ALLERGIC GRANULOMATOSIS, ALLERGIC ANGIITIS, AND PERIARTERITIS NODOSA *

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During the past 25 years a relation between allergic states and vascular lesions of the type seen in periarteritis nodosa has been firmly established by study of human disease and by experimental evidence. Gruber [1] suggested that periarteritis nodosa is a hyperergic vascular response to infection. Cohen, Kline, and Young [2] postulated a causal relationship between allergy, as exemplified by severe asthma, and periarteritis nodosa developing in its course. Wilson and Alexander,[3] on reviewing the literature, found association of these two diseases in 18 per cent of 300 cases of periarteritis nodosa. Cases of this type have been studied also by Rackemann and Greene,[4] who described the clinical syndrome in some detail, and by Harkavy,[5] who interpreted this syndrome as an expression of vascular allergy. Rich [6,7] and other authors [8] found vascular lesions in patients who developed reactions to foreign serum or drugs (sulfonamides, iodine, dilantin), which Rich believed to be identical with those of periarteritis nodosa. Rich and Gregory [9] were able to reproduce these lesions experimentally in animals.

While most of the authors concerned themselves with pathologic changes in the vascular system, there are a number of reports in the literature indicating that, in addition, widely dispersed extravascular lesions may occur in connective tissue (Rössle,[10] Bergstrand,[11] Rich,[12] Smith [13]). Such lesions are characterized by inflammatory exudate rich in eosinophilic leukocytes, by necrosis of the exudate, and by severe alteration of collagen with granulomatous (epithelioid and giant cell) reaction.

The present report deals with cases of severe asthma which presented the clinical syndrome described by Rackemann and Greene,[4] and by Harkavy,[5] and which, on pathologic examination, exhibited the granulomatous extravascular lesions noted above, as well as necrotizing, inflammatory, and granulomatous vascular changes.

Most of our material is derived from cases autopsied in the Department of Pathology of the Mount Sinai Hospital, New York City. Of 23 patients in whom death was accompanied, or preceded, by severe asthma (status asthmaticus), 9 showed a strikingly uniform clinical

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picture. In addition to asthma, there were fever and hypereosinophilia, and symptoms of cardiac failure, renal damage, and peripheral neuropathy resulting from vascular embarrassment in various systems of organs. A patient with a similar syndrome was autopsied at the Long Island College Hospital * and another at the Barnert Memorial Hospital.* In addition, 2 patients with this syndrome are still alive and are being followed at the Mount Sinai Hospital. One patient, who later died at home, was treated at the Mount Sinai Hospital in 1941; at that time a specimen of a skin nodule was taken. No autopsy was obtained on this patient. Of the 14 cases exhibiting the clinical syndrome, specific anatomical lesions were found in 13. These 13 cases form the basis of the present report.

Clinical Data

Review of the data of our 13 cases (9 female, 4 male) yields a rather uniform clinical picture.

The age at the onset of asthma varied from 7 to 58 years. This preceded the terminal illness by an average of 3 years, with variation from a few months to 10 years. The course of the asthma was that of rapidly increasing severity until fever and hypereosinophilia appeared. Although one patient actually died in status asthmaticus, in the majority symptoms of asthma abated and sometimes completely disappeared during the course of the terminal illness.

Several patients exhibited sensitivity to various allergens and, sometimes, to bacteria cultured from the paranasal sinuses. Only a few reported a family history of allergy. Infection of the paranasal sinuses was present in the majority of cases; *Staphylococcus aureus, Staphylococcus albus,* and Pneumococcus were isolated from sinus washings in some of these. In one instance (M. M.) a pneumococcus was found in the sputum as well, during attacks of migratory pneumonia. In another instance (R. E.) blood cultures yielded a gram-negative rod during the initial stages of fever, identified as *Haemophilus para-influenzae.*

The duration of the terminal illness in the fatal cases varied from 3 months to 5 years. One patient is still alive 5½ years, and another, 1½ years after the onset of fever and eosinophilia.

Fever was present in all cases. It was very irregular; in some patients the temperature reached 40° C., but in the majority did not exceed 39°, or even 38° C. Usually the fever abated some time before death. There was marked leukocytosis, occasionally as high as 60,000 per cmm., and intense eosinophilia reaching 84 per cent of the total white count. Table I gives the absolute eosinophil count rather than percentage fig-

* We wish to thank Dr. Jean Oliver, and Dr. L. G. Shapiro and members of his staff for permission to publish these 2 cases.

TABLE I

Clinical Data in 13 Cases of Allergic Granulomatosis

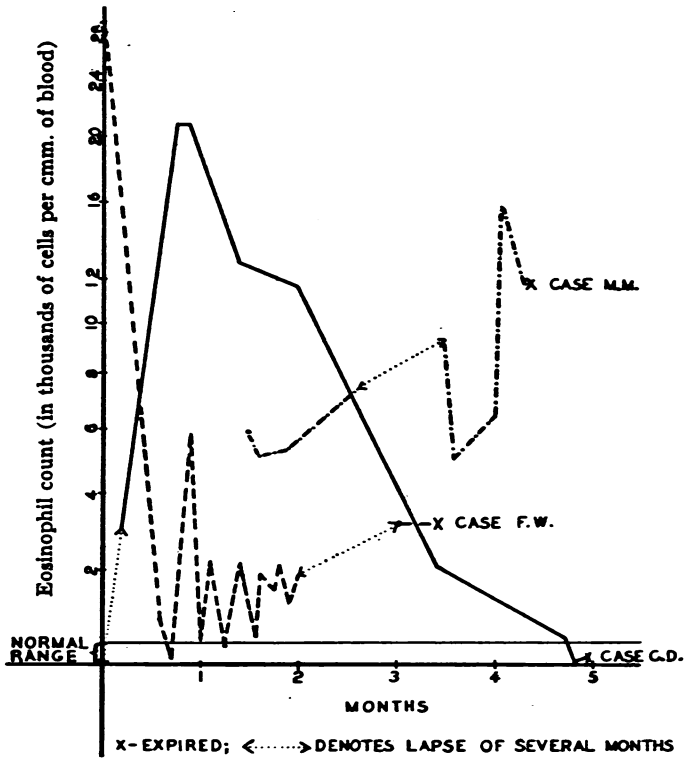
Case	Sex	Age at the time of death	Age at the onset of asthma	Evidence of sensitization	Family history of allergy	Sinusitis and other infections	Duration of terminal illness	Range of eosinophilia	Highest blood pressure	Organ manifestations								Cause of death	Remarks
										Lungs	Heart	Gastro-intestinal tract	Kidneys	Skin, purpura / Skin, nodules	Lymph-adenopathy	Peripheral neuropathy	Central nervous system	Joints	
		yrs.	*yrs.*				*mos.*	*cells/cmm.*	*mm. Hg*										
S.W.	M	38	35	+	o	+	3	90–8,100	120/90	+P	+Fl	+	o	+ o	o	+	o	o	Perforated peptic ulcer	
C.D.	F	45	44	o	o	o	6	60–21,500	150/110	+P	+Fl	+	±	o +	+	+	+	o	Cardiac failure	BUN, 75
S.S.	F	9	7	+	+	+	16	1,200–19,600	168/120	+P	+Fl	+	+	+ +	+	o	+	o	Cardiac failure	
B.Z.	F	28	18	+	o	+	8	200–6,500	150/11	+PL	+	+	+	o +	o	+	+	o	Uremia	BUN, 106
F.H.	F	24	18	o	o	+	60	0–29,000	136/90	+PL	+Fl	+	±	+ +	+	o	o	+	Cachexia	
H.C.	F	55	47	o	o	+	10	0–5,000	150/90	+PL	o	+	+	o o	o	o	+	o	Status asthmaticus	
M.M.	F	23	18	+	+	+	24	5,000–15,700	182/128	+PL	o	+	±	o o	o	+	+	o	Subarachnoid hemorrhage	Tr. pr., 1:1,280
F.W.	F	34	32	+	o	o	15	150–28,500	170/130	+P	+	+	+	+ o	+	+	+	o	Cerebral hemorrhage	BUN, 62 Tr. pr., 1:1,280
A.K.	M	44	40	o	o	o	3	5,600	125/85	+P	+	+	o	o o	o	o	+	o	? (No head examination)	
H.P.	M	63	58	o	o	+	6	2,500–13,000	130/90	o	+	o	+	+ o	+	+	+	+	Cerebral hemorrhage	
E.G.	F	21	17	+	o	+	20	2,100–11,000	150/110	+PL	+Fl	+	±	+ +	o	+	o	+	Cardiac failure	
R.L.	F	*	45	+	o	+	*	0–8,400	120/80	o	+	+	±	+ +	+	+	o	+		Tr. pr., 1:1,280
R.E.	M	†	9	o	o	+	†	130–28,400	170/120	+P	+	+	+	+ +	+	+	o	o		Positive blood culture (see text, p. 278) Tr. pr., 1:1,280

M = male, F = female; + = present or positive, ± = doubtful, O = absent or negative; P = pneumonia, PL = Loeffler's pneumonia, Fl = failure; BUN = blood urea nitrogen; Tr. pr. = serum precipitin test with trichinella antigen.

* Last seen in April, 1950, at the age of 56. Duration of illness at that time, 66 months.

† Last seen in April, 1950, at the age of 12. Duration of illness at that time, 20 months.

ures. In individual cases the eosinophil count fluctuated markedly during the course of the illness (Text-fig. 1). Occasionally it followed a peaked curve with a rapid drop shortly before death. In some cases it was persistently high, while in others it fluctuated between very high and normal. Such findings stress the importance of repeated differential blood counts. As in any wasting disease, anemia and weight loss were common accompaniments, the latter often being very marked, and out of proportion to the degree of fever.



Text-figure 1. Behavior of eosinophil count in three cases of allergic granulomatosis.

Recurrent episodes of pneumonia were present in nearly every case. Five presented the typical clinical and roentgenologic findings of Loeffler's pulmonary infiltration. Association of Loeffler's pneumonia with asthma and periarteritis nodosa has been reported (Hennell and Sussman [14]).

Numerous symptoms indicated involvement of various organ systems. Elevation of blood pressure was noted in 7 cases, particularly in those of longer duration, usually appearing in the latter part of the illness. Heart failure due to myocardial damage was frequent. Abdominal pain and diarrhea, often bloody, were present in nearly every

case. As a rule, there was mild hematuria and albuminuria; nitrogen retention occurred in only 3 cases. The majority of patients exhibited a variety of cutaneous manifestations, erythematous, maculopapular, or pustular. Of significance is the frequency of purpura (non-thrombocytopenic). The other lesion that merited special attention was a deep cutaneous or subcutaneous nodule, occurring on the head, trunk, and extremities. Such nodules were encountered in 7 cases; in 5 of these they furnished the anatomical basis (by biopsy) for the diagnosis of allergic granuloma. Generalized, though mild, lymphadenopathy was observed in over one-half of the cases. Manifestations of involvement of the central and peripheral nervous systems were very common. The former varied from disorientation to convulsions and coma; 3 of the patients died of cerebrovascular accidents. Peripheral neuropathy with variable motor, sensory, and trophic disturbances of the extremities and of the cranial nerves was observed in 8 of 13 cases.

Symptoms referable to joint involvement were not common: in 3 instances they were mild; in another they were severe enough to warrant the diagnosis of rheumatoid arthritis.

Of interest was the occurrence of a positive precipitin test with trichinella antigen in all 4 patients on whom the test was performed. Although the precipitin titer was very high (1:1, 280), the skin tests with trichinella antigen were negative. Similar findings have been reported in periarteritis nodosa.[15]

A summary of the clinical data is found in Table I.

Anatomical Findings

Because of the uniformity of findings, only a brief summary of the gross observations is presented. In the majority of cases the gross findings were those of periarteritis nodosa. There were nodular swellings along the course of small arteries of many organs, including the heart, liver, spleen, kidneys, gastro-intestinal tract, gallbladder, pancreas, and others. These vascular changes were accompanied by infarcts, hemorrhage, and scars in the affected organs. In a number of cases there was grossly recognizable vascular involvement of the lungs, consisting of thickening of branches of the pulmonary arteries and narrowing of their lumina, and occasional occlusion by a thrombus. In several instances there was patchy pneumonic consolidation, mostly confined to the lower lobes. In 4 cases the bronchi were filled with tenacious mucus.

Of all the organs, the heart was most prominently affected. Five cases showed pericarditis, 2 of them in an acute fibrinous stage. The heart usually was enlarged, both ventricles being involved. In addition

to the vascular changes mentioned, there were varying degrees of patchy myocardial scarring, and, in some cases, endocardial fibrosis accompanied by adherent mural thrombi, sometimes present in all four chambers. In no instance were there any valvular changes suggestive of rheumatic disease.

In 2 instances additional changes, which merit a more detailed description, were encountered in various organs.

Case A. K.* was characterized by the presence of widespread nodules, similar in appearance to those seen in miliary tuberculosis. They were well demarcated, firm, and glistening white or yellow, measuring up to 2 mm. in diameter. The lungs were thickly studded with these nodules and markedly increased in volume and weight (nearly 3,000 gm.). The spleen was considerably enlarged, weighing 460 gm., and showed innumerable nodules up to 1 cm. in diameter (Fig. 1). The same nodules were seen in the liver and in both kidneys, where they often coalesced to form larger masses.

Miliary nodules and larger aggregates were found also in the spleen of case H. P. This spleen was slightly enlarged (190 gm.) and was riddled with innumerable grayish, sometimes confluent nodules, averaging 1 to 2 mm. in diameter (Fig. 2). In this case there were no gross changes in the arteries, apart from arteriosclerosis of large vessels. However, the portal vein, just beyond the bifurcation, presented a raised, brownish plaque, about 2 cm. in diameter, which appeared to involve the entire thickness of the wall. In the heart, in addition to the gray streaks through the myocardium, there was marked thickening of the endocardium, particularly at the apex of the left ventricle, caused by deposition of gray, semi-translucent tissue under the smooth endothelial lining. The kidneys contained many cysts, probably on an arteriosclerotic basis. The parenchymal markings were somewhat obscured. The pelves and the ureters had unusually thick and rigid walls, and their mucosa was brownish gray and nodular. The ureters were slightly dilated.

Microscopic Changes

The histologic changes in all 13 cases were essentially similar except for minor variations. They are, therefore, described together in order to avoid repetition.

Connective Tissue

The important feature in nearly all cases (12 of 13), were lesions of extravascular connective tissues, including the stroma of various organs. Such lesions were, on occasion, very widespread, but more often they were found in just a few sites, or even in only one (Table II).

* The autopsy in this case was performed by Dr. Peter Gruenwald.

TABLE II

Anatomical Findings in 13 Cases of Allergic Granulomatosis
Location of Principal Extravascular and Vascular Lesions

Case	Extravascular lesions	Arterial lesions			Venous lesions
		Active	Healed	Granulomatous	
S.W.	Epicardium	Lungs, heart, kidneys, gastro-intestinal tract	Lungs, liver, gastro-intestinal tract	Kidneys, gastro-intestinal tract	
C.D.	Epicardium	Heart, liver, spleen, pancreas, kidneys, uterus, gallbladder, gastro-intestinal tract	Lungs, liver, pancreas, kidneys, gastro-intestinal tract	Heart, pancreas, kidneys, gallbladder, gastro-intestinal tract	
S.S.	Epicardium, periaortic tissue, liver, skin (biopsy)	Lungs, gastro-intestinal tract	Heart, liver, spleen, gallbladder, gastro-intestinal tract	Lungs, gastro-intestinal tract	Gastro-intestinal tract
B.Z.	Skin (biopsy)	Heart, spleen, kidneys, (healing)	Heart, liver, kidneys, gastro-intestinal tract		
F.H.	Skin (biopsy)	Uterus (healing)	Lungs, liver, kidneys, uterus, gastro-intestinal tract		
H.C.	Epicardium				
M.M.	Epicardium, myocardium, lungs	Heart, liver, kidneys, pancreas, diaphragm, gallbladder, gastro-intestinal tract	Heart, liver, spleen, pancreas, kidneys, gastro-intestinal tract	Heart, liver, kidneys, gallbladder	Heart (myocardial veins)
F.W.		Liver, kidneys, gallbladder, nerves, gastro-intestinal tract, adrenals, muscles	Lungs, heart, liver, adrenals, nerves, gastro-intestinal tract, muscles	Gastro-intestinal tract	Heart (large coronary vein)
A.K.	Lungs, spleen, liver, kidneys	Lungs, spleen, liver, kidneys, gallbladder		Lungs, liver, gallbladder, kidneys	Lungs (pulmonary veins), spleen (trabecular veins)
H.P.	Epicardium, myocardium, endocardium, spleen, kidneys, perirenal fat, ureters	Spleen (trabecular and follicular arteries), ureters	Ureters, adrenals	Spleen (trabecular arteries), ureters	Liver (portal vein), spleen (trabecular veins)
E.G.	Skin (biopsy)	Unknown			Unknown
R.L.	Skin (biopsy)	Gallbladder (biopsy)	Unknown		Unknown
R.E.	Skin (biopsy)	Unknown			Unknown

Inflammatory changes were always present, varying in intensity from diffuse sheets of exudate (Fig. 3), to small localized collections of inflammatory cells. The composition, as well as the extent, of the exudate seemed to depend on the phase of the inflammation, whether acute, subacute, or chronic. In the acute stage the predominant cell was the eosinophilic leukocyte which constituted as much as 70 to 80 per cent of the exudate. The number of eosinophils decreased as the acute inflammation subsided, but they were seldom entirely absent. Further characteristic elements were macrophages and giant cells, either of foreign body or of Langhans' type; these became more prominent as the process tended toward the subacute and chronic stages. In addition, there were varying numbers of plasma cells, lymphocytes, and neutrophils.

The most frequent site of inflammation was the heart, and, more particularly, the epicardium; but its manifestations were observed, as well, in the lungs, bile ducts, spleen, kidneys, ureters, perirenal fat, lymph nodes, muscles—in short, in any part of the body.

The most characteristic extravascular lesion was a granulomatous nodule (Figs. 4 and 5) associated with, or replacing, the inflammatory exudate and often located near a small vein. These nodules ranged in size from about 50 μ to 1 mm. or more, the latter being visible to the naked eye. They showed a central, eosinophilic core surrounded by radially arranged macrophages and giant cells. The eosinophilic core consisted of two elements: necrotic cells and severely altered collagen fibers. These two elements were not always clearly discernible at the same time, and not necessarily present in every instance. The cells involved in the process of necrosis were predominantly eosinophilic leukocytes, and, to a lesser extent, macrophages and local tissue cells. Small, dense aggregates of eosinophils occurred within the exudate in the acute stage. The leukocytes were at first intact, but subsequently underwent disintegration, with scattering of the eosinophilic granules and pyknosis and fragmentation of the nuclei (Fig. 6). The macrophages around such a focus assumed the appearance and the radial arrangement of epithelioid cells, although often their cytoplasm was less abundant and the nuclei more shrunken and distorted than those of true epithelioid cells. With Mayer's hematoxylin stain the fragmented nuclei frequently gave the necrotic center of the nodule a bluish cast; however, occasionally this was due to deposition of calcium salts. Apparently the cellular débris was removed, as in the majority of the nodules one could see only fragmented, granular, eosinophilic material without a trace of the pre-existing cellular elements. In some foci, epi-

thelioid cells predominated among the cellular elements in and around the area of necrosis, while giant cells were inconspicuous or entirely absent. In such cases the necrotic focus occupied the center of a nodule of epithelioid cells, and, as the lesion spread peripherally, additional layers of cells became necrotic. Such structures sometimes resembled epithelioid tubercles.

The second structural element of the granulomatous nodule consisted of severely altered collagen fibers. In the acute stage, collagen changes often were overshadowed by necrotic inflammatory cells, unless studied by connective tissue stains. With these stains it was possible to demonstrate an increasing acidophilia of the thin fibers, followed by complete loss of tingibility and eventual total disappearance. Fiber changes were best seen in lesions in which cellular exudate was negligible, particularly in the more chronic cases. The collagen change was of the nature of so-called fibrinoid swelling. The fibers became very thick, straight, and developed increased affinity for acid dyes. Along the edges of such fibers, splintering of short, thin fragments was observed; these were somewhat wavy, "spirochete"-like, or rod-like, and tended to break up into highly acidophilic granular masses. With special stains, such as the modified Mallory stain, the altered fibers showed transitions from blue-green to yellow. In polarized light, the fibers exhibited complete loss of the normal birefringence.

One might expect that much of the inflammatory exudate would undergo resorption; however, the more severe alterations in the tissues, particularly those leading to necrosis, apparently resulted in scarring with proliferation of fibrous tissue. The final scar did not differ from scar tissue in general, except when there were remnants of specific inflammation or necrotic foci. Scarring was most prominent around the blood vessels, and in the heart where it occurred in all three layers. In the epicardium, there was replacement of fat and fine reticular fibers by thick collagen bundles; in the myocardium, interstitial fibrosis extending from the septa indicated, at least in part, preceding interstitial inflammation; the endocardial scars often were accompanied by mural thrombosis. On occasion, secondary collagen change occurred in the scar tissue, usually accompanied by typical granulomatous proliferation.

Blood Vessels

Lesions of blood vessels were present in 9 of 10 autopsied cases, although on occasion, as in case H. P., they were few and inconspicuous. In the tenth case (H. C.), there were only a few scarred arterial lesions suggestive of arteriosclerosis rather than of a previous inflammation

and necrosis. The arterial alterations were essentially similar to those usually seen in periarteritis nodosa, as far as the character of lesions and organ distribution were concerned (Table II). At the same time they were related to the changes in the extravascular connective tissue described in the preceding paragraphs. All stages of necrotizing arteritis could be seen in nearly every case, although the healed, fibrosed lesions usually predominated. This is not surprising, in view of the long clinical course in the majority of cases. In the acute phase one could observe typical segmental "fibrinoid" necrosis of vessel wall, with marked swelling, destruction of the muscle and elastic tissue, and often, formation of an aneurysm. This was accompanied by an inflammatory response in and around the vessel, with predominance of eosinophilic leukocytes. The lumen often was blocked by a thrombus or by markedly proliferated endothelial cells, as emphasized by Bergstrand.[11] Narrowing of the lumen also frequently resulted from the reparative fibrosis and scarring of the affected wall. The final appearance of a healed lesion was indistinguishable from the end stage of any type of arteritis.

An important feature in many arterial lesions was the presence of macrophages and giant cells around necrotic areas, the macrophages frequently assuming the radial arrangement and appearance of epithelioid cells (Figs. 7, 8, and 9). This granulomatous response was found in at least some of the arteries in 7 of 9 cases showing active or healing lesions (Table II). In 2 instances (C. D., S. S.) many of the macrophages in the arterial media had vacuolated, foamy cytoplasm, as if loaded with lipids.

Alterations of the veins were less frequent and less prominent than those of the arteries. They were encountered in 5 cases (Table II). They bore considerable resemblance to the lesions in the extravascular connective tissue, rather than to those in arteries, consisting of acute inflammatory foci within the wall, usually accompanied by typical granulomata (Figs. 3 and 10). In some of these, healing was followed by formation of a scar.

Although the histologic appearance of the lesions described was rather uniform throughout the body, there were some peculiarities noted in individual organs, which merit special consideration. Among these were the heart, lungs, and kidneys, as well as the liver, spleen, lymph nodes, and skin.

Heart

Of all the organs in the body, the epicardium was the most common seat of granulomatous nodules (Fig. 5; 6 of 10 autopsied cases, Table II). The nodules were, as a rule, accompanied by inflammation and fibrosis, as previously described. The most constant lesion of the myo-

cardium was interstitial eosinophilic inflammation; this was present in 7 cases, varying in extent from an occasional focus to diffuse myocarditis. Granulomatous nodules, when they occurred, usually were situated in the connective tissue septa, on occasion closely simulating the myocardial Aschoff body of rheumatic fever. As previously mentioned, fibrosis of the myocardium was common; it probably resulted from anoxia secondary to vascular lesions, as well as from scarring of inflammatory foci. Valvular lesions usually were absent, but often the mural endocardium was involved, probably by extension from the myocardium. This resulted in patchy and diffuse subendocardial inflammation followed by fibrosis. In one case (H. P.) a small granuloma was found on a chorda tendinea of the mitral valve.

Lungs

Involvement of branches of the pulmonary artery was common (6 of 9 cases; Fig. 9). The veins were involved in one case (Fig. 10, Table II). In approximately one-half of the cases there were parenchymatous lesions in the form of a more or less extensive pneumonic process, involving septa as well as the alveoli (Figs. 11 and 12). In the acute stage the exudate was characterized by predominance of eosinophilic leukocytes, mixed with giant cells. The latter were very numerous in case M. M. Frequently, healing terminated in focal fibrosis (case H. P.). In 2 cases (M. M., A. K.) there were typical granulomatous nodules in the septa. These findings are very similar to those reported in Loeffler's pneumonia,[16,17] as already noted by several authors.[11,18,19]

Histologic evidence of bronchial asthma (hyalinization of basement membrane, increased mucous secretion, eosinophilic infiltration of the bronchial walls) was present in most of the cases, but was never very marked.

Kidneys

Acute or chronic renal vascular lesions and their sequelae were common. Frequently there was diffuse or focal interstitial nephritis with predominance of eosinophilic leukocytes. In some cases, this was accompanied by granulomatous nodules. In one instance (H. P.), the inflammation extended into the peripelvic fat and involved the entire length of both ureters. Most of the cases showed focal glomerular lesions (Fig. 13), usually involving only one or a few capillary loops, and rarely affecting the majority of glomeruli. Usually only the terminal stage, that is, fibrosis with complete obliteration of the involved loops and capsular adhesions, was seen. These changes bore considerable similarity to healed Löhlein's lesions. However, in 2 cases (M. M., H. P.) one could observe also acute lesions which consisted of marked

swelling and intense eosinophilia of the capillary walls, with necrosis of cells and fragmentation of the nuclei. Frequently the afferent arterioles and the pre-arterioles were involved in the same process, so that the fibrinoid change could be traced from an arcuate artery to the glomerular capillaries.

Tubular lesions were not constant and were mostly non-specific. In several instances many tubules contained granular material resulting from disintegration of eosinophilic leukocytes and lining cells of the tubules.

Liver

Lesions in the liver usually were confined to the blood vessels with resulting damage to the parenchyma. An occasional case (A. K.) showed extravascular granulomatous nodules. Of special interest in one case (S. S.) was affection of a large bile duct. This consisted of necrosis of the wall, infiltration by bile pigment, marked inflammation with exudation of eosinophils and plasma cells, and, finally, proliferation of fibroblasts.

Spleen

In the majority of cases there were no specific lesions in the spleen other than those of hilar or trabecular arteries. In one instance (H. P.) the follicular arteries showed prominent fibrinoid and hyaline changes, and in 2 cases there was inflammation of the trabecular veins (H. P., A. K.). In the same 2 cases, the spleen was the seat of extensive and striking parenchymatous changes. As mentioned, the gross appearance was suggestive of miliary tuberculosis; it was caused by discrete and conglomerate granulomatous nodules in various stages of development (Fig. 4). Many of these nodules were scattered at random throughout the red pulp; others lay in close relation to the trabeculae, encroaching upon the latter. The collagen fibers were spread apart by the infiltrating cells, sometimes appearing swollen and eosinophilic, sometimes thin and pale. Many of the fibers disappeared, with marked attenuation of the trabeculae. Healing of the nodules occurred by the usual process of fibrosis (case H. P.).

Lymph Nodes

Because of frequent generalized lymphadenopathy, many lymph nodes were removed at autopsy for histologic examination. Usually they showed non-specific, although sometimes quite extensive, inflammatory changes. In one case (H. P.), a lymph node removed for biopsy 5 months before death, at the height of the acute illness, revealed diffuse granulomatous inflammation with obliteration of architecture, proliferation of reticulum cells, eosinophilic infiltration, and an occasional

giant cell of Langhans' type. This picture was suggestive of early Hodgkin's disease. However, at autopsy, numerous lymph nodes showed only chronic inflammation with predominance of plasma cells.

Skin

Sections of cutaneous nodules were available in 6 cases. These nodules were located just beneath or within the dermis, and showed conglomerate and confluent granulomatous lesions with necrosis of collagen, and epithelioid, giant cell, and eosinophilic reaction (Fig. 14). The location of the nodules was sometimes paravascular; but, in no instance were lesions observed in the vessel walls.

In 3 cases, the granulomata were located in the subcutaneous tissue, and were identical with the nodules seen in the viscera (S. S., F. H., R. E.). In 2 others (E. G., B. Z.) the nodules were situated in the dermis and were less distinctly circumscribed (Figs. 15 and 16). They were characterized predominantly by severe fibrinoid alteration of collagen. In the sixth case (R. L.) there was homogenization of collagen in the lesion, similar to that seen in the nodules of rheumatoid arthritis. In this case there were severe joint symptoms.

Nerves

Sections of peripheral nerves were available in only one case (F. W.). These showed acute inflammation and necrosis of the walls of the nutrient arteries.

Comment

As mentioned above, of 14 cases exhibiting asthma, fever, and hypereosinophilia, 13 presented characteristic lesions. These consisted of infiltration of connective tissue with eosinophilic leukocytes, and fibrinoid change of collagen with granulomatous (epithelioid and giant cell) reaction in connective tissue and in the blood vessel walls. The remaining case * showed at the time of necropsy only completely fibrosed scars in the walls of many arteries and scars in the retroperitoneal connective tissue and the pericardium. In cases B. Z. and F. H. there were only a few subsiding lesions at the time of death in addition to the numerous vascular scars, and the diagnosis of allergic granulomatosis rests on biopsy of cutaneous nodules. This emphasizes the diagnostic importance of these nodules.

The presence of giant cells around necrotic collagen in the blood vessel wall has been noted by some of the early observers in reporting cases

* This case as well as cases S. S. and F. H. have been reported previously in detail by Harkavy.[5]

of periarteritis nodosa associated with asthma (Otani [20]). Similarly, giant cell reaction and fibrinoid alteration of extravascular collagen have been reported in cases of periarteritis nodosa ascribed to drug allergy (iodine,[7] dilantin [8]). There are cases on record in which giant and epithelioid cell reaction was found in the absence of allergic history,[18,21] but in at least some of them the author (Ophüls [21]) admits that the history was incomplete and that the anatomical changes in the lungs were strongly suggestive of asthma. Clearly, review of the literature cannot be relied upon to determine the relative frequency of granulomatous reaction and of extravascular lesions of collagen in cases with allergic background and those without such a background, because the clinical stories and, particularly, the microscopic descriptions are very often presented in an abbreviated form. At least a partial answer can be obtained only by comparison of available cases.

As might be expected, most of the cases reported in this series were indexed under the heading of periarteritis nodosa in the Pathology Laboratory of the Mount Sinai Hospital. Under the same heading there were 20 odd cases with no history of allergy, particularly none of asthma. We reviewed the clinical records and the pathologic material of all cases, numbering 15, in which histologic slides were available. Only one of these showed fleeting eosinophilia up to 1,300 cells per cmm. (14 per cent of 9,400 white cells); a few had an occasional eosinophil count of between 400 and 1,000, while in all other cases eosinophils were below 400, or absent. These findings are in agreement with those of Wilson and Alexander [3] who, in their review of 300 published cases of periarteritis nodosa, found that high eosinophilia was present in 94 per cent of cases associated with asthma and in only 6 per cent of those without a history of asthma.

The histologic slides in these 15 cases were searched for evidence of extravascular alteration of collagen and for epithelioid and giant cell reaction around altered collagen, whether extravascular or within the vessel wall. Extravascular changes were observed in 2 instances. In one, there were definite foci of fibrinoid alteration in the posterior mitral leaflet, accompanied by formation of ridge-like projections on the auricular surface of the valve. Less advanced collagen changes were found in the fibrous septa of the myocardium, usually near small blood vessels; these lesions were surrounded by myocytes and Aschoff cells, and were closely reminiscent of rheumatic nodules. In the second case, small foci of severe collagen alteration, apparently not connected with blood vessels, were seen in the splenic trabeculae. In the remaining cases of this group there were no extravascular lesions, and in none of

the 15 cases could we find epithelioid or giant cells around the altered collagen.

Recently, Zeek, Smith, and Weeter [22] described the morphologic lesions of what they called "hypersensitivity angiitis." Included in this group were patients who developed reaction to various drugs, particularly sulfonamides, and also one case of severe asthma. At autopsy they exhibited necrotizing arterial lesions in many organs, and, in addition, frequent involvement of veins, pulmonary vessels, splenic trabeculae and follicular arterioles, and necrotizing lesions in the renal glomeruli. In addition, there occurred edema of the interstitial tissue of the viscera and small foci of necrosis, and, occasionally, the interstitial tissue was infiltrated with inflammatory cells of various types, including eosinophils. As can be seen, these lesions are very similar to those observed in our series, although Zeek made no mention of epithelioid and giant cell reaction except to state that foreign body giant cells never occurred in experimental "true" periarteritis nodosa.

It has been the contention of many authors (Otani,[20] Zeek *et al.*,[22] Mallory [23]) that what is called periarteritis nodosa is not a single entity, but a heterogenous group of cases whose common denominator is the necrotizing arterial lesion. Zeek believed that there are at least two distinct types: the above-mentioned hypersensitivity angiitis and the "true" periarteritis nodosa. It seems to us that there are valid reasons, both clinical and anatomical, for defining the group here presented under the name of allergic angiitis and allergic granulomatosis (Churg and Strauss [24]). Relation of this group to the hypersensitivity angiitis of Zeek remains to be established. Its allergic etiology seems to be clearly proved, at least as long as asthma is considered an allergic disease. This does not mean that other cases classified as periarteritis nodosa may not also have an allergic etiology. However, if one excludes cases associated with asthma, and those due to drug and serum sickness, all of which constitute probably less than one-third of the entire group of periarteritis nodosa, there is very little clinical evidence of sensitization in the remaining two-thirds of the cases. It is true that arterial lesions very similar to those of periarteritis nodosa have been produced by injection of foreign serum in animals. We have no personal experience with these lesions. It seems to us, however, that it would be important to determine whether these vascular alterations truly reproduce periarteritis nodosa or, with due regard to species difference and the mode of sensitization, allergic or hypersensitivity angiitis.

In the cases here presented, allergic granuloma occurred in combination with angiitis, except for one instance in which vascular involvement

could not be demonstrated. There is no doubt that eosinophilic and granulomatous inflammation can exist quite independently of vascular involvement. These lesions have been observed in the lungs of patients with Loeffler's "pulmonary infiltration with eosinophilia,"[16,17] in the livers of children exhibiting marked eosinophilia (Zuelzer and Apt[25]), and in the hearts of individuals who developed allergic reaction to arsphenamides (Šikl[26]). The allergic nature of Loeffler's syndrome is generally accepted. In the cases described by Zuelzer and Apt there also is considerable evidence for the allergic mechanism giving rise to the granulomata in the liver. The occurrence of similar lesions in the appendiceal wall invaded by parasites, such as ascaris and strongyloides, gives support to this concept (Wenger[27]). It seems that when the anatomical involvement spares the vascular system, the clinical course is likely to be much milder and often self-limited, while the majority of cases with widespread vascular lesions end fatally.

Little can be said about the morphogenesis of allergic granulomatosis. Presumably, as a result of sensitization to inhalants, bacteria, or drugs, the antigen-antibody reaction produces or liberates a chemical substance or substances which damage collagen fibers and attract eosinophilic leukocytes. Whether collagen damage always precedes inflammatory exudation cannot be stated with certainty, although it often appears to do so. Unfortunately, we know nothing about substances that attract eosinophils. Although the altered collagen appears as in other types of periarteritis nodosa, there must be a difference in its chemical composition, because it excites epithelioid and, particularly, giant cell reaction. This difference may be due to substances responsible for the original damage to the collagen, or perhaps to some factor contributed by the eosinophilic leukocytes. In favor of the latter concept is the occurrence of giant cells in association with eosinophilic pneumonia, but in the absence of obvious collagen changes. Also, somewhat similar necrotic and granulomatous lesions were observed in certain cases of Hodgkin's disease, in lymph nodes rich in eosinophils.

Summary and Conclusions

The occurrence of a clinical syndrome of severe asthma, fever, and hypereosinophilia, together with symptoms of vascular embarrassment in various organ systems, has been established. Thirteen observed cases of this syndrome formed the basis of this study.

The basic anatomical changes in these 13 cases consisted of widespread vascular lesions of the type seen in periarteritis nodosa, and of characteristic tissue alteration in the vessel wall and in the extravascular collagen system.

This tissue alteration, common to all cases here reported, comprised necrosis of eosinophilic exudate, severe "fibrinoid" collagen change, and granulomatous proliferation of epithelioid and giant cells. This is considered a histopathologic entity termed "allergic granuloma."

The finding of the granulomatous lesions, both within vessel walls and in connective tissue throughout the body, suggests that this syndrome constitutes an entity apart from classical periarteritis nodosa. This assumption was corroborated by review of 15 cases of periarteritis nodosa without asthma, none of which revealed extravascular granulomata or granulomatous vascular changes.

Of frequent occurrence in this syndrome are cutaneous and subcutaneous nodules showing the typical connective tissue alteration. These are of significant value for diagnosis by biopsy. Of further possible diagnostic significance is granulomatous lymphadenitis.

It is suggested that other allergic syndromes (Loeffler, Zuelzer, Šikl) may represent the more benign forms of allergic granulomatosis, while angiitis is its most malignant expression.

ADDENDUM

As of January, 1951, patients R. L. and R. E. were living at the ages of 57 and 13 years, respectively. Duration of illness at that time was 73 and 29 months, respectively.

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DESCRIPTION OF PLATES

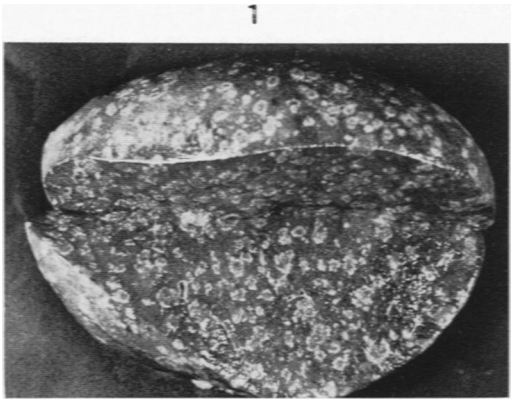
PLATE 48

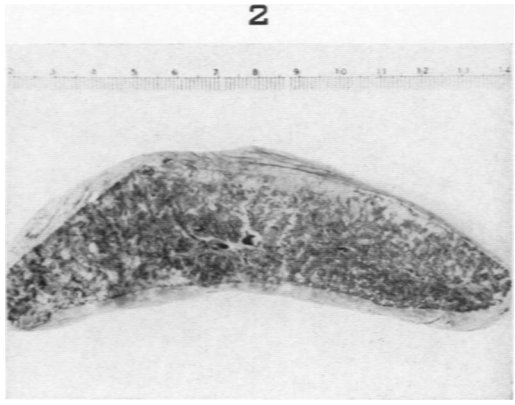
FIG. 1. Case A. K. Gross appearance of the spleen. Subcapsular and parenchymal nodules.

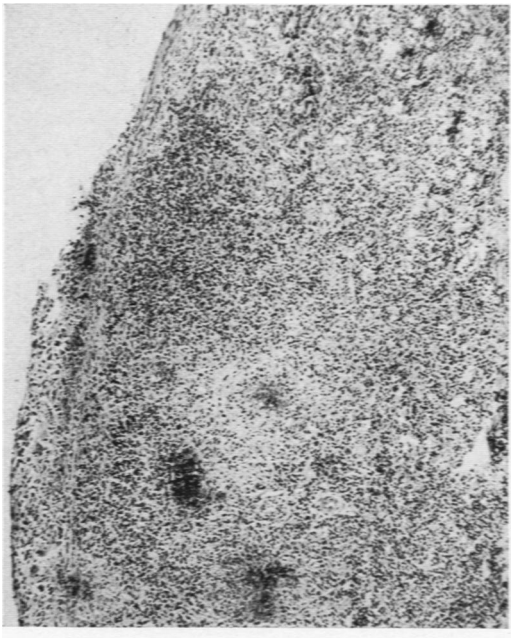
FIG. 2. Case H. P. Section of spleen. Discrete and confluent nodules in the pulp.

FIG. 3. Case H. P. Portal vein. Diffuse inflammatory infiltration with predominance of eosinophils, and scattered granulomata within the exudate. × 55.

FIG. 4. Case H. P. Spleen. Typical granuloma showing necrotic center surrounded by radially arranged epithelioid cells and a few giant cells. × 295.







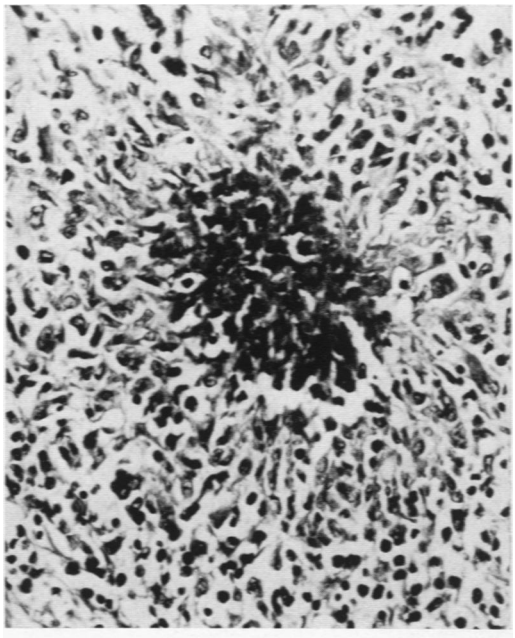


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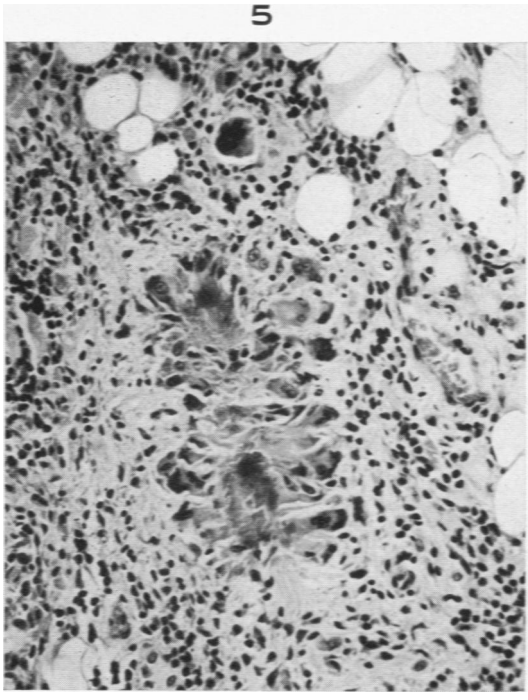
PLATE 49

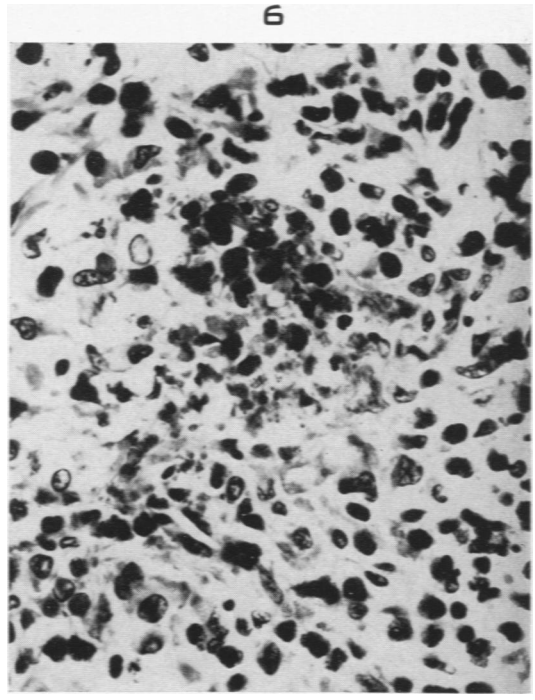
FIG. 5. Case H. C. Epicardium. Granuloma with numerous giant cells. × 200.

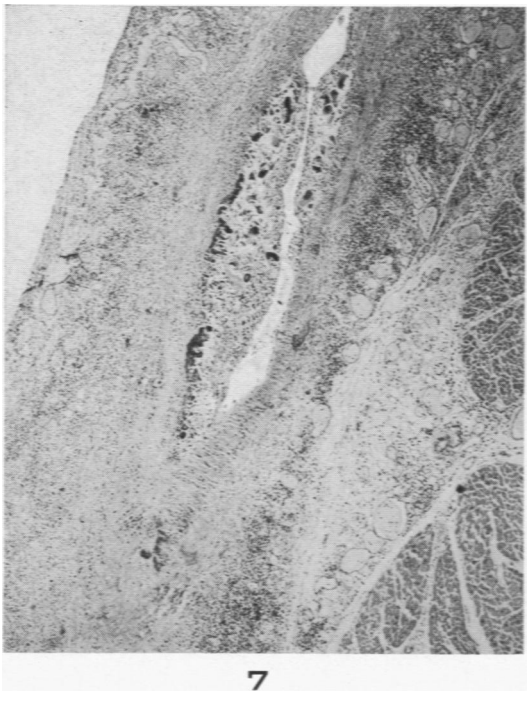
FIG. 6. Case H. P. Inflammatory exudate showing focus of clumping and disintegration of eosinophils. × 525.

FIG. 7. Case M. M. Coronary artery. Subintimal granulomata around necrotic collagen. × 30.

FIG. 8. Same as Figure 7, at a higher magnification. × 200.







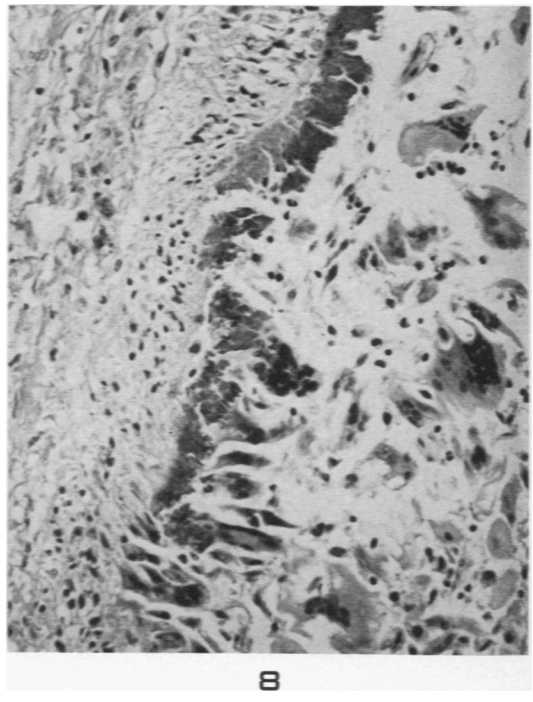


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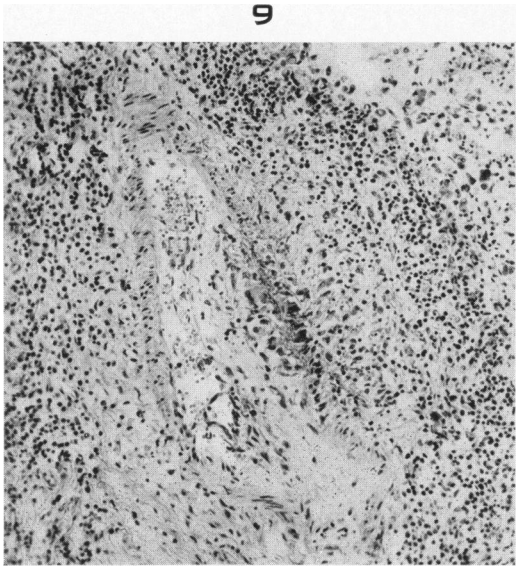
PLATE 50

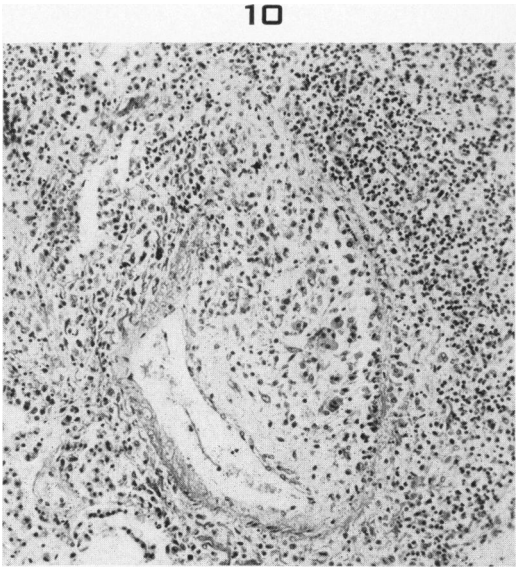
FIG. 9. Case S. S. Lung. Branch of a pulmonary artery showing marked narrowing of the lumen and a granuloma in the wall. × 100.

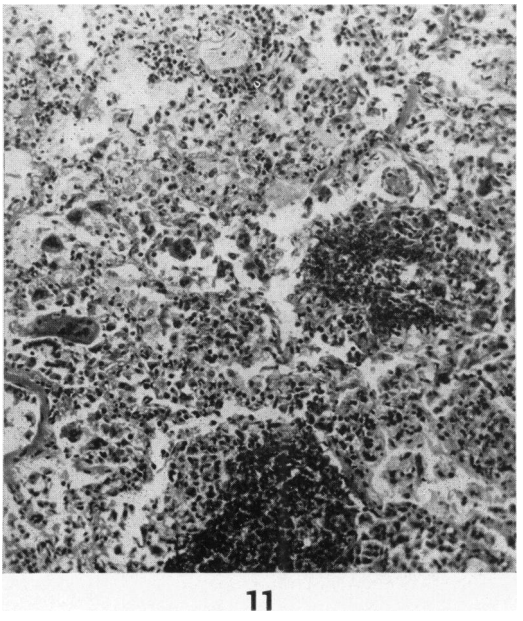
FIG. 10. Case A. K. Lung. Branch of a pulmonary vein showing a large subintimal granuloma. × 100.

FIG. 11. Case M. M. Lung. Eosinophilic pneumonia with necrosis of exudate, and giant cells. × 100.

FIG. 12. Same as Figure 11, at a higher magnification. Giant cells, edema, and infiltration of alveolar septa with eosinophils. × 375.







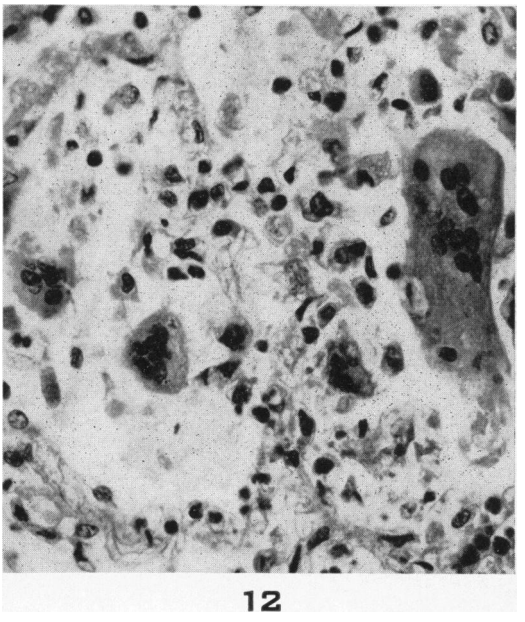


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PLATE 51

FIG. 13. Case M. M. Kidney. Focal necrotizing glomerulitis. × 330.

FIG. 14. Case S. S. Subcutaneous tissue. Diffuse inflammatory exudate and conglomerate granulomata. × 35.

FIG. 15. Case B. Z. Skin. Dermal granulomatous nodule with marked collagen change. × 60.

FIG. 16. Same as Figure 15, at a higher magnification. Junction of necrotic collagen with epithelioid cell zone. Many polymorphonuclear leukocytes may be noted. × 415.

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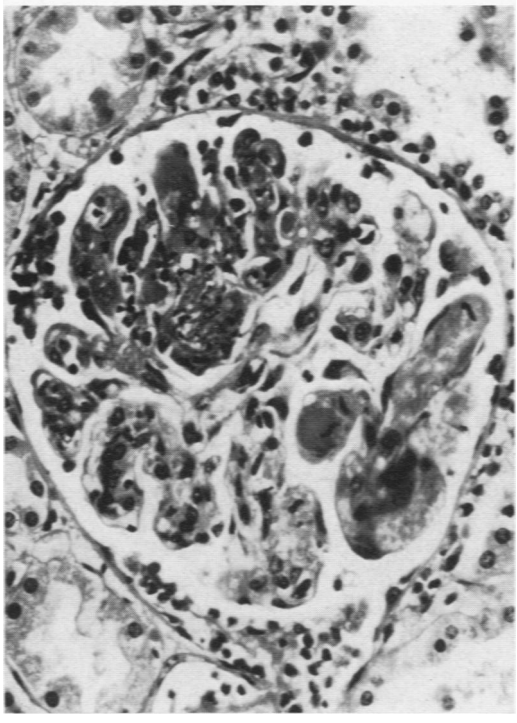

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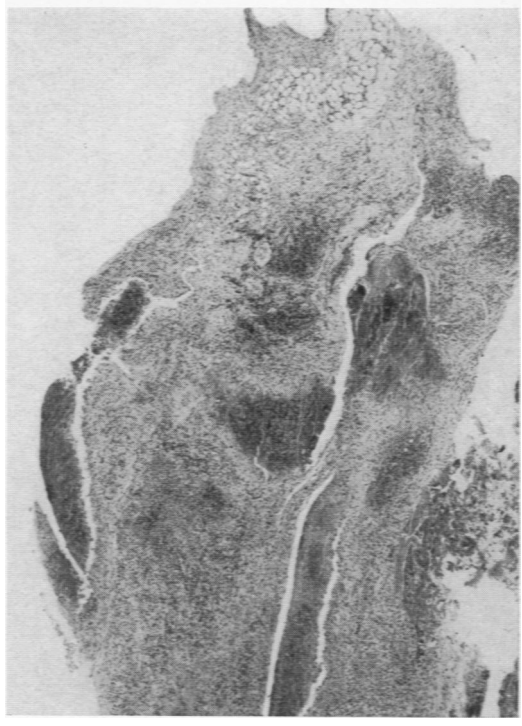

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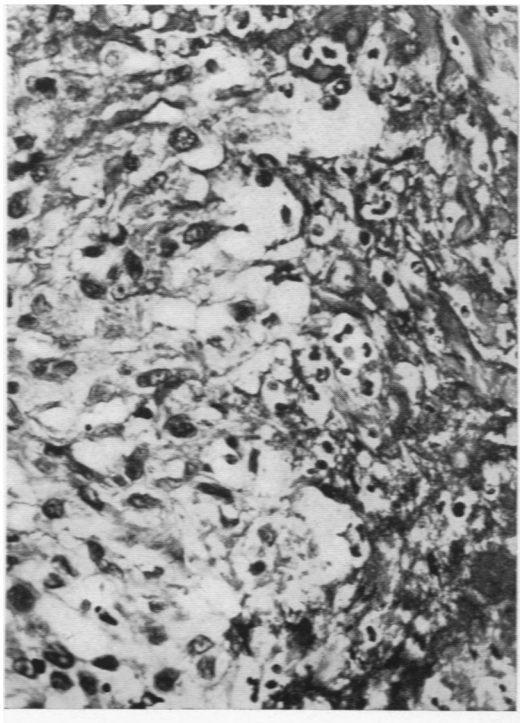

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