

CARDIOVASCULAR ALLERGY DUE TO PENICILLIN, SULFADIAZINE, AND BACTERIAL SENSITIZATION

RESULTS OF TREATMENT WITH CORTISONE AND ACTH

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THE important clinical effects of ACTH and cortisone in the treatment of certain common allergic diseases, such as asthma, urticaria, and various dermatoses have been reported by a number of investigators (Bordley,¹ Randolph and Collins,² Rose,³ Carey,⁴ Sulzberger,⁵ Feinberg,⁶ Cooke,⁷ and others). Almost all of the workers are agreed that these substances are of considerable value in controlling certain phases of the afore-mentioned disorders, notably status asthmaticus, acute serum type reactions due to drug allergy, and various skin eruptions. Their effects may be spectacular in the reversible, though severe, allergic manifestations. This is especially true in those diseases of relatively short duration, as in cases with pulmonary eosinophilic infiltrations⁸ or allergic arthritis, where conditions are subject to spontaneous remissions. Under such circumstances the course of the disease may be abruptly curtailed and the patient may recover completely even though the exciting agent is not always detected or removed. This has been observed by the writer in some cases of penicillin sensitization marked by acute serum sickness type of response. In the more chronic allergic conditions, such as protracted bronchial asthma, urticaria, and eczema, the clinical course may be controlled just as long as the hormonal therapy is maintained. If the basic causative agents continue to operate because they are obscure or cannot be eliminated, a return of the symptoms is inevitable. The same holds true, as will be shown, in cases of vascular allergy. In these patients, however, the eventual outcome will depend upon the number and character of the irreversible lesions. In individuals with protracted manifestations of vascular allergy and general debility, ACTH or cortisone therapy may even prove to be harmful because of the tendency to intercurrent infections which may be masked by treatment. The following cases of vascular allergy illustrate these points.

CASE REPORTS

CASE 1. S. M., a 50-year-old woman, was admitted to Mount Sinai Hospital in December, 1949, because of fever, weakness, and purpuric rash of one month's duration. Her past history disclosed that she was subject to arthralgias in her youth and during a ten-year period prior to her admission she suffered with an allergic rhinitis, polypoid sinusitis, and cough. She was skin-tested and found to be sensitive to grasses, ragweed, house dust, coffee, and chicken. Because of the nasal obstruction, polypectomies had been performed, one eight years previously, and a second, two years previously. Two months before admission, October, 1949, she developed a cough, low grade fever, and recurrence of her polyps, causing a return of nasal obstruction. To eliminate the latter she was subjected to a third polypectomy. Prior to this operation she was injected prophylactically with penicillin and postoperatively was given more penicillin together with aureomycin. Two weeks later she developed a daily fever of between 101° and 102° F., cough, wheezing, tachycardia, and purpuric spots on the knuckles of her hand. The penicillin was stopped temporarily and the purpura cleared. In

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view of the persistence of the fever and respiratory symptoms, her physician decided to give her another million units of penicillin as well as penicillin aerosol. This was followed by extensive hemorrhagic vesicular and purpuric rash over the upper and lower extremities. Additional treatment with Chloromycetin, potassium iodide, barbiturates and massive doses of antihistamines, aggravated rather than ameliorated these manifestations. A blood count showed 10,000 white blood cells and 35 per cent eosinophils. Blood cultures were negative. She had a positive trichinella precipitin test in a dilution of 1:1280. A muscle biopsy was reported as manifesting changes "compatible with collagenous disease."

In view of the severity of her symptoms she was transferred to the Mount Sinai Hospital, Dec. 17, 1949, for ACTH therapy.

Examination on admission disclosed an acutely and chronically ill patient with a diffuse hemorrhagic vesicular rash involving the lower back and abdomen, wrists and forearms as well as the tongue, thighs, and buttocks. Some of the lesions were discrete, ranging from 1 to 3 cm. in size, some appeared as hemorrhagic blebs and others as hemorrhagic necrotic areas forming confluent serpigenous ulcers which revealed muscle and fascia in the depth of the wound. The temperature was 103° F. The lungs were negative. The heart did not appear enlarged but there was a tachycardia of 120. At the apex of the heart there was a protodiastolic gallop rhythm as well as a systolic blowing murmur which was also heard over the precordium. The abdominal and neurological examinations were negative.

The significant laboratory findings were HGB 9.0; RBC 2,700,000; WBC 11,250 with a moderate shift to the left and 10 per cent eosinophils which subsequently rose to 28 per cent. ESR was 120 mm. in one hour (Westergren). The urine specific gravity was 1.023; albuminuria 2 plus; B.U.N. was 22 mg. per cent. The blood sugar, chlorides, and creatinine were within normal limits, as were the serum albumin, globulin, alkaline phosphatase, calcium, phosphorus, cholesterol and cholesterol esters, and prothrombin time.

The electrocardiogram, Jan. 5, 1950, showed sinus tachycardia, low voltage of the QRS complexes with low T-waves in all leads. (Fig. 1.) Chest film disclosed irregular infiltrations throughout both lung fields and bilateral effusions. The electroencephalogram showed diffuse cerebral dysfunction.

In view of the patient's pulmonary lesions she was again given penicillin to prevent infection. This was followed by pruritus and edema of the left eyelid, indicative of hypersensitiveness. The penicillin was immediately discontinued. Skin and muscle biopsy at this stage was reported as showing lesions compatible with a diagnosis of erythema multiforme. Despite this, a clinical diagnosis of diffuse hyperergic vascular disease was made. Cortisone therapy was started Dec. 23, 1949, with 150 mg. per day in divided doses for seven days. This was then reduced to 100 mg. per day for five days. During this twelve-day period the temperature slowly fell from 103° to 101° F. where it remained. The sedimentation rate, however, persisted at 115 mm. The gallop rhythm and tachycardia disappeared within eight days and the eosinophils after three days. While there was a slight general improvement there was no remarkable change in the general clinical picture, the hemorrhagic necrosis continued to spread although the superficial purpura had faded. She was accordingly started on ACTH, Jan. 7, 1950, after a preliminary trial of aureomycin combined with DOCA and ascorbic acid therapy, which proved to be of no avail. On a dosage of 140 mg. of ACTH per day, the temperature fell to normal within 24 hours and the purpuric rash disappeared. The pulmonary lesions and the bilateral pleural effusions cleared within six days. Although the ulcers on the leg began to heal, those on the skin and tongue showed no evidence of resolution. The ACTH was gradually reduced over a four-week period and finally discontinued February fifth because the patient became irritable, disoriented and had crying spells. The total dose given during the month was 2.50 Gm. On the twenty-third and twenty-fifth day of treatment a casual specimen of urine showed 1-3 plus sugar but a fasting blood drawn the following day showed 95 mg. per cent of sugar. After discontinuance of ACTH most of the deep ulcers on the legs healed rapidly except one. Six days after ACTH was stopped the temperature began to rise reaching 101° F., the ESR rose to 122 mm. per hour, and the eosinophilia, tachycardia and edema of the extremities reappeared. The pulmonary lesions, how-

ever, did not return. On March 2, 1950, ACTH therapy was resumed at the dose of 100 mg. per day and most of these abnormalities disappeared except the ESR which remained above 100 mm. in one hour. The blood pressure rose to 150/90. She developed a mustache and a small goatlike beard. The dosage of ACTH was again gradually reduced to 50 mg. per day and then to 25 mg. per day on March 16, 1950.

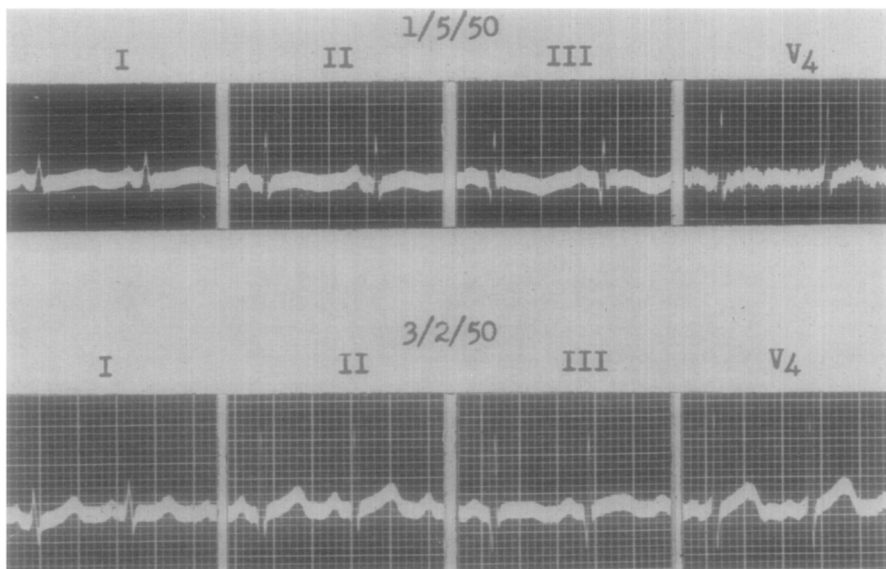


Fig. 1.—(Case 1, S. M.) 1/5/50, low voltage of QRS complexes with low T-waves in all leads. 3/2/50, the T-waves are of normal amplitude and the record is now normal.

Following this the patient began to run a febrile course with temperatures rising to 103-105° F. Examination disclosed an abscess of the buttocks which yielded staphylococcus aureus A. on culture. A blood culture was negative. Aureomycin and streptomycin were administered with but a slight fall in temperature despite a maintenance dose of 25 mg. of ACTH per day. On the 25th of March she vomited 400 c.c. of chocolate colored fluid and the following day she presented the picture of shock and jaundice. The liver was not palpable. A tentative diagnosis of serum hepatitis associated with diffuse vascular disease was made. The serum bilirubin was 4.2 mg. Cephalin flocculation 3 plus. Thymol turbidity 2 plus. The urine showed a trace of bile but no urobilinogen. The patient lapsed into coma and died on the 97th hospital day.

A summary of the autopsy findings as reported by Paul Klemperer showed (1) infected deep ulcerations of skin over sacrum, buttocks and thighs; (2) allergic granulomatosis of the aorta, generalized necrotizing arteritis and focal fibrosis, diffuse myocardial fibrosis; (3) partial atelectasis, edema and congestion of the lungs; (4) ulceration and erosion of the entire gastrointestinal tract, acute gastric ulcers with passive bleeding; (5) acute hepatic necrosis. A culture of the heart blood from ventricle showed no growth. (Figs. 2, 3, and 4.)

CASE 2. J. V., a 43-year-old woman, was first seen in April, 1950, at the Barnert General Hospital in Paterson, N. J., in consultation with Dr. J. Selikoff. She gave a history of good health till January, 1947, when she developed coryza and cough which persisted through the spring. She went to the Allergy Clinic of the Roosevelt Hospital where she was found sensitive to trees, grasses, ragweed, and dust. Treatment consisted of antihistaminics, dust and vaccine injections. In February, 1950, she developed an upper respiratory infection followed by wheezing. She was told she had a pansinusitis and was advised to take penicillin. Accordingly her physician injected her with 300,000 units of penicillin daily on March 8, 9,

and 10. One week later she developed fever of 102° to 103° F., polyarthritis, generalized urticaria, and angioedema. The penicillin was discontinued and she felt better. Because of the persistence of the joint pains she consulted another physician who made a diagnosis of infectious arthritis and gave her more penicillin together with aureomycin. This caused an exacerbation of her previous symptoms and on March 20, 1950, she again developed fever, arthritis, extensive purpura and ecchymoses involving the skin of the trunk and extremities, ulcerative purpura of the buccal mucosa, and gingivae and tongue, as well as buttocks. The arthritis was severe and affected the ankles and fingers of both hands, wrists and the temporomandibular joint. X-ray examination of the lungs disclosed diffuse infiltrations. Auscultation of the heart revealed only tachycardia. The electrocardiogram showed inversion of T-waves in all leads. The Hgb was 10.4 Gm., RBC 3 million, platelets 240,000 and WBC between 6 to 11,000 with 26 per cent of eosinophil cells. The sedimentation rate varied between 7 to 45 mm. in one hour. Prothrombin time was 18 seconds, control, 18 seconds. Serum albumin and globulin were normal. The urine showed albumin and red blood cells. There was also blood in the stool. She was treated with aspirin, codeine, demerol, and sulfonamides. Each of these caused hypersensitivity reactions, manifested by distinct aggravation of all her symptoms and gastric distress. Biopsy of one of the purpuric lesions disclosed changes compatible with "allergic granulomatosis." A diagnosis of vascular allergy due to penicillin hypersensitiveness was made. Cortisone therapy was advised, and started on April 7, 1950, approximately three weeks after the onset of her symptoms.

The initial dose of cortisone was 200 mg. per day in divided doses. This was gradually reduced to 80 mg. per day as her condition improved between April and July, 1950. The improvement was marked by a fall in temperature, disappearance of the pulmonary lesions, as well as of the purpura, subsidence of the polyarthritis, and healing of the ulcerating purpuric lesions in the mouth and buttocks. The albumin in the urine was also reduced. Except for a moonlike swelling of the face, the clinical course seemed satisfactory. In the midst of this apparent progress she developed an abscess in the buttocks associated with a rise in temperature to 100° F. This was incised and drained on June 14, 1950. Culture of the pus yielded staphylococcus aureus. In the presence of the infection the purpura and arthralgias began to reappear and the cortisone dosage was increased from 50 to 80 mg. per day. Up to this point she had received 3 Gm. of cortisone. Because of delayed healing of the wound, cortisone was temporarily suspended. Following this the wound healed rapidly but the arthritis returned and the purpura became more marked as did the tachycardia with pulse ranging between 100 to 120. The heart sounds showed no abnormalities on auscultation. In view of this recession it was decided to transfer her to the Mount Sinai Hospital for ACTH therapy.

On admission, August 19, 1950, besides the clinical manifestations above described, the significant laboratory findings were Hgb 9.1, RBC 3.3 million, WBC 8,100 with 7 per cent of eosinophils. Sedimentation rate was 37 mm. in one hour. The bleeding time was 3 minutes. Coagulation time 11½ minutes, clot retraction normal. The urine showed a specific gravity of 1012. There was albuminuria with granular and hyalin casts, and some red and white blood cells. The blood urea nitrogen was 35 mg. per cent. Urea clearance was 8 and 22 c.c. Blood albumin, globulin, creatinine, cholesterol, and cholesterol esters were normal. X-ray examinations of the chest and sinuses showed no abnormality. The electrocardiogram showed right bundle branch block.

One week after admission she developed cough, fever of 103° F. and signs of bronchopneumonia. X-ray disclosed a pneumonic infiltration at the base of the right lung. The white blood cell count rose to 14,950 with 26 per cent of eosinophils. The sputum culture showed a mixture of nonsignificant organisms. She was treated with terramycin and 75 mg. of ACTH per day. This was followed by an immediate fall in temperature. To avoid masking the underlying infection, ACTH was eliminated and terramycin was continued until the pulmonary lesions and temperature subsided. The respite was short. The purpura, anemia, and fever up to 102° F. returned. Notwithstanding repeated transfusions there was no increase in hemoglobin. During the sixth hospital week she was again started on a daily

Fig. 2.

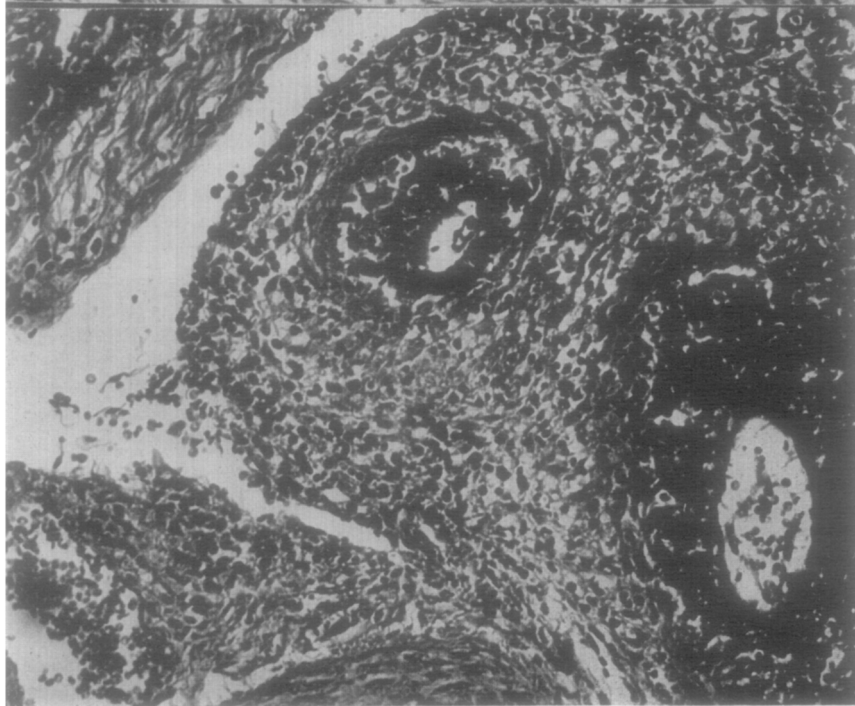
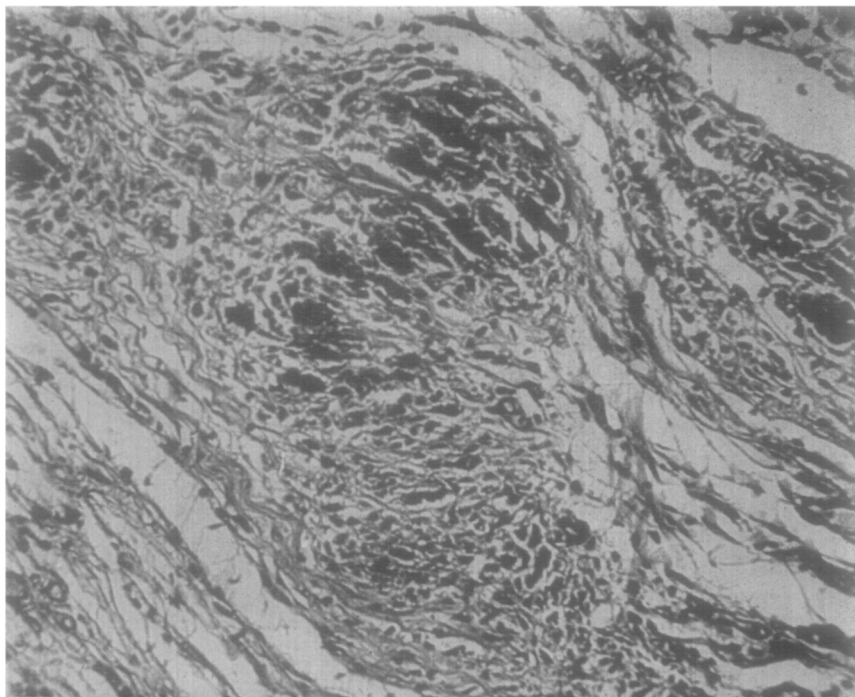


Fig. 3.

Fig. 2.—(Case 1, S. M.) Granuloma in the adventitia of the aorta. Swelling and fragmentation of the collagen with fibroblastic reaction.

Fig. 3.—(Case 1, S. M.) Acute necrotizing arteritis associated with eosinophilic exudate.

dose of 100 mg. of ACTH which was stopped temporarily because of an attack of pulmonary edema. At this point the blood urea nitrogen rose from 47 to 80 mg. per cent. After controlling the pulmonary edema with diuretics, ACTH was resumed. Despite this she developed neuritis of the right hand and feet. It was felt that this was due both to the hyperergic vascular disease and poor nutritional state. Massive doses of vitamins combined with physical therapy and ACTH, brought about a gradual improvement in the neuritis. She received a total of 2935 mg. of ACTH in varying doses during 3½ months. Any dose below 40 mg. per day failed to control the fever or joint pains. During the third hospital month she developed an infected pilonidal cyst which required both chemotherapy and an increase in ACTH dosage. She insisted on going home and was discharged December 12, 1950, on 100 mg. of oral cortisone daily. Her fundamental disease was unchanged as indicated by the abnormalities in the electrocardiogram and evidences of renal disease such as albumin and red blood cells in the urine and elevated blood urea nitrogen (80 mg. per cent). The electrolyte balance was maintained by salt-poor diet and occasional doses of diuretics.

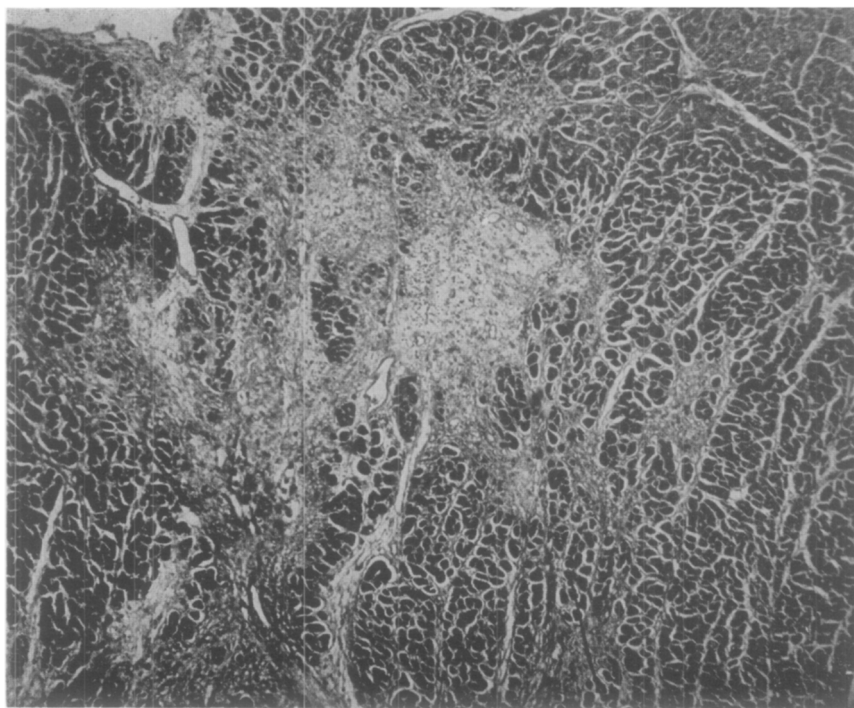


Fig. 4.—(Case 1, S. M.) Diffuse fibrosis of the myocardium.

During the two weeks after returning home her condition deteriorated rapidly. While receiving cortisone therapy, she developed an acute peritonitis which was considered to be due to an intestinal perforation secondary to a mesenteric arteritis. She died three days after the appearance of these symptoms. No autopsy was obtained.

During the nine months of her illness she received approximately 4 Gm. of cortisone and 3 Gm. of ACTH.

Biopsy report (April, 1950) by Dr. J. Churg of the Barnert General Hospital, of purpuric area of skin removed from back of elbow, was as follows: "There is distinct edema of the epidermis and marked diffuse perivascular infiltration with neutrophilic and eosinophilic leukocytes and some lymphocytes and histiocytes. The leukocytes show marked tendency to nuclear fragmentation with scattering of nuclear fragments. The inflammation

Fig. 5.

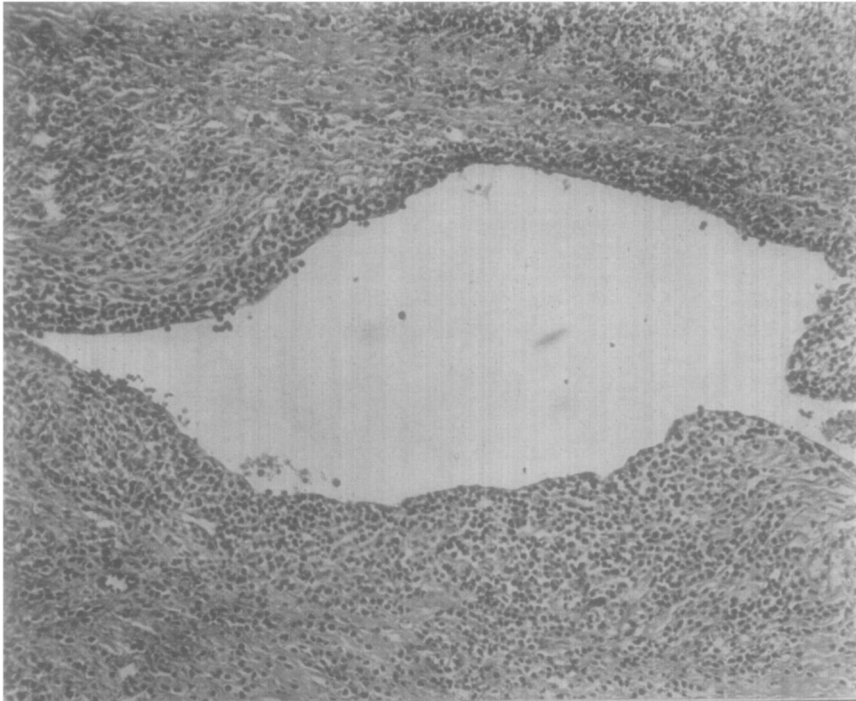


Fig. 6.

Fig. 5.—(Case 3, A. K.) Eosinophilic phlebitis.

Fig. 6.—(Case 3, A. K.) Periportal infiltration with eosinophils.

is most intense in the subpapillary layer, but in some places it extends to the deep line of resection. In the areas of the most intense inflammation the collagen appears altered, the fibers are poorly outlined, swollen and slightly basophilic. The vessels participate strongly in the process: the capillaries, particularly those of the subpapillary layer, are markedly engorged. Some capillaries, as well as some small venules and arteries, show acute inflammation and focal necrosis of the wall. However, none of the vessels show changes characteristic of periarteritis nodosa. There are many small areas of blood extravasation in the subpapillary layers and the papillae."

A second biopsy of the skin and muscles on October 19, 1950, disclosed marked arteritis and muscle atrophy. These changes were considered compatible with a diagnosis of allergic granulomatosis.

CASE 3. A. K., a 45-year-old man with a history of hay fever for twenty years and intermittent attacks of asthma, was first seen in January, 1949. He stated that on Dec. 18, 1945, he suffered a severe respiratory infection for which he received sulfadiazine. Several days later he developed pruritus, progressive malaise, nausea, and weakness followed by gradual enlargement of the abdomen. The latter became quite pronounced in 1947, causing him to see a number of physicians, including a hematologist, Dr. N. Rosenthal, who found an enlarged liver and spleen, a white blood count of 30,000 with 60 per cent eosinophils and Hgb 10 Gm. His condition remained unchanged until 1949 when he caught cold and developed a stuffy nose and asthma. Because the symptoms grew steadily worse he consulted the writer in January, 1949. Examination disclosed infected sinuses, and infiltrations at the bases of both lungs associated with wheezing respiration. The heart sounds were of poor quality, but there was no evidence of valvular disease. The pulse was 80 and the blood pressure 130/70. The spleen extended three finger breadths below the costal margin and the liver two finger breadths. X-ray examination of the lungs revealed a pneumonic infiltration at the left lung base and enlargement of the heart to the left. An electrocardiogram disclosed sinus rhythm, rate 90, depression of RST₂ and 4, T₂, diphasic, T₃ inverted. The sinus washings disclosed a "Taylor" pneumococcus on culture. Skin tests showed positive reactions to foods and pollens. A number of blood counts indicated an average of 30,000 white blood cells and 50 to 60 per cent eosinophil cells. He was treated with intramuscular injections of penicillin and the infection in the lungs and sinuses improved. Penicillin aerosol however, produced asthmatic attacks and was therefore discontinued. In view of the clinical and electrocardiographic evidence of myocardial damage associated with eosinophilia, the diagnosis of hyperergic vascular disease with eosinophilic myocarditis was made.

From February to October, 1949, the patient's condition gradually deteriorated. He experienced precordial pains and episodes of tachycardia. The electrocardiogram continued to be abnormal, still showing RST repressions, T-wave inversions in the standard lead, RS-T elevations in a VR, T-wave inverted in a VF. The unipolar leads from V₁ to V₆ showed very distinct RS-T depressions. The spleen and liver became gradually augmented in size and scattered purpuric spots appeared over the abdomen. On October 29, 1949, he experienced acute severe pains in the upper left quadrant, with precipitous enlargement of the spleen to the pelvic brim. On palpitation the abdomen was rigid and the splenic area exquisitely tender. There was no ascites. The temperature was 99° F. and the pulse 100. The white blood cell count was 18,300 with 30 per cent eosinophils. The platelets were 80,000 per cubic mm. A diagnosis of acute splenic infarction with perisplenitis was made. He was admitted to Mount Sinai Hospital where a splenectomy was performed to preclude a possible rupture of the infarcted organ.

Pathological examination of the excised spleen and biopsies of the liver and a lymph node showed the following: (1) Splenomegaly (weight 1,100 Gm.) with stenosing endophlebitis and focal obliterating arteritis as well as periarteriolar sclerofibrosis; diffuse eosinophilic infiltration of the splenic pulp with occasional myelocytes and megakaryocytes; increase of fibrillar reticulum together with multiple anemic infarcts; (2) the liver showed periportal eosinophilic infiltration; (3) an excised lymph node revealed eosinophilic lymphadenitis with focal fibrosis (Figs. 5 and 6).

Following splenectomy the blood platelets rose to 170,000. The white blood cell count was 29,000 with 60 per cent eosinophils. This subsequently rose to 44,000 with 75 per cent eosinophils. The patient developed a subphrenic abscess which was incised and drained. Although he made a good recovery his general condition continued to grow worse. Congestive heart failure developed with bilateral effusion in the chest. The venous pressure rose to 210 mm. of water. The liver increased in size to four finger breadths below the costal margin. The urine showed albumin with hyalin and granular casts. The blood urea rose to 94 mg. per cent, uric acid 4.8, sodium 150 meq., potassium 6.6 meq. He was given mercurial diuretics, a low-salt diet, ammonium chloride and a transfusion of packed red cells. He was also started on 40 mg. of ACTH per day. On this regimen he at first felt generally better. The total white count fell and the eosinophils dropped to 6 per cent. However, cardiac failure persisted, as shown by a venous pressure of 210 mm. of water, with a rise to 240 mm. on upper quadrant compression. ACTH was finally discontinued because the cardiac condition grew worse. The white blood cell count returned to its former levels although the absolute eosinophil counts were lower. He was discharged from the hospital Sept. 9, 1950, only to be readmitted on Sept. 30, 1950, because of marked edema of the legs and ascites, severe precordial pains and blurring of vision. He also developed a Babinski and Chaddock on the right leg. Soon after his admission he became stuporous. There was rigidity of the neck, the eyes were widely open but unseeing and there appeared purposeless movement of the extremities, spasticity of the legs and arms, with clonus of the right ankle. The spinal fluid was clear, the pressure was 220 mm. initially and ultimately 160 mm. Pandy reaction was one plus, WBC 23 cells per cubic millimeter, sugar 68 mg. per cent, chlorides 742 mg. per cent, protein 60 mg. The eye grounds showed no papilledema. The patient developed a right hemiparesis with paralysis of the right arm. The neurologist's opinion was that the patient suffered from diffuse cerebral vascular disease more marked on the right than on the left.

He developed Cheyne-Stokes breathing and his temperature rose to 104° F. The white blood cell count increased precipitously to 149,000. The radial pulses became faint, the blood pressure fell to 40/0, and the patient died on Oct. 3, 1950. Post-mortem examination was refused. A diagnosis of diffuse hyperergic vascular disease with eosinophilic myocarditis, probably due to sulfonamide sensitivity or bacterial allergy was entertained.

CASE 4. R. S., a 17-year-old girl, was admitted to the Brooklyn Thoracic Hospital in December, 1948, with the following history. For the past four years she had suffered with vasomotor rhinitis and dry winter cough. Two months prior to admission these symptoms became associated with general fatigue, low grade fever, and night sweats. In view of these manifestations she was suspected of having tuberculosis.

On examination of the lungs, only a few scattered râles at the bases were audible on auscultation. The heart was normal except for a tachycardia (Fig. 7). X-ray examination of the chest, however, showed distinct infiltrations throughout both lungs suggestive of the Loeffler type. This was further substantiated by the migratory and variable nature of the lesions during the succeeding months. They fluctuated from interstitial infiltrations to massive involvement of one lobe or another. At one time atelectasis of one lobe with a shift of the heart to the side of the collapsed lung was noted. The electrocardiogram showed sinus tachycardia with a rate of 110 to 140. Nasal smears disclosed eosinophilia. The sinus washings yielded hemolytic streptococci, pneumococcus type 12 and *Staphylococcus albus*. The sputum culture showed a mixture of hemolytic streptococci, pneumococci, and *Staphylococcus aureus*. She was found clinically sensitive to banana, tomato, crab, pineapple, cheese, and spinach although she showed reactions to dust, horradendrum, alternaria, etc. The white blood count varied between 12,000 to 29,000 with 20 to 29 per cent of eosinophils. Hgb was 68 to 70 per cent. A biopsy of the deltoid muscle showed no evidence of hyperergic vascular disease. The diagnosis considered was eosinophilic pulmonary infiltrations.

Treatment consisted of penicillin injections (to which she was found sensitive), aureomycin, dihydrostreptomycin, various antihistaminics, and salicylates without any beneficial

effect. On her return home in May, 1949, she was also given mapharsen in the belief that the condition was one of tropical pulmonary eosinophilosis. This caused a rise in temperature to 105° F. and diarrhea, without influencing the course of the disease.

She was admitted to the Mount Sinai Hospital in July, 1949, for further observation. An investigation for a possible focus of infection resulted in the finding of a moderate infection in the antra, and of two lower molar teeth. Sinus washing and removal of the infected teeth was followed by treatment with a combination of Chloromycetin and aureomycin. This resulted in the development of purpuric spots under the nail beds and was therefore discontinued. The tachycardia and the pulmonary infiltrations persisted.

During a period of temporary remission of the lesions in the lungs, she returned home. Here her condition grew progressively worse. She developed anemia, necessitating transfusions, as well as fever of about 101° F. The tachycardia became more severe and led to cardiac insufficiency. The heart became enlarged to the left and she developed congestive failure despite intensive digitalis therapy and salt-free diet. She lost weight and looked emaciated. At this stage cortisone became available and she was again transferred to the Mount Sinai Hospital on Oct. 13, 1949, for treatment with this hormone.

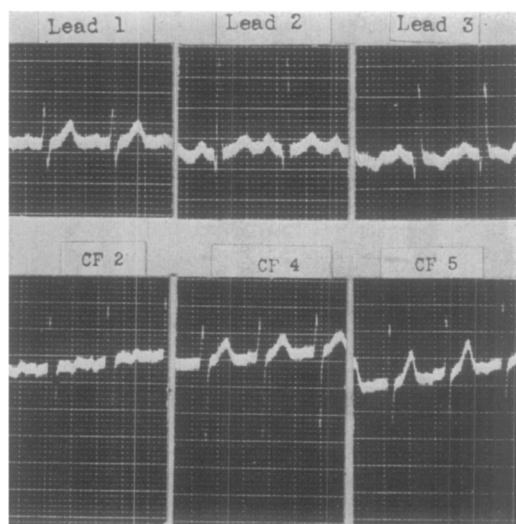


Fig. 7.—(Case 4, R. S.) Before treatment with cortisone, May, 1949. The ECG reveals normal sinus rhythm. There is a tendency toward a right axis deviation. Small Q₂ and Q₃ present T₃ inverted. Tachycardia 125.

During her hospital stay the clinical course was marked by the presence of cachexia, peripheral neuritis of the left leg, anemia, tachycardia with a suggestion of a diastolic gallop, fever between 101° to 104° F. and subcutaneous nodules on the forehead one centimeter in diameter. The important laboratory findings were Hgb of 10 Gm. and 12,000 WBC with 19 per cent of eosinophils. The urine showed a specific gravity of 1029 and 2 plus albumin. The ESR was 72 mm. The blood cultures, urea, uric acid, albumin, and globulin, total protein showed no abnormalities. An electrocardiogram revealed right bundle branch block (Wilson type). QRS measured .12 second and Rt axis deviation (Fig. 8). X-ray examinations of the lungs showed recurrent migratory infiltrations. Biopsy of the skin revealed nonspecific inflammatory changes.

She received 150 mg. of cortisone per day for 8 days, 50 mg. for 6 days, and 25 mg. for 8 days. Under this therapy the white blood cell count dropped to 5,000 and the eosinophils to 7 per cent. The x-ray of the lungs showed complete disappearance of the pulmonary lesions. The urine became free of albumin and the blood count normal. The patient gained weight and felt well. The cortisone was discontinued and she went home Dec. 27, 1949.

About the middle of January, 1950, she suffered a relapse, necessitating a renewal of cortisone therapy. This was administered to her by Dr. Emanuel Schwartz. She was started on 200 mg. per day, which was gradually reduced to 50 mg. Just as before, the pulmonary lesions and other symptoms subsided within a week. The cortisone however, was continued. On the thirty-sixth day of treatment after an injection of 50 mg. of cortisone she went into an anaphylactic-like shock marked by wheezing respiration and heart rate of 160. This lasted only a few minutes, and the patient was well within 48 hours. To determine the cause of her abnormal response Dr. Schwartz tested her with cortisone and its vehicle. He found her sensitive to the latter, and concluded that the vehicle was responsible for the shock reaction. Of five control patients tested with the aqueous vehicle three were negative, and one gave a slight reaction.

Following this episode she recovered completely and has remained relatively well with the exception of mild recurrences of sneezing and cough with asthmatic attacks from time to time. The asthmatic episodes were readily controlled with oral cortisone. Although at the last examination in October, 1950, she had no major complaints, the electrocardiogram still showed the presence of a bundle branch block of the Wilson type, indicative of irreversible myocardial damage (Fig. 9).

The diagnosis was cardiovascular allergy, involving lungs, heart and probably some peripheral vessels, etiology unknown, but possibly infectious in nature.

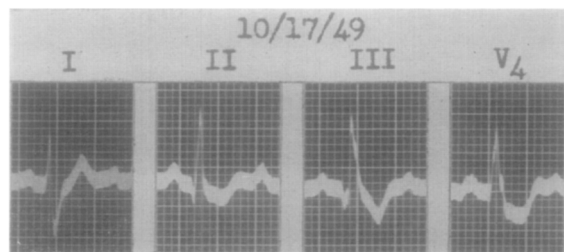


Fig. 8.—(Case 4, R. S.) During treatment with cortisone. QRS slurred, notched and widened and measures 0.12 sec. Rt. Axis deviation. RS-T in leads 2, 3, and 4 depressed, T_2 and T_3 inverted.

DISCUSSION

An analysis of the preceding four cases disclosed the following significant features in the pathogenesis of the vascular disease. All of these patients were allergic individuals with a history of vasomotor rhinitis, sinusitis, and asthma. Because of the intercurrent respiratory infections they received antibiotic therapy consisting of injections of penicillin in varying amounts as well as sulfadiazine (Case 3). Sometime in the clinical course each of the patients exhibited symptoms of hypersensitiveness to these substances in the nature of a severe serum sickness type of reaction with implication of the connective-vascular tissues in the lungs, heart, kidneys, joints, and skin. In the first two cases penicillin was regarded as probably responsible for the hyperergic vascular disease. This assumption was based on the observations that (1) the clinical manifestations appeared after an incubation of one or two weeks following treatment with penicillin, (2) temporary withdrawal of this antibiotic resulted in a recession of the presenting symptoms and (3) its readministration led to an accelerated reaction with prompt exacerbation of all the previous symptoms. Among the earliest signs exhibited by these patients were polyarthritides, pulmonary infiltrations, eosinophilia, and purpura. Although the latter was previ-

ously described as a result of penicillin sensitivity,^{9, 10, 11, 12, 13} none of the recorded cases manifested such extensive necrotizing purpuric lesions with concurrent involvement of the cardiovascular system as noted in these two cases. Most of the reports of penicillin allergy deal with the development of skin reactions, such as urticaria, angioedema, exfoliative dermatitis, arthralgia, occasional pulmonary infiltration, and/or asthma. Recently a case of angioneurotic edema with transient electrocardiographic aberrations which returned to normal within a week, was reported by Felder and Felder.¹⁴ They ascribed the reversible electrocardiographic changes to edema of the myocardium or anoxemia due to diminished coronary flow.

In contrast to these reversible reactions following penicillin sensitization, the biopsy sections of the first two cases under discussion disclosed irreversible inflammatory alterations of the collagen tissue, capillaries, and venules, as well as necrotizing arteritis. None of the vessels, however, showed any of the characteristic changes of periarteritis nodosa. These observations were further corroborated by the autopsy findings in Case 1, as described above in detail, revealed extensive lesions in the blood vessels characterized by necrotizing arteritis with eosinophils, granulomatous formations in the aorta, focal myocardial fibrosis, as well as allergic reactions in the liver and gastrointestinal tract.

Dr. Paul Klemperer, who reviewed the histological sections of Case 1, expressed the opinion that "in order to define the morbid process underlying the pathologic-anatomic findings in this case the latter must be taken in their

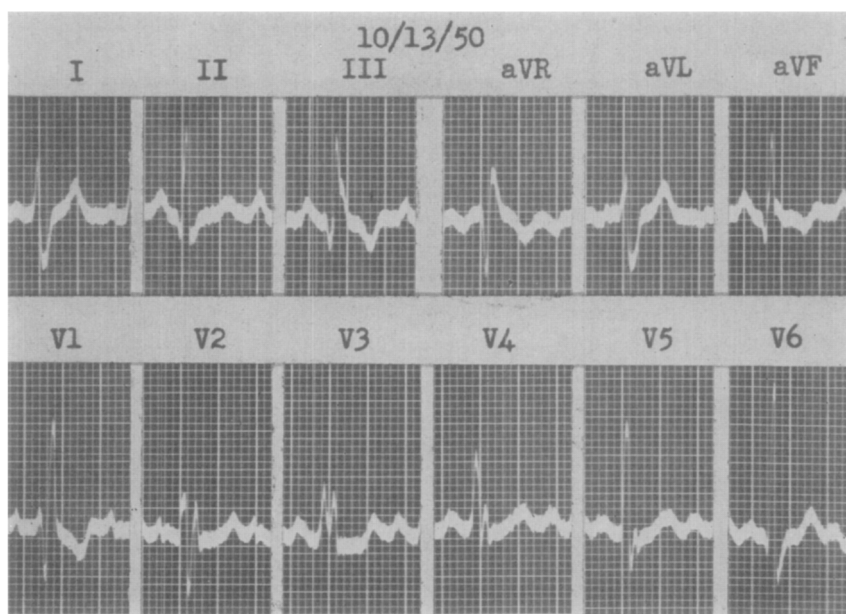


Fig. 9.—(Case 4, R. S.) 10/13/50, 1 year after treatment. The ECG reveals RBBB of the Wilson type with QRS measuring 0.11 sec. There was no change in the ECG during the course of treatment or follow-up period. Rate 125.

totality." Thus the necrotizing arterial lesions were only one of the pathological manifestations of this morbid process, and he therefore felt that it would be incorrect to label this case simply as periarteritis nodosa. Arterial lesions did not account for the second important finding, i.e., the widely distributed foci of myocardial scarring which were not associated with any conspicuous involvement of the arteries. There was, however, evidence of inflammation which could very well explain the "myocardial destruction." The third component in this pathologic syndrome was the granuloma of the aorta which was considered by Klemperer to be identical with the granulomatous lesions described by Churg and Strauss under the title of Allergic Granulomatosis, Allergic Angiitis, and Periarteritis Nodosa.¹⁵ These investigators regard the periarteritis nodosa-like lesions seen in asthmatics associated with granulomatous alterations within the vessel walls and in connective tissue, as an entity apart from classical periarteritis nodosa. They reached this conclusion from a study of 15 cases of periarteritis nodosa without asthma, none of which revealed extravascular granulomata or granulomatous vascular changes. In other words, Churg and Strauss, in agreement with Zeek, Smith, and Weeter,¹⁶ believe that necrotizing arteritis and/or periarteritis nodosa with granulomatous reactions in connective tissue occurring in patients who give a history of allergy, are the result of hypersensitivity, whereas true periarteritis nodosa is not dependent upon an allergic mechanism. It is not the purpose of this report to enter into any discussion of this point of view. It is considered sufficient to note that, although a positive history of allergy in any given case adds support to the concept that an allergic factor is involved in the pathogenesis of the presenting vascular disease, a negative history does not necessarily eliminate such a possibility nor does the absence of extravascular granulomatous changes exclude the existence of hypersensitiveness.

A fourth element in the disease complex in Case 1 in addition to the lesions in the heart and blood vessels, was the necrosis of the liver "distinguished histologically by destruction of the reticulum fibres." Despite the possibility of the existence of a virus infection or shock as a cause, hepatic necrosis may also be a manifestation of hypersensitiveness. In favor of this assumption is the fact that parenchymatous lesions with central lobular necrosis of the liver have been reported in experimental serum sensitization. Clinically, hepatic necrosis has also been observed by Kaegel¹⁷ of Roessles' Institute in a case of serum sickness following tetanus antitoxin injection, as well as a result of sensitization to drugs, such as cinchophen, mapharsen, and sulfonamides. In some of the cases of sulfonamide sensitization described by Moore, McMillan, and Duff¹⁸ necrosis of the liver was so marked that it closely simulated the gross and microscopic appearance of acute yellow atrophy. Granulomatous lesions in the parenchyma associated with complete disappearance of liver cells and partial destruction of the reticulum were also observed in some of their patients. Since penicillin may induce reactions similar to those caused by the sulfonamides or other drugs, as evident in the cases under discussion, it is conceivable that it may also be responsible for similar reactions in the liver. That transitory involvement of the liver may follow penicillin sensitization is indicated in the case reported by

Felder and Felder.¹⁴ Although there was no evidence of jaundice in his patient damage to the liver was shown by a four plus cephalin flocculation reaction, thymol turbidity, 6.3 units; alkaline phosphatase, 13.2 Bodansky units; total protein, 4.63 Gm., cholesterol 249 mg., and cholesterol esters 103 mg. As the patient improved, within two weeks the cephalin flocculation reaction became negative, the thymol turbidity 3 units; alkaline phosphatase 2 Bodansky units; cholesterol 305 mg. cholesterol esters 249 mg. per cent and total protein 6.8 Gm.

A fifth significant finding in Case 1 was the presence of ulceration and erosions throughout the entire gastrointestinal tract and gastric ulcers with passive lesion bleeding. In all probability the lesions in the gastrointestinal tract just as those in the skin were due to vascular disease following penicillin sensitivity. Similar findings were recently reported by Berne¹⁹ in a patient with presumptive penicillin sensitivity who had also received sulfadiazine. In this case the duodenum, small intestine, and cecum disclosed superficial ulcerations of the mucosa with diffuse hemorrhagic necrosis. Microscopically, the arteries and veins in the submucosa showed acute necrotizing angitis with thrombosis and surrounding areas of infiltrations with polymorphonuclear leukocytes and lymphocytes. The vascular changes were most conspicuous in the ileum.

Whether the bleeding from the gastric ulcers in this case is to be attributed solely to penicillin sensitivity or in part to ACTH therapy is still a question. Perforation and hemorrhage of peptic ulcers have been previously described by Habib,²⁰ Beck,²¹ and Smyth²² during ACTH therapy but the activation of multiple ulcers has never been reported as far as the author is aware.

The sixth important feature in this case was the absence of any lesions in the lungs at autopsy in contrast to the positive roentgenologic findings during life, attesting to the reversibility of the pulmonary reaction.

After evaluating these various pathological manifestations Klemperer concluded that they were "anatomic expressions of an allergic diathesis." Thus the underlying morbid process was obviously attributable to sensitization.

Whereas the vascular reactions in Cases 1 and 2 were presumably related to penicillin sensitivity as such, it should be noted that the clinical manifestations resulting therefrom, especially the purpura, could be accentuated by the administration of other apparently unrelated antibiotics such as aureomycin and Chloromycetin, as well as various drugs such as aspirin, codeine, demerol, and sulfonamides.

Two possible etiologic factors were considered to be responsible for the allergic cardiovascular manifestations in Case 3: they were sulfadiazine and/or bacterial sensitization. In favor of the former was the fact that several days after ingestion of the sulfadiazine the patient developed urticaria with generalized itching and weakness which was still present three years later (1949) when seen by the writer. This history and the finding of advanced electrocardiographic changes, hepatosplenomegaly, and marked eosinophilia in an atopic individual suggested the diagnosis of cardiovascular allergy with eosinophilic myocarditis resulting from sulfadiazine sensitivity. The decided increase in the size and the hard consistency of the liver and spleen stimulated the thought that the

disease process in these organs was of long duration. In fact, this condition was found in 1947, when the patient was seen by the hematologist who first noted the marked eosinophilia. Skin tests with sulfadiazine were not made because of their questionable value. The diagnosis of sulfonamide sensitization therefore had to be made by inference based on the history of exposure to these drugs and the pathological changes following therefrom, as reported in the literature. That sulfonamide sensitization may induce hyperergic vascular disease with involvement of the liver and spleen as well as eosinophilic myocarditis has been described by French,²³ Moore, McMillan, and Duff,¹⁸ Rich,²⁴ Black-Schaffer,²⁵ Lichtenstein and Fox,²⁶ Lederer and Rosenblatt,²⁷ and others.

Most of these recorded cases came to autopsy 6 to 7 weeks after the sulfonamide therapy and had been in a more or less acute phase of the disease. The spleen in these patients showed polyvasculitis, i.e., necrotizing arteritis and trabeculitis. The liver showed various degrees of cellular eosinophilic infiltrations. One of the cases of eosinophilic myocarditis associated with generalized vascular allergy, reported by the writer²⁸ in 1943, although regarded as one due to bacterial hypersensitiveness, had also received sulfathiazole 1½ years prior to death. In addition to these reports, periarteritis nodosa (proved by biopsy in one case), and necrotizing vascular lesions involving the spleen and other organs following sulfadiazine sensitivity have recently been described by Goodman,²⁹ and Duria and Brodziak.³⁰

The second possibility, that bacterial allergy may also have been responsible for the cardiovascular syndrome in this case was likewise explored. The presence, in January, 1949, of an infected antrum, which yielded an unidentified pneumococcus ("Taylor" pneumococcus), could not be regarded as a primary causative factor in a disease which had been in progress for several years, unless it could be proved that the sinus infection had existed prior to, or throughout this period. Inasmuch as this could not be done, it was argued that the antral infection caused by the pneumococcus or by an unidentified microorganism in a person susceptible to respiratory allergy, might have acted as an additional excitant and thus influenced the course of an established hyperergic vascular process initiated by sulfadiazine sensitization. This, it was felt, could also explain the duration of the disease, since the intensification of allergic syndromes as a result of the synergistic action of several allergens is not uncommon. Despite the fact that both the sinus infection and the pneumonia were controlled by penicillin therapy, the vascular disease progressed. This was indicated by a general decline in the condition of the patient and the sudden infarction of the spleen which was subsequently removed. The presence of a focal obliterating endarteritis with periarterial sclerofibrosis, stenosing eosinophilic phlebitis and diffuse eosinophilic infiltration of the splenic pulp in the excised organ, substantiated the diagnosis of hyperergic vascular disease. It also served to explain the enormous enlargement of the spleen as well as the infarctions. The eosinophilic infiltrations in the liver accounted for its increased size, apart from the superimposed passive congestion due to myocardial insufficiency.

The literature discloses no record of such a large spleen with so many infarcted areas with the possible exception of a case reported by Magnus³¹ in

1937. His patient, aged 21, had asthma, three years in duration, and severe diarrhea prior to his death. There was no record as to the type of asthma nor the medication used in this case. Autopsy disclosed necrotizing arteritis which had produced widespread necrosis of the pancreas, kidneys, spleen, and the alimentary tract. It was thought that the vascular lesions were due to some "toxic" factor. The blood vessel changes resembled periarteritis nodosa but the absence of periarterial leukocytic infiltration and aneurysm formation was against such a diagnosis. The author also commented on the fact that in polyarteritis nodosa acute extensive necrosis of the spleen is uncommon.

In our case there was also no evidence of lesions typical of periarteritis nodosa. There was no doubt that the vascular changes were allergic in nature. Following splenectomy the irreversible vascular disease remained unchanged notwithstanding treatment with ACTH. Because of the salt-retaining effects of this hormone, the electrolyte balance could not be maintained in spite of the salt-free diet, diuretics, and potassium chloride, and the patient died both from cardiac failure and cerebral vascular disease.

The underlying cause for the recurrent pulmonary eosinophilosis which had persisted for a year and a half in the fourth case of this group was obscure. Although hypersensitiveness to some infection was suspected, this was never fully established. The hyperergic vascular disease in this patient was essentially limited to the lungs and heart. The pulmonary lesions were reversible, as evident by the fact that prior to cortisone therapy they would disappear spontaneously from time to time only to return. The cardiac involvement, however, was progressive. This was indicated by the presence of a right bundle branch block and an attack of failure before the administration of cortisone. Cortisone proved to be temporarily effective in reducing the temperature, the eosinophil count and the sedimentation rate. It also caused the complete disappearance of the reversible infiltration in the lungs even though it was administered $1\frac{1}{2}$ years after the development of the pulmonary disease. The proteinuria and the mild peripheral neuritis likewise subsided. The remission brought about by cortisone lasted about four weeks, necessitating a subsequent resumption of the treatment. Within a week after the institution of the second course of cortisone the pulmonary lesions and associated manifestations were completely controlled. It is worthy of note that on the thirty-sixth day of convalescence while the patient was still receiving 50 mg. of cortisone per day and was free of symptoms, she suddenly developed a transient anaphylactic-like shock. Dr. Emanuel Schwartz, who administered the second course of cortisone, attributed this to sensitization of the vehicle. Since the shock reaction until this day the patient has not had any recurrence of the pulmonary infiltrations. Except for brief asthmatic seizures which have been readily controlled by cortisone she has been relatively well.

In contrast to the favorable results attained in this patient, cortisone as well as ACTH failed to influence the progress of the hyperergic vascular disease in the major shock organs in the other three cases. In Cases 1 and 2 the fever, purpura, the ecchymotic necrotic lesions, and the joint pains were relieved as long as the hormones were being administered, only to recur in less severe

form whenever the cortisone or ACTH was discontinued. While the intercurrent eosinophilic pulmonary lesions disappeared completely under the hormonal therapy, just as in Case 4, the basic disease affecting the myocardium and the kidneys continued to advance in spite of the early administration of these hormones, i.e., about a month after the onset of symptoms. Protraction of the illness may have been partly due to the intensification of the sensitizing process by the repeated administration of penicillin, unfortunately carried on for lack of appreciation of the probability that this antibiotic was responsible for the clinical manifestations. Other antibiotics such as aureomycin and Chloromycetin used in the treatment, may have exerted a synergistic sensitizing effect and aggravated the disease. This was clearly illustrated in Case 4. In order to control the focal infection in the sinuses and teeth considered as etiologic factors, this patient was given Chloromycetin combined with aureomycin since she was known to be sensitive to penicillin. Four hours later she developed purpura under the nail beds which disappeared after discontinuance of these antibiotics.

The untoward development of a staphylococcus infection in the buttocks in Cases 1 and 2, as well as the sudden appearance of a pulmonary and pilonidal cyst infection in Case 2, in the course of the cortisone and ACTH therapy, further militated against the effectiveness of these hormonal drugs. This was evidenced by an exacerbation of the previously controlled symptoms, i.e., fever, purpura, arthralgias, etc., requiring an increase in the dosage of cortisone and ACTH, respectively, in order to suppress them. Treatment with antibiotics of the intercurrent infections in view of the established allergy to those agents was obviously out of the question. In both instances the abscesses were incised and drained, and the wounds treated conservatively. It seems more than a coincidence that both of these patients developed buttock abscesses while under the hormonal therapy. The possibility of intercurrent infections masked by ACTH or cortisone therapy has been referred to in the literature. The fact that experimentally small laboratory animals even though receiving large doses of ACTH became worse and died exactly as the untreated controls, has been recently reported by Finland, Kass and Ingbar³² at the second clinical ACTH conference. In a discussion of this subject Finland raised the question whether it is possible that where there is already necrosis of tissue, ACTH or cortisone may actually aggravate the underlying infection whether or not antibiotic drugs are used. Working along similar lines Schwartzman has recently shown that ACTH and cortisone in combination, or cortisone alone, produce a marked acceleration of experimentally induced poliomyelitis infection (strain MEFI) in mice, and an extraordinary enhancement of susceptibility to this infection in hamsters, giving rise to a violent and uniformly fatal disease. ACTH alone failed to produce this effect, possibly due, according to Schwartzman,³³ "to elaboration of an unknown factor capable of reversing the enhancing effect of cortisone."

SUMMARY

Four atopic individuals with hyperergic vascular disease characterized by extensive purpura, pulmonary infiltrations with eosinophilic myocarditis, hepatosplenomegaly and renal involvement are reported.

Penicillin hypersensitiveness appeared to have been responsible for the clinical syndrome in the first two patients. Allergy to sulfadiazine and bacterial infection was regarded as the probable exciting factors in the vascular disease in Case 3, and bacterial infection was suspected in Case 4. Concurrent sensitivity to other antibiotics and drugs may have acted synergistically to accentuate the morbid process in all four cases.

Treatment with cortisone and ACTH was effective in controlling the reversible phases of the disease, such as eosinophilic pulmonary infiltrations, purpura, joint pains, fever, etc. It failed to halt the irreversible lesions in the heart and kidneys.

The writer wishes to express his appreciation to Dr. Paul Klemperer for the interpretation of the pathological material and to Dr. Louis Soffer and Mortimer Bader for their co-operation in the study of the effects of ACTH and cortisone while the patients were in the wards of the Mount Sinai Hospital.

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