SARCOID AND SARCOID-LIKE GRANULOMAS
A Study of Twenty-Seven Post-Mortem Examinations *

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The cases classified in the literature as sarcoid and sarcoidosis represent a heterogeneous group both clinically and pathologically. The difficulty of characterizing sarcoid may readily be seen by examining the definition of this disease process prepared by the Conference on Sarcoid of the National Research Council: [1]

"Sarcoidosis is a disease of unknown etiology. Pathologically it is characterized by the presence in any organ or tissue of epithelioid cell tubercles with inconspicuous or no necrosis and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The characteristic lesions may be replaced by fibrosis, hyalinization or both.

"Clinically, the lesions may be widely disseminated. The tissues most frequently involved are lymph nodes, lungs, skin, eyes and bones, particularly of the extremities.

"The clinical course usually is chronic with minimal or no constitutional symptoms; however, there may be acute phases characterized by a general reaction with malaise and fever. There may be signs and symptoms referable to the tissues and organs involved.

"The intracutaneous tuberculin test is frequently negative; the plasma globulins are often increased.

"The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued chronic course of the disease."

In the present study an effort is made to clarify the relationship among the sarcoid and sarcoid-like granulomas seen in 27 necropsied cases collected at the Armed Forces Institute of Pathology.

Classification and Analysis

The cases for this study were selected from the following groups: (1) with undiagnosed non-caseous granulomas, 13 cases; (2) with granulomas of sarcoidosis, 10 cases; (3) with granulomas of sarcoidosis with clinical and pathologic evidences of secondary tuberculosis, 4 cases. Twenty-three patients were male and 4 female. This discrepancy in sex distribution is related to the predominance of males in the Army, reflected in the material in the files of the Armed Forces Insti-

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tute of Pathology. The ages ranged from 18 to 68 years. Seven of the 27 patients were Negroes.

The granulomas usually could be readily classified as either tuberculoid or foreign body type. The tuberculoid granulomas (Fig. 1) were characterized by a large number of epithelioid cells and by relatively few giant cells. The foreign body granulomas (Fig. 2) were characterized by many giant cells and by the paucity or absence of epithelioid cells. It was often difficult, however, to assign a granuloma to one or another of these categories since all degrees of variation between the typical forms were noted. In some instances granulomas of both types were seen within the same organ and within different organs of the same patient.

The giant cells contained inclusion bodies of several types: (1) plate crystal slits—the so-called cholesterol slits (Fig. 3), (2) asteroid or spiculated bodies (Fig. 4), (3) Schaumann bodies—the round or oval non-crystalline laminated inclusions (Fig. 5), (4) non-lipid crystalline material (Fig. 6). On this basis it was possible to classify the granulomas into four groups according to the type of inclusion bodies found in the giant cells.

The cases are classified and summarized in Table I. Three of the cases (nos. 1, 25, and 26) have already been reported,[2,3] and several of the remaining cases were included by Ricker and Clark[1] in their study of 300 cases of sarcoidosis. Two of the cases (nos. 19 and 20) have been reported by Pinkerton and Iverson[4] as probable cases of histoplasmosis.

Group I consists of only 2 cases with granulomatous lesions of the foreign body type in the lungs. The giant cells contained asteroid bodies and large plate crystal slits. Although in case 1 the granulomas were extensive, in neither this case nor in case 2 could death be attributed directly to them. Because the lesions were present only in the lungs, it was impossible to exclude an exogenous etiologic agent.

In the 12 cases of group II (nos. 3 to 14) with giant cells containing only asteroid bodies, granulomatous lesions were observed in a variety of organs. Although most of these lesions were of foreign body type, in 5 cases granulomas of tuberculoid type were noted also, sometimes in almost equal number. A few giant cells containing small plate crystal slits were present in cases 10, 12, and 13 of this group, but they were not as prominent as in the cases of group I. In only one patient (case 9) could death be attributed to the granuloma, since no other cause could be found to account for the terminal hemoptysis. Neither sarcoidosis nor tuberculosis was suggested clinically in any

of the cases. A disturbance of fat metabolism was noted in 7 of the 12 cases.

Giant cells containing both asteroid bodies and Schaumann bodies were observed in the 7 cases composing group III (cases 15 to 21). The granulomatous lesions were of both the foreign body and tuberculoid types and they appeared in many organs. A few giant cells in 6 cases contained small plate crystal slits, but these were not as prominent as in the cases of group I. The probable cause of death in 3 cases was the granuloma or terminal tuberculosis. No evidence of any relationship to metabolic disturbances was noted in cases of this group. A clinical diagnosis of sarcoidosis was made in case 17. In case 18, although there was some caseation necrosis of the epididymis, liver, and kidneys, repeated tuberculin tests were negative. In cases 19 and 20 there was a serum hyperglobulinemia. Tuberculin tests were not done in either case 19 or case 20.

In one of the 7 cases there was morphologic or biologic evidence of tuberculosis in addition to the non-specific granuloma. In this patient the signs and symptoms of disease became apparent 1 year before death. Several tuberculin tests were negative, and smears of the sputum showed no acid-fast bacilli. Five months before death there was an exacerbation of the disease, all of the previous Mantoux sites suddenly became positive, and subsequent tuberculin tests were positive. At about the same time acid-fast bacilli were demonstrated in the sputum and in a left axillary mass, and, shortly before death, in the spinal fluid. At necropsy, caseation necrosis was observed in lungs, liver, and spleen, and in some bronchial and para-aortic lymph nodes. The lobes of the lung and the lymph nodes that contained the asteroid bodies and the Schaumann bodies and crystals did not show caseation necrosis. Acid-fast stains of several tissue sections of non-necrotic bronchial lymph nodes revealed no acid-fast bacilli.

Pinkerton and Iverson,[4] in a more recent study of cases 19 and 20, observed large numbers of fungi, probably *Histoplasma capsulatum,* in the necrotic adrenal glands. The organisms were difficult to identify with the usual tissue stains, but were readily seen when periodic acid-Schiff's reagent was used. They concluded that these 2 cases probably represent uncomplicated histoplasmosis.

Granulomatous lesions were observed in almost all organs in the cases of group IV (cases 22 to 27) characterized by giant cells containing only Schaumann bodies. These lesions were of both foreign body and tuberculoid type, although the tuberculoid type predominated. In cases 24, 26, and 27 a few giant cells contained small plate

TABLE I

Classification and Analysis of Twenty-seven Cases of Sarcoid and Sarcoid-like Granulomas

Case no.	A.F.I.P. no.	Race, sex	Age	Clinical diagnosis	Organs and tissues† containing granulomas	Tissue acid-fast stains	Necrosis	Type of‡ granuloma	Possible disturbances in fat metabolism	Special tests	Cause of death
Group I. Asteroid bodies and large plate crystal slits within giant cells											
1	203190	W F	68	Tuberculosis or carcinoma	Lung *SL	–	–	F			Cocaine reaction
2	94944	W M	68	Coronary occlusion	Lung *SVR	–	–	F	Obesity		Coronary thrombosis
Group II. Only asteroid bodies within giant cells											
3	184035	C M	22	Methyl alcohol poisoning	Lung * Liver *E Spleen *	– – –	– – –	F			Acute methyl alcohol poisoning
4	181599	W M	30	Pulmonary embolism	Lung *VR Lymph nodes (hilar)	–	– –	F	Obesity; fatty infiltration of liver		Pulmonary embolism
5	120711	W F	55	Carcinoma of cecum or regional ileitis	Lung *V Spleen (?)		– –	F	Obesity; hypothyroidism; fatty infiltration of liver		Acute suppurative ileitis
6	95602	W M	44	Coronary occlusion	Pancreas *	–	–	F	Obesity; pancreatic necrosis; fatty infiltration of liver		Acute hemorrhagic necrosis of pancreas
7	124086	M		Cerebral malaria (?)	Lung *	–	–	F	Fat embolism following trauma		Pulmonary and systemic fat embolism
8	109562	W M		Appendicitis	Lung *VR Liver *VR Spleen	– – –	– – –	F			Ruptured appendix
9	149058	W M	22	Hemoptysis, cause undetermined	Lung * Spleen *R Lymph node (bronchial)* Liver *	– – 	– – – –	F	Fatty infiltration of liver	Sputum, acid-fast stains, negative	Hemoptysis, possibly due to granuloma
10	106812	C M	22	Generalized hemorrhage	Spleen *SRE Lymph nodes *VRE Lung R Liver R	– –	– – – –	Ft			Purpura

11	74926	W F	62	Intestinal obstruction with perforation	Spleen * Lung Lymph nodes * Liver	– –	– – – –	Ft		Tuberculin, negative; animal inoculation, negative	Intestinal obstruction
12	109226	W M	34	Unexplained sudden death	Lung *S Heart Spleen Liver	–	– – – –	FT			Coronary thrombosis
13	96128	W M	49	Myocardial infarction	Lung SR Lymph nodes *VR Liver VR Spleen E Adrenal rest tumor Heart(?) Thyroid gland(?)	– – –	– – – – – – –	FT	Hypothyroidism		Myocardial infarction
14	91001	W M	47(?)	Diabetes mellitus	Lung *VR Spleen Liver (?) Thyroid gland(?)	–	– – – –	Ft	Diabetes mellitus		Diabetic acidosis
					Group III. Asteroid bodies and Schaumann bodies within giant cells						
15	113763	W M	20	Accidental death	Lymph nodes *SVR Lung OR Liver	– –	– – –	Ft			Trauma
16	85448	W M	28	Suicidal death	Lung *VR Lymph nodes *SVRE Kidney *VRE Spleen VRE Liver SVRE Heart OE	– –	– – – – – –	FT			Trauma
17	96016	C M	26	Sarcoidosis	Lung OCVR Lymph nodes *SOVRE Spleen RE Liver	–	– – – –	Tf		Protein, normal; x-ray of extremities, negative; tuberculin, negative	Granuloma
18	169363	W M	27	Malignant hypertension; undiagnosed generalized granuloma	Lymph nodes *V Lung *L Kidney OVE Lymphatics (ureteral and hepatic) Epididymis Liver Diaphragm Stomach Pons	–	– – + – + + – – –			Protein 6.2 with A/G 3.8/2.4; tuberculin, negative	Granuloma

TABLE I (Continued)

Case no.	A.F.I.P. no.	Race, sex	Age	Clinical diagnosis	Organs and tissues† containing granulomas	Tissue acid-fast stains	Necrosis	Type of‡ granuloma	Possible disturbances in fat metabolism	Special tests	Cause of death
Group III. Asteroid bodies and Schaumann bodies within giant cells (*Continued*)											
19	121747	W M	54	Chronic glomerulonephritis, pulmonary tuberculosis	Tongue SOVL	−	−			Protein, 9.5 with A/G 5.2/4.3; animal inoculation, negative; (*H. capsulatum* demonstrated in adrenal gland)	Histoplasmosis
					Lung *SOCVRL		+				
					Stomach SOL		−				
					Kidney O	−	+				
					Spleen E	−	+				
					Adrenal gland	−	+	Ft			
					Liver E		−				
					Lymph nodes		−				
					Heart		−				
					Thyroid gland		−				
					Pancreas		−				
					Pectoralis muscle		−				
20	119987	W M	30	Miliary tuberculosis	Lymph nodes SOCR	−	−			Protein, 9.7 with A/G 5.1/4.6; x-ray of extremities, negative; (*H. capsulatum* demonstrated in adrenal gland)	Histoplasmosis
					Spleen *SVR	−	−				
					Lung OCRE	−	−				
					Liver SOC		−	FT			
					Adrenal gland R	−	+				
					Rib R	−	−				
					Kidney O	−	−				
21	148970	C M	30	Tuberculous meningitis	Lymph nodes (bronchial) OCVR	−	−			X-ray of extremities, negative; tuberculin negative, later positive; spinal fluid, acid-fast stained smear, positive	Granuloma; terminal tuberculosis
					Lymph nodes (bronchial and aortic) VR		+	FT			
					Lung *OVR		+				
					Liver		+				
					Spleen VR		+				
Group IV. Only Schaumann bodies within giant cells											
22	124456	W F	32	Regional ileitis, pulmonary embolism	Ileum OVR	−	−				Pulmonary embolism
					Liver CE		−	Ft			
23	173430	W M	18	Chronic cholecystitis	Lymph node OR		−				Cardiac failure during cholecystectomy
					Liver E	−	−	Tf			

24	172709	C M	25	Sarcoidosis	Heart E	−	−			Protein, 6.4 with A/G 1.9/1; x-ray of extremities, negative	Granuloma
					Lung SLE	−	−				
					Lymph nodes	−	−				
					Liver	−	−				
					Brain		−				
					Pituitary gland		−				
					Thyroid gland L		−				
					Prostate		−	Tf			
					Pancreas E		−				
					Epididymis		−				
					Kidney OE		−				
					Psoas muscle(?)		−				
					Retina		−				
					Spleen		−				
25	203191	W M	46	Coronary occlusion	Lymph nodes OC	−	−		Obesity		Coronary thrombosis
					Heart	−	−				
					Spleen	−	−				
					Liver		−	T			
					Pancreas		−				
					Kidney		−				
					Lung	−	−				
26	163480	C M	26	Tuberculosis, lung	Lymph node (cervical) SOCR		−			Protein, normal; x-rays of extremities, negative; sputum acid-fast stains, positive	Granuloma; tuberculosis
					Lymph node (interbronchial and pancreatic) OC	−	+				
					Liver C		+	FT			
					Lung CL		+				
					Stomach		−				
27	151036	C M	35	Unexplained sudden death	Brain R	−	+				Granuloma; probable tuberculosis
					Dura SOR	−	+				
					Lymph nodes R	−	−				
					Lung		−				
					Spleen		−				
					Liver R		−				

† Symbols indicate morphologic changes:
* = Asteroid body
S = Plate crystal slits
O = Schaumann bodies
C = Non-lipid plate crystals
V = Vacuoles in giant cells
R = Extracellular round spaces
L = Lipophages
E = Eosinophils

‡ Key to symbols:
F = Almost all foreign body type
f = Few foreign body type
T = Almost all tuberculoid type
t = Few tuberculoid type
FT = Equal numbers of foreign body and tuberculoid types

crystal slits, but they were not prominent. The only case in this group in which any relation to metabolic disease was suggested was an example of obesity. In 3 of the 6 cases the probable cause of death was the granuloma or complicating tuberculosis. By biopsy, a diagnosis of sarcoid was made in case 24, but no tuberculin test was done. Cases 26 and 27 had superimposed tuberculosis in addition to the non-specific granulomas. In case 26 the sputum was positive for tubercle bacilli, and at necropsy there was necrosis of the lymph nodes, lung, and liver. Caseation necrosis of the brain and dura was present in case 27, but no tubercle bacilli could be demonstrated.

It may be seen that the granulomas form a spectrum, and thus it is impossible to define clearly the lesions of any one group. The spectrum ranges from granulomas of foreign body type containing asteroid bodies, through those of mixed type containing asteroid bodies, Schaumann bodies, and non-lipid crystals, to granulomas of primarily tuberculoid type containing Schaumann bodies and non-lipid crystals. In groups I and II the granulomas were usually unexpected findings at necropsy and were unrelated to the cause of death. They occurred in a limited number of organs and were associated in some instances with abnormalities of lipid metabolism. In group IV the granulomas occurred in all organs and were not associated with any recognizable disturbance in lipid metabolism. In many of these cases death was directly attributable to the granulomas or to complicating tuberculosis. The intermediate group had some characteristics of both extreme types.

Because the morphologic features of the groups of granulomas demonstrated here overlap, it would appear impossible to define specifically the lesions of sarcoid and sarcoidosis.

Discussion

The cases in groups I and II (in which the giant cells contained asteroid bodies) are probably related to local or systemic abnormalities in lipid metabolism. This relationship was first perceived by Hirsch,[5] who pointed out that the asteroid bodies occur frequently in close association with plate crystal slits ("cholesterol slits"). Upon chemical analysis of splenic tissue containing such lesions he found large amounts of stearin and palmitin. Furthermore, he produced rosette-shaped crystalline inclusion bodies within giant cells of tubercle-like lesions in the lungs of rabbits by means of cholesterol-palmitin mixtures given intravenously. The crystals gradually became changed in the tissues so that they were no longer soluble in the usual fat

solvents. He postulated that asteroid bodies form in the same manner.

Previously reported studies of material from case 1 of this series[2] indicated that the lipid plate crystals were not cholesterol or an ester of cholesterol although they gave a positive Liebermann-Burchard reaction. It was concluded that the crystals were an unidentified lipid, probably a steroid. It was shown that the same lipid which crystallized in plates was capable of crystallizing in the shape of asteroids, suggesting that the asteroid bodies in the giant cells might be related to the plate crystals with which they were closely associated. However, since it could not be demonstrated that the asteroid bodies in the tissue were crystalline in structure, it may be postulated that the lipid crystals act only as a template which is later removed, leaving behind a telltale cytoplasmic reaction. This does not conflict with the recent observation of Cunningham[6] that the asteroid body itself is possibly protein in nature.

Since asteroid bodies within giant cells have been described in association with a variety of disease processes,[1,2,6-9] they probably are not disease specific.

Because of the confusion that exists in the classification of granulomas of this type it is suggested that descriptive terms be used in naming the granuloma,[9,10] for example, generalized (or localized) foreign body (or tuberculoid) giant cell granuloma with asteroid inclusions.

The cases of group III will be considered after those of group IV. The cases in group IV in which the giant cells contained Schaumann bodies, and in some cases non-lipid crystalline material, probably represent a heterogeneous group. Some of these might be classified as sarcoid and sarcoidosis. The inclusion bodies from 2 of these cases have been studied and reported in detail in a previous paper.[3] The crystals were shown to contain ferric iron but no silicon, calcium, or beryllium. They were thought to be comprised of inorganic material. The possibility was suggested that the intracytoplasmic crystalline material forms Liesegang rings,[11] and thus makes up the Schaumann body.

Lesions similar to these have been described in berylliosis,[12] asbestosis,[13] talcum powder granuloma,[14] and silicosis.[8] None of these substances is thought to be the causative agent in the granulomas reported here. When more is known about the nature of the inclusion bodies in these granulomas, it is probable that additional etiologic agents will be discovered.

The cases in group III in which the giant cells contained asteroid

bodies, Schaumann bodies, and in some cases non-lipid crystals are probably of the same type as the cases in group IV except that there is a resulting or coexistent local or systemic abnormality in lipid metabolism. The organisms of histoplasmosis have been demonstrated in 2 of the cases.[4] Although some observers have reported seeing intermediary forms between asteroid bodies and Schaumann bodies, no intermediary forms were found in any of these cases.

The cases in groups III and IV are morphologically most compatible with the definition of sarcoidosis advanced by the National Research Council. Few of the patients, however, exhibited the clinical manifestations accepted as criteria. In both of these groups the underlying disease was sometimes complicated by tuberculosis, much as silicosis is frequently complicated by tuberculosis.

Summary

Sarcoid and sarcoid-like granulomas were found at necropsy in a variety of organs and tissues in the 27 cases presented here. Although there was considerable overlapping, the cases were divided into four groups as follows: group I (2 cases) with asteroid bodies and large plate crystal slits within giant cells; group II (12 cases) with only asteroid bodies within giant cells; group III (7 cases) with asteroid bodies and Schaumann bodies within giant cells; group IV (6 cases) with Schaumann bodies and non-lipid crystalline material within giant cells. The possible significance of the various types of inclusion bodies was discussed. Reasons were given for supposing that the lesions of groups I, II, and III were related wholly or in part to local or systemic disturbances in lipid metabolism, and that those of groups III and IV were more heterogeneous, some possibly related to those generally classified as sarcoid or sarcoidosis. Two cases in group III have more recently been diagnosed as histoplasmosis.

It was difficult to define clearly the lesions of sarcoid and sarcoidosis because the lesions formed a spectrum of granulomas.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Granuloma of tuberculoid type. Spleen. Case 21. Hematoxylin and eosin stain. × 185. (Armed Forces Institute of Pathology neg. 103669.)

FIG. 2. Granuloma of foreign body type. Lung. Case 21. Hematoxylin and eosin stain. × 185. (A.F.I.P. neg. 103672.)

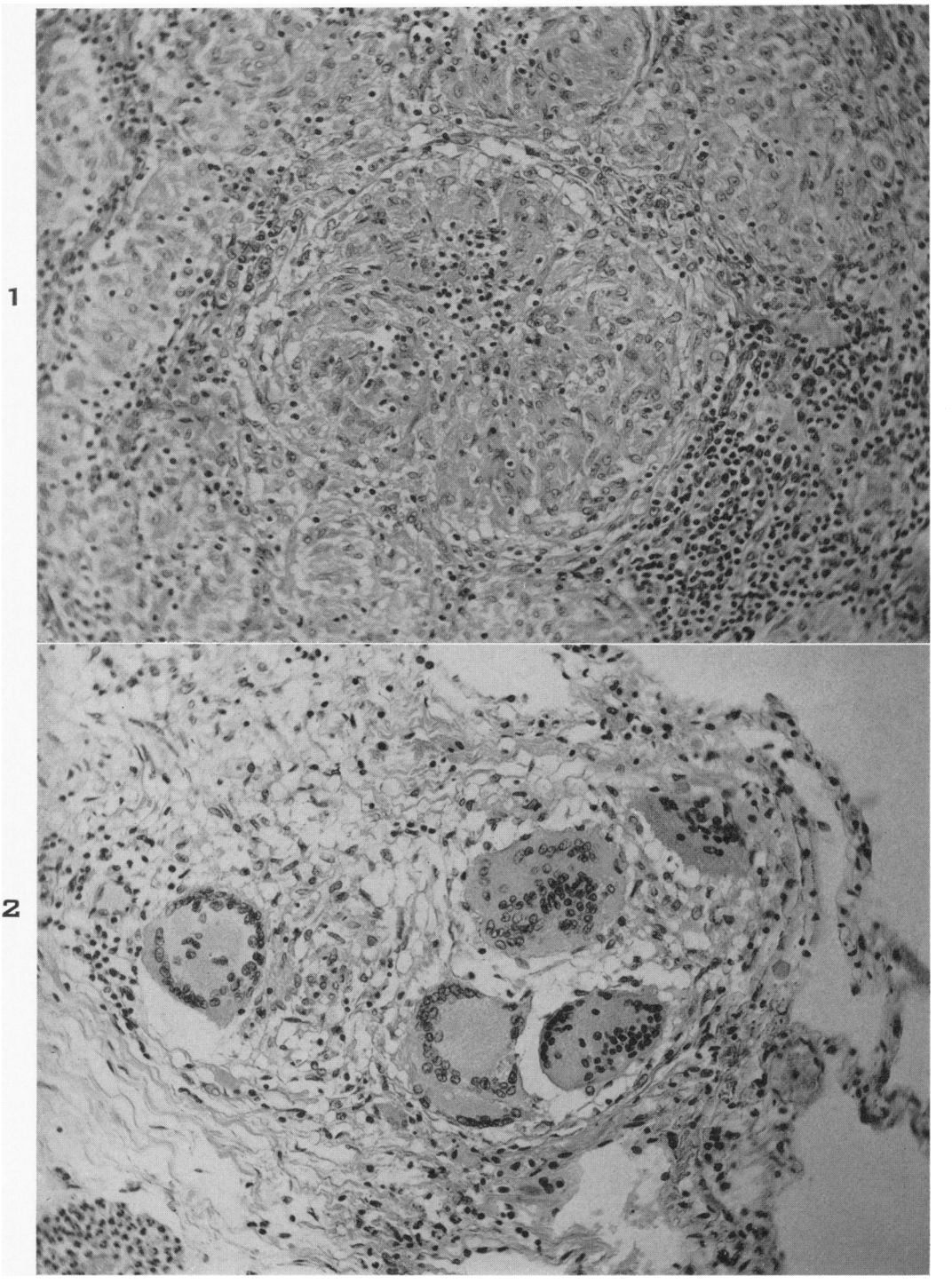
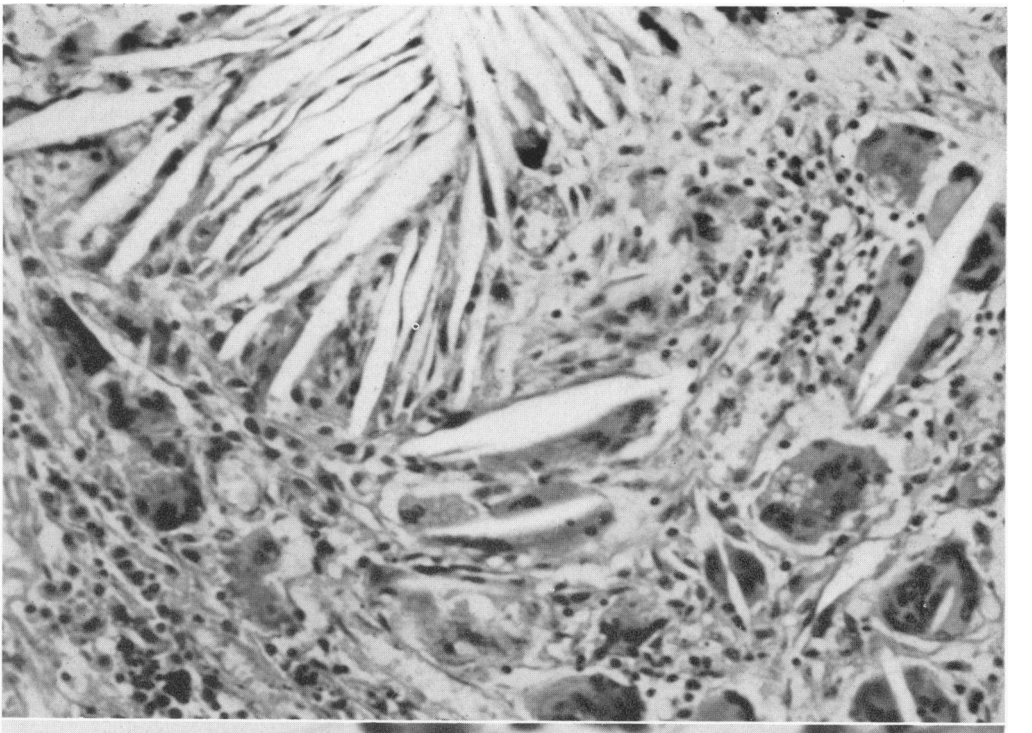


FIG. 3. Granuloma containing many plate crystal slits. Lung. Case 2. Hematoxylin and eosin stain. × 295. (A.F.I.P. neg. 86129.)

FIG. 4. Giant cell containing asteroid body. Lung. Case 16. Hematoxylin and eosin stain. × 900. (A.F.I.P. neg. 103515.)



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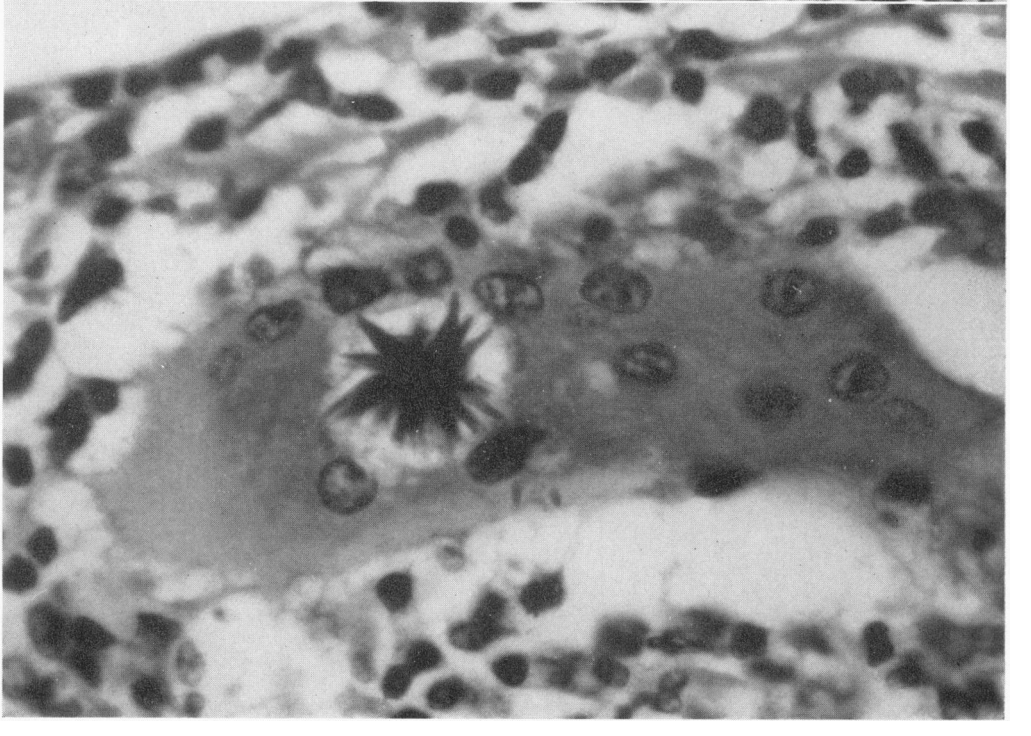

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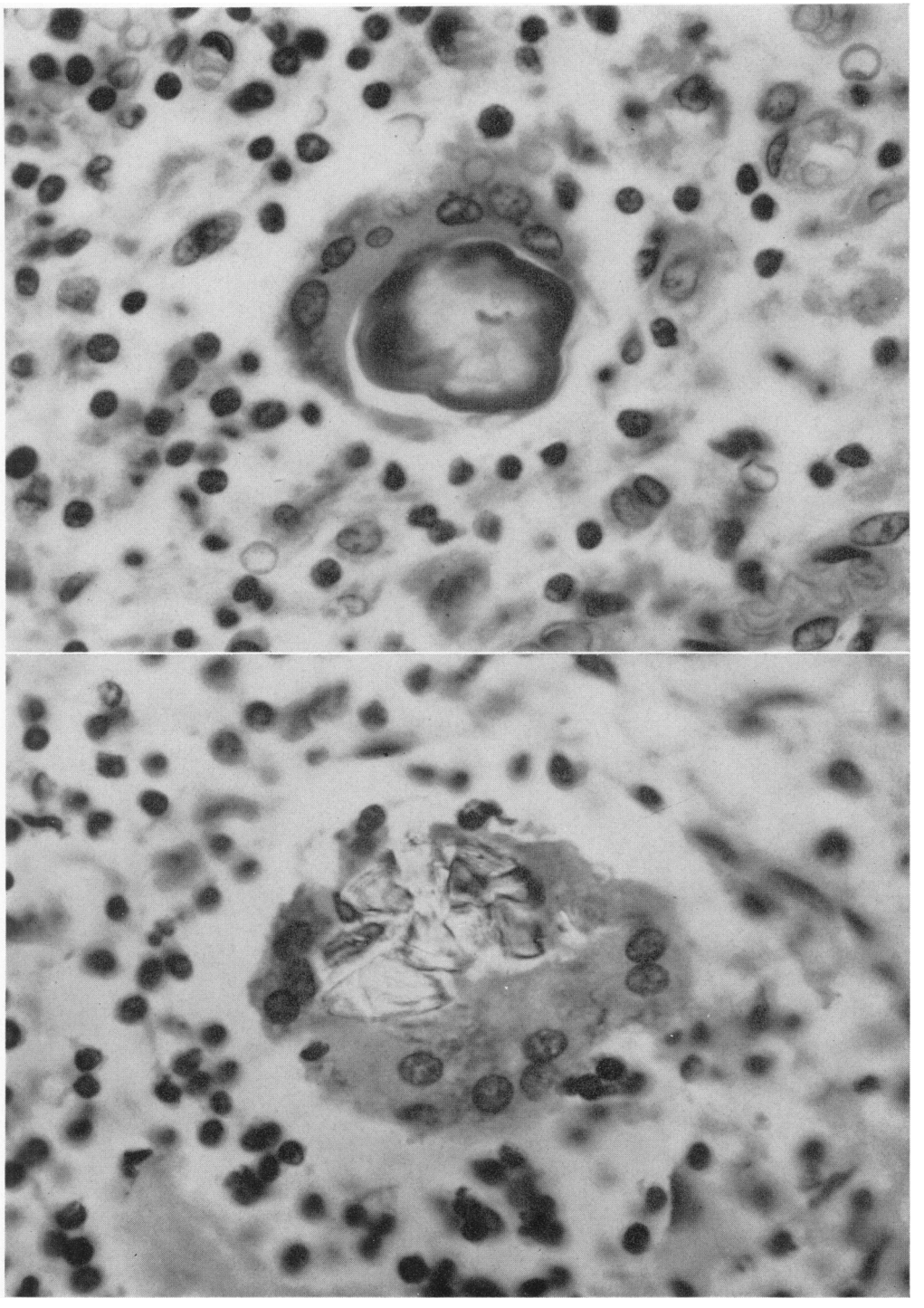
FIG. 5. Giant cell containing Schaumann body. Lymph node. Case 25. Hematoxylin and eosin stain. × 900. (A.F.I.P. neg. 103677.)

FIG. 6. Giant cell containing non-lipid crystals. Lymph node. Case 20. Hematoxylin and eosin stain. Polarized light. × 900. (A.F.I.P. neg. 104549.)



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