

FATAL NECROTIZING ANGIITIS ASSOCIATED WITH HYPERSENSITIVITY TO PENCILLIN O AND IODIDES

Report of Case

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UP TO A FEW YEARS AGO, periarteritis nodosa was rare and its cause unknown, but with more cases being reported and studied there appears to be little doubt that the condition is sometimes due to hypersensitivity reactions. This concept was suggested by Gruber¹ in 1925 and later substantiated by the work of Rich,² Rich and Gregory,³ Clark and Kaplan,⁴ and Germuth.⁵ According to Collens and Wilensky,⁶ most of the evidence at present suggests that periarteritis nodosa is fundamentally an antigen-antibody reaction involving the blood vessels. However, the groundwork for considering periarteritis nodosa more definitely on the basis of hypersensitivity created by drugs goes back to the fundamental studies of Landsteiner and Chase⁷ with haptenes in the production of anaphylactic sensitivity.

Because of the varied morphology of periarteritis nodosa, Zeek⁸ has preferred to use the term "necrotizing angiitis" to cover the entire group of vascular lesions, both arterial and venous, in which the fully developed stage is characterized by fibrinoid necrosis and inflammation. She distinguishes five different types morphologically and clinically, namely (1) hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatic arteritis, (4) periarteritis nodosa, and (5) temporal arteritis. The first two, she has said, may be due to hypersensitivity, but in classic periarteritis nodosa, hypertension is considered to be the important factor. While her classification is attractive, there is difficulty at times in recognizing each type pathologically and clinically.

Hypersensitivity appeared to play a definite role in the case of necrotizing angiitis that we are reporting. The case is unusual in that (1) it is one of the very few in which penicillin O has been suspected as the cause, (2) it was further complicated by the development of iodide sensitivity, (3) it may represent cross sensitization to penicillin O or a combination of sensitivity to both penicillin and iodides, and (4) it was not characterized by any healing in the arterial walls following cortisone therapy, which may well indicate that the dosage used was inadequate.

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REPORT OF A CASE

A 39-year-old white housewife, mother of seven children, who came to the Mayo Clinic on Nov. 8, 1953, had bronchial asthma, vasomotor rhinitis, nasal polyps, and bilateral chronic maxillary sinusitis. She had a history of being allergic to penicillin since 1950. The ear, nose and throat consultant recommended that she have bilateral nasoantral windows made, as well as nasal polypectomy and ethmosphenoidectomy. These procedures were carried out on November 13 after cortisone preparation for 2 days prior to operation. Preparation with cortisone was indicated because she had had 20-tablet courses of cortisone therapy 12 months, 5 months, and 3 months previously for relief of asthma. The amount of cortisone acetate used was 200 mg. intramuscularly 2 days before, 200 mg. the day before, and 100 mg. the day of operation. Postoperatively, the amount was rapidly reduced to none, and radium was applied to the nasal cavities in an attempt to prevent recurrence of polyps.

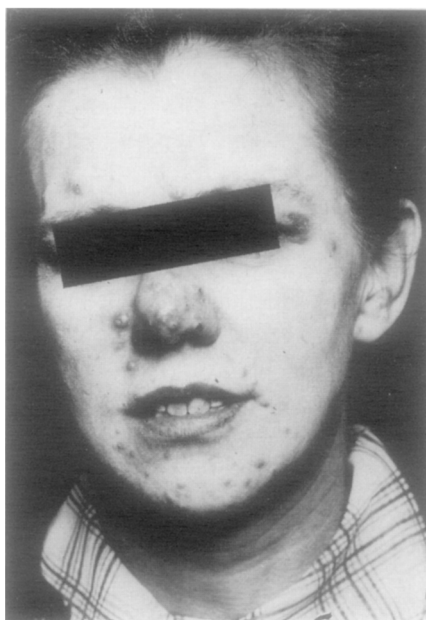


Fig. 1.—Appearance of bullae on face.

Because of her known sensitivity to penicillin G, she was given penicillin O, on the theory then current that it was hypoallergenic, in doses of 1,000,000 units along with 0.5 Gm. of streptomycin intramuscularly daily for 6 days postoperatively. In addition, she was given a nasal aerosol containing penicillin O and variable quantities of streptomycin, amounting to a total of 700,000 units of penicillin O and 0.0675 Gm. of streptomycin. The aerosol was mixed with Alevaire and administered at 2-hour intervals day and night for 6 days. There was no apparent immediate untoward reaction and she was dismissed a week later.

In December, 1953, she had pneumonia and was treated by her family physician with "nonallergenic" penicillin (O), approximately three or four injections, as well as with chlortetracycline (Aureomycin), four capsules daily for 1 week. At that time she said that her nose had continued to feel "plugged and stuffed" since her nasal operation. She recovered from this infection but was admitted to our dermatology service on Jan. 8, 1954, because of an eruption of the hands, face, and elbows of 3 weeks' duration. She had first noticed an erythematous papule over the dorsum and knuckles of the right hand.

Later bullae appeared, and, after a few days, vesicles were evident on the opposite hand as well as on the arms and legs. Bullae appeared on her face after her admission to the hospital (Fig. 1). She remained in the hospital for 6 days and was dismissed with a diagnosis of erythema multiforme. Her skin cleared and remained so until January 19, when a few hours after taking a teaspoonful of an iodide mixture for her asthma she broke out again with a skin reaction similar to the one she had presented on January 8 (Fig. 2). She was advised to avoid iodides in the future.

The patient remained fairly well, though weak and "run down," until about February 1, when she contracted a cold following chilling in subzero weather. Her asthma recurred and necessitated hospitalization in her home community where she again received penicillin O, cortisone, epinephrine, oxygen and other supportive agents. About February 20, she began to have soreness in the calves of her legs when walking, edema of the ankles and hands, burning in her feet and hands, and weakness of the hands and legs. Arthralgia



Fig. 2.—Appearance of eruption on hands.

was present in the wrists and ankles. About March 4, purpuric and ecchymotic areas developed about the ankles, feet, hands, sacrum, buttocks, and right ear. She was hospitalized in her home community on March 6 and was treated with vitamins K and B₁₂. Her asthma recurred and she was transferred to the Rochester Methodist Hospital 9 days later, where she was under observation and treatment until her death on April 15, 1954.

When the patient was admitted on March 15, 1954, the condition of her legs seemed to be somewhat improved. The burning had decreased considerably, though pruritus remained, and the edema was subsiding; however, she was still weak and clumsy. Her hands were swollen, stiff, weak, and incoordinated. Her blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic, her temperature 98.2° F., and her pulse rate 140 per minute. She appeared thin, pale, and chronically ill. She had a purpuric and ecchymotic eruption about the right ear, hands, sacrum, buttocks, ankles, and feet. Some old vesicular lesions on the legs appeared to contain pus. She had a creamy yellow discharge from the left external auditory meatus and a purulent postnasal discharge. Sibilant and sonorous râles were heard over the lung fields on expiration and inspiration. Expiration was prolonged, and chest expansion was limited. The right hand, forearm, and elbow were swollen. The fingers were stiff. Weakness of the arms and legs was believed to be the cause of her incoordination. The anteroinferior portion of the left tympanic membrane was perforated; the final diagnosis was chronic suppurative otitis media.

Dermatologic examination revealed that the skin reaction was somewhat different from the iodide eruption seen in January. The latter had cleared in 6 days, while the present one had been evident for 10 or 12 days and was hemorrhagic. It was thought that penicillin was most likely responsible unless the patient had taken iodides while in the hospital in February. The urticaria had been present about 3 days. The consultant in hematology believed that the patient had a vascular type of purpura, probably part of a sensitivity reaction, and noted that the high eosinophilia (55 per cent) was unusual although seen in some asthmatics in whom periarteritis nodosa develops. We who saw the patient clinically thought she had a drug reaction to penicillin O, although evidently she had no apparent immediate reaction to it when it was given in November, 1953. However, the preoperative administration of cortisone may have protected her. Penicillin G had provoked asthma in the preceding 3 years. Results of the lupus erythematosus clot test were negative.

On March 18, 1954, a diagnosis of periarteritis nodosa secondary to penicillin O was made and cortisone therapy was begun, starting with 200 mg. a day and later decreasing to 75 mg. a day. On March 23, a neurologic diagnosis of polyneuritis of the allergic type was made. Serum was obtained before cortisone therapy was started, and passive transfer studies with this in normal donor's skin showed no reactivity to penicillin G, penicillin O, or procaine. No tests were done with iodides as an antigen. Following the use of cortisone the patient seemed to gain in strength for 2 or 3 days, when supraventricular tachycardia (rate of 164) with palpitation and weakness developed unexpectedly. Quinidine and digitalis were given. About this time the urine began to show albumin and blood cells. Also, the blood pressure rose to hypertensive levels. The retinal arterioles showed narrowing, grade 2, with focal constrictions, grade 1, but no sclerosis. Vision was good.

Pain in the extremities continued to grow worse, requiring treatment with meperidine (Demerol) and morphine. On April 6, biopsy of the left gastrocnemius muscle confirmed the clinical diagnosis of periarteritis, and a bone-marrow study 4 days later showed severe eosinophilia and perivascular cuffing with plasma cells. On April 8 the patient had some epigastric and right upper quadrant distress with resistance on palpation in these regions. She also had dysphagia and was thought to be having intracranial involvement. The pain in the legs became almost intolerable, and any activity made it worse. Two or 3 days previously, her voice had become hoarse and the question of vocal cord weakness arose. Her urine showed a progressive increase in number of erythrocytes and in albumin. More petechiae developed and the abdomen became distended.

On April 14 the patient became disoriented and had visual hallucinations. Her blood pressure increased to 208/120 mm. Hg, her pulse rate increased to 124 per minute, and later some jerking developed in her left leg and arm. She became comatose and died on April 15, the terminal episode being due to cerebral involvement.

X-ray and laboratory data are given in Table I. In November, 1953, and January, 1954, routine urinalyses showed no blood cells. On March 16 the urine showed micro-hematuria, grade 1, and this increased up to the time of her death. Albuminuria appeared on March 31 and persisted until death. The value for hemoglobin decreased somewhat from November, 1953, to April, 1954. Leukocytosis was present from January, 1954, reaching its maximum about the middle of March. The differential counts showed marked eosinophilia most of the time, reaching its peak about the time the patient's condition was getting worse. The sedimentation rate was high even in January when she had the skin eruption probably due to iodides, then dropping until the terminal phase. The values for electrolytes were essentially normal up to within 1 week of death. Her temperature during her last hospitalization, as well as during the other two, remained normal or subnormal until the final day of life. Her coagulation and prothrombin times were within normal limits but the bleeding time was slightly increased. Inoculation of rabbit cornea with fluid removed from one of the bullae when she had a reaction to iodides in January did not produce any evidence of herpes virus. The results of all routine skin tests for allergy were negative except for a grade 3 reaction to cattle hair.

TABLE I. X-RAY AND LABORATORY DATA

ITEM	YEAR 1953	YEAR 1954						
	11-10	1-9	3-16	3-20	3-27	3-31	4-3	4-10
Thoracic roentgenogram	Neg.	Neg.	Neg.					
Urine								
Pyuria (grade)	*	1	1			4	2	1
Erythrocyturia (grade)			1			2	2	2
Albuminuria (grade)						2	2†	3
Blood								
Hemoglobin (Gm./100 c.c.)	13.2	12.8	11.9‡	11.2		12.2		11.2‡
Leukocytes (1,000s/c. mm.)	10.4	12.3	81.0	58.0	27.1	25.6		17.0
Differential count (%)								
Lymphocytes	26.5	10.5	10	9	8	13		16
Monocytes	4.5	4.0	4	2	5	4		2
Neutrophils	42.5	30.5	31	29	24	39		54
Eosinophils	25§	55	55	55§	61§	44		28
Sedimentation rate (mm. in 1 hr.)¶		75#		47	30	27		47
Flocculation test for syphilis	Neg.			Neg.				

*Occasional pus cell.

†Also grade 1 cylindruria (granular).

‡Erythrocyte count, 4,270,000 and 3,820,000 on 3-16-54 and 4-10-54, respectively.

§Also basophils, 1.5, 2, and 1 per cent on 11-10-53, 3-20-54, and 3-27-54.

||Also myelocytes, 3 and 1 per cent on 3-20-54 and 3-27-54.

¶Other blood data on 3-16-54: platelet count 294,000, bleeding time 7.5 min., coagulation time 6.25 min., clot retraction time 2 hr., and blood smear showing extreme eosinophilia. On 3-19-54: result of LE clot test negative. On 4-2-59: blood urea 28 mg./100 c.c., serum sodium 131, potassium 4.5, and chlorides 90.8 mEq./L.

#Sedimentation rate was 71 and 38 mm. on 1-12-54 and 3-19-54.

It seemed, in retrospect, that most of the vascular and renal changes had come in the final 4 weeks. Her progress had appeared to be satisfactory until she had become overly tired one day, and following this she started the downhill trend, but this may have been coincidental.

At necropsy, external examination revealed ecchymotic areas on the thighs, arms and shoulders, and petechiae over the abdomen, thighs, legs and feet. In the heart and pericardium were many small nodules 1 to 2 mm. in diameter, firm and yellow, and situated along the small vessels of the pericardium. Small focal infarcts were present throughout the myocardium. Hemorrhagic areas, a few millimeters in diameter, were seen throughout both upper lobes of the lungs, while small infarcts could be seen and palpated over the surface of both lower lobes. The bronchi were prominent, and bloody mucus and pus were present in both the trachea and the bronchi. Bronchiectasis was noted in the right upper lobe and both lower lobes, being most marked in the right lower lobe. Small hemorrhages could be seen throughout the spleen, and nodules were palpable along the splenic vessels. No evidence of infarcts was grossly visible. Perivascular nodules and small areas of infarction were evident in the liver. The gall bladder showed on its surface many nodules 1 to 3 mm. in diameter, along the course of the small vessels.

A mass approximately 5 cm. in diameter and hemorrhagic in appearance was present along the lesser curvature of the stomach; it proved to be a hematoma containing clotted blood. An ulcer, measuring 1 by 2 cm., was seen on the posterior wall of the stomach, approximately 5 cm. proximal to the pylorus. The small intestine and the colon contained many small infarcts, varying in diameter from a few millimeters up to 2 cm.; these were most abundant in the lower part of the ileum. The pancreas manifested nodularity similar to that seen in the heart, spleen and liver. There was bilateral cortical atrophy of the adrenals, and the cortices appeared rather pale. The kidneys were pale and had numerous petechiae over their surfaces. No evidence of gross infarction was seen. Palpation revealed small nodules in the bladder and diaphragm. The breasts, thyroid, and parathyroids appeared grossly normal.

A hemorrhagic infarct involved the right frontal lobe of the brain, and another involved the right temporal lobe. The fourth ventricle was filled with blood, and subarachnoid hemorrhage was seen over the spinal cord.

Histologically, numerous lesions of necrotizing arteritis were found throughout many of the organs studied, including the kidneys, heart, gastrointestinal tract, gall bladder, pulmonary-artery branches, follicular arterioles of the spleen, liver, pancreas, muscle, adrenal glands, uterus, bladder, peripheral nerves, and central nervous system. Arterioles and capillaries were commonly involved as well as small and medium-sized arteries. Two types of arteritis were seen. In the lungs, peripheral nerves, liver, and gastrointestinal

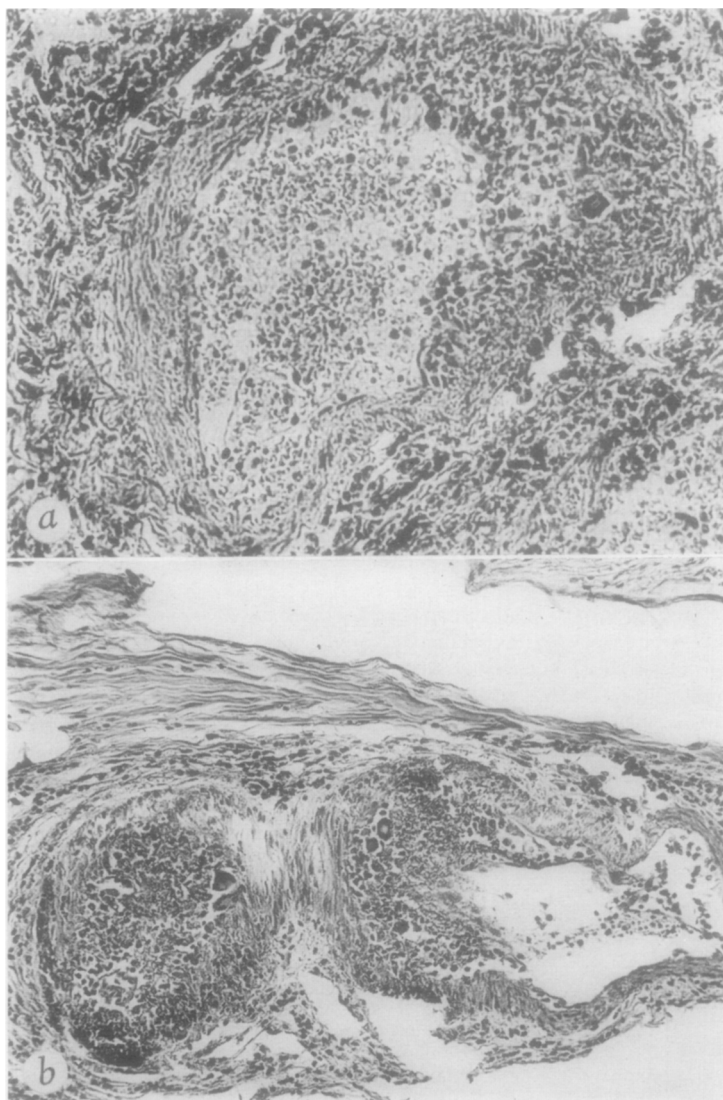


Fig. 3.—*a*, Small pulmonary artery showing granulomatous arteritis. Extensive inflammatory exudate consisting mainly of round cells and an occasional giant cell replaces much of intima and media in one part of vessel wall (hematoxylin and eosin; $\times 200$). *b*, Artery from right sciatic nerve showing granulomatous arteritis. Inflammatory exudate has destroyed much of intima and media at vessel branching. Giant cell reaction is prominent (hematoxylin and eosin; $\times 150$).

tract were seen vessels with granulomatous inflammation. The inflammatory reaction was predominantly intimal or adventitial and consisted of varying numbers of lymphocytes, plasma cells, polymorphonuclear leukocytes, epithelioid cells, and giant cells of foreign body or Langhans' type (Fig. 3). Eosinophilic infiltration was prominent in many areas of arterial inflammation. Other vessels in the organs noted showed the more characteristic acute arteritis as seen in typical cases of periarteritis nodosa. This consisted of fibrinoid necrosis of the vessel wall with acute inflammatory exudate throughout the various coats of the wall (Fig. 4, *a*). All the lesions seen were of either the acute or the subacute type corresponding in characteristics to the stages of acute inflammation or stage of granulation inflammation as described by Arkin.⁹ No extravascular granulomas were seen, but extravascular inflammatory reactions of other forms were notable.

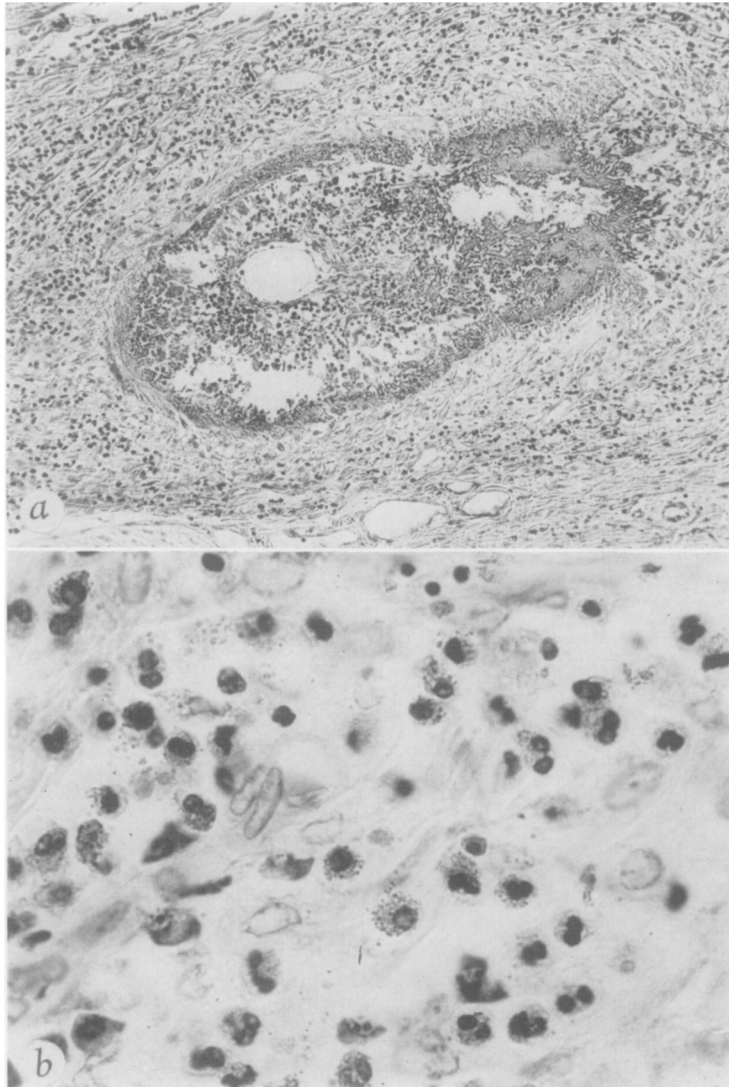


Fig. 4.—*a*, Artery in liver showing acute arteritis. Fibrinoid necrosis has destroyed much of media. Intima manifests inflammation with polymorphonuclear and round cells (hematoxylin and eosin; $\times 95$). *b*, Interstitial inflammatory reaction in hilus of liver. Inflammatory response is almost entirely eosinophilic (hematoxylin and eosin; $\times 725$).

Interstitial inflammation was seen in areas of the heart, liver, and peripheral nerves (Fig. 4, *b*). The inflammatory exudate was predominantly eosinophilic and plasma cell in character. In the cardia of the stomach there was an interstitial inflammatory nodule consisting of a central core of pyknotic nuclei and some fibrinoid material surrounded by macrophages which were in turn surrounded by an inflammatory exudate of eosinophils, lymphocytes, and plasma cells. In the kidneys were somewhat similar focal areas having a fibrinoid center with mononuclear inflammatory reaction surrounding it (Fig. 5).

Numerous areas of fibrinoid necrosis of glomerular tufts of the kidneys were seen (Fig. 6, *a*). Epithelial proliferation of the glomeruli was prominent, with adhesive capsulitis and crescent formation (Fig. 6, *b*). Periglomerular inflammatory reaction with polymorphonuclear leukocytes and lymphocytes was common. Occasional glomeruli showed areas of fibrosis. Tubules manifested severe degenerative changes. In the interstitial tissues a prominent inflammatory reaction with lymphocytes and plasma cells was seen.

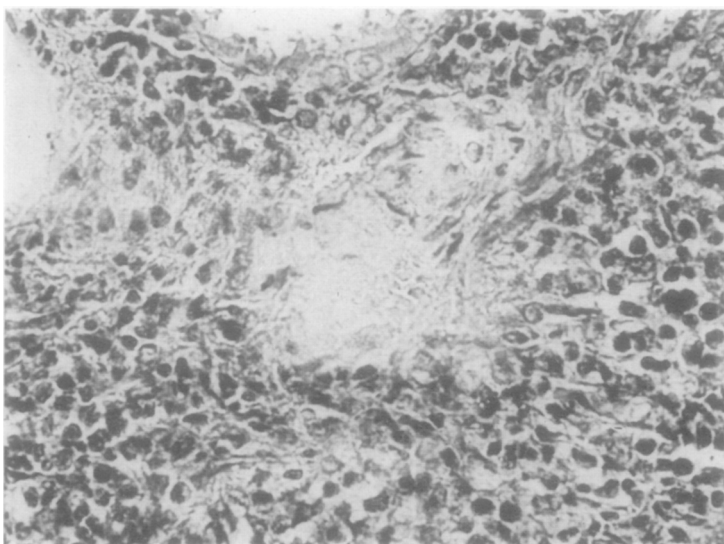


Fig. 5.—Extravascular inflammatory reaction in interstitial tissue of kidney. Central core of fibrinoid necrosis is surrounded by a broad zone of macrophages, round cells, and polymorphonuclear cells (hematoxylin and eosin; $\times 300$).

Associated pathologic findings included diffuse areas of bronchopneumonia, bronchiectasis, and changes consistent with chronic asthmatic bronchitis. The appearance of the gastric ulcer noted on gross examination was not inconsistent with that seen in gastric ulcerations complicating steroid administration. A number of small arteries and arterioles in the submucosa and adventitia in the area of the gastric ulcer were involved with acute arteritis and hyalinized thrombi. In the area of hematoma in the stomach an artery showed extensive necrosis. In one area of this vessel there was a deficiency in a segment of the wall through which the lumen communicated with the surrounding hematoma (Fig. 7). The nasal polyp was not unusual and contained no arterial lesions. Numerous lesions of acute arteritis were evident in the central nervous system, predominantly in the pia-arachnoid, although occasional involvement of vessels was seen within the brain substance itself. The adrenal cortices showed atrophy consistent with long-term administration of steroids.

The anatomic diagnoses were: (1) periarteritis nodosa (drug allergy); (2) intracerebral hemorrhage, right frontal, and infarct, right temporal lobe; (3) subarachnoid hemorrhage with hemorrhage in the fourth ventricle; (4) infarcts of the intestines, lungs, and brain; (5) hypertrophic bronchitis (asthma clinically); (6) purulent bronchitis with bronchiectasis; (7) pulmonary emphysema; (8) atrophy of the adrenal glands (cortisone

therapy); (9) hemorrhages in the skin (questionable nodular lesions); (10) periarteritis of the gall bladder; (11) hypertrophy of the kidneys; (12) grade 1 arteriosclerosis of the aorta, coronary arteries, and cerebral vessels; (13) ulcer of the stomach; (14) hematoma in the lesser curvature of the stomach; and (15) ulcer of the gall bladder.

Comment on Pathologic Findings.—Numerous reviews of the pathology of periarteritis nodosa are presently available in the literature.⁹⁻¹³ Studies within the past 2 decades have stressed the hypothesis that many cases formerly included under the broad classification of periarteritis nodosa are actually cases of allergic or hypersensitivity phenomena.¹⁴⁻¹⁶ Some observers think that the pathologic picture of periarteritis nodosa differs from that of hypersensitivity

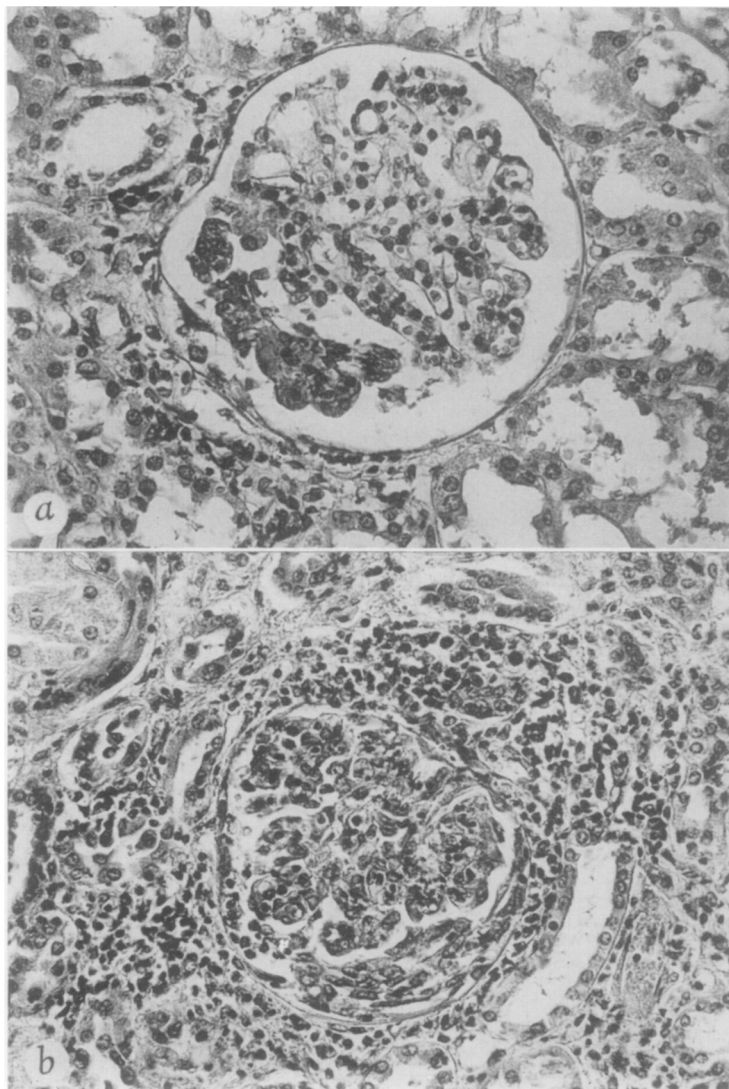


Fig. 6.—Glomeruli of kidney. *a*, Fibrinoid necrosis involving focal areas of glomerular tuft (hematoxylin and eosin; $\times 300$). *b*, Prominent epithelial proliferation with crescent formation, and periglomerular inflammatory reaction with lymphocytes and polymorphonuclear cells (hematoxylin and eosin; $\times 300$).

angiitis.¹⁷ In periarteritis nodosa, primarily the small and medium-sized muscular arteries are affected. The lesions are of varying ages from acute to healing, involvement of pulmonary-artery branches and splenic follicular arterioles is infrequent, and granuloma formation with epithelial cells and giant cells is extremely rare. Allergic angiitis, on the other hand, is characterized by involvement of small arteries, venules, and arterioles. Involvement of pulmonary-artery branches and splenic follicular arterioles is common, all the lesions are of a similar age (usually acutely exudative in appearance), and necrotizing glomerulonephritis is frequently found. Case reports of angiitis following drug reactions stress "extravascular" lesions, including focal necrosis, focal granulomas, interstitial inflammatory lesions



Fig. 7.—Artery in stomach showing extensive necrosis of arterial wall. Communication of vessel lumen with surrounding hematoma due to deficiency in a segment of the wall is seen (hematoxylin and eosin; $\times 57$).

(especially of the heart and kidney), and prominent eosinophilia.¹⁸⁻²⁰ Churg and Strauss²⁰ delineated a further division of necrotizing angiitis, termed "allergic granulomatous angiitis." This entity is characterized pathologically by extravascular inflammatory lesions, focal and diffuse, as well as extramuscular granulomas. The vessels show the usual vasculitis seen both in periarteritis nodosa and in granulomatous arteritis. In the cases of Churg and Strauss, all stages of lesions were seen, but healing lesions predominated. Veins were not uncommonly involved.

In the present case there were lesions that fit fairly well into the category of both allergic angiitis and allergic granulomatous angiitis. This is not unexpected in that allergic granulomatous angiitis is a combination of the lesions of allergic vasculitis and allergic granulomatosis. The clinical history of multiple drug reactions, as well as certain facets of the histologic picture, including acute rather than healed lesions and necrotizing glomerulitis, favors

this being truly an allergic angiitis. On the other hand, the history of long-term clinical asthma and marked eosinophilia, along with histologic evidence of granulomatous polyarteritis and extravascular inflammatory lesions with fibrinoid center, supports the view that this was a case of allergic granulomatous angiitis. That these views are not inconsistent has been noted above, and actually supports the concept that various forms of necrotizing angiitis are merely stages in a spectrum of responses to similar pathogenic stimuli. In either case, the over-all pathologic picture supports the idea that an allergenic agent was responsible for the patient's clinical picture.

Incidentally, the renal findings are consistent with the picture of focal necrotizing glomerulitis as described by Davson and associates²¹ and Wainwright and Davson.²² In their cases presenting this lesion, the remainder of the findings were those primarily of allergic angiitis, not unlike those recorded in the present case.

COMMENT

This case of necrotizing angiitis is similar to those reported by Rich² and occurring after the use of sulfonamides and heterologous serum, with the finding of collagenous degeneration and arterial lesions showing hyaline and fibrinoid changes microscopically. We believe that penicillin O was probably responsible for the development of the necrotizing angiitis and that for this patient this drug was not hypoallergenic. However, the sensitivity to iodides cannot be entirely discounted. Perhaps the groundwork for hypersensitivity reaction was being laid by the administration of penicillin O, and sensitivity to iodides may have been the basis for the incident that started the patient to react systemically, culminating in the necrotizing angiitis found generally. If this case is one of hypersensitivity to penicillin O, it illustrates that cross sensitization can and does occur with related drugs. The case illustrates that it is best to avoid similar drugs in a patient who has been sensitive to a drug, and a drug with a different chemical structure should be used.

Another point that needs emphasis in this case is that the dosage of cortisone probably was not large enough to ensure healing of the arterial lesions. Some investigators advocate very large doses, as much as 0.5 to 1 Gm. daily, in order to produce healing of such lesions. In retrospect, it would appear that this patient was not doing well in January, 1954, since at that time her blood was showing evidence of abnormality in that she had leukocytosis, an increased sedimentation rate, and a high eosinophilia (55 per cent). The groundwork for the systemic condition may have been present at that time. Her resistance appeared to be low, as shown by the fact that she was having recurrent upper respiratory infections. With cortisone therapy, such infection could have been masked further. At any rate, drug reactions can be serious, and may be fatal, as is illustrated by this case. It is our conviction that internists should always be on the alert for drug sensitivity and be prepared to treat it, as well as to avoid continuation of the use of drugs that may produce hypersensitivity reactions similar to those in this case.

SUMMARY

A case of fatal necrotizing angitis is thought to have resulted from the administration of penicillin O to a patient known to be sensitive to penicillin G. The patient also had an iodide allergy and hence it cannot be stated definitely that this did not have a place in the production of the necrotizing angitis. Several of us who saw the patient thought that the penicillin O was probably more important than the iodides in the final outcome of the case. Postmortem findings were typical of allergic angitis described by Zeek, while some features were characteristic of the allergic granulomatous type described by Churg and Strauss. Skin reactions to penicillin G and O and procaine were all negative. The patient died despite cortisone therapy; the dosage level may have been inadequate. This case, as well as others which have been described in the literature, especially those of Gruber and Rich, shows that drug allergy is important in the pathogenesis of some of the so-called cases of periarteritis nodosa.

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