistent with gout. As in the previous two cases, there was no family history of the disease. Although gout is rare in negro females, it has been reported by others.[5,6] It

may be of significance that the gout appeared shortly after panhysterectomy, since the occurrence of gout in women is more common after the menopause.[7] Conceivably, the two episodes of thrombophlebitis also were related to the gout in view of previous reports of this association.[8]

The diagnosis of sarcoidosis was based on the biopsy findings in the liver and was supported by the presence of enlarged lacrimal glands, the suggestive history of uveitis, the patient's race and birthplace in the rural Southeast, and the finding of hyperglobulinemia and hypercalcemia. Conceivably, the renal calculi present earlier in life were also related to her sarcoidosis. Although the predominence of granulomatous lesions in the liver with the production of a cirrhotic picture is unusual in sarcoidosis, one of us (GK) has reported one such case[9] and has seen several others.

It is reasonably clear that the gout antedated the psoriasis by three years. Hepatomegaly, later shown to be due to sarcoidosis, was not discovered until two years later. However, it is not known when the hepatomegaly developed, since there is no record of a prior abdominal examination. The history of renal calculi very early in life, taken together with the later finding of slight hypercalcemia, suggests that sarcoidosis could have been present in childhood. Also consistent with the hypothesis that the disease was of very long standing was the advanced degree of fibrosis of apparent granulomatous origin found in the liver.

OBSERVATIONS

In a search for possible interrelationships between sarcoidosis, psoriasis, and gout, the clinical records of patients previously hospitalized with each of these diseases were reviewed for evidence of the coexistence of the others. Included were 73 successive cases of histologically confirmed sarcoidosis, and 100 random selected cases each of well-documented psoriasis and gout. In looking for evidence of sarcoidosis in the latter two groups, particular attention was paid to the condition of the skin and the eyes, the size of the lymph nodes, liver, and spleen, the x-ray findings in the chest, the levels of serum globulin, calcium and alkaline phosphatase, and any history of antecedent ocular inflammation or salivary gland enlargement.

In addition, 25 of the sarcoidosis cases and 45 of the psoriasis cases were re-investigated for hyperuricemia, employing the Brown modification[10] of the Folin method for uric acid. Serum concentrations in excess of 6.0 mg. per cent in males and 5.0 mg. per cent in females are considered abnormal in this laboratory.

Sarcoidosis. None of the 73 patients with sarcoidosis exhibited psoriasis or the features of classical gout. However, six of the 25 whose blood uric

TABLE 1. OBSERVATION ON 73 CASES OF SARCOIDOSIS (EXCLUSIVE OF THREE PATIENTS WITH COEXISTENT PSORIASIS AND GOUT)

Case no.	*Sex*	*Serum uric acid (mg.%)*	*NPN (mg.%)*	*PSP excretion (%)*	*Serum Ca (mg.%)*	*Serum P (mg.%)*	*Joint symptoms*	*Skin lesions*
1	M	*7.8**	*53*	..	9.4	4.4	+	Seborrheic dermatitis
2	M	*7.4*	16**	..	9.9	3.0	0	0
3	F	*6.9*	30	57	9.4	2.7	+	0
4	F	*6.3*	30	..	9.8	4.7	0	0
5	F	*5.5*	39	54	*13.8*	3.2	0	0
6	F	*5.4*	36	..	9.0	4.1	0	0
7	M	5.7	32	..	*11.6*	3.6	0	0
8	M	5.7	19**	..	10.5	4.5	0	0
9	M	5.6	27	..	10.3	3.6	0	0
10	M	5.4	10**	..	11.1	2.3	0	Seborrheic dermatitis
11	F	5.0	11**	..	...	..	0	0
12	F	5.0	25	..	10.4	4.7	0	0
13	F	4.7	32	..	9.4	4.3	0	0
14	F	4.6	30	..	9.7	3.7	+	Seborrheic dermatitis
15	F	4.6	30	..	10.2	5.0	0	0
16	F	4.4	37	..	10.2	3.6	+	0
17	F	4.4	33	..	*11.4*	4.3	+	0
18	F	4.4	12**	..	9.9	2.7	0	0
19	M	4.3	31	..	10.5	2.7	0	0
20	M	4.0	35	..	10.2	3.4	0	0
21	M	4.0	*7**	..	10.2	4.5	0	0
22	F	3.9	40	..	10.0	3.3	0	Sarcoidosis
23	M	3.7	30	..	10.3	3.0	0	0
24	M	3.7	27	..	9.0	4.5	0	0
25	F	3.3	27	..	...	..	0	0
26	M	..	30	..	9.5	3.4	0	Lichen planus
27	M	..	33	..	9.4	4.4	+	0
28	F	..	27	..	...	..	+	0
29	M	..	28	..	9.9	2.8	+	0
30	F	..	23	..	10.2	3.6	+	Sarcoidosis
31-73	M,F	..	..	..	...	..	0	Seborrheic dermatitis (1) Vitiligo (1) Acne rosacea (1) Dermatitis, type ? (1)

* Abnormal values italicized.

** BUN.

acid was determined had hyperuricemia (Table 1). In only one of these (No. 1) was there azotemia. Another (No. 5) had hypercalcemia, but renal function was unimpaired. Hence, 20 per cent of the group tested had an otherwise unexplained elevation of serum uric acid, an incidence considerably higher than that previously reported in nongouty individuals.[7, 11]

Migratory joint pain, often accompanied by swelling, was reported as a significant symptom in nine of the 73 cases investigated. Two of these (No. 1 and 2) had hyperuricemia, but the character of the joint manifestations did not suggest gout in either. In No. 1, the sensitized sheep-cell test for rheumatoid arthritis was positive, while in the remaining cases the joint symptoms were interpreted as manifestations of the sarcoidosis.

Psoriasis. In reviewing the records of 100 cases of psoriasis, no unequivocal instances of coexistent sarcoidosis or gout were encountered. However, there was suggestive evidence of these diseases in several (Table 2).

Sixteen of the group had arthritis. Although the latter was not typical of gout in any, in Case 9 it was accompanied by a hyperuricemia of 6.8 mg. per cent, and in Case 26 it began acutely in one of the great toes, although subsequently other joints were affected, and the serum uric acid was found to be normal. Ten of the remaining 14 patients with joint symptoms had what was regarded as classical rheumatoid arthritis.

Although the diagnosis of sarcoidosis was not established in any of the group, 11 patients exhibited roentgenographic signs of otherwise unexplained pulmonary fibrosis, significant hyperglobulinemia, hepatomegaly, or splenomegaly, either alone or in combination (Table 2). Case 15 was of particular interest in that the patient had psoriasis, slight hyperuricemia, pulmonary fibrosis, recurrent corneal ulcers, marked hyperglobulinemia (5.08 gm. per cent), and, on two occasions, was found to have small hepatic granulomata in needle biopsy specimens. Sarcoidosis was considered a distinct possibility, but the hepatic granulomata were deemed too small to warrant an unequivocal diagnosis. Liver biopsy in three of the other patients with hepatomegaly failed to reveal granulomas. In the remaining cases with hepatomegaly, hyperglobulinemia, or pulmonary fibrosis the possibility of sarcoidosis had not been considered, and, hence, had not been investigated.

Eighteen of the 47 patients with psoriasis whose blood uric acid was determined were found to have hyperuricemia (Table 2). Renal function was impaired in Cases 10 and 13, and was not investigated in five others, but was normal in the remainder, so that in at least 20 per cent of the group the hyperuricemia was otherwise unexplained.

TABLE 2. OBSERVATIONS ON 100 CASES OF PSORIASIS (EXCLUSIVE OF THREE CASES WITH COEXISTENT SARCOIDOSIS AND GOUT)

Case no.	Sex	Serum uric acid (mg.%)	NPN (mg.%)	Arthritis	Chest x-ray	Hepatomegaly	Splenomegaly	Eye signs	Serum proteins (gm.%)		
									Total	Alb	Glob
1	M	*10.1*	40	0	..	0	0	0	N**	N	N
2	M	*8.0*	28	0	Neg.	0	0	0	N	N	N
3	M	*7.6*	30	0	Neg.	0	0	0	N	N	N
4	M	*7.4*	27	0	Neg.	0	0	0	N	N	N
5	M	*7.2*	..	0	..	0	0	0	...	...	...
6	M	*7.2*	25	0	..	0	0	0	...	...	...
7	M	*7.1*	17	0	..	0	0	0	...	...	...
8	M	*6.9*	35	0	Neg.	0	0	0	N	N	N
9	M	*6.8*	36	+	..	0	0	0	N	N	N
10	F	*6.7*	14*	0	..	0	0	0	...	...	...
11	F	*6.5*	*23**	0	Neg.	+	0	0	...	...	...
12	F	*6.5*	..	0	Neg.	0	0	0	...	...	...
13	F	*6.5*	22*	0	..	0	0	0	...	...	...
14	F	*6.3*	..	0	Neg.	0	0	0	...	...	...
15	M	*6.1*	30	0	Pulmonary fibrosis	0	0	Recurrent corneal ulcers	*7.60*	*2.52*	*5.08*
16	M	*6.1*	..	0	..	0	0	0	...	...	...
17	F	*5.9*	9*	0	..	0	0	0	...	...	...
18	F	*5.1*	..	0	Neg.	+	0	0	...	...	...
19	M	5.8	..	0	Neg.	0	0	0	...	...	...
20	M	5.3	..	0	Neg.	0	0	0	N	N	N
21	F	5.0	..	0	..	0	0	0	...	...	...

Case no.	Sex	Serum uric acid (mg.%)	NPN (mg.%)	Arthritis	Chest x-ray	Hepatomegaly	Splenomegaly	Eye signs	Serum proteins (gm.%) Total	Alb	Glob
22	M	4.7	..	0	..	0	0	0	...	...	...
23	F	4.6	..	0	Neg.	0	0	0	...	...	...
24	F	4.6	..	0	Neg.	0	0	0	N	N	N
25	F	4.5	..	0	Neg.	0	0	0	...	...	...
26	F	4.3	28	+	Neg.	0	0	0	...	...	...
27	M	4.2	38	+	Neg.	0	0	0	7.17	3.08	4.09
28	M	4.2	..	0	Neg.	0	0	0	...	...	...
29	F	4.2	..	0	..	0	0	0	...	...	...
30	F	4.1	..	0	..	0	0	0	...	...	...
31	F	4.0	..	0	Neg.	0	0	0	...	...	...
32	F	4.0	..	0	Neg.	0	0	0	6.13	2.87	3.26
33	F	4.0	..	0	Neg.	0	0	0	...	...	...
34	M	4.0	35	0	Neg.	0	0	Corneal ulcers	...	...	...
35	M	3.9	..	0	..	0	0	0	...	...	...
36	M	3.9	..	0	..	0	0	0	...	...	...
37	M	3.9	..	0	Neg.	0	0	0	N	N	N
38	F	3.8	..	0	..	0	0	0	...	...	...
39	F	3.8	..	0	..	0	0	0	...	...	...
40	F	3.6	..	0	Neg.	0	0	0	...	...	...
41	F	3.4	..	0	..	0	0	0	...	...	...
42	M	3.3	..	+	Neg.	0	0	0	...	...	...
43	F	3.2	..	0	..	0	0	0	...	...	...
44	F	3.1	17*	+	Neg.	0	0	0	...	...	...
45	F	3.0	28	+	Neg.	0	0	0	...	...	...

46	F	3.0	.	+	Neg.	0	0	0	...	...	...
47	F	3.0	36	0	Neg.	0	0	0	...	...	...
48	F	..	..	+	..	0	0	0	...	...	...
49	F	..	..	+	Neg.	0	0	0	...	...	...
50	M	..	..	+	Neg.	0	0	0	*5.67*	*2.08*	*3.59*
51	F	..	..	+	Bronchiectasis	0	0	0	...	...	...
52	F	..	..	+	Neg.	0	0	0	*8.88*	4.13	*4.75*
53	M	..	..	+	Neg.	0	0	0	N	N	N
54	M	..	..	+	Neg.	0	0	0	...	...	...
55	M	..	..	+	Pulmonary fibrosis	0	0	0	...	...	...
56	F	..	..	+	Neg.	0	0	0	...	...	...
57	F	..	..	0	..	0	0	0	7.98	3.22	*4.76*
58	M	..	..	0	Neg.	+	0	0	7.80	3.60	*4.20*
59	M	..	..	0	..	+	0	0	...	...	...
60	F	..	..	0	Neg.	+	+	0	...	...	...
61	M	..	..	0	..	+	0	0	7.88	3.84	*4.04*
62	M	..	..	0	Pulmonary fibrosis	0	0	0	6.30	*2.70*	3.60
63	F	..	..	0	Inactive tuberc.	0	0	0	7.81	*2.08*	*4.73*
64–77	M	..	..	0	Neg. (9)	0	0	0	N (5)	N (5)	N (5)
78–100	F	..	..	0	Neg. (16)	0	0	0	N (9)	N (9)	N (9)

Abnormal values italicized.

* BUN.

** N = normal.

Gout. In none of the 100 cases of gout investigated was there skin lesions suggestive of either sarcoidosis or psoriasis. However, two of the group had pulmonary fibrosis and one had hypercalcemia of undetermined etiology. Although there was no obvious collateral evidence of sarcoidosis in these cases, the diagnosis had not been considered at the time of hospitalization, and, hence, had not been adequately excluded by appropriate studies.

REVIEW OF THE LITERATURE

Although there are no previous reports of coexistent sarcoidosis, psoriasis, and gout, the literature contains references to every other possible combination of these diseases, including sarcoidosis and psoriasis, sarcoidosis and gout, and psoriasis and gout.

Sarcoidosis and psoriasis. The classical skin lesions of sarcoidosis are readily differentiated from those of psoriasis on the basis of their appearance, distribution, and histological features. However, in their monograph on sarcoidosis, Longcope and Freiman[12] describe a form of cutaneous sarcoidosis that resembles psoriasis and cite one case in their own series (No. 16) and another reported by Combes.[13] Since in neither of these patients were the characteristic granulomata of sarcoidosis demonstrated in the skin, the possibility of coexistent sarcoidosis and psoriasis cannot be excluded. A search of the literature for cases with similar skin lesions in which typical sarcoidal lesions were demonstrated proved fruitless. However, one report of coexistent sarcoidosis and psoriasis was uncovered.[14] Whether the paucity of references to the combination of sarcoidosis and psoriasis reflects its rarity, or is attributable to the failure of writers on sarcoidosis to report the occurrence of so common and apparently unrelated a disorder as psoriasis, is uncertain.

The conjunctivitis, corneal ulceration and iritis that are known to occur in the course of psoriasis[15–17] are reminiscent of the ocular complications of sarcoidosis. However, the absence of collateral evidence of sarcoidosis in such cases, and the fact that the only lesions examined have not been granulomatous in nature,[17] make it highly improbable that the eye manifestations in the two diseases share a common pathogenesis.

Lorincz[18] has suggested that psoriasis may represent an inherited pattern of reaction in the skin that may be elicited by a variety of etiological factors. Hence, if there is any connection at all between psoriasis and sarcoidosis, it is conceivable that the latter may occasionally serve as a nonspecific stimulus in provoking the former. An analogous situation is seen in the well-known association between sarcoidosis and erythema

nodosum,[19] another skin disorder that is neither granulomatous in nature nor specifically related to sarcoidosis.

The alternative possibility, that psoriasis may occasionally give rise to sarcoidosis, or that, in some instances, both diseases are due to the same etiological factor, cannot be excluded with certainty.

Sarcoidosis and gout. In addition to Hutchinson's two cases,[1, 2] only one other instance of gout[20] was encountered in a review of over 90 cases of sarcoidosis associated with arthritis. Reports of hyperuricemia in sarcoidosis are equally scarce.[21, 22, 23] However, with the exception of the present investigation, the blood uric acid has not been studied in any large group of patients with sarcoidosis. Indeed, even in the cases with arthritis reviewed by us, it was determined in only two.[24, 25] Admittedly, the transient and migratory character of the usual joint symptoms[4, 26–29] and the presence of granulomatous lesions in the synovial membranes of patients with sarcoidosis[4] are inconsistent with gout. Nevertheless, considering the fact that the arthritis may be limited to a single joint,[12, 24] and that the radiographic bone changes in sarcoidosis and gout may be indistinguishable,[12] it is conceivable that, if the possibility of gout were investigated more often, the incidence would prove to be higher than previous reports indicate.

A variety of inflammatory disorders of the eye, including uveitis and chorioretinitis, are known to occur in patients with gout.[31–33] Although these are similar to the ocular manifestations of sarcoidosis, they appear to be related to the deposition of urates rather than to a granulomatous reaction.

Obviously, gout is such a common disorder that its mere coexistence with sarcoidosis in a few instances cannot be considered adequate evidence of a relationship between these diseases. However, our finding of hyperuricemia in 20 per cent of an unselected group of 25 patients with sarcoidosis is more suggestive. One possibility to be considered is that the hyperuricemia was a manifestation of the renal dysfunction known to occur in patients with sarcoidosis as a consequence of complicating hypercalcemia[34] or granulomatous involvement of the kidney.[35] This appears unlikely, since all but one of the cases with hyperuricemia had normal renal function, and only one exhibited hypercalcemia, although admittedly subtle changes in tubular function were not excluded. An alternative possibility is that the hyperuricemia was due to an acceleration of purine metabolism of the type seen in leukemia, dependent in this instance on the excessive proliferation of the reticuloendothelial cells from which sarcoid granulomata stem.

Psoriasis and gout. Of the possible combinations of sarcoidosis, psoriasis, and gout, only that of psoriasis and gout has been reported with any degree of frequency. In one large series of patients with gout totaling 520,[36] psoria-

sis was present in 4.0 per cent, an incidence considerably in excess of that found in the general population, which is said to range between 0.27 and 1.4 per cent.[37, 38] Although these data suggest a relationship between psoriasis and gout, the specificity of this relationship is in doubt, since the incidence of psoriasis has been found to be equally high in rheumatoid arthritis and only slightly less so in osteoarthritis.[39]

Comparable data on the incidence of gout in psoriasis are not available. However, hyperuricemia has been reported in a high proportion of patients with psoriasis, being present in 35 per cent of 307 cases studied by two groups of investigators.[40, 41] Our own observations confirm these reports, but contradictory evidence, based on the study of a smaller number of patients, has been presented by others.[42]

If, as these data suggest, the incidence of hyperuricemia in psoriasis is as high as 35 per cent, it is hardly likely that it is attributable exclusively to chance alone, to unrecognized renal insufficiency, or to the use of agents known to raise the blood uric acid level.[43–46] One possibility that merits consideration is that the hyperuricemia is the consequence of an increase in purine metabolism, as in leukemia, related in this instance to the greatly accelerated proliferation of epidermal cells known to occur in psoriasis.[18] The fact that there is no correlation between the blood uric acid concentration and the severity of the psoriatic lesions[42] would appear to be contradictory. However, a similar discrepancy may be seen in leukemia, where the uric acid concentration does not necessarily parallel the number of leukocytes in the peripheral blood.

COMMENT

The evidence cited suggests some possible relationships between sarcoidosis, psoriasis, and gout, but does not settle the question of whether their coexistence in the three cases reported was a chance occurrence or the consequence of an interaction among these diseases.

Considering the striking differences in their pathogenesis and morphological features, and the variations in their time of onset, it is unlikely that all three diseases were initiated or precipitated by a single stimulus. The alternative possibility, that one of them provoked the others, appears more reasonable in view of the interrelationships previously discussed. The fact that the three diseases occurred in a different sequence in each case (psoriasis, gout, and sarcoidosis in Case 1; sarcoidosis, gout, and psoriasis in Case 2; gout, psoriasis, and sarcoidosis in Case 3), would appear to be contradictory. However, as previously indicted, it was not possible to date the onset of sarcoidosis or hyperuricemia with accuracy, so that no con-

clusions regarding the precise sequence of events in these cases are warranted. Obviously only a careful search for evidence of the triad in future cases of sarcoidosis, psoriasis, and gout can establish whether or not there is any relationship among these diseases.

SUMMARY

Three cases of coexistent sarcoidosis, psoriasis, and gout are presented. Evidence, based on a review of the literature and an investigation of patients with each of these diseases seen in the same hospital over a five-year period, is cited in support of the view that the occurrence of all three diseases in these individuals may not have been due to chance alone.

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