HEPATIC MANIFESTATIONS OF SARCOIDOSIS AND OTHER GRANULOMATOUS DISEASES*

A Study Based on Histological Examination of Tissue Obtained by Needle Biopsy of the Liver

GERALD KLATSKIN and RAYMOND YESNER

It is evident from both clinical and autopsy studies that sarcoidosis is usually a generalized disease. What was once regarded as a primary disorder of the skin is now known to include a wide variety of apparently unrelated clinical syndromes, having as their common denominator a similar histopathology. The clinical features of the disease, which vary according to the distribution of lesions in the special tissues and organs, are now so well known to clinicians that sarcoidosis is being recognized with increasing frequency. Although studies of autopsy[1-16] and biopsy[17-20] material indicate that the liver is one of the organs most frequently affected, the clinical manifestations of hepatic sarcoidosis have received little attention. This aspect of the disease takes on added significance now that liver tissue is readily available for histological examination by needle biopsy.

Since the etiology of sarcoidosis is still in doubt and since its clinical manifestations are usually not pathognomonic, the diagnosis must of necessity depend on the histological demonstration of typical lesions. When the skin and superficial lymph nodes are not involved, needle biopsy of the liver may be the only practical means of establishing the diagnosis. The chief objections to needle biopsy are that serious, and occasionally fatal, complications may follow the procedure,[21] and that the small samples of tissue obtained may fail to include lesions when they are actually present in the liver; but the dangers are negligible provided the procedure is carried out skillfully and adequate precautions are taken in the selection and postoperative care of patients. In the authors' experience of 650 biopsies there have been relatively few minor, and no fatal, complications. As for errors in sampling, evidence will be presented to show that they are considerably less than might be anticipated from the size of the specimen obtained at biopsy.

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* From the Department of Internal Medicine, Yale University School of Medicine, and the Department of Pathology, Veterans Administration, Newington, Connecticut. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration. Aided by a grant from the Fluid Research Fund, Yale University School of Medicine.

From published data it would appear that sarcoidosis of the liver seldom gives rise to symptoms. A few instances of jaundice[7, 22, 23] and ascites[24] have been reported, but it is not clear whether these were all due to sarcoidosis or to other coincidental causes. Hepatomegaly is a more frequent finding[9, 25, 26] and occasionally poses a difficult diagnostic problem, especially when accompanied by splenomegaly. Banti's syndrome, Hodgkin's disease, and cirrhosis have been frequent diagnostic errors. The problem is somewhat complicated by the fact that the enlargement of the liver in sarcoidosis may be secondary to congestive failure rather than to granulomatous infiltration. The functional status of the liver in sarcoidosis has not been studied systematically, but sporadic reports indicate that it is usually normal or only slightly impaired.[25, 27]

Characteristically, the lesions in the liver occur as scattered, sharply circumscribed, discrete granulomata, predominantly in the portal triad, but occasionally elsewhere in the lobules. Generally, the lobular architecture is little disturbed, and there are few changes in the parenchymal cells. In a few instances, however, an increase in periportal connective tissue has been observed,[16] and in two cases typical cirrhosis has been found at autopsy.[8, 15] Schaumann[15] expressed the opinion that the cirrhosis in his case was related to sarcoidosis, but it is not clear from his description whether the cirrhosis resulted from fibrous tissue replacement of sarcoidal lesions or from the general effects of a chronic debilitating disease. The well-recognized tendency for the lesions of sarcoidosis to heal by fibrous tissue replacement as in the lung suggests that, in some instances at least, cirrhosis may be the end result of healing granulomata.

While the histopathology of sarcoidosis is characteristic, it cannot be regarded as pathognomonic, since sarcoid-like lesions can be produced by a variety of agents, of which the unknown cause of sarcoidosis is only one.[28] It is obvious, therefore, that the diagnosis of sarcoidosis cannot be based on the histological findings in the liver alone, unless a number of other diseases have been excluded. Of these brucellosis and tuberculosis constitute the most frequent differential diagnostic problems. However, granulomata of the liver have also been described in a variety of diseases, including erythema nodosum,[28] beryllium intoxication,[29] syphilis,[30] tularemia,[31] histoplasmosis,[32, 33, 34] blastomycosis,[35, 36] and leprosy.[37] The differentiation of sarcoidosis from these diseases is based on histological criteria in some instances, on the demonstration of specific etiologic agents in others, and on clinical features in the remainder. In some cases the diagnosis cannot be established with certainty even after characteristic granulomata have been demonstrated histologically, and appropriate clinical and bacteriological studies carried out. The complexity of the diagnostic problem stems from the uncertainties regarding the etiology of sarcoidosis. The disease has been variously described as a form of tuberculosis,[10, 38, 39] as a virus infection,[7, 40, 41] and as a characteristic but non-specific response to a variety of etiological agents, including the tubercle bacillus, the brucella organism, beryllium, and possibly others.[42]

The following is a report of an investigation of the clinical, functional, and histological status of the liver in sarcoidosis, and in a number of other diseases known to produce similar granulomata in the liver. Its objectives were: (a) to determine the frequency and clinical significance of hepatic lesions, and to evaluate needle biopsy of the liver as a diagnostic measure in sarcoidosis, and (b) to determine whether the hepatic lesions of sarcoidosis can be differentiated from those of other granulomatous diseases.

Materials and methods

All subjects admitted to the hospital with a diagnosis of proved or suspected sarcoidosis were included in the study. The following procedures were carried out

routinely: (a) a careful physical examination with special emphasis on the state of the liver; (b) blood count, urine analysis, and serological (Mazzini) test for syphilis; (c) a group of liver function tests[48]; (d) serum protein determination; (e) one or more intracutaneous tests with Purified Protein Derivative (PPD first strength = 0.00002 mg., second strength = 0.005 mg.); (f) x-ray examination of the chest and extremities, and (g) needle biopsy of the liver.

TABLE 1

HEPATIC GRANULOMATA DEMONSTRATED IN 650 NEEDLE BIOPSIES

	No. biopsied	*Granulomata present*
Sarcoidosis—total	**20**	**15**
histologically confirmed	15	15
presumptive diagnosis	5	0
Tuberculosis—total	**18**	**7**
acute miliary	4	4
pulmonary	8	2
glandular	3	0
osseous*	2	1
renal	1	0
Erythema nodosum—total	**3**	**2**
tuberculin-negative	2	1
tuberculin-positive	1	1
Brucellosis—total	**2**	**1**
active	1	1
inactive	1	0
Beryllium intoxication—total	**1**	**0**
Viral infections—total	**4**	**3**
infectious mononucleosis	2	1
influenza B	1	1
type unknown	1	1
Mycotic infections—total	**2**	**1**
histoplasmosis	1	0
actinomycosis	1	1

* Case 23 with osseous tuberculosis and tuberculin-positive erythema nodosum included in both groups.

The Vim-Silverman needle[44] and the intercostal approach were employed in obtaining specimens of liver tissue. The tissue was usually fixed in Carnoy's solution, occasionally in 10 per cent formalin, imbedded in paraffin in the usual manner, sectioned at 5 microns, and stained with a modification of Masson's trichrome stain, with hematoxylin-eosin, and by the Ziehl-Neelsen technique for acid-fast bacilli. Occasionally sections were also stained for reticulum by Laidlaw's technique. If no lesions were demonstrable in the first set of slides examined, the block of tissue was sectioned serially in its entirety and re-examined. In several instances, where the lesions found were not typical, a second biopsy was performed.

Similar clinical and histological studies were carried out in all subjects with known or suspected granulomatous disease of other types (Table 1). Included in this group

TABLE 2

CLINICAL FEATURES OF HISTOLOGICALLY-CONFIRMED CASES OF SARCOIDOSIS

					Symptoms			*Distribution of lesions*										
Case no.	*Sex*	*Age*	*Race*	*Chief complaints*	*Duration*	*Wt. loss‡*	*Max. fever*	*Skin*	*Periph. nodes*	*Thorac. nodes*	*Lungs*	*Hepato-megaly*	*Spleno-megaly*	*Bone*	*Eye*	*Paro-tids*	*Miscellaneous*	*Complications*
1	F	34	N	malaise, cough pain in joints	5y.	4	102.4	++*	+*	++	+++	++*	P*	0	0	0	?heart	Banti's synd., splenectomy cholelithiasis
2	F	32	N	fatigue, dyspnea, chest pain	1½m.	3	102.8	0	+	+++	++	++*	0	0	0	0	?kidney	
3	M	54	W	blur. vis., weakness, vomiting, cough, dyspnea	1y.	20	102.8	0	0	0	+	++*	++	0	++	0	?heart	
4	F	43	N	none†	?	0	0	0	0	+++	0	+*	0	0	0	0	0	fibrocalcific tb. rt. apex
5	F	11	N	weakness, abdom. pain, fever	10m.	10	104.	0	++*	0	0	+++*	+++	0	0	0	0	
6	F	32	N	chest pain, fever, cough	2½y.	10	100.5	0	±	+++	0	+*	0	0	0	0	0	syphilis, treated
7	M	33	W	none†	?	0	0	0	0	+++	0	0*	0	0	0	0	0	
8	M	32	N	painful eyes, blurred vision	3wk.	0	0	0	0	++	0	0*	0	0	+++	0	lachrymals*	glaucoma

9	M	26	W	dyspnea, cough	2y.	6	0	0	+	++	++	0*	0	0	0	0	0	
10	M	41	N	fatigability, anorexia†	?	20	0	0	0	++	0	+*	0	0	0	0	0	fistula-in-ano
11	M	52	W	weakness, finger-cramps, cough, chest pain, dysp.	3y.	25	104.4	0	++	+	0	+*	+	0	0	0	marrow*	pericarditis
12	M	60	W	weakness, dyspnea, cough, urin. frequency	3y.	35	0	0	P*	0	+++	++*	0	0	0	0	0	renal failure metastatic calcification, osteoporosis, compression fractures vertebrae
13	F	34	W	fatigability	6y.	0	99.6	? P	±	0	0	+*	+	0	P	0	0	choroidal deposits
14	M	29	W	fatigability, sweats†	6m.	16	0	0	++	++	0	++*	++	0	0	0	0	thrombosed hemorrhoids rhoids
15	F	34	W	parotid swelling, fever, cough, dysp.	3y.	0	102.	?+	±	+	++	0*	0	0	0	+++	0	

* Sarcoids demonstrated histologically.

† Hospitalized for investigation of abnormal pulmonary findings discovered during routine x-ray examination.

‡ Maximal weight loss, in pounds.

± Palpable lymph nodes regarded as normal; + = slight, ++ = moderate, +++ = marked enlargement.

P Lesions present in the past.

were four subjects with outspoken acute or chronic liver disease, who on routine liver biopsy exhibited typical sarcoidal lesions. The diagnosis of sarcoidosis had not been suspected in any of these, nor could evidence of other similar lesions be found on subsequent investigation.

The criteria used in establishing the diagnosis of sarcoidosis were: (a) the demonstration of typical lesions histologically, (b) a clinical picture compatible with the disease, and (c) the exclusion of specific etiological agents known to produce similar lesions. These were chosen on the assumption that the etiology of the disease is still unknown. Subjects with clinical or histological features of sarcoidosis, but with evidence of active tuberculosis, brucellosis, erythema nodosum, or beryllium intoxication were considered separately, since the relationship of these conditions to sarcoidosis is still a matter of dispute.

Every effort was made to exclude tuberculosis and brucellosis by appropriate cultural and serological studies. When pulmonary lesions were demonstrated by x-ray, sputum or gastric washings were concentrated and examined for tubercle bacilli by staining, by culture on Dubos media, or by guinea-pig inoculation. Only in case 3, with pulmonary lesions suggestive of early pneumonoconiosis, was it not possible to obtain a suitable specimen of sputum or gastric washings for study. One or more blood cultures for brucella organisms were obtained in each of the subjects exhibiting significant fever. Tests for brucella agglutinins were carried out in most of the group. Where lymphadenopathy was a prominent feature, or when the blood picture suggested infectious mononucleosis, tests for heterophile antibodies were performed. In a few instances skin tests for histoplasmosis and coccidioidomycosis were carried out.

Significantly enlarged lymph nodes and suspicious skin lesions were biopsied wherever possible. In a number of instances the bone-marrow, and in one case each the lachrymal gland, the parotid gland, and the spleen were examined microscopically.

Results—Sarcoidosis

The diagnosis of sarcoidosis was suspected clinically in 33 patients admitted to the hospital during the period of investigation. The disease could be excluded with reasonable certainty in 13, i.e., by the demonstration of tubercle bacilli in 5, and by the demonstrations of other causes for the clinical manifestations in 8. Of the remaining 20 cases, histological confirmation of the diagnosis was obtained in 15 (cases 1 to 15), but was lacking in 5.

The clinical and laboratory features of the histologically-confirmed group are presented in Tables 2 and 3. In general they did not differ significantly from those described in other large series.[9, 18, 45]

Clinical evidence of liver disease (Table 4). Hepatomegaly was a frequent finding, occurring in 11 of the 15 confirmed cases. This appeared to be related to the presence of granulomata, since it was not found in any of the 5 cases of probable sarcoidosis without hepatic lesions. However, 4 cases with hepatic granulomata had no hepatomegaly, and there was a poor correlation between the number of lesions demonstrated histologically and the degree of enlargement. In none could the enlargement be attributed to associated congestive failure. As a rule, the liver was only moderately enlarged, soft, and non-tender, and in only one instance, case 5, was it sufficiently enlarged and tender to suggest a primary disorder of the liver.

TABLE 3

LABORATORY DATA ON HISTOLOGICALLY-CONFIRMED CASES OF SARCOIDOSIS

Case no.	Hematology								Tuberculin		Serum chemistry					Serology			Bacteriology			Histology				
	R.b.c.	Hemoglobin	W.b.c.	P.m.n.	Lymph	Mono.	Eos.	Sed. rate	PPD 1	PPD 2	Proteins	Albumin	Globulin	Ca	P	Brucella	Heterophile	Mazzini	Sputum	Gast. Wash.	Blood	Liver	Nodes	Skin	Spleen	Marrow
	x10⁶/ cmm.	gm./ 100 cc.	x10³/ cmm.	per cent				mm. 1 hr.			grams per 100 cc.			mg. per 100 cc.												
1	3.84	12.0	12.9†	74	19	3	0	—	+++	—	8.94	2.41	6.53	10.29	3.63	0	—	+++	0	—	—	+	+	+	+	0
2	4.38	12.5	7.4	80	9	6	5	32	0	0	7.09	2.95	4.14	—	—	0	—	0	0	—	0	+	0	—	—	—
3	3.73	11.0	3.8	72	12	16	0	43	0	+	6.73	2.59	4.14	—	—	0	—	0	—	—	0	+	—	—	—	0
4	4.68	12.0	7.7	57	41	—	2	34	0	0	7.88	3.54	4.34	—	—	—	—	0	0	0	—	+	—	—	—	—
5	4.90	12.0	3.9	67	25	6	2	—	0	0	8.40	3.00	5.40	10.20	5.00	0	0	0	—	—	0	+	+	—	—	0
6	3.52	11.0	5.0	64	33	3	0	—	++	—	8.22	3.37	4.85	—	—	0	—	++‡	0	—	0	+	—	—	—	—
7	4.45	14.0	6.4	71	26	3	0	23	0	+++	7.56	4.14	3.42	—	—	—	0	0	—	—	—	+	—	—	—	—
8	—	12.5	2.8	46	46	2	6	16	0	++	7.80	5.30	2.50	—	—	—	—	0	—	—	—	+*	—	—	—	—
9	—	15.5	4.5	64	23	5	7	14	0	0	7.50	—	—	9.80	4.10	—	—	0	0	—	—	+	0	—	—	—
10	4.11	13.0	5.9	64	31	0	5	—	0	0	8.50	—	—	—	—	—	—	0	—	0	—	+	—	—	—	0
11	—	11.0	10.3	66	25	4	5	—	0	+	7.40	3.20	4.20	9.30	3.40	0	0	0	—	0	0	+	0	—	—	+
12	3.60	13.0	8.9	78	18	4	0	—	0	0	7.01	3.58	3.43	12.89	5.16	0	—	0	—	0	0	+	+	—	—	—
13	4.03	13.0	12.5	59	37	4	0	—	0	+	6.26	4.44	1.82	—	—	0	0	0	—	—	0	+	—	—	—	0
14	4.64	13.5	6.9	65	31	0	4	5	+	—	7.00	—	—	—	—	—	0	0	—	0	—	+	0	—	—	—
15	3.81	11.0	7.0	62	34	4	0	—	0	+++	6.34	3.00	3.34	—	—	0	—	0	0	—	0	+	—	—	—	—

+ Under heading Histology signifies presence of sarcoid lesions demonstrated histologically; elsewhere +, ++ and +++ signify mild, moderate and strong reaction, respectively.

* Biopsy of lachrymal gland also positive for granulomata.

† Leukopenia on previous admission, before splenectomy.

‡ History of treated syphilis.

Tenderness was evident in 2 other cases, and the liver was described as firm in a third.

Splenomegaly occurred in 6 of the 11 subjects with hepatomegaly, and was accompanied by leukopenia and mild anemia in 3 (cases 1, 3, 5), suggesting Banti's syndrome. In one of these (case 1), a splenectomy had been performed 5 years prior to this investigation. In 5 of the 6 cases with splenomegaly and hepatomegaly the diagnosis of Hodgkin's disease or malignant lymphoma had been suspected.

Except for mild jaundice in case 5, and splenomegaly as indicated, there were no other collateral signs of liver disease, such as spider nevi, palmar erythema, increased collateral venous circulation, ascites or edema, in any of the group. X-ray examination of the gastrointestinal tract was carried out in 6 subjects, but no esophageal varices or other abnormalities were demonstrated, except for coincidental cholelithiasis in case 1.

Gastrointestinal symptoms occurred in all but 4 of the cases, but these could not be correlated with the presence of hepatomegaly, nor with the number of hepatic granulomata demonstrated histologically. Moreover, similar symptoms were present in 2 of the 5 unconfirmed cases of sarcoidosis, who had neither hepatomegaly nor demonstrable hepatic granulomata, suggesting that most of the symptoms were due to the general constitutional effects of the disease rather than to specific hepatic lesions. Only one subject, case 5, had mild jaundice which appeared to be directly related to extensive granulomatous involvement of the liver and marked hepatomegaly. Anorexia was present in approximately half the group, and nausea, vomiting, or indigestion in a third each. Five subjects complained of abdominal pain, but in only one (case 5) could it be attributed to enlargement and tenderness of the liver.

Hepatic function. The results of the tests of hepatic function are summarized in Table 4. One or more abnormalities were observed in 12 of the 15 cases. On the whole they indicated only minor impairment of function, and, in several instances, were probably related to alterations in the serum protein pattern rather than to hepatic dysfunction. Only in case 5 did the results suggest moderately severe hepatic damage. In general there was a poor correlation between the results of the tests and the presence of hepatomegaly or the number of granulomata demonstrated histologically. However, no abnormalities of hepatic function were observed in the 3 cases tested with unconfirmed sarcoidosis and without hepatic granulomata.

The serum bilirubin was increased significantly in case 5, and, to a lesser degree, in case 3. Significant bromsulphthalein retention occurred in 5 of the 13 cases tested, but was minor in one, and only moderate in the others. Thymol turbidity was increased slightly in 6, and the cephalin-cholesterol flocculation test was mildly to moderately positive in 5 of the 13 cases tested. These abnormalities appeared to be better correlated with high serum globulin concentrations than with evidence of liver damage, judged

TABLE 4

EVIDENCE OF LIVER DISEASE IN HISTOLOGICALLY-CONFIRMED CASES OF SARCOIDOSIS

Case no.	*Liver*				*Symptoms*							*X-ray*		*Liver function tests*						
	Biopsy	*Enlargement*	*Tenderness*	*Consistency*	*Splenomegaly*	*Anorexia*	*Indigestion*	*Diarrhea, constip.*	*Abd. pain*	*Nausea, vomit.*	*Jaundice*	*G. I.*	*Gall bladder*	*One min. bilirub.*	*Total bilirub.*	*Ceph. flocc.*	*Thym. turb.*	*BSP*	*Prothrombin*	*Alk. phosph.*
1	+	++	0	soft	P	++	+	0	+	++	0	0	stones	—	1.00	2+	*7.5*	*36./*	*60*	8.9K
2	+++	++	0	soft	0	0	+	C+	+	0	0	—	—	0.27	0.75	1+	2.0	—	—	—
3	++	++	++	soft	++	++	0	0	0	++	0	0	0	0.29	*1.22*	1+	3.0	*/18.6*	*55*	4.89
4	+	+	0	soft	0	0	0	0	0	0	0	0	0	0.19	1.04	1+	*6.0*	/6.0	100	4.02
5	+++	+++	++	soft	+++	++	0	0	+++	++	+	—	—	*0.53*	*3.99*	*2+*	*6.0*	*/32.7*	*50*	*56.92*
6	++	+	0	firm	0	0	0	0	0	0	0	—	—	0.19	0.24	*3+*	*7.5*	/3.3	72	4.84
7	+++	0	0	—	0	0	0	0	0	0	0	—	—	0.09	0.60	1+	*8.8*	/5.9	72	*6.50*
8	+	0	0	—	0	0	0	0	0	0	0	—	—	0.20	0.40	0	2.0	/5.5	100	4.80
9	+	0	0	—	0	0	++	C+	+	+	0	hyper-motility	0	—	—	—	—	—	90	2.90
10	+	+	0	soft	0	+	0	0	0	0	0	0	0	0.10	0.20	0	3.8	*/7.0*	*48*	3.90
11	++	+	0	soft	+	0	0	C++	0	0	0	0	0	—	—	2+	1.2	/4.0	87	*10.60*
12	+	++	0	soft	0	+	0	0	0	0	0	—	—	0.09	0.72	3+	*7.7*	/5.5	100	*5.30*
13	+	+	0	soft	+	0	+	d+	0	0	0	—	—	0.03	0.27	0	0	6.0/	74	*6.40*
14	+	++	+	soft	++	++	0	0	0	0	0	—	—	0.10	0.30	0	1.0	0	*68*	2.50
15	+	0	0	—	0	+	+	0	++	n+	0	—	—	0.17	0.52	0	3.0	*/19.2*	*62*	3.24

Biopsy: + = 1-5 granulomata, ++ = 6-10 granulomata, +++ = > 10 granulomata per section.
Physical findings and symptoms: + = slight, ++ = moderate, +++ = marked.
Liver function tests: abnormal values *italicized*. Normal values = 1-minute serum bilirubin < 0.30 mg. per cent; total serum bilirubin < 1.2 mg. per cent; cephalin-cholesterol flocculation < 2+ in 48 hours; thymol turbidity < 5.0 units; bromsulphalein retention 10%/6%, or less, 30 min./45 min. after injection of 5 mg./kg.; prothrombin > 70 per cent of normal control; alkaline phosphatase < 5.0 units (Bodansky), or < 15.0 K units (King-Armstrong).

by the serum albumin level and bromsulphthalein retention. The prothrombin level was decreased in 6 subjects, but was below 50 per cent of normal in only one. In every instance it was possible to raise the level by the administration of vitamin K.

The serum albumin level was below 3.5 grams per cent in 7, and below 3.0 grams in 3 of the 12 subjects tested. In all but one this was associated with an abnormally high globulin level, exceeding 4.0 grams per cent. These alterations were poorly correlated with the number of hepatic granulomata demonstrated histologically and with other evidence of hepatic dysfunction, suggesting that they were, in part at least, due to extra-hepatic factors.

The serum alkaline phosphatase concentration was increased in 5 subjects, but in 3 the increase was of only borderline significance. Case 5, with the most extensive liver damage, had a level of 56.92 Bodansky units associated with a mild degree of jaundice. However, 5 months earlier, before the appearance of jaundice and when the serum bilirubin concentration was within normal limits, the alkaline phosphatase level was 44.03 units. This degree of hyperphosphatasemia is unusual in liver disease, except in the presence of severe obstructive jaundice or hepatic malignancy, and suggested the possibility of bone lesions. However, x-ray studies and bone-marrow biopsy failed to disclose evidence of sarcoidosis. It is probable, therefore, that the hyperphosphatasemia in this case was due to granulomatous infiltration of the liver. In case 11 the alkaline phosphatase level was 10.60 units. Although x-ray examination of the bones failed to reveal cystic areas, a bone-marrow biopsy demonstrated the presence of granulomata. It is difficult to determine whether the hyperphosphatasemia in this case was due to bone or liver involvement, since many granulomata were also present in the liver. In neither case 5 nor 11 was the serum calcium elevated. On the other hand, in case 12 there was a significant hypercalcemia, associated with decalcification of the bones, metastatic calcification of the soft tissues, and renal failure, but the serum alkaline phosphatase level remained low (5.30 Bodansky units). Harrell and Fisher,[27] who first called attention to the occurrence of hyperphosphatasemia in sarcoidosis, observed the same lack of correlation between the serum phosphatase level and the presence of bone lesions or hypercalcemia, and suggested that the former might, therefore, be related to involvement of the liver. The present findings would appear to corroborate this conclusion.

Liver biopsy and other diagnostic measures. Liver biopsy revealed granulomata in all 15 confirmed cases (Tables 3 and 5). In case 10 the first biopsy disclosed the presence of intrasinusoidal collections of epithelioid cells suggestive but not typical of sarcoidal lesions. However, classical lesions were demonstrable in a second biopsy specimen obtained 2 weeks later. In case 11 typical lesions were demonstrated in the first biopsy specimen, but not in a second obtained a month later. This was the only case in

the series in which the diagnosis of sarcoidosis had not been suspected before liver biopsy.

No hepatic lesions were demonstrated in the five presumptive cases of sarcoidosis. Unfortunately, the biopsy was not repeated in any of these subjects. Only one had enlarged peripheral lymph nodes and suspicious skin lesions. Biopsy of both these tissues failed to reveal granulomata. A bone-marrow biopsy in another case was likewise negative.

Histological confirmation of the diagnosis of sarcoidosis was based on the liver biopsy findings in 12 of the 15 cases. In the remaining 3, the liver biopsies were positive, but the diagnosis had been established by an earlier splenectomy in case 1, and by lymph-node biopsy in cases 5 and 12. The liver biopsy findings were later confirmed in other tissues in 2 of the 12 subjects in whom the diagnosis was based on hepatic granulomata (case 8, lachrymal gland; case 11, bone-marrow), but no confirmatory lesions could be found in 4 lymph-node and 3 bone-marrow biopsies carried out in the remaining 10. Thus, histological confirmation of the diagnosis rested on the liver biopsy findings alone in 10 of the 15 cases, even though all accessible, suspiciously involved tissues were excised for histological study. However, 3 of these subjects (cases 6, 13, 15) had small palpable lymph nodes which were not regarded as abnormal, and which, therefore, were not biopsied. Some of these may have contained granulomata, in view of reports that apparently normal lymph nodes frequently contain diagnostic lesions.[15] Tonsillar biopsy has also been recommended as a useful diagnostic measure,[15] but none was carried out in this series.

If it is assumed that all the presumptive diagnoses of sarcoidosis were correct, the incidence of positive liver biopsies was 75 per cent. This does not differ significantly from the incidence of sarcoidal lesions in the liver found at autopsy (63 per cent*), which suggests that the sampling error was insignificant, despite the small size of the tissue specimens obtained by needle biopsy.

The liver biopsy findings take on added significance when the results of other diagnostic measures are analyzed. The tuberculin test is usually given considerable weight in the differential diagnosis of sarcoidosis, although it is well known that it may be misleading. Only 6 of the 15 confirmed cases of sarcoidosis exhibited negative tuberculin reactions to the first and second strengths of P.P.D. (Table 3).

The x-ray findings in the chest frequently suggested or confirmed the clinical impression of sarcoidosis, but seldom warranted an unequivocal diagnosis. Intrathoracic adenopathy or pulmonary lesions compatible with sarcoidosis were observed in 13 of the 15 histologically-confirmed cases

* Based on autopsy reports of 74 cases taken from the literature.[1-16, 46-55] Most of the published autopsy reports on sarcoidosis were included, but a number were omitted because of inadequate data, the presence of extensive tuberculosis obscuring the distribution of sarcoidal lesions, or because the original reports were not available.

TABLE 5

DIFFERENTIAL DIAGNOSIS IN HISTOLOGICALLY-CONFIRMED SARCOIDOSIS

Case no.	*Roentgenologist's diagnoses (before biopsy)*	*Clinicians' diagnoses (before biopsy, after chest x-ray)*	*Initial biopsy establishing diagnosis*	*Later biopsies confirming diagnosis*	*Negative biopsies*
1	Bilateral pneumonia Probable tuberculosis Sarcoidosis (after splenectomy)	Banti's syndrome Tuberculosis Sarcoidosis (after splenectomy)	spleen*	liver lymph node skin	marrow
2	Hodgkin's disease ? Sarcoidosis*	Hodgkin's disease Tuberculosis Sarcoidosis	liver	0	lymph node
3	Pulmonary fibrosis ? Pneumoconiosis	Lymphosarcoma Hodgkin's disease Pulmonary fibrosis Banti's syndrome Sarcoidosis*	liver	0	marrow
4†	Probable Hodgkin's disease Minimal tuberculosis, L.U.L.	Hodgkin's disease Sarcoidosis* Tuberculosis	liver	0	0
5	Normal	Liver abscess Acute hepatitis Hodgkin's disease Banti's syndrome Malignancy Sickle anemia Sarcoidosis*	lymph node	liver	marrow
6	Probable Hodgkin's disease	Aortic aneurysm Hodgkin's disease Sarcoidosis* Tuberculosis	liver	0	0

7†	Sarcoidosis,* or Hodgkin's disease	Sarcoidosis Hodgkin's disease Coccidioidomycosis Tuberculosis	liver	0	0
8	Sarcoidosis ? tuberculosis ? lymphoblastoma	Sarcoidosis*	liver	lachrymal gland	0
9	? tuberculosis ? sarcoidosis*	Sarcoidosis	liver	0	lymph node
10†	? sarcoidosis* ? Hodgkin's disease	Sarcoidosis Hodgkin's disease	liver	0	marrow
11	? Hilar adenopathy	Pericarditis Collagen disease Lymphoma Tuberculosis Brucellosis	liver*	marrow	lymph node
12	Pulmonary fibrosis	Pulmonary fibrosis Hyperparathyroidism	lymph node*	liver	0
13	Normal	Hodgkin's disease Brucellosis Sarcoidosis*	liver	0	marrow
14†	? Sarcoidosis*	Lymphoma Sarcoidosis Infectious mononucleosis	liver	0	lymph node
15	Bronchopneumonia ? tuberculosis Sarcoidosis (later film)	Sarcoidosis*	liver	0	0

* First suggested diagnosis of sarcoidosis.

† Hospitalized for investigation of abnormal pulmonary findings discovered during routine x-ray examination.

(Table 2). In 7 of these, including 4 whose disease was discovered during a routine chest x-ray examination, the x-ray findings first called the attention of the clinician to the possibility of sarcoidosis. However, the clinician's interpretation of these findings was influenced by his knowledge of other clinical and laboratory features. A better appraisal of the relative value of the x-ray examination in the differential diagnosis of sarcoidosis can be obtained by analyzing the opinions rendered by expert roentgenologists who examined the initial films with a minimum of clinical data available. Sarcoidosis was mentioned as a possibility in only 6 of the 13 cases showing abnormalities, and in every instance but one an alternative diagnosis was mentioned (Table 5).

The x-ray findings in the chest were of relatively greater importance in the groups with a presumptive diagnosis of sarcoidosis. Roentgenological abnormalities compatible with sarcoidosis were the first clue to the nature of the diagnosis in all 5 cases. In 4 of these, sarcoidosis was suggested by the roentgenologist.

The x-ray findings in the extremities were of no value in this series, since not one of the 18 confirmed and presumptive cases examined exhibited the cystic areas occasionally seen in sarcoidosis.

The alterations in the protein pattern described by Harrell and Fisher[27] were observed in many of the subjects, although not as frequently as positive liver biopsies. Of the 15 histologically-proved cases, 7 had serum protein levels above 7.5, while 7 of the 12 tested had serum globulin levels above 3.5 grams per cent (Table 3). However, these changes proved to be of little value in the differential diagnosis of sarcoidosis because of their non-specificity.

The serum calcium concentration is frequently increased in sarcoidosis.[27] In this series only 1 of the 5 determinations carried out revealed significant hypercalcemia (12.89 mg. per cent) associated with mild hyperphosphatemia (5.16 mg. per cent). However, these findings proved to be of little diagnostic value in this subject (case 12). The patient was studied at another hospital where the discovery of hypercalcemia, hypercalcinuria, and bone decalcification associated with renal failure led to the diagnosis of hyperparathyroidism, and the performance of a parathyroidectomy. The correct diagnosis was not established until somewhat later when lymphadenopathy became apparent and a biopsy was performed.

Minor changes in the hematological picture were observed in a few subjects, but in none were they helpful in establishing the diagnosis of sarcoidosis (Table 3). Five subjects exhibited leukopenia, and one a mild monocytosis. Slight normochromic anemia occurred in 6 cases, and the sedimentation rate was increased in all but one of the 7 tested.

Histopathology of the liver. The histological features of the liver biopsy specimens obtained in sarcoidosis and in the other granulomatous diseases studied are outlined in Table 6. The outstanding finding in both groups was

the presence of multiple, discrete granulomata with minimal changes in the remaining parenchyma.

In general, the granulomata observed in the sarcoidosis group resembled those described by others, both in the liver[18, 19, 20] and in other tissues.[9, 11] However, the similarities between the hepatic lesions in sarcoidosis and the other granulomatous diseases studied proved to be much greater than anticipated from previous reports, and it was found that, with few exceptions, the lesions could not be differentiated on the basis of histological criteria alone. The striking similarity of the lesions in sarcoidosis, erythema nodosum, tuberculosis, and brucellosis is illustrated in Figures 1, 2, 3, and 4.

Judging by the ease with which granulomata were demonstrated by needle biopsy, and from the *number* of lesions in single sections, ranging from 1 to more than 12, it was apparent that the livers in the subjects with sarcoidosis were heavily seeded with granulomata. Similar numbers of lesions were found in the other granulomatous diseases studied, although the incidence of positive liver biopsies was significantly lower in some forms of tuberculosis (Table 1).

The *size* of the granulomata tended to remain submiliary in all groups, but they were by no means uniform. The largest lesions comprised collections of 25 to 50 epithelioid cells; the smallest, of less than 12. In most subjects both small and large lesions could be found in the same section, and usually the small lesions outnumbered the large.

The *contour* of the lesions in sarcoidosis tended to be round and discrete with sharp borders (Fig. 1B), while that in tuberculosis and brucellosis was more often irregular or lobulated, suggesting the coalescence of multiple lesions (Figs. 2D, 4B). However, lobulated or irregular lesions were also observed in some cases of sarcoidosis (Fig. 1D), and round, sharply outlined lesions in some cases of tuberculosis (Fig. 1C). Moreover, the contour of the granulomata often varied in the same section, so that this criterion was of little value in differentiating hepatic granulomata. Others[56] have emphasized as a point of differentiation the tendency of tuberculous lesions to coalesce.

The *localization* of the lesions in sarcoidosis did not differ significantly from that in tuberculosis and brucellosis. Granulomata were found both within the parenchyma and in the portal zones in all three diseases. The lesions in erythema nodosum and in the virus and mycosis groups all occurred within the lobular parenchyma. However, differences in localization should not be overemphasized, especially when based on the examination of single sections. In many instances, lesions which were clearly intralobular in one section proved to have connections with a portal zone when traced through serial sections, and even then it was not always possible to determine the site of origin of such lesions. Previous reports[11, 40]

TABLE 6

SUMMARY OF HISTOLOGICAL FEATURES IN LIVER BIOPSY MATERIAL

Case no.	*Hepatic granulomata*										*Giant cells*			*Associated changes*							
														Portal zones			*Parenchyma*				
	No. lesions/ section	*Size*	*Location*	*Shape*	*Border*	*Collagen envel.*	*Central reticulum*	*Density*	*Cellular infil.*	*Cellular border*	*No. per section*	*Inclusions*	*Necrosis*	*Connective t. prolif.*	*Cellular infiltration*	*Bile duct proliferation*	*Fatty infiltration*	*Necrosis*	*Cellular infiltration*	*Focal R. E. hyperplasia*	*Clinical diagnosis*
1	3	L, S	P, H	round	sharp	+	+	+	0	1	3	0	0	+	0	+	0	+	l, e	+	sarcoidosis
2	12	L, S	P, H	lobul.	sharp	+	+	++	l, e	e, p	0	—	+f	0	l, e, p	0	0	0	e	+	sarcoidosis
3	8	L, S	P, H	lobul.	sharp	+	—	+++	0	1	5	+c	0	0	0	0	+	0	0	+	sarcoidosis
4	3	L, S	H	irreg.	irreg.	0	—	++	1	1	0	—	0	0	0	0	+	0	0	+	sarcoidosis
5	>12	L, S	P, H	round	sharp	0	+	+++	0	p	0	—	0	+	0	0	0	0	0	+	sarcoidosis
6	10	L, S	H	irreg.	irreg.	0	+	++	0	0	1	0	0	0	0	0	0	0	0	+	sarcoidosis
7	16	L, S	P. H	lobul.	sharp	0	+	+++	0	0	3	0	0	0	0	0	+	0	0	+	sarcoidosis
8	2	S	P, H	round	sharp	0	—	+	0	0	0	—	0	0	0	0	0	0	0	+	sarcoidosis
9	3	S	P, H	round	sharp	+	—	+	0	0	6	0	0	0	0	0	0	0	0	0	sarcoidosis
10	2	L, S	P. H	irreg.	irreg.	0	—	+++	0	1	2	0	+f	0	0	0	+	0	0	+	sarcoidosis
11	6	M	P, H	round	sharp	++	—	+	p, l, e	p, l, e	6	+v	0	+	p, l, e	0	0	+	0	0	sarcoidosis
12	4	L, S	P, H	irreg. round	irreg. sharp	0 +	+	+++	1	1	4	+c	+	0	0	0	+	0	0	+	sarcoidosis
13	< 1	S	P	round	irreg.	0	+	++	0	0	0	0	0	+	0	+	0	0	0	0	sarcoidosis
14	1	S	H	irreg.	irreg.	0	—	++	0	l, m	0	0	0	0	0	0	0	0	0	0	sarcoidosis
15	< 1	S	H	round	sharp	0	—	++	0	0	0	—	0	0	0	0	0	0	0	0	sarcoidosis

16	3	L	H	round	sharp	+	—	++	0	0	3	0	0	0	0	0	0	0	0	0	miliary tuberculosis
17	4	L, S	H	round irreg.	sharp irreg.	0	±	++	l, m	1	0	—	+	0	1	0	0	+	l, m	+	miliary tuberculosis
18	2	L, S	P	irreg.	irreg.	0	—	+++	0	1	5	0	+++c	0	0	0	0	0	0	0	miliary tuberculosis
19	3	L	P, H	irreg.	irreg.	0	—	+	0	1	2	0	+++	0	1	0	0	0	0	0	miliary tuberculosis
20	6	S	P, H	irreg.	irreg.	0	0	++	1	0	0	0	+f	0	0	0	0	0	0	+	pulmon. tuberculosis
21	1	M	P	lobul.	irreg.	0	—	++	0	0	1	0	+++	0	0	0	+	0	0	0	pulmon. tuberculosis
22	1	M	P, H	lobul.	sharp	+	—	+++	0	1	0	—	0	0	0	0	0	0	0	0	tuberculin-neg., erythema nodosum
23	2	L, S	P, H	irreg. lobul.	irreg. sharp	0	+	++	1	1	3	0	+	0	0	0	0	0	0	0	tuberculin-pos., erythema nodosum
24	7	L, S	P, H	irreg. lobul.	irreg. sharp	0	—	++	1	1	3	0	+++	++	l, pl.	0	+	0	l, pl.	+	brucellosis
25	2	S	H	irreg.	irreg.	0	—	++	0	0	0	—	0	0	l, m	l, m	0	+	l, m	++	infect. mononucleosis
26	4	L, S	H	irreg.	irreg.	0	—	++	1	1	0	—	+	0	0	0	0	0	0	0	influenza B
27	2	M, S	H	irreg.	irreg.	0	—	++	0	0	0	—	+	+	p, l, pl, m	0	+	+	m	+	fever, ? viral
28	1	S	H	irreg.	irreg.	0	—	++	1	1	0	—	+	0	1	0	0	0	0	+	actinomycosis
29	10	L, S	P, H	round	sharp	0	—	+	0	0	5	0	0	+	+	0	0	0	0	+	inf. hepatitis
30	1	L	P, H	round	sharp	+	—	++	0	l, e	3	+a	0	+++	0	0	++	0	0	0	cirrhosis, diabetes
31	>12	L	P, H	lobul.	sharp	+	—	+	l, e	l, e	>12	++v	+	++	l, e	++	0	0	0	0	cirrhosis
32	2	S, M	P, H	irreg.	irreg.	0	—	++	0	1	1	0	0	++	m	0	+	+	1	0	cirrhosis

Symbols: Size: L = >24 epithelioid cells, M = 12-24 cells, S = <12 cells. Location: P = portal, H = intralobular. Density: + = loose, ++ = moderately compact, +++ = compact. Cell types: p = polymorphonuclears, l = lymphocytes, e = eosinophiles, m = monocytes, pl = plasma cells. Necrosis: f = fibrinoid, c = caseous. Inclusions: c = crystalline, a = asteroids, v = vacuoles.
+ = mild, ++ = moderate, +++ = marked.

have emphasized the predominance of sarcoidal lesions in the portal zones and tuberculous lesions within the lobular parenchyma.[11, 40]

The lesions in sarcoidosis were composed of masses of *epithelioid* cells, varying in shape, size, and arrangement, depending in part on the compactness of the lesion. Neither the histological appearance of these cells individually, nor their arrangement or compactness, differed from those found in the other granulomatous diseases studied. The staining properties of the epithelioid cells differed very markedly from those of hepatic parenchymal or other inflammatory cells, and were especially well brought out by the Masson trichrome staining technique. In sections so stained even the smallest lesions stood out in bold relief against the background of normal liver tissue.

The paucity of *inflammatory cells* within and around the granulomata in sarcoidosis has been emphasized as a point of differentiation from other granulomata. In general, the lesions in tuberculosis and brucellosis did show a more dense collar of lymphocytes than those in sarcoidosis, in which disease such cells were often lacking, but there were too many exceptions in both groups to validate this as a reliable criterion for histological differentiation. The distribution of lymphocytes and other leukocytes within the granulomata was of no greater value, since they occurred only infrequently and in small numbers in all the diseases studied.

Giant cells were demonstrated in 8 of the 15 cases of sarcoidosis, in 5 of the 7 cases of tuberculosis, in one of the 2 cases of erythema nodosum and in the one case of brucellosis studied, but neither their number nor type served to differentiate between these diseases. Typical Langhans' and foreign body giant cells could be found in each of the groups, and often within the same lesion when studied in serial sections. Giant cells of unusual size, and containing an unusually large number of nuclei, are said to be characteristic of sarcoidosis.[9, 40] In the present series neither the size nor the nuclear content of the giant cells differed significantly in the various disease groups studied.

Giant-cell inclusions of the asteroid[2] and Schaumann-body type[57] are frequently found in the granulomata of sarcoidosis, although they are by no means pathognomonic.[25] Only 2 of the histologically-confirmed cases of sarcoidosis exhibited crystalline inclusions, possibly an early stage of the asteroid body, and case 30 with cirrhosis and a presumptive coincidental sarcoidosis had a typical asteroid body. No Schaumann bodies were observed, but it is known that these occur more frequently in the lymph nodes than in other tissues.[57] Teilum[58] has suggested that the inclusion bodies in sarcoidosis represent globulin precipitates related to hyperglobulinemia. In this series there was no correlation between the occurrence of inclusion bodies and the concentration of serum globulin. No inclusion bodies were observed in tuberculosis or brucellosis. Although inclusions do

occur in granulomatous diseases other than sarcoidosis, they rarely occur in tuberculosis.[25]

The presence of a *reticulum* framework in the granulomata of sarcoidosis is regarded as an important point in its differentiation from tuberculosis.[11] A fine reticulum network was demonstrated in each of the 6 cases of sarcoidosis examined. In 2 subjects with tuberculosis no reticulum was demonstrated in one, and only a few scattered fibers in the other. In subject 23, a case of tuberculin positive erythema nodosum, the hepatic granulomata were thought to be tuberculous, but they exhibited a reticulum framework as in sarcoidosis.

There was a striking difference between the degree of *necrosis* observed in the granulomata of sarcoidosis, tuberculosis, and brucellosis. Necrosis was absent in 12 and was only minor in extent in 3 of the 15 cases of sarcoidosis. In 7 cases of tuberculosis, on the other hand, all but one showed necrosis, and it was frequently extensive. Necrosis was also extensive in the one case of brucellosis. It is of interest that caseation necrosis occurred in only one of the 7 cases of tuberculosis, a patient who had had signs of miliary tuberculosis for 6 months (Fig. 2D). Although the demonstration of marked necrosis favored either tuberculosis or brucellosis, its absence could not be used to differentiate these diseases from sarcoidosis. In 3 of the tuberculous subjects the foci of necrosis were very small, and could not be differentiated from those seen in some cases of sarcoidosis, and in all the tuberculous subjects and in the one with brucellosis, there were small granulomata without necrosis adjacent to the larger necrotic lesions. One subject with miliary tuberculosis exhibited granulomata with no necrosis whatever.

A thin *collagen envelope* was demonstrated in some of the lesions in 6 cases of sarcoidosis. In one subject (case 11) the envelope was laminated, suggesting the amorphous paramyloid bands described by Teilum.[54] Sarcoid lesions are known to undergo fibrosis and hyalinization during the stage of healing,[11] but in the present series there did not appear to be any relationship between the presence of collagenous connective tissue encapsulation and the known duration of the disease. Similar encapsulation was observed in one case of tuberculosis and in a case of tuberculin-negative erythema nodosum, but not in brucellosis.

Focal areas of intrasinusoidal *reticulo-endothelial hyperplasia* were common in both sarcoidosis and other granulomatous diseases. In some sections it was possible to demonstrate intermediate stages between these ill-defined, irregular collections of swollen Kupffer cells and sharply outlined, small epithelioid granulomata, suggesting that the former were in some instances, at least, the forerunners of the latter.

Minor associated changes in the liver, unrelated to the granulomatous lesions themselves, were observed in many of the confirmed cases of sarcoidosis. These consisted of mild degrees of periportal fibrosis and

cellular infiltration, and less commonly of mild fatty infiltration, focal necrosis or cellular infiltration of the parenchyma. In none did these changes suggest an early cirrhosis. The relationship of sarcoid-like hepatic lesions to the development of cirrhosis in 3 subjects (cases 30, 31, and 32) will be discussed in another section.

A much greater degree of connective tissue proliferation and cellular infiltration of the portal zones and of cellular necrosis and inflammatory reaction in the parenchyma was observed in brucellosis. The possible relationship of these lesions to the development of cirrhosis will be discussed in another section.

No significant alterations in hepatic structure, other than the presence of granulomata, were observed in tuberculosis.

Acid-fast stains for tubercle bacilli were uniformly negative, except in one of the 4 subjects with miliary tuberculosis who exhibited typical tubercle bacilli adjacent to a granuloma.

Sarcoid-like hepatic lesions associated with other diseases

The striking similarities between the hepatic lesions of sarcoidosis and those of other granulomatous diseases may be paralleled by indistinguishable clinical features, a fact which emphasizes the necessity for carefully considering all the granulomata in any study of sarcoidosis, whether it be from the point of view of the clinician interested in diagnosis, or from that of the investigator concerned with its pathogenesis.

The following is a résumé of the clinical and laboratory evidence of liver involvement in the more common granulomatous diseases encountered during this investigation. The data illustrate the difficulties which these diseases may present in the differential diagnosis of sarcoidosis, and demonstrate some interesting relationships which may be of significance in the pathogenesis of sarcoidosis.

Acute miliary tuberculosis. The liver is frequently seeded with tubercles during the course of acute miliary tuberculosis, and in occasional cases the seeding may be so dense that the clinical picture is dominated by jaundice and hepatomegaly. As might be expected, therefore, needle biopsy of the liver has proved to be of diagnostic value in this disease.[59, 60]

Four subjects with acute miliary tuberculosis were investigated. The clinical features of the disease are summarized in Table 7. The symptoms had an acute onset and were of relatively brief duration in cases 16 and 17, while the clinical course was less acute and more protracted in cases 18 and 19. Hepatomegaly was evident only in the more chronic form of the disease, but hepatic granulomata and abnormalities of liver function were demonstrated in all four cases. In case 16 mild jaundice appeared on the third day of streptomycin therapy and subsided within a period of two weeks. The jaundice was associated with an increase in serum bilirubin,

TABLE 7

SUMMARY OF FINDINGS IN FOUR CASES OF DISSEMINATED MILIARY TUBERCULOSIS

	Case 16							*Case 17*	*Case 18*	*Case 19*
Age, sex, race	43, F, W							45, M, N	42, F, N	28, M, N
Symptoms and signs										
duration	18 days							10 days	6 months	3 months
pulmonary (x-ray)	+							0 (+ later)	0	+
pleural effusion	+							0	+	0
pericardial effusion	0							0	+	0
ascites	0							0	0	0
hepatomegaly	0							0	+	+
splenomegaly	0							0	+	0
jaundice	+							0	0	0
meningitis	later							0	+	+
lymphadenopathy	0							±	±	0
Tuberculin test	neg. (later +)							+	—	—
Serum proteins, gm.%	7.16							6.93	7.08	7.20
serum albumin	2.60							2.38	3.13	—
serum globulin	4.56							4.55	3.95	—
Liver function tests	*7/18*	*7/20*	*7/26*	*8/1*	*8/17*	*9/19*	*10/11*			
ser. l'bilirubin, mg.%	1.44	—	0.48	0.50	0.14	0.22	0.07	0.05	0.05	0.30
ser. total bilirubin, mg.%	2.66	—	1.18	1.32	0.66	0.28	0.47	0.80	0.58	1.50
ceph.-chol. flocc.	—	4+	4+	4+	4+	3+	0	4+	3+	4+
thymol turbidity, u.	—	14.5	16.0	13.5	14.0	9.0	7.5	11.0	16.2	2.5
ser, alk. phosph., B. u	—	40.4	25.8	—	35.3	26.1	14.1	9.37	2.9	—
urine urobilinogen	—	—	—	—	—	—	—	1.80	—	—
BSP retention, % in 45′	—	44.1	—	16.5	—	14.7	12.3	32.7	7.5	2.5
Tubercle bacilli										
sputum	0 (gu. pig)							+ (gu. pig)	—	0
gastric washings	+ (gu. pig)							—	—	0
spinal fluid	0 (smear)							—	0 (smear)	+ (smear)
Liver biopsy	+							+	+	+
Diagnosis established	Chest x-ray							Liver biopsy	Liver biopsy	Chest x-ray Spinal fluid

strongly positive cephalin-cholesterol and thymol turbidity tests, and a striking elevation of serum alkaline phosphatase. The pathogenesis of the jaundice was not clear. Unfortunately, the liver biopsy specimen, which revealed many granulomata, was not obtained until the jaundice had subsided. The relatively short duration of the jaundice (despite the continued presence of many tubercles), its close association with the commencement of streptomycin therapy, and the unusually high serum alkaline phosphatase level, suggested the possibility of a drug reaction of the type seen in early arseno-therapy.[61] Tuberculosis can, of course, involve the biliary tree[62] and produce a similar picture, but this mechanism seemed unlikely in view of the brief duration of the jaundice. In the other cases, the laboratory evidence of liver damage was less striking, and the strongly positive cephalin-cholesterol flocculation and thymol turbidity reactions observed may have been more closely related to the hyperglobulinemia associated with tuberculous infection than to specific hepatic lesions.

The diagnosis of miliary tuberculosis was based on the liver biopsy findings in two of the four cases. In case 17 tubercles and acid-fast bacilli were demonstrated in the liver a week before miliary lesions were evident in the chest x-ray (5th week of the disease), and a month before acid-fast bacilli were demonstrated by guinea-pig inoculation of a sputum concentrate. Likewise in case 18, the diagnosis was based on the finding of typical caseating tubercles in the liver. Acid-fast bacilli were never demonstrated in stained smears or cerebrospinal, pleural, or pericardial exudate, and pulmonary lesions did not become evident by x-ray before death. Unfortunately sputum and gastric washings were not obtainable because of the patient's critical state.

In cases 16 and 19 the clinical diagnosis was based on the x-ray findings in the chest. Later, tubercles were demonstrated in the liver, but they contained no acid-fast bacilli and exhibited no caseation necrosis. They were compatible with, but not diagnostic of, tuberculosis. Confirmation of the diagnosis depended on the recovery of tubercle bacilli from exudates in both cases.

These results illustrate both the value and the limitations of needle biopsy of the liver in the diagnosis of miliary tuberculosis. The early acute phase of the disease, especially before the appearance of pulmonary lesions or meningitis, may simulate a wide variety of febrile diseases. The demonstration of hepatic granulomata narrows the range of possibilities to the granulomatosis group, but does not exclude such diseases as brucellosis or the more florid forms of sarcoidosis, unless tubercle bacilli or caseation necrosis can be demonstrated in the sections. Often the granulomata are not distinctive and the diagnosis of miliary tuberculosis cannot be made without collateral bacteriological or clinical evidence.

Other forms of tuberculosis. Miliary tubercles are found with great regularity in the livers of fatal cases of chronic tuberculosis. In Saphir's

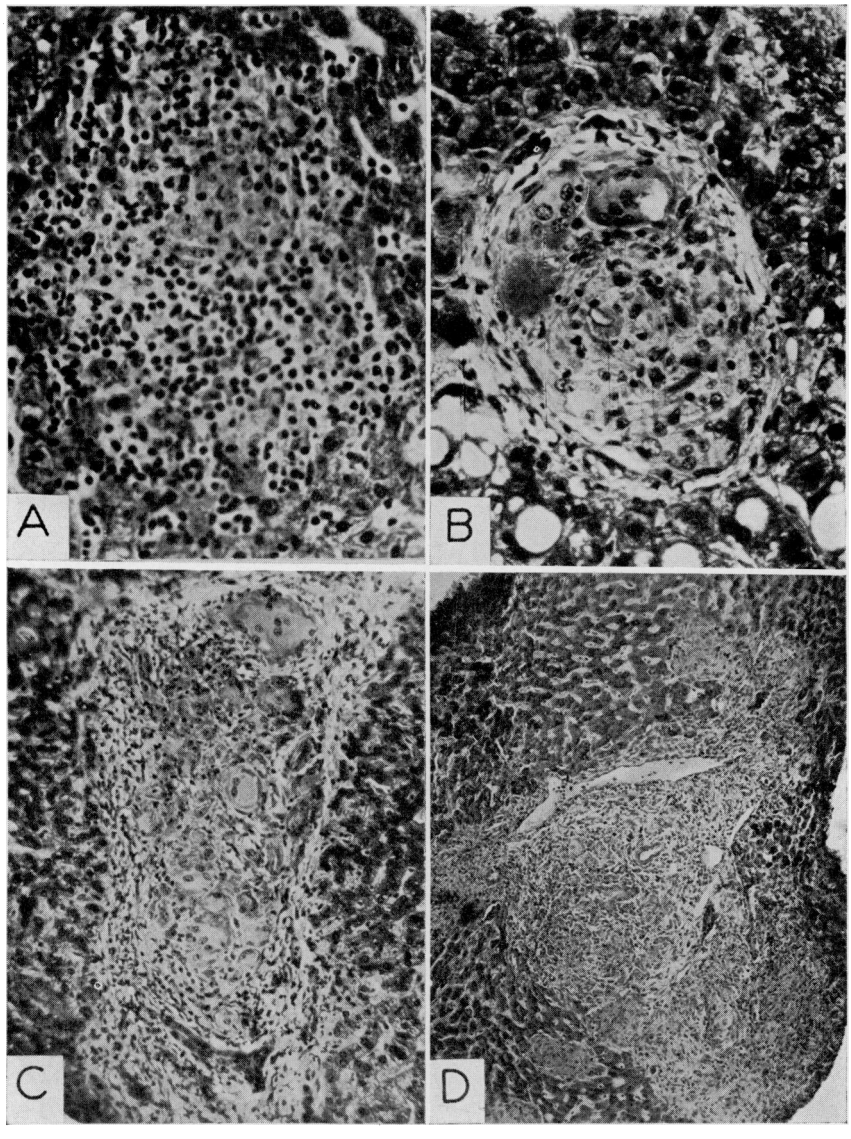

FIG. 1. Hepatic granulomata in sarcoidosis. A. Case 4. Irregular intralobular lesions with poorly defined margins and considerable lymphocytic infiltration (x440). B. Case 12. Sharply circumscribed intralobular lesion with connective tissue capsule. Note giant cell with large vacuole containing crystalline material (x440). C. Case 3. Sharply circumscribed portal zone lesion with connective tissue capsule (x220). D. Case 2. Large lobulated portal zone lesion (x125).

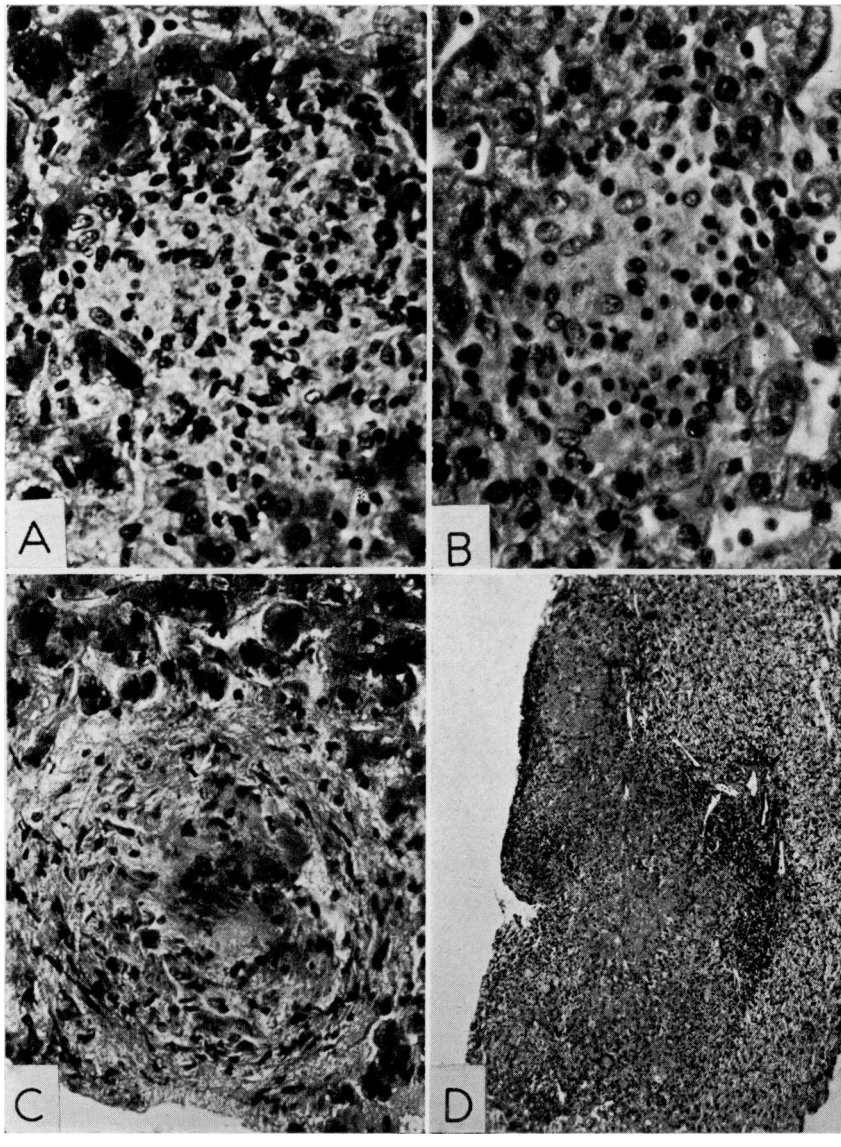

FIG. 2. Hepatic granulomata in tuberculosis. A. Miliary tuberculosis (case 17). Irregular intralobular lesion with moderate lymphocytic and monocytic infiltration. Acid-fast stain revealed tubercle bacilli adjacent to a similar lesion (x550). B. Pulmonary tuberculosis (case 20). Small, poorly circumscribed intralobular lesion with slight lymphocytic infiltration (x750). C. Miliary tuberculosis (case 16). Sharply circumscribed intralobular lesion with thick connective tissue capsule and little inflammatary exudate (x440). D. Miliary tuberculosis (case 18). Large irregular portal zone lesion with dense surrounding lymphocytic infiltration and areas of central caseation necrosis (x85).

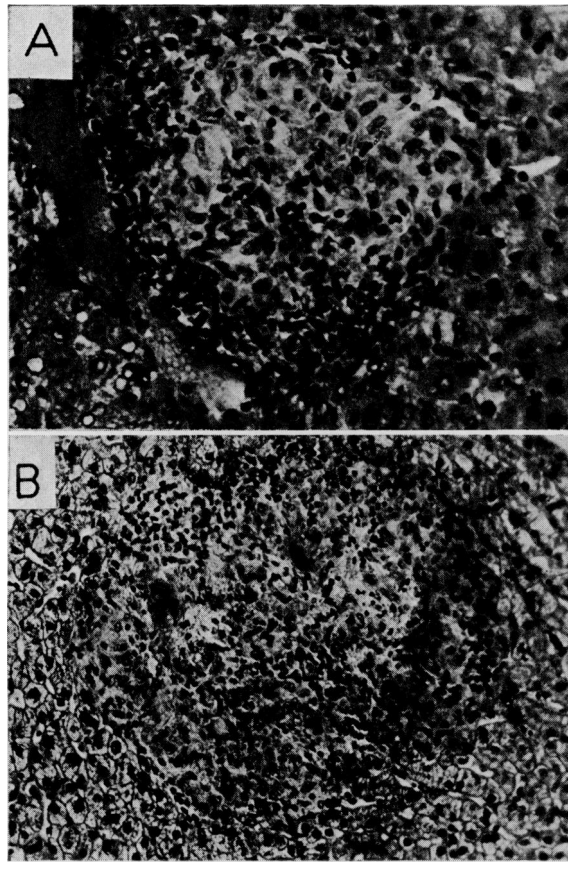

FIG. 3. Hepatic granulomata in erythema nodosum. A. Tuberculin-negative erythema nodosum (case 22). Sharply circumscribed lesion adjacent to a small sublobular vein showing slight surrounding lymphocytic reaction (x440). B. Tuberculin-positive erythema nodosum associated with active tuberculosis of the spine (case 23). Lobulated intralobular lesion with poorly defined borders, moderate lymphocytic reaction, and slight central necrosis. Central reticulum network demonstrated by special stain (x250).

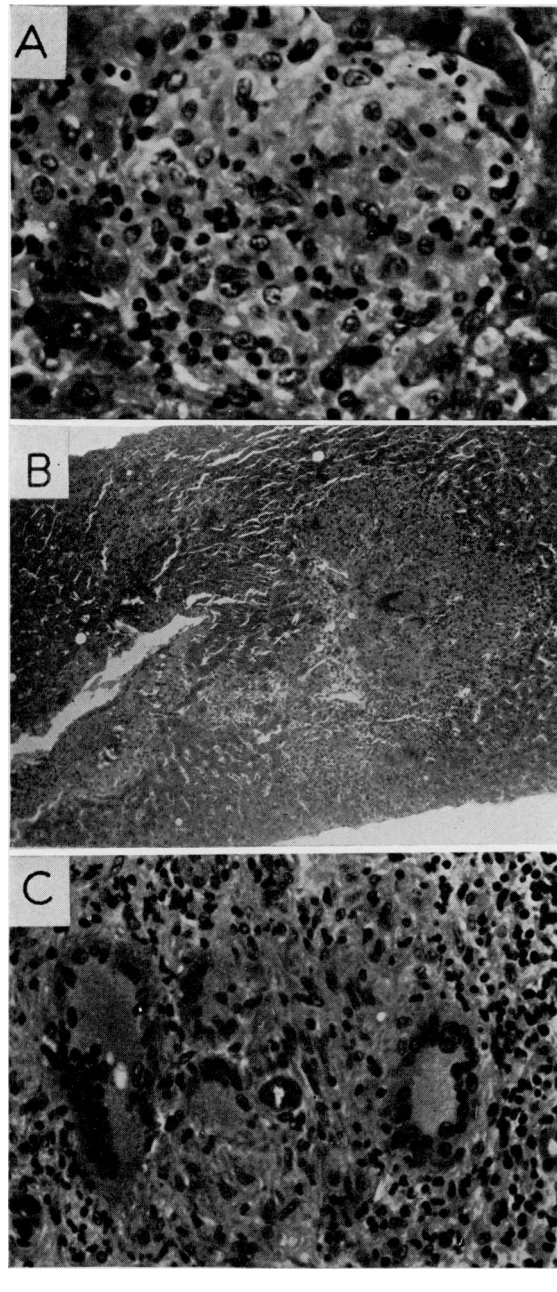

FIG. 4. Hepatic granulomata in brucellosis (case 24). A. Sharply circumscribed lobulated intralobular lesion with slight lymphocytic inflammation (x650). B. Very large irregular portal zone lesion extending to a central vein and along the wall of a sublobular vein. Marked lymphocytic infiltration and small areas of central necrosis (x110). C. High power view of Fig. 4B, showing giant cells with many nuclei, epithelioid cells, and lymphocytic infiltration (x440).

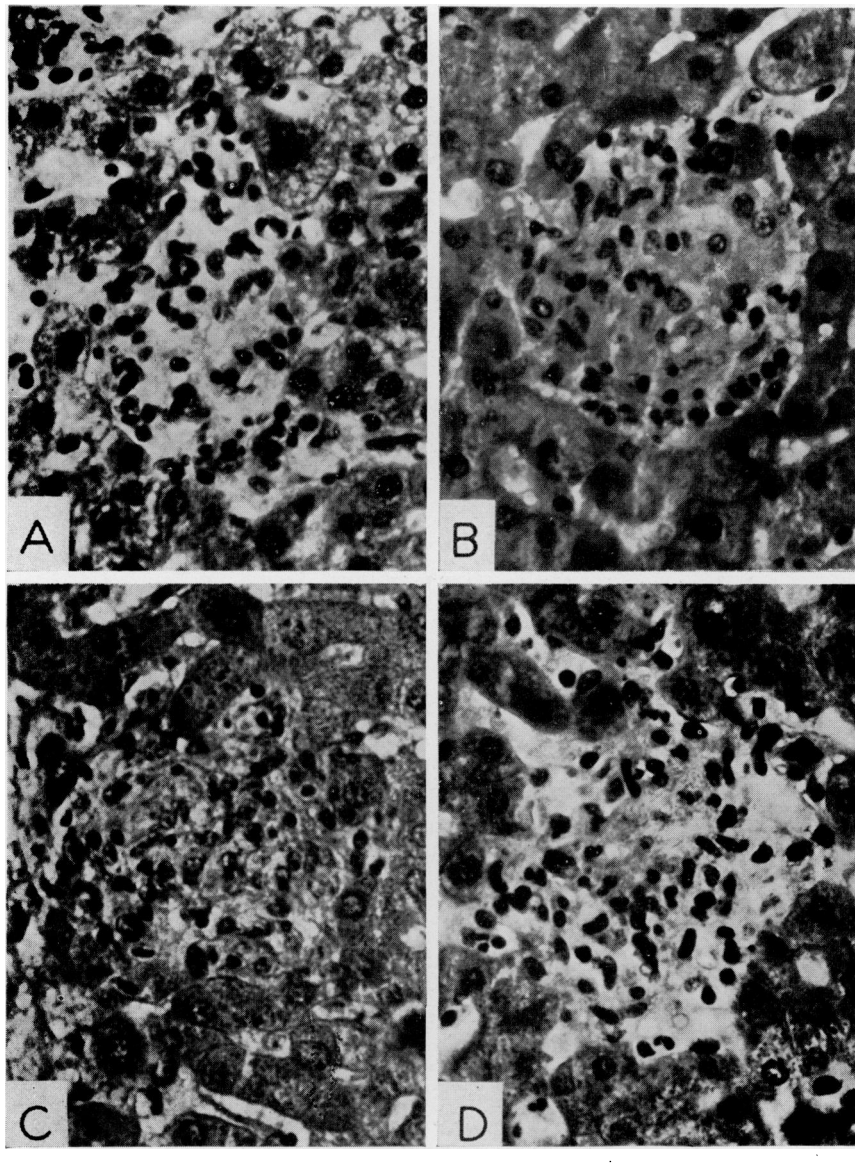

FIG. 5. Small atypical hepatic granulomata associated with infection. A. Infectious mononucleosis (case 25) x740. B. Influenza B (case 26) x750. C. Disseminated actinomycosis (case 28) x720. D. Viral infection, type not determined, (case 27) x700.

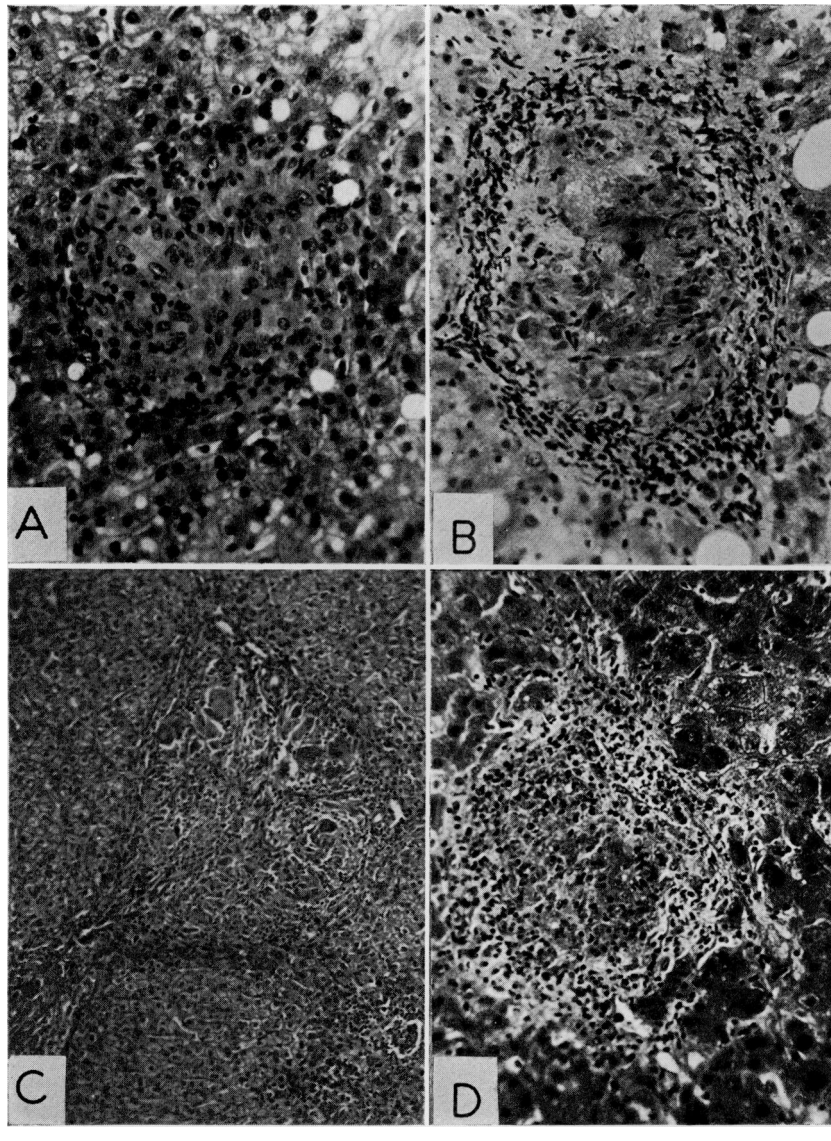

FIG. 6. Hepatic granulomata in subjects with "primary" liver disease. A. Infectious hepatitis (case 29). Intralobular lesion interpreted as evidence of coincidental sarcoidosis (x750). B. Cirrhosis (case 30). Intralobular lesion interpreted as evidence of coincidental sarcoidosis (x300). C. Granulomatous cirrhosis (case 31). Extensive granulomatous infiltration of portal zones and parenchyma distorting the normal lobular architecture, interpreted as evidence of sarcoidal cirrhosis (x140). D. Cirrhosis (case 32). Intralobular lesion with considerable surrounding lymphocytic reaction (x275). Nature of lesion not determined.

series[63] they occurred in 80 out of 100 cases of chronic ulcerative pulmonary tuberculosis. The hepatic tubercles did not appear to be related to the presence of intestinal lesions, suggesting that hematogenous spread was by way of the hepatic artery. Lorentz[64] reviewed the autopsy findings in 100 cases of chronic tuberculosis, including 14 with major lesions in extrapulmonary sites, and found that all but one had tubercles in the liver. In this series there was a very close relationship between the occurrence of hepatic and intestinal lesions, implying an hematogenous spread of tubercle bacilli by way of the portal vein. In the light of this experience Lorentz concluded that such hematogenous spread occurred in every case of florid tuberculosis. The clinical significance of these observations has received little attention until recently. Clinicians have long recognized the manifestations of overwhelming hematogenous dissemination of tubercle bacilli, but have not been able to detect the minor episodes that occur during the course of chronic tuberculosis, unless they have resulted in obvious disease of such tissues as the lung, genito-urinary tract, or bone. Recently, however, van Beek and Haex[59] have been able by means of liver biopsy to demonstrate hematogenous dissemination in all types of chronic tuberculosis, not only of the lungs, but also of the glands and viscera. Their findings are more in keeping with autopsy experience than those of van Buchem,[19] who could find no hepatic granulomata in the 9 cases of active exudative pulmonary tuberculosis he biopsied. Van Beek and Haex[59] stressed the importance of sectioning biopsy specimens serially in searching for hepatic tubercles. Van Buchem[19] does not appear to have used this technique, which may account for his results. Recognition of the fact that miliary tubercles, sometimes indistinguishable from sarcoids, may occur in the liver with pulmonary or grandular tuberculosis is of the greatest importance in interpreting the liver biopsy findings in suspected sarcoidosis.

Liver biopsies were performed in 13 cases of active tuberculosis. The disease was predominantly pulmonary in 8, glandular in 3, renal in 1, and osseous in 2. All blocks of tissue were sectioned serially, and in 5 cases the biopsy was repeated. Miliary granulomata were demonstrated in 3 of the 13 cases. Case 23, in which osseous tuberculosis was complicated by tuberculin-positive erythema nodosum, will be described in the section on erythema nodosum. A brief summary of the findings in the remaining two cases follows.

Case 20. W. Mc., a 35-year-old Negro, was found to have bilateral pulmonary infiltration, a questionable cavity in the left upper lobe, and marked hilar adenopathy in May 1949 during a routine community x-ray survey. These changes were interpreted as indicating far advanced pulmonary tuberculosis. An x-ray of the chest taken in 1943 was normal. He had no symptoms except for mild cough of several weeks' duration, attributed to a recent upper respiratory infection.

Physical examination revealed nothing of note except for pulmonary findings compatible with bilateral tuberculosis.

The patient was admitted to a tuberculosis sanatorium in September 1949 and

remained there until April 1950. During that period he was asymptomatic; serial x-rays of his chest revealed no change; monthly sputum concentrates were negative for acid-fast bacilli on smear and culture, and one gastric-washing was negative for acid-fast bacilli on culture and guinea-pig inoculation. Tuberculin tests with first and second strengths of PPD were both negative. In April 1950 the patient developed a prolonged, unexplained fever, and three weeks later was transferred to this hospital for further investigation.

Physical examination revealed mild generalized lymphadenopathy, pulmonary findings as before, and fever.

Repeated blood cultures and brucella agglutination tests were negative. Hyperglobulinemia was present (total proteins 7.44, albumin 3.16, globulin 4.28 mg. per cent). Liver function tests revealed the following: one-minute serum bilirubin 0.07 mg. per cent, total serum bilirubin 0.52 mg. per cent, cephalin-cholesterol focculation 3+, thymol turbidity 10 units, serum alkaline phosphatase 6.4 Bodansky units, bromsulphthalein 5.4 per cent retention in 45 minutes, and prothrombin 74 per cent. X-ray examination of the chest showed no significant change since the initial examination in April 1949, and once again was interpreted as indicative of bilateral pulmonary tuberculosis, although the diagnosis of sarcoidosis was suggested as a possibility. No changes in the bones were demonstrated by x-ray.

Liver biopsy revealed the presence of granulomata, consisting of epithelioid cells without giant cells (Fig. 2B). The lesions were regarded as compatible although not typical of sarcoidosis, since many were poorly circumscribed and lacked a reticulum network. Acid-fast stain revealed no bacilli. Biopsy of an axillary lymph node revealed large masses of epithelioid cells surrounded, in some areas, by zones of eosinophilic amorphous material, changes which were interpreted as indicative of "probable Boeck's sarcoid," although the pathologist indicated that tuberculosis could not be excluded. Unfortunately, none of the gland was saved for guinea-pig inoculation.

The patient was discharged from the hospital on April 29, 1950, with the diagnosis of sarcoidosis. He was still mildly febrile but felt well. His clinical improvement continued as an ambulatory patient. In June 1950 the guinea-pig inoculated with gastric washings obtained on April 28 was found to be positive for tuberculosis.

Comment. This case illustrates the difficulty of differentiating sarcoidosis from tuberculosis. The diagnosis of sarcoidosis was based on the histological findings in both the liver and a lymph node, the relatively benign course of the disease, a negative tuberculin reaction, hyperglobulinemia, the absence of tubercle bacilli in the sputum, and the stability of the pulmonary lesions over a long period of observation. Until tubercle bacilli were demonstrated by guinea-pig inoculation of gastric washings, it was assumed that the pulmonary lesions were due to sarcoidosis. In retrospect, it seems probable that they were tuberculous in nature, and that the acute febrile illness represented a hematogenous spread. The granulomata in the liver were composed largely of epithelioid cells, the type of lesion described by van Beek and Haex[59] in early hematogenous dissemination. They, too, failed to observe acid-fast bacilli or caseation under such conditions. It is, of course, possible to take the point of view that the patient had two unrelated diseases, sarcoidosis and tuberculosis, or, as suggested by Scadding[42], that this was an example of tuberculous sarcoidosis, but the weight of evidence in the light of van Beek and Haex's work favors a tuberculous etiology for all the lesions.

Case 21. J.P., a 34-year-old white male, was admitted to the hospital on March 20, 1950, complaining of dysphagia, sore throat, and hoarseness of five weeks' duration. For one year he had noted a productive cough, increased fatigability, and moderate weight loss. Night sweats appeared two weeks before admission.

Physical examination revealed moderately enlarged, firm, non-tender submaxillary and axillary lymph nodes, signs of cavitation over the right upper lobe of the lungs and a pleuro-pericardial friction rub over the left anterior chest. The liver and spleen were not palpable. There were no skin or ocular lesions and the parotids were not enlarged.

X-ray examination of the chest revealed advanced exudative cavernous tuberculosis of the right upper lobe and minimal tuberculosis of the left upper lobe. A concentrate of sputum was positive for acid-fast bacilli on stained smear. The tuberculin test was strongly positive and the sedimentation rate was increased. Liver function tests and the serum protein concentrations were normal.

Liver biopsy revealed a typical granuloma with irregular margins in a portal zone. It showed only slight lymphocytic reaction around it, but exhibited considerable non-caseous central necrosis and contained a single giant cell. No acid-fast bacilli were demonstrable.

On supportive therapy plus streptomycin and tibione, there was prompt symptomatic improvement and the pleuro-pericardial friction rub and hoarseness disappeared. The temperature was slightly elevated for two days, but did not exceed 100°F. thereafter. The patient has been followed for three months and is still under observation. He continues to improve and has shown no clinical evidence of hematogenous dissemination. Liver biopsy repeated on April 3, 1950, failed to disclose tubercles, but the specimen obtained was very small.

Comment. This is another example of a clinically unrecognized hematogenous spread of tubercle bacilli to the liver during the course of active pulmonary tuberculosis. The granulomata in the liver were fewer in number than in case 20, but they were larger, were confined to the portal triads, and showed more necrosis, features indicating greater age, according to van Beek and Haex.[59] Although no tubercle bacilli were demonstrated in these lesions, their irregular contour and the degree of necrosis they exhibited were compatible with a tuberculous etiology. The exclusion of other necrotizing granulomata, such as brucellosis, however, was based on the accompanying clinical and bacteriological features, rather than on histological criteria.

Erythema nodosum. It is generally believed that erythema nodosum is a manifestation of hypersensitivity to a variety of agents, including bacteria, viruses, fungi, and chemical compounds.[28, 65] In an exhaustive investigation carried out in Sweden, Löfgren[66] found evidence of a tuberculous etiology in the majority of his cases. However, in a similarly large series studied in Boston by Favour and Sosman,[65] the beta-hemolytic streptococcus appeared to be the most frequent etiological factor.

The typical skin manifestations of erythema nodosum are occasionally accompanied by disseminated lesions involving the hilar lymph nodes, the lungs, the peripheral lymph nodes, and, more rarely, the eyes.[67] The nature of these lesions has aroused great interest. Löfgren[66] believes that the hilar

adenopathy is due to tuberculosis in tuberculin-positive cases, but that disseminated lesions in tuberculin-negative cases are probably manifestations of sarcoidosis. Kerley[27] attaches no importance to the results of the tuberculin reaction and asserts that all cases of erythema nodosum with visceral lesions are due to sarcoidosis.

The recent observations of van Beek and Haex[28] have been cited in support of the hypothesis that hilar adenopathy in tuberculin-positive erythema nodosum is due to tuberculosis. These investigators found, on liver biopsy in such cases, granulomata which resembled the hepatic tubercles seen in miliary tuberculosis. Although they were unable to demonstrate acid-fast bacilli in the lesions, they interpreted their findings as evidence of recent hematogenous dissemination of tubercle bacilli. They attached little importance to their failure to demonstrate organisms in hepatic tissue, since the same difficulty was encountered in the case of miliary tuberculosis. However, their conclusions regarding the tuberculous nature of the lesions, based on histological criteria and supported only by a positive tuberculin reaction and, in some cases, by evidence of tuberculosis in other tissues, cannot be accepted without reservation, in view of the difficulty of distinguishing between tuberculosis and other types of hepatic granuloma on histological grounds alone. Moreover, the authors presented no data on the hepatic findings in tuberculin-negative erythema nodosum. Whether tuberculous and non-tuberculous types of erythema nodosum can be differentiated on the basis of the tuberculin reaction is debatable, but it is clear that the presence of hepatic granulomata cannot serve to distinguish between them.

The interrelationships between erythema nodosum, sarcoidosis, and tuberculosis are poorly understood. There are several striking similarities between erythema nodosum and sarcoidosis. They are both regarded, by some at least, as a non-specific response to a number of etiological agents, both may exhibit disseminated lesions of similar distributions and histological structure, and both have been considered as a special type of response to the tubercle bacillus in some cases. The evidence suggests that both sarcoidosis, or a sarcoid-like syndrome, and erythema nodosum may be produced by a variety of etiological agents, including the tubercle bacillus, and that in some cases the same agent may produce both diseases simultaneously.

During the course of this study, 3 cases of erythema nodosum were investigated. In 2 of the 3 cases, granulomata resembling sarcoids were demonstrated on liver biopsy. One of the cases was tuberculin-negative and had no evidence of tuberculosis, the other was tuberculin-positive and had Pott's disease and a pleural effusion, presumably of tuberculous etiology. The clinical features in these two cases are summarized below.

Case 22. W.C., a 29-year-old white male, was admitted to the hospital on May 5, 1949, with a history of migratory polyarthritis and fever for 3 weeks, and a tender,

nodular eruption of the legs of 5 days' duration. He was seen by his physician a week after the onset of his illness and given a course of penicillin with no relief of symptoms. Later he received moderate doses of acetylsalicylic acid which appeared to relieve the arthritis and fever. His physician had noted inflammation of the pharynx, but the patient denied having had a sore throat.

Physical examination revealed typical lesions of erythema nodosum over both legs, but no other abnormalities. The eyes were normal, the parotids were not enlarged, and there were no significantly enlarged peripheral lymph nodes. The liver and spleen were not palpable, and there were no abnormal cardiac findings. The joints appeared to be normal.

X-ray examination of the chest revealed marked bilateral enlargement of the hilar and mediastinal nodes without pulmonary infiltration or cardiac enlargement. The tuberculin test was negative to the first and second strengths of PPD. The blood count was normal, but the sedimentation rate was increased to 36 mm. in one hour. X-ray examination of the hands failed to reveal any abnormalities. Total serum proteins were 6.3, serum albumin 2.8, and serum globulin 3.5 gm. per cent. Throat culture revealed no pathogens, and the antistreptolysin titer was within normal limits.

Needle biopsy of the liver revealed a few moderate-sized granulomata which resembled sarcoids (Fig. 3A). No acid-fast bacilli were demonstrated. Biopsy of one of the skin lesions revealed fat necrosis, lymphocytic and macrophagic infiltration, and surrounding fibroblastic proliferation. No epithelioid or giant cells were seen.

The patient ran a high remittent fever for two and one-half weeks which failed to respond to salicylate therapy. It then fell by lysis and was normal at the end of 3 weeks. During the height of the fever there was an increase in the intensity of the first sound at the apex of the heart, and a soft systolic murmur appeared at the aortic area. Concurrently the P=R interval increased to 0.22 seconds, and there was vague arthralgia without objective signs of arthritis, suggesting the possibility of rheumatic fever. The erythema nodosum lesions began to subside a few days after admission and were completely gone at the end of 3 weeks. The patient was discharged from the hospital on July 26, 1949.

He was seen again eleven months later, on June 1, 1950, at which time he felt well and exhibited no abnormalities on physical examination, except for a small palpable axillary lymph node. X-ray examination of the chest at this time showed a slight decrease in the size of the hilar adenopathy previously described. The electrocardiogram still showed a P=R interval of 0.22 seconds.

Comment. This case illustrates the difficulty of interpreting the significance of hepatic granulomata in erythema nodosum. The histology of the lesions was compatible with either sarcoidosis or tuberculosis. Tuberculosis appeared to be adequately excluded, but the negative tuberculin test, the long duration of the hilar adenopathy without symptoms and the reversal of the albumin-globulin ratio were compatible with sarcoidosis. However, many of the clinical features suggested a streptococcal infection complicated by rheumatic fever, conditions in which sarcoid-like lesions have not been described. The possibility that the erythema nodosum was an unrelated complication of a hitherto unrecognized sarcoidosis could not be excluded, but seemed unlikely in view of the frequent association of erythema nodosum and hilar adenopathy. It is of interest that the histological appearance of the erythema nodosum skin lesions did not resemble those of sarcoidosis, a feature noted by Löfgren,[86] even in cases presumed to be due to sarcoidosis.

Case 23. M.B., a 32-year-old Negress, was admitted to the hospital on June 1, 1950, complaining of painful nodules on her legs of two weeks' duration. For the preceding four months she had been troubled with constant, bilateral, flank pain aggravated by movements of the spine. About two weeks before the onset of her rash she began to complain of increasing fatigability, anorexia, progressive weight loss, fever, night sweats, dry cough, dyspnea, and pleural pain.

Physical examination revealed many typical lesions of erythema nodosum over the posterior and lateral aspects of both legs, signs of a large pleural effusion on the right, and signs of Pott's disease of the thoracic spine. The liver was slightly enlarged, soft and non-tender, but there was no splenomegaly or lymph-adenopathy.

X-ray examination confirmed the presence of a large pleural effusion on the right and revealed extensive destruction of the 11th and 12th dorsal vertebrae compatible with the diagnosis of tuberculosis. The tuberculin test was strongly positive. Aspirated pleural fluid revealed a specific gravity of 1.024 and a cell count of 3,500 per c.m.m., of which 95 per cent were lymphocytes. Guinea-pig inoculation of the sediment failed to reveal evidence of tuberculosis. Gastric washings were likewise negative for acid-fast bacilli. Liver function tests revealed the following: one-minute serum bilirubin .04, total bilirubin 0.30 mg. per cent; cephalin-cholesterol flocculation 1+, thymol turbidity 6.0 units; serum alkaline phosphatase 6.8 Bodansky units; urine urobilinogen 0.15 Ehrlich units per 100 cc., bile negative; serum proteins 6.8, serum albumin 2.45, serum globulin 3.73 gm. per cent. The sedimentation rate was 48 mm. in one hour.

Liver biopsy revealed many small and large granulomata (Fig. 3B), most of which resembled sarcoids and exhibited a reticulum network. Others were irregular in shape with indistinct margins and small areas of necrosis, suggesting tubercles, although no acid-fast bacilli were demonstrated.

Comment. The nature of the vertebral lesion, the lymphocytic pleural exudate, the strongly positive tuberculin reaction and the close association between the appearance of constitutional symptoms and the rash strongly suggested that the erythema nodosum in this case was due to tuberculosis. Presumably, the hepatic granulomata were also tuberculous and indicated hematogenous dissemination, as suggested by van Beek and Haex.[59] However, their histological features did not differ significantly from those in case 22, in which the erythema nodosum was regarded as non-tuberculous. Of special interest was the occurrence of hepatic granulomata in the absence of hilar adenopathy.

It is evident, therefore, that hepatic granulomata may occur in both tuberculin-negative and tuberculin-positive erythema nodosum, that they may be present in the absence of hilar adenopathy, and that their presence cannot be interpreted as proof of a tuberculous etiology, much less of a recent hematogenous spread.

Brucellosis. There is clinical and pathological evidence that the liver is frequently involved in brucellosis. Hepatomegaly,[68] alterations in hepatic function,[60] and jaundice[68] often accompany the disease, and autopsy studies of the liver usually reveal scattered granulomata, focal necrosis, and periportal cellular infiltration.[70] Cirrhosis is an occasional complication,[71–74] and it is thought by some that brucellosis is the direct cause,[75] or an important contributory factor in its pathogenesis.[60] Recently Spink and his associates[60] have reported on the liver biopsy findings in 10 patients with active brucel-

losis. Granulomata were demonstrated in every instance and were usually associated with a cellular infiltrate, especially in the portal areas. They emphasized that the granulomata were nonspecific and could not be distinguished from those of sarcoidosis and, less commonly, from those of tuberculosis and syphilis. Moreover, they made the important point that the diagnosis of sarcoidosis should not be made on the basis of hepatic lesions unless brucellosis has been excluded. Their attempts to culture brucella organisms from liver tissue failed.

Only 2 cases of brucellosis were available for study during this investigation. In one the disease was inactive and no hepatic lesions were demonstrated. In the other, liver biopsy revealed granulomata histologically and brucella organisms on culture. The clinical features in the latter case are summarized below.

Case 24. M.A., a 37-year-old white male, was admitted to the hospital on February 7, 1950, complaining of fever, drenching night-sweats, cough, and chest pain of four days' duration. He was known to have had an attack of brucellosis, complicated by acute cholecystitis, in 1947. In the interim he had felt well except for occasional flatulence and one brief bout of fever. Although the patient appeared ill, no abnormalities were noted on physical examination. The liver and spleen were not palpable.

Blood cultures were positive for *B. abortus* on 6 occasions. Similar organisms were also cultured from aspirated liver tissue, bone marrow, and urine. Brucella agglutinin tests were persistently negative. The gall bladder was not visualized after a double dose of Diodrast. X-ray examination of the chest revealed no abnormalities. Liver function tests revealed a total serum bilirubin of 0.4 mg. per cent, cephalin-cholesterol flocculation 2+, thymol turbidity 2.0 unit, serum alkaline phosphatase 4.7 Bodansky units, bromsulphthalein retention 11 per cent in 45 minutes, and prothrombin 64 per cent. Total serum proteins were 6.7 gms. per cent.

Liver biopsy before treatment revealed many large and small granulomata. Some resembled the lesions of sarcoidosis very closely (Fig. 4A); others were more irregular, exhibited more necrosis, and were more heavily infiltrated with inflammatory cells than is usual in that disease (Figs. 4B,C). The portal triads were moderately thickened by proliferating connective tissue and moderate round cell infiltration, but the lobular architecture was not distorted. There were also small focal areas of round cell infiltration within the lobular parenchyma. The biopsy was repeated one week and 7 weeks following a two-week course of aureomycin therapy. On both occasions the liver still showed small granulomata.

Beryllium intoxication. Following exposure to beryllium some individuals develop severe pulmonary symptoms due to a granulomatous pneumonitis.[76]

Autopsy studies in fatal cases indicate that the granulomatous process is not confined to the lungs, for miliary granulomata resembling sarcoids have been described in a number of tissues including the liver.[29-77] The resemblance to sarcoidosis is not limited to the histological picture, but extends to many of the clinical features, and especially to the roentgenological appearance of the lungs.[78] Scadding,[42] who believes that sarcoidosis is a specific tissue response to a variety of unrelated etiological agents, has suggested that beryllium sarcoidosis is only one of the several types that may occur, and has indicated the necessity for excluding beryllium intoxication in in-

vestigating the nature of any case of sarcoidosis. Until recently it has been assumed that a careful occupational history sufficed to exclude exposure, but the recent report,[77] supported by postmortem histological and chemical evidence, that beryllium intoxication may occur in individuals living near plants employing beryllium compounds, has greatly complicated the diagnostic problem. The possibility of such exposure must, therefore, be borne in mind in interpreting sarcoid-like granulomata found in liver biopsy material.

Only one case of presumed beryllium intoxication was available for investigation.* There was a definite occupational history of exposure to beryllium compounds for two years, following which the patient developed progressive dyspnea, orthopnea, cyanosis, and cough. When seen five years later he was completely incapacitated and presented the signs of a decompensated cor pulmonale with polycythemia, hepato-splenomegaly, clubbing of the fingers, and edema. Liver function tests were normal except for 8 per cent bromsulphthalein retention at 45 minutes, and a 2+ cephalin-cholesterol flocculation. X-ray examination revealed a fine, diffuse, nodular infiltration of both lungs compatible with beryllium pneumonitis, and cor pulmonale. Biopsy of the liver failed to disclose the presence of granulomata.

The diagnosis of beryllium intoxication appears to have been reasonably well established in this case. However, the x-ray findings in the chest and the cardio-respiratory symptoms were also considered compatible with an advanced sarcoidosis. It was only the occupational history which differentiated the two diseases. Even if the liver biopsy had been positive for granulomata it would not have aided in the differential diagnosis, since the lesions in the two diseases are indistinguishable.

Syphilis. Granulomata are said to occur in the liver during early acquired syphilis,[80] and according to Spink and his associates[69] may occasionally resemble those of brucellosis and sarcoidosis. No cases of primary or secondary syphilis were available for study during this investigation.

Leprosy. Miliary granulomata are frequently found in the liver in leprosy,[37] and may be very difficult to differentiate from sarcoids. Indeed, the clinical and histological features of sarcoidosis may be mimicked so closely by leprosy that the lepra bacillus or a related organism has been suggested as the etiological agent in sarcoidosis.[79] Unfortunately, no subjects were available for investigation.

Virus infections. A number of investigators have suggested a virus etiology in sarcoidosis,[7,80] and recently Löfgren and Lundbeck[41] have reported the isolation of a specific virus from gastric washings and biopsy material in six cases of sarcoidosis. Moreover, miliary granulomata may occur in other virus infections, and may occasionally give rise to difficulties interpreting liver biopsy findings.

* Since this paper was written granulomata have been demonstrated in biopsy tissue obtained from the liver and the skin of a patient with beryllium pneumonitis.

The liver is frequently affected in infectious mononucleosis, a presumed virus infection. Clinically, hepatomegaly and altered liver function occur with great frequency and jaundice is a not uncommon complication. Histologically, the liver usually shows marked hyperplasia of the reticulo-endothelium, and the sinusoids are packed with actively proliferating abnormal lymphocytes, simulating the picture of leukemia.[18, 81] Focal areas of parenchymal necrosis may occur and are usually infiltrated with large mononuclear cells.[82] These may resemble epithelioid granulomata, and, indeed, in the bone marrow granulomata indistinguishable from those of brucellosis, sarcoidosis, and tuberculosis have been described.[83] It is quite possible that similar granulomata may occur in the liver and make the differential diagnosis from sarcoidosis difficult.

Liver biopsy was performed in two non-jaundiced cases of infectious mononucleosis. Both showed the usual changes described, and in addition in one (case 25) there were small sinusoidal collections of large mononuclear cells resembling small atypical sarcoids (Fig. 5A).

Similar small granulomata were demonstrated in the liver during the acute phase of an influenza B infection in case 26 (Fig. 5B), and during the course of an acute febrile illness associated with a rash, thought to be viral in nature (case 27, Fig. 5D).

Mycotic infections. A number of disseminated mycotic infections give rise to visceral and pulmonary granulomata. Of these, histoplasmosis most closely resembles sarcoidosis, both histologically and clinically.[32–34] Granulomata have been described in the liver, amongst other tissues, so that the possibility of histoplasmosis must be considered when sarcoid-like lesions are demonstrated by liver biopsy. Typical *Histoplasma capsulatum* are often found within reticulo-endothelial cells in the liver, but they may be difficult to demonstrate without special stains[84].

One case of histoplasmosis with extensive pulmonary involvement and a strongly positive histoplasmin skin test was investigated. The clinical features suggested sarcoidosis as an alternative diagnosis. Liver biopsy failed to disclose any lesions.

A case of disseminated actinomycosis was also investigated (case 28). The disease was of many years' duration and had involved the subcutaneous tissues, lymph nodes, lungs, and bone before *Actinomyces bovis* was recovered. A liver biopsy revealed several, small, mid-zonal granulomata composed of epithelioid cells (Fig. 5C). No giant cells, actinomyces, or caseation were evident.

Hepatic granulomata have also been described in coccidioidomycosis,[85] and blastomycosis,[85, 86] amongst mycotic infections, and in granuloma inguinale[86] and tularemia.[31] However, neither the clinical nor the histological features in these diseases are sufficiently like sarcoidosis to cause difficulties in diagnosis. Moreover, in all but tularemia the etiological agent can be demonstrated in histological sections of infected tissues.

"Primary" liver disease with sarcoid-like hepatic lesions

In the course of investigating a large number of patients with overt liver disease by needle biopsy, sarcoid-like hepatic granulomata were found in 4 subjects, in whom the diagnosis of sarcoidosis had not been suspected, and in whom no other clinical or histological evidence of the disease could be found. These findings were difficult to interpret and several possibilities were considered.

In occasional cases of sarcoidosis the hepatic lesions may predominate and simulate the picture of primary liver disease, as in case 5. However, typical sarcoids can usually be demonstrated in other tissues in such cases. Although there are clinical reports of sarcoidosis affecting a single organ, they have seldom been confirmed by postmortem examination. It is obvious, however, that many lesions may escape detection by the techniques available to the clinician. It was possible, therefore, that some of the group under consideration fell into this category. Under such conditions, the hepatic granulomata would be indicative of a sarcoidosis either coincidental to, or provocative of the underlying liver disease. There is evidence in the literature to support both possibilities. Scadding and Sherlock[20] reported the occurrence of granulomata in a liver biopsy specimen obtained from a subject with carbon tetrachloride poisoning. The lesions were interpreted as evidence of sarcoidosis, although no other signs of the disease were found. Moreover, sarcoidosis has been reported at autopsy as an incidental finding unrelated to the cause of death.[11, 13, 53] On the other hand, reports of the occurrence of jaundice[7, 22, 23] and cirrhosis[8, 15] during the course of frank sarcoidosis, suggested that the underlying liver disease might be secondary to the granulomata in some of the present group. Finally, in view of the difficulty in distinguishing between the various types of hepatic granulomata, the possibility was considered that the lesions were not due to sarcoidosis, but represented non-specific reactions to the various etiological factors responsible for the underlying liver disease.

The following 4 case reports illustrate the possible diverse interpretations of hepatic granulomata found in subjects with overt liver disease and no other evidence of sarcoidosis.

Case 29. F.F., a 30-year-old white male, was admitted to the hospital on June 22, 1949, because of jaundice of two days' duration. Six days before admission his illness had begun with anorexia, nausea, and mild arthritic symptoms. He had enjoyed good health prior to the onset of his acute illness.

Physical examination revealed moderate jaundice and a slightly enlarged tender liver. There were no skin nor mucous membrane lesions, lymphadenopathy, splenomegaly, ocular lesions, or parotitis.

The leukocyte count on 6/23/49 was 8,500 with 35 per cent neutrophils, 64 per cent lymphocytes, of which several were regarded as atypical, and 1 per cent monocytes. Five days later the count was 6,200 with 67 per cent neutrophils, 29 per cent lymphocytes, and 4 per cent eosinophils. Heterophile agglutinins were positive 1:28 on 7/1/49, 1:28 on 7/30/49, and 1:14 on 8/26/49. Brucella agglutinins were negative. The tuberculin reaction was negative to the first strength and positive to the second strength of

PPD. The total serum proteins were 6.75, the albumin fraction 3.24, and the globulin fraction 3.51 gm. per cent on 6/25/49. These were restudied at frequent intervals and continued to show a slight elevation of globulin. On 8/25/49, at which time the jaundice had completely subsided, the total serum proteins were 6.99, the albumin fraction 3.37, and the globulin fraction 3.62 gm. per cent. X-ray examination of the chest, hands, and feet revealed no abnormalities. Liver function tests were carried out at frequent intervals. Only a few representative studies are given below:

	6-24	*6-30*	*7-14*	*7-28*	*8-11*	*8-25*	*9-21*
One-minute serum bilirubin, mg.%	2.78	1.18	0.31	0.14	0.13	0.07	0.05
Total serum bilirubin, mg.%	5.42	2.71	0.69	0.55	0.55	0.35	0.55
Cephalin-cholesterol flocculation	3+	3+	3+	2+	2+	2+	2+
Thymol turbidity, units	19.3	26.5	17.5	14.5	17.5	25.5	17.0
BSP retention, % at 45 minutes	..	..	..	19.0	22.0	14.5	6.5
Urine bile	4+	3+	0	0	0	0	0
Urine urobilinogen, Ehrlich units/2 hrs.	1.9	39.2	3.0	3.0	1.8	1.6	2.9

A liver biopsy performed on 7/27/49, the 42d day of disease, revealed a large number of granulomata compatible with the diagnosis of sarcoidosis, and minor changes in the portal zones and parenchyma indicative of a healing hepatitis (Fig. 6A).

The clinical diagnosis was infectious hepatitis, and the patient was treated accordingly. The course was afebrile and the patient made a rapid and uneventful clinical recovery, all clinical signs of hepatitis having subsided in two weeks. However, minor abnormalities in liver function, as indicated above, persisted until the date of his discharge from the hospital, 99 days after the onset of his illness.

The patient was readmitted to the hospital two months later for re-evaluation. He felt perfectly well at the time, and physical examination revealed no abnormalities. Liver function tests were carried out and all were within normal limits. The x-ray examination of the chest was still negative. The liver biopsy was repeated and once again sarcoid-like granulomata were found, but there were no signs of hepatitis.

Comment. The history and clinical course in this case were typical of infectious hepatitis. The initial blood count and the positive heterophile agglutinin test, however, suggested the possibility of infectious mononucleosis, a disease which might account for both the acute hepatitis and the granulomata. However, the absence of lymphadenopathy, splenomegaly, and sore throat, and the low titer of heterophile agglutinins were very much against the diagnosis. Moreover, it appeared unlikely that granulomata due to infectious mononucleosis would be found two months after recovery. As for the blood picture, it is well known that the differential white count in infectious hepatitis may resemble that in infectious mononucleosis. On the other hand, hepatic granulomata have not been described in infectious hepatitis, either in the acute phase or during convalescence[87, 88]; nor could the attack of jaundice be attributed to sarcoidosis in view of the prompt recovery despite the persistence of granulomata in the liver. It seemed highly probable, therefore, that this was a case of infectious hepatitis superimposed on an unrelated sarcoidosis. No other evidence of sarcoidosis was found, but deep-seated lesions in inaccessible lymph nodes or viscera could not be excluded.

Case 30. W.S., a 49-year-old white male, was admitted to the hospital on February 2, 1950, because of abdominal pain. For 2 years he had had typical symptoms of chronic cholecystitis and cholelithiasis, and for 4 months symptoms of diabetes mellitus. He had also had a chronic cough for many years, and had spent three months in a tuberculosis sanatorium, where no evidence of active tuberculosis could be found. There was a history of moderate alcohol intake, but the diet had been adequate until anorexia developed six months before admission. The patient's mother had died of diabetes mellitus at the age of 56.

Physical examination revealed moderate obesity, a moderately enlarged, firm liver with tenderness over the gall bladder area, and slight splenomegaly. There were no skin lesions, pulmonary signs, lymphadenopathy, ocular abnormalities, or parotitis to suggest sarcoidosis, and no collateral clinical evidence of cirrhosis, such as icterus, spider nevi, gynecomastia, enlarged abdominal veins, ascites, or edema.

Urine analysis revealed mild albuminuria and marked glycosuria, but no other abnormalities. The fasting blood sugar was 293 and the serum cholesterol 165 mg. per cent. X-ray examination of the chest and hands revealed no abnormalities. Five sputum concentrates and three gastric washings were negative for tubercle bacilli on stain, culture, and guinea-pig inoculation. The tuberculin test was negative to the first strength, but was not repeated with the second strength of PPD. The total serum proteins were 6.3, the albumin fraction 3.7, and the globulin fraction 2.6 gms. per cent. Serum calcium was 9.8, serum inorganic phosphorus 3.0 mg. per cent. Liver function tests performed shortly after admission revealed: total serum bilirubin 0.5 mg. per cent, cephalin-cholesterol flocculation 1+, thymol turbidity 2.0 units, serum alkaline phosphatase 3.4 Bodansky units, and bromsulphthalein retention 26.5 per cent at 45 minutes. Six weeks later these tests were repeated with almost identical results, except for a decrease in bromsulphthalein retention to 16 per cent. Bleeding, clotting, and prothrombin times were normal. A cholecystogram disclosed the presence of cholelithiasis. A roentgenogram of the esophagus failed to demonstrate varices.

Liver biopsy revealed: (a) derangement of the lobular architecture by marked interlobular fibrosis and fatty metamorphosis compatible with Laennec's cirrhosis, (b) vacuolization of the parenchymal-cell nuclei, such as is often seen in diabetes mellitus, and (c) a single large granuloma composed of epithelioid cells and central giant-cells, surrounded by a rim of fibroblasts and lymphocytes (Fig. 6B). There was no evidence of necrosis, and no acid-fast bacilli were demonstrated on stained section. One giant-cell contained a poorly defined asteroid body. Liver biopsy was repeated in 6 weeks with essentially the same findings.

Comment. There seems to be little doubt that the symptoms in this case were due to cholelithiasis and diabetes mellitus. The type of cirrhosis found at biopsy could have been related to either the diabetes or the alcoholism, or to both. The diabetes appeared to be the more important factor, since the alcohol intake had been neither very large nor accompanied by an inadequate diet. The family history of diabetes mellitus militated against the possibility that the diabetes was secondary to hepatic or biliary disease. The histological features of the hepatic granulomata and the absence of other known causes for such lesions suggested sarcoidosis, although no other clinical or histological evidence of the disease could be demonstrated. It was unlikely that the cirrhotic picture was secondary to granulomatous infiltration, in view of the paucity of the lesions and the presence of two other more common etiological factors. It appeared probable, therefore, that

the sarcoidosis was an incidental finding in a patient with diabetes and cirrhosis. Whether the sarcoidosis was confined to the liver is not certain, but it appears unlikely in the light of past autopsy experience.

*Case 31**. L.W., a 38-year-old white woman, first consulted her physician in February, 1949, because of nervousness, migraine headaches, and abdominal distension of about 8 months' duration. Physical examination revealed marked hepatomegaly and splenomegaly. No other abnormalities were noted.

The patient was admitted to a hospital where the following laboratory data were obtained: erythrocyte count 3.73 million, hemoglobin 10.65 gms., leukocyte count 5,000, differential count normal; sedimentation rate 43 mm. in one hour; urine analysis normal except for a trace of albumin. Total serum proteins were 6.25 gms. per cent with 3.25 gms. of albumin and 3.0 gms. of globulin. The serum cholesterol was 297 mg. per cent. Liver function tests revealed a total serum bilirubin of 0.75 mg. per cent, cephalin-cholesterol flocculation 3+, bromsulphthalein retention 20 per cent at one-half hour, and prothrombin 75 per cent of normal. X-ray examination of the chest, gastrointestinal tract, gall bladder, and spine revealed no abnormalities. Brucella agglutination tests were negative.

A biopsy of the liver was obtained through a small abdominal incision. Stained sections revealed an extensive granulomatous infiltration tending to disrupt the normal lobular architecture (Fig. 6C). Close to the capsule the granulomata were circumscribed and confined to the portal zones, which exhibited increased fibrosis and lymphocytic and eosinophilic infiltration. In the deeper layers, however, the granulomata were less well defined and occurred in both portal and mid-zonal areas. The lesions were composed of loosely arranged epithelioid cells, large numbers of giant cells, both of the foreign-body and Langhans' type, and were infiltrated and surrounded by many lymphocytes and a few eosinophiles. No areas of caseation necrosis were seen, but several of the lesions contained small foci of fibrinoid degeneration.

Following her discharge from the hospital early in 1949, the patient was treated symptomatically and appeared to improve. In July, 1950, approximately two years after the onset of her illness, she developed severe hematemesis and required a large number of blood transfusions before her symptoms abated. The hemorrhage was thought to be due to a ruptured esophageal varix.

Comment. This case illustrates that granulomatous infiltration of the liver may be of sufficient severity to simulate the picture of cirrhosis. The histological features were compatible with sarcoidosis. While no other features of the disease were demonstrated, it seemed probable that the spleen was also involved. The poorly circumscribed character of the lesions and the extensive lymphocytic reaction around them suggested the possibility of brucellosis and tuberculosis. However, the afebrile clinical course and the negative agglutination tests were against the former, and the negative chest x-ray, the absence of pulmonary symptoms, fever, or adenopathy appeared to exclude the latter. The increased periportal fibrosis and the disruption of the lobular architecture by the granulomatous process clearly indicated how granulomatosis of the liver could lead to cirrhosis during the phase of healing. The sudden appearance of massive hematemesis

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* The authors are indebted to Dr. O. L. Kirklin, Indianapolis, Indiana, for the clinical data and microscopic sections in this case.

compatible with rupture of an esophageal varix suggested that such progression had occurred in this case.

Case 32. N.P., a 54-year-old white male, was admitted to the hospital on November 21, 1949, complaining of painless jaundice and weakness of two weeks' duration. These symptoms were accompanied by dark urine, clay-colored stools, mild gaseous distention, and a 16-lb. weight loss. There were no chills, fever, biliary colic, anorexia, nausea, vomiting, or indigestion.

A history was obtained of "liver trouble" in 1926, but the patient could recall no details of this illness, and denied having had gastrointestinal symptoms prior to the onset of his present illness. The patient had consumed a minimum of one quart of beer daily for some time, but the diet had been good. For several months the patient had eaten 4 to 5 unwashed apples daily, which had previously been sprayed with a lead-arsenic mixture.

Physical examination revealed mild hypertension, obesity, moderate icterus of the skin and sclerae, hepatomegaly with a soft non-tender liver edge palpable a hand's-breadth below the costal margin, slight splenomegaly, and small palpable lymph nodes in the right axilla. There were no skin or ocular lesions, parotitis, or pulmonary findings to suggest sarcoidosis, and no collateral clinical signs of cirrhosis.

The blood count and smear were normal. The urine contained bile, 1+ albumin, a trace of sugar, and a few leukocytes. Subsequent analyses continued to show mild albuminuria and a few leukocytes, but no other abnormalities. A fasting blood sugar was 135 mg. per cent shortly after admission, but was never repeated. The non-protein nitrogen was 40 mg. per cent. The Kahn test was negative. Gastric analysis was normal. The feces were brown and contained occult blood. Liver function tests were carried out periodically and are summarized as follows:

	11-20	*12-5*	*12-9*	*12-29*	*1-2*	*1-26*
One-minute serum bilirubin, mg.%	5.55	1.95	1.35	0.85	...	0.20
Total serum bilirubin, mg.%	7.90	2.60	2.40	1.10	0.50	0.40
Cephalin-cholesterol flocculation	3+	...	3+	1+	1+	0
Thymol turbidity, units	10.1	...	3.75	1.0	1.25	2.25
Serum alkaline phosphatase, units	6.5	...	4.0	2.9	6.4	3.6
Bromsulphthalein retention, 45 min., %	...	14.0	14.0	11.0	1.0	2.5
Prothrombin, per cent	48	68	52	74	68	58

The total serum proteins were 7.0 gm. per cent. Agglutination tests for brucellosis were carried out on two occasions with negative results. A portion of the second liver biopsy specimen was cultured, but no brucella organisms were recovered. The tuberculin test was negative to the first strength, but was strongly positive to the second strength of PPD.

X-ray examination of the chest revealed cardiac enlargement, but no hilar adenopathy or pulmonary infiltration. Roentgenograms of the esophagus, gastrointestinal tract, and hands were normal. A cholecystogram showed poor filling of the gall bladder and a rounded area of calcification in the liver thought to be a calcified hemangioma.

Liver biopsy performed on November 30, 1949, revealed normal liver tissue except for: (a) a few small granulomata composed of epithelioid-cell clusters, (b) a mid-zonal area of focal necrosis infiltrated with lymphocytes and endothelial cells, (c) scattered hyaline necrosis of individual parenchymal cells, (d) a few dilated canaliculi filled with plugs of bile, and (e) moderate portal fibrosis. The necroses were interpreted as indicative of a focal hepatitis, possibly of toxic origin, and it was recommended that the biopsy be repeated to exclude sarcoidosis, in view of the presence of atypical granulomata. Accordingly a second biopsy was performed on January 24,

1950. This specimen revealed normal liver tissue with a number of circumscribed granulomata, chiefly in the portal areas, composed of epithelioid cells and a few giant cells. The granulomata were interpreted as indicating "probable sarcoidosis" (Fig. 6D).

The patient's course was afebrile, and on bed-rest and a normal diet the jaundice faded rapidly and the liver receded to the coastal margin. His appetite was excellent throughout his hospitalization and he had no complaints. He was discharged from the hospital on February 2, 1950, and was advised to return in two months for further observation.

On March 24, 1950, the patient was brought to the hospital in an ambulance and was dead on arrival. According to his family he had been well until two weeks before his death, at which time he began to complain of constant right upper quadrant pain. They attributed this to his having been drinking hard cider pressed from the same unwashed apples previously described. Three days before his death he disappeared from his home and was found wandering in the woods, after having fallen into a pond, and having been badly exposed. He was returned to his home feeling very weak. On the morning of his death he was found to be in a state of collapse at his bedside. Shortly thereafter he had a massive hematemesis and passed several tarry stools. An ambulance was called and he expired en route to the hospital.

The following is a brief summary of the findings at postmortem examination. There were multiple superficial ulcerations of the mucosa of the lower esophagus and of the lesser curvature of the stomach, with a large amount of clotted blood in the stomach. These were associated with a chronic esophagitis and chronic gastritis, but no esophageal varices were demonstrated. The liver was enlarged and exhibited both gross and microscopic evidence of a fine, diffuse cirrhosis. No circumscribed hepatic granulomata were found in 7 sections, but several showed small collections of epithelioid cells in the portal areas without giant cells. The spleen was slightly enlarged, weighing 375 grams, but contained no granulomata. A group of mediastinal and coeliac lymph nodes were enlarged and were found to contain numerous multinucleated giant cells of the foreign-body type with vacuoles and prominent asteroid bodies, and vacuolated macrophages. There was no associated fibrosis. The heart was considerably enlarged (700 grams), and the lungs were the site of an organizing non-suppurative pneumonitis. There were small collections of serous fluid in the pleural and abdominal cavities. Microscopic examination failed to reveal the presence of granulomata in any of the other viscera or lymph nodes examined.

The tissues and gastric contents were subjected to an exhaustive toxicological study, but no evidence of heavy-metal or alkaloid poisoning was found.

Comment. The history of possible exposure to arsenic, the clinical course, and the initial liver biopsy suggested an acute toxic hepatitis. However, the absence of fatty metamorphosis in the liver and the failure to detect significant amounts of arsenic in the tissues were important points against an acute arsenical hepatitis. While the age of the fibrosis found in the liver could not be estimated with certainty, it seemed more compatible with that of a Laennec's cirrhosis related to chronic alcoholism, than to the residuals of a recent acute hepatitis. In that event the attack of jaundice might be interpreted as indicative of hepatic failure on a cirrhotic basis.

The nature of the hepatic granulomata found on biopsy remains obscure. While they resembled sarcoids, no similar lesions were found at autopsy. The marked infiltration of the mediastinal and coeliac glands with foreign-body giant cells and macrophages did not resemble the lesions of the active phase of sarcoidosis, nor, in the absence of fibrosis, did they resemble those

of the healing phase. This case illustrates the difficulty of interpreting the significance of hepatic granulomata. A presumptive diagnosis of acute toxic hepatitis and coincidental sarcoidosis was made on the basis of the liver biopsy findings. It was not until the postmortem examination was carried out that it became evident that the diagnosis was incorrect. However, even then a thorough investigation of all the tissues failed to elucidate the nature of the granulomatous reaction.

Summary and conclusions

The clinical, functional, and histological status of the liver was investigated in 20 cases of sarcoidosis, and, for purposes of comparison, in a number of other diseases associated with granulomatous lesions.

Submiliary granulomata were demonstrated by needle biopsy of the liver in all 15 histologically-confirmed cases of sarcoidosis, but in none of the 5 with a presumptive diagnosis, and in 10 of the former, histological confirmation of the diagnosis rested on the liver biopsy findings alone. The incidence of hepatic sarcoids demonstrated by needle biopsy did not differ significantly from that observed at autopsy, indicating that the sampling error was small.

Hepatomegaly was present in 11 of the 15 cases exhibiting hepatic granulomata, and was accompanied by splenomegaly in 6. Mild gastrointestinal symptoms and minor alterations in hepatic function occurred in most of the subjects with hepatic sarcoidosis, but the evidence suggested that some of these were related to the systemic effects of the disease, rather than to the presence of specific hepatic lesions. In one subject, however, the granulomatous infiltration was sufficiently extensive to produce moderately severe hepatic dysfunction and symptoms, including jaundice.

Submiliary granulomata were also demonstrated by needle biopsy of the liver in miliary, pulmonary, and osseous tuberculosis, in erythema nodosum, and in brucellosis. These were often associated with slight hepatomegaly and minor alterations in hepatic function, as in sarcoidosis. Smaller, somewhat atypical granulomata were demonstrated in infectious mononucleosis, influenza B, in an unidentified viral infection, and in actinomycosis. No hepatic lesions were found in a subject with beryllium intoxication, or in one with histoplasmosis. The occurrence of miliary hepatic granulomata in early syphilis, leprosy, tularemia, and other mycotic infections was discussed, although no subjects were available for investigation.

There were striking resemblance in morphology between the hepatic lesions of sarcoidosis on the one hand, and those of tuberculosis, erythema nodosum, and brucellosis on the other. Although many of the granulomata in tuberculosis and brucellosis exhibited a greater degree of necrosis and surrounding inflammatory reaction than those in sarcoidosis, most of the lesions could not be differentiated on histological grounds alone. Caseation necrosis and acid-fast bacilli were demonstrated only once each in the

hepatic granulomata of 7 subjects with tuberculosis. Brucella organisms were successfully cultured from the liver biopsy specimen in a subject with active brucellosis.

The hepatic lesions in tuberculin-negative erythema nodosum did not differ from those in tuberculin-positive erythema nodosum, and could not be distinguished from those of sarcoidosis and tuberculosis. The interrelationships between these three diseases were discussed.

Granulomata resembling those of sarcoidosis were discovered on routine liver biopsy in a case of acute hepatitis and in 3 cases of cirrhosis, in whom no other signs of sarcoidosis could be found. The evidence suggested that the lesions were due to a coincidental sarcoidosis in the case of hepatitis and in one of the cirrhotics. In the third case the lesions were also probably due to sarcoidosis, but the cirrhosis appeared to be secondary to the sarcoidal granulomatous infiltration. In the fourth case the nature of the lesions could not be determined, even after postmortem examination, but sarcoidosis appeared to be excluded.

The results of this investigation indicate that needle biopsy of the liver is of great value in confirming the diagnosis of sarcoidosis histologically, especially when readily accessible lesions in the skin and peripheral lymph nodes are not available for study, but that the histological findings must be supplemented by other clinical and laboratory data to exclude granulomatous diseases which resemble sarcoidosis.

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