Virchows Arch. Abt. A Path. Anat. 359, 97—104 (1973)
© by Springer-Verlag 1973

Fatal Necrotizing Angiitis after Sulfadimethoxine Therapy Presenting as Anaphylactoid Purpura

J. N. Cox, J. L. de Moerloose, J. R. Humbert, and L. Paunier

Department of Pathology and the Department of Pediatrics and Genetics, University of Geneva, Geneva

Received December 3, 1972

Summary. A fatal case of diffuse systemic necrotizing angiitis is described in a 14 year old boy presenting with Schönlein-Henoch purpura and developing renal failure. It is proposed that a long-acting sulfonamide (sulfamidethoxine) caused the disease, thus serving to reinforce previously published warnings against the indiscriminate use of long-acting sulfonamides.

Introduction

The clinical symptoms of the Schönlein-Henoch syndrome are well documented (Dodge *et al.*, 1963; Fitzsimmons, 1968; Starky and Thileu, 1960) and although its etiology remains obscure (Ballard *et al.*, 1970; Vernier *et al.*, 1961) it is currently believed to be a generalized vasculitis (Cruchard *et al.*, 1960; Gairdner, 1948; Vernier *et al.*, 1961).

Several autors attribute this syndrome to a hypersensitivity reaction whose clinical expression depends on the individual's sensitivity (Girard, 1972; McCombs, 1965); according to this concept, the Schönlein-Henoch syndrome may be only one clinical manifestation of a spectrum observed in cases of generalized systemic allergic angiitis.

We have recently observed the case of a 14 year old boy with a fatal Schönlein-Henoch syndrome. There was a systemic necrotizing angiitis in all the organs examined. The patient had been treated for tonsillitis with a long-acting sulfonamide (sulfadimethoxine) prior to hospitalization; in the absence of other known agents which could induce such a hypersensitivity reaction we speculate that the sulfonamide caused the disease in this patient.

Clinical History

This 14 year old male child, devoid of a family history of allergic diseases, was treated, for tonsillitis, with sulfadimethoxine (Madribon) for 8 days. The treatment was interrupted for two weeks during which time penicillin was given for 2 days, and was then readministered for 3 more days before he was referred to the Department of Pediatrics, Geneva, with the clinical diagnosis of anaphylactoid purpura, supported by the appearance of a petechial rash on the lower extremities and arthralgias of shoulder, hip and knee joints the day before admission. There was marked edema of the ankles and feet; the blood pressure was normal at 14/8 cm Hg.

Pertinent laboratory findings on admission included a leucocyte count of 18.000/mm^3, with 89% neutrophils, an erythrocyte sedimentation rate of 50 mm/hour, a haemoglobin of 11.4 g %, haematocrit 38% and platelets 191.000/mm^3. The tourniquet test was positive

and blood was present in the stools. The Addis count was 420.000 red cells/min. The urine contained 0.25 g/l albumin. Blood urea nitrogen was 930 mg/l and creatinine was 39 ml/min/1.73 m². Antistreptolysin titer was 280 units and remained at this level throughout the course of the disease. Beta-1-C-globulin was normal at 40 units (Ayoub and Hoyer, 1969; Borgeaud *et al.*, 1970). He was treated with penicillin 2 million units/day for 2 days, aspirin 4 g/day and diazepam (Valium) 6 mg/day.

During the first week of hospitalization the temperature oscillated between 38° and 39° C. The purpuric rash and the arthralgias, except that of the left elbow, disappeared. Hypertension (15/10 cm Hg) developed and was treated with a salt-free diet. Edema of the lower extremities persisted.

The haemoglobin had now dropped to 9.8 g/100 ml and the blood urea nitrogen varied between 1.000 and 1.300 mg/l. The creatinine clearance decreased to 31 ml/min/1.73 m². The Addis count was 25.000 red cells/min.

Arthralgias reappeared during the second week and neurological symptoms were observed. These included a decrease in sensibility of the right hand and a hypotonia and paralysis of the extensors of the left forearm. The blood pressure rose to 17/11 cm Hg in spite of reserpine treatment, to which apresoline was added. The Addis count rose to 640.000 red cells/min.

Tonico-clonic convulsions appeared on the 16th hospital day; an electro-encephalogram showed an irritative focus in the parietal region of the left hemisphere. These seizures were controlled by phenobarbital.

The patient's condition deteriorated progressively. The creatinine clearance decreased to 15 ml/min/1.73 m², and the urea nitrogen rose to 2.200 mg/l. A kidney biopsy was performed and on the same occasion specimens were taken from the liver, calf muscle and a purpuric skin lesion for histologic studies. Peritoneal dialysis was undertaken at the end of the third week which resulted in a fall in blood urea nitrogen to 675 mg/l, but this rose again to 1.100 mg/l. In two days the urinary output decreased to 400 ml/day and the edema of the legs reached to the waist. The patient finally died in renal failure and cardio-respiratory arrest in spite of a second emergency dialysis.

The rosette test for sulfadimethoxine was positive at $5^0/_{00}$ and for penicillin at $6^0/_{00}$ (control: $1^0/_{00}$) in samples of blood taken prior to his death.

Patholgy

Gross Pathological Changes. Gross pitting edema of the lower extremities was present. The kidneys (right: 200 g, left: 250 g) were enlarged, pale, and had a fleabitten surface. The liver (1930 g) was enlarged and congested. The brain was edematous (1460 g) with purpuric hemorrhages over its whole surface. The lungs were heavy, edematous and dark-red with areas of parenchymal consolidation.

Histology. All organs were examined histologically; the techniques used included haematoxylin-eosin, van Gieson-Verhoeff, phosphotungstic acid haematoxylin (PTAH), methenamine silver stain according to Jones, P.A.S., Masson-Verhoeff and Weigert stains.

The principal lesion observed was a necrotizing angiitis, and was found in both the biopsy material and the post-mortem specimens. These lesions consisted of extensive fibrinoid necrosis of the walls of the small and medium size muscular arteries, which in several instances were occluded by fibrinous thrombi. These vessels were surrounded by a dense histio-leukocytic infiltration containing in areas numerous eosinophils. Practically all the organs examined showed this vasculitis and in some cases the veins were involved.

The organs most severely involved were: the kidneys (Fig. 1), spleen, muscle with an accompanying myositis (calf, psoas, diaphragm), digestive tract (Fig. 2a

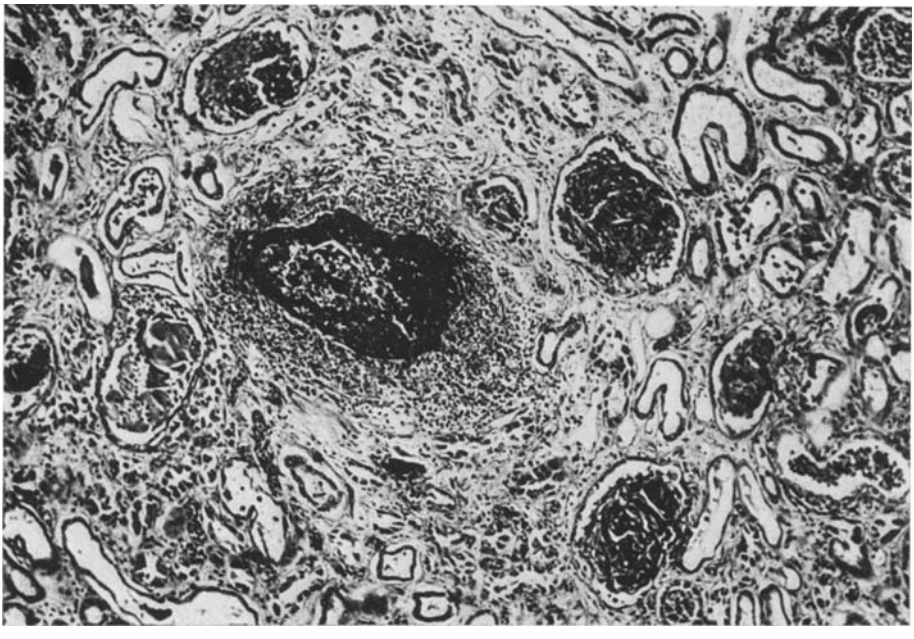

Fig. 1. Kidney (autopsy). Fibrinoid necrosis of arterial wall with fibrinous thrombus obliterating the lumen and cuffing of the area by an histio-leukocytic infiltration. There is tubular necrosis in the immediate vicinity. (H. E., × 30)

and b), gall bladder, endocrine glands (adrenals, thyroid, pancreas), brain, heart, joints (synovial tissue of the knee joint), and testis where numerous infarctions were observed.

The lesions were fewer in the liver, lungs (pulmonary and bronchial arteries), tonsils and vasa-vasorum of the thoracic and abdominal aorta. The lymph nodes examined were free of lesions, but the vessels within the surrounding adipose tissue were involved.

The skin lesions both in the biopsy and post-mortem material consisted of marked perivascular cuffing by lymphocytes, plasma cells, neutrophils and a few eosinophils. There was no necrosis.

Besides these acute, exsudative lesions, there were older ones, in the form of scarred and partially obliterated vessels principally in the muscles of the pharynx (Fig. 3a and b), the liver (Fig. 4a and b) and the myocardium.

The kidneys showed, outside of the vascular lesions, a widespread focal, proliferative glomerulonephritis at different stages of development in the biopsy specimen, In the post-mortem material, the glomerular lesions were diffuse. The glomeruli were severely damaged with extensive scarring of the majority, crescent formation and synechiae to the capsular membrane in others. By the Masson stain fibrine deposits were observed in some instances, on the capillary membrane of the glomeruli. Exsudation was minimal in the glomeruli.

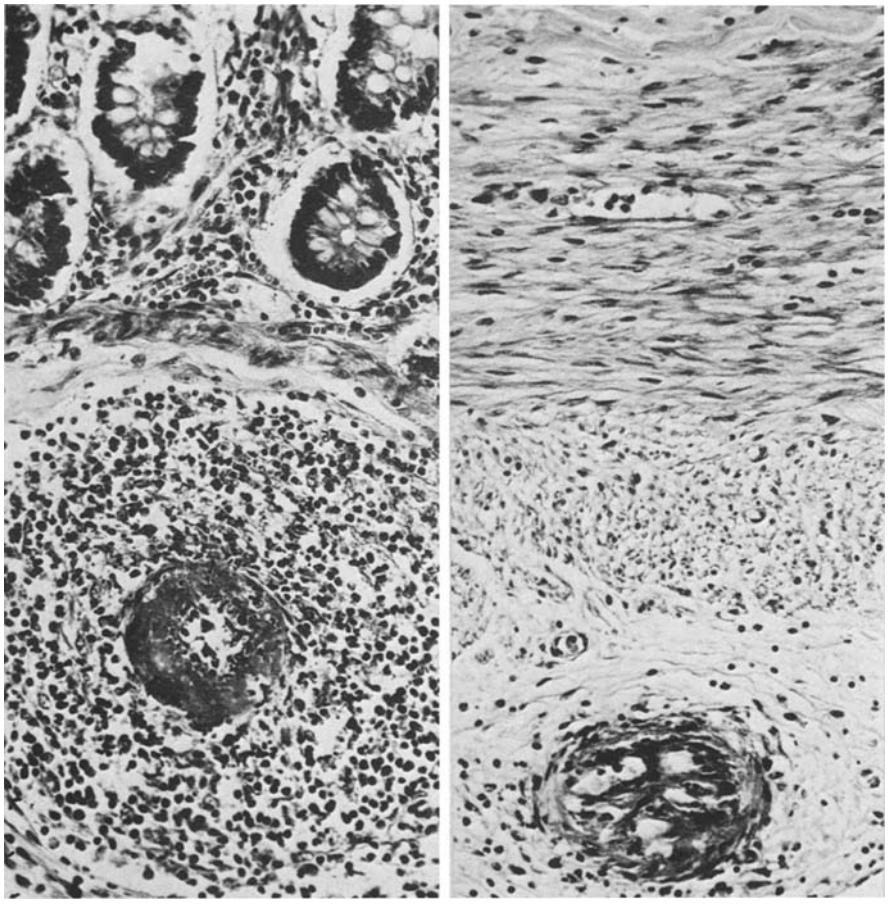

Fig. 2a and b. Appendix: a Acute vasculitis within the submucosa. b Within the serosa. These lesions are seen throughout the gastro-intestinal tract. (H. E., × 120)

Discussion

Various clinical syndromes have been described, in which systemic necrotizing vasculitis is a prominent feature. While each of these syndromes may present specific clinical and laboratory characteristics, their differential diagnosis is extremely difficult to establish from autopsy or biopsy material, because of the wide overlap of morphological features.

Schönlein-Henoch purpura is one of these well defined clinical syndromes in which widespread vasculitis is frequently found. The vascular lesions in this syndrome have been described in kidney biopsies of patients affected with the nephropathy of rhumatoid purpura. The most frequent lesions in the kidney include endocapillary proliferation; segmentary or focal glomerulonephritis (with endo- and extra-capillary proliferation) with fibrous synechiae between the capillary loops and Bowman's capsule forming crescents; or a diffuse endo- or extra-

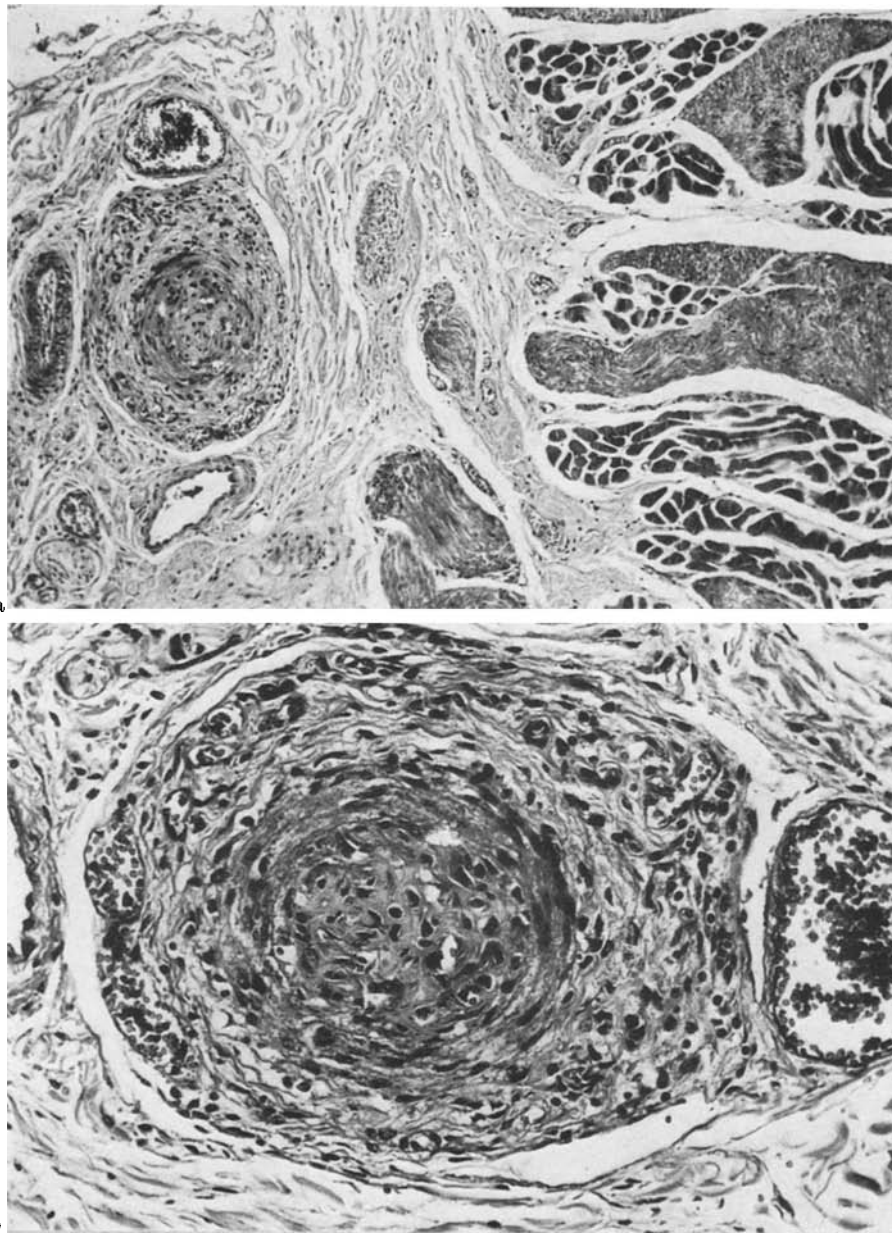

Fig. 3a and b. Muscle of the pharynx: a Organized obliterative thrombus of the artery (H. E., × 30). b Detail (H. E., × 120)

capillary glomerulonephritis involving all the glomeruli and accompanied by various degrees of epithelial proliferation. Fibrinoid necrosis of the vessels is rare, and rarely as extensive as in our case (Habib and Levy, 1972; Meadow *et al.*,

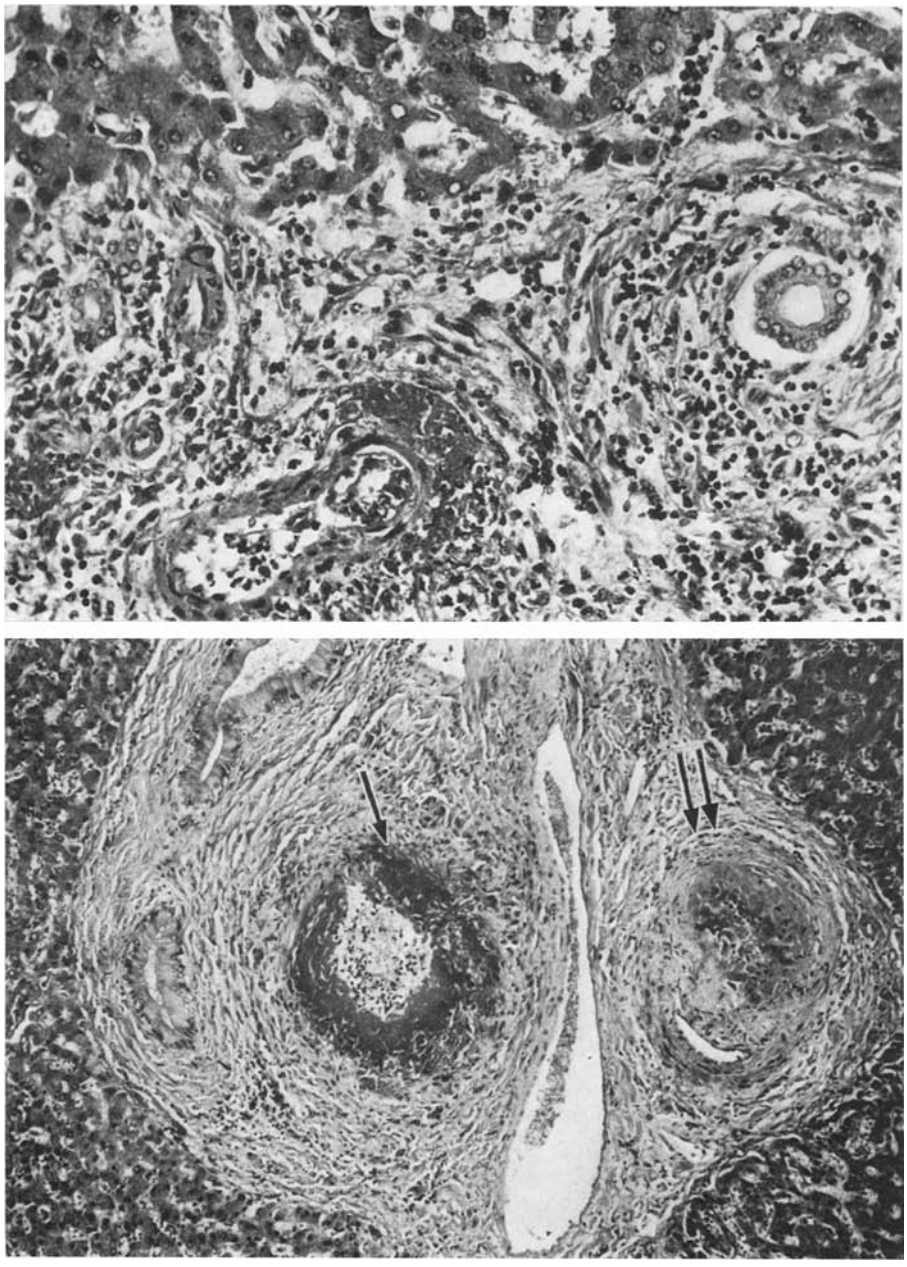

Fig. 4a and b. Liver: a Acute vasculitis of artery within the portal tract (H. E., × 60). b ↑ acute lesion, ↑↑ organized old lesion with same portal tract (H. E., × 30)

1972). The vascular lesions exhibited by our patient in all organs examined resemble most closely those of hypersensitivity angiitis (Doerr, 1970; Zeek, 1953) named also "allergic vasculitis" (McCombs, 1965).

The possible physiopathological processes involved in the genesis of necrotizing vasculitis are worth some comment. It is now admitted that systemic allergic vasculitis results from damage done to vessel walls by antigen-antibody complexes in association with complement (Kinlaw and McCune, 1961). This mechanism can be demonstrated in experimental hypersensitivity lesions (Dixon, 1965) and operates in particular in serum sickness and drug hypersensitivity reactions. The immune complexes responsible for triggering these phenomena have been well studied in cases of essential cryoglobulinemia (Barnett *et al.*, 1970). It may be relevant in this context to recall the demonstration of IgA, IgG, fibrinogen and complement in most of the kidney vascular lesions of Schönlein-Henoch patients (Barnett *et al.*, 1970; Whitsed and Penny, 1971).

The finding in our patient of vascular lesions suggestive of a hypersensitivity reaction raises the question of the etiology. Eleven different diseases are mentioned in connection with the 72 cases of allergic vasculitis reviewed by McCombs (1965). Twelve of these patients had reactions attributed to antibiotics, in particular penicillin and sulfonamides. Zeek's patients (1953), who had drug reactions etiologically implicated in their systemic vasculitis frequently pursued a rapidly fatal course (within a few weeks).

The only possible triggering agent in our case seems to be the antibiotics (sulfonamides and penicillin) or perhaps the ill-defined pharyngitis for which he was given antibiotic therapy. Even though there are still some contraversies over the value of the rosette test, the positive results in this case would serve as an indicator to show that there were some sensitivity to both drugs. The biopsy and autopsy material suggest that treatment with sulfonamide may have been the main culprit. Thus, the vascular lesions are of two distinct types: one takes the form of obliterated scarred vascular lesions, without inflammatory reactions, and can be considered the result of the first clinical manifestations of the illness six to eight weeks prior to the patient's death; the other type of lesions is much more diffuse, is observed in all organs examined, presents as an acute vascular necrosis with infiltration by histiocytes and granulocytes, and probably occured closer to the patient's death (they were not very widespread (kidney and muscle) on the biopsies taken 2—3 weeks previously). This suggests the presence of a triggering agent that must have acted on two different occasions to create these separate vascular lesions; the bimodal sulfonamide therapy is compatible, in its timing and interval, with being the etiological agent involved.

Furthermore, the clinical history reveals that our patient's symptoms had begun shortly after administration of a sulfonamide for his tonsillitis, and had subsided gradually after withdrawal of the substance. They reappeared when sulfonamides were reintroduced. The short course of penicillin did not seem to modify favourably the course of the disease, but rather it may have played some role in accelerating the process towards its fatal outcome.

Allergic vasculitis due to sulfonamides, especially the long-acting form as used in our patient, is well known (Doerr, 1970; French, 1946; Lichtenstein, 1946). In one case, the clinical picture was almost identical to that observed in our patient, with rapidly progressive renal failure and death (Sherlock and White, 1944). Although it is impossible to state with certainty that the long-acting sulfonamides caused our patient's disease and death, it is highly probable that it did. Long-acting sulfonamide drugs have little or no place in modern pediatric

therapy, and our report serves as another warning against the use of this potentially dangerous drug.

The rosette tests for Penicillin and Sulfadimethoxine were performed by Dr. J. P. Girard. We thank Miss C. L. Seignemartin for secretarial services, also Mrs. M. Engler and Messers J. C. Rumbeli and E. Denkinger for their technical and photographic assistance.

References

Ayoub, E. M., Hoyer, J.: Anaphylactoid purpura: streptococcal antibody titers and beta-1-C-globulin levels. J. Pediat. **75**, 193–201 (1969).

Ballard, H. S., Eisinger, R. P., Gallo, G.: Renal manifestations of the Henoch-Schönlein syndrome in adults. Amer. J. Med. **49**, 328–335 (1970).

Barnett, E. V., Bluestone, R., Cracchiolo, A., Goldberg, L. S., Kantor, G. L., McIntosh, R. M.: Cryoglobulinemia and disease. Ann. intern .Med. **73**, 95–107 (1970).

Borgeaud, M., Paunier, L., Humair, L.: La bêta-1-C globuline dans les néphropathies de l'enfant. Helv. paediat. Acta **25**, 585–601 (1970).

Cruchaud, A., Bouvier, C. A., Humair, L.: Les artérites nécrosantes par sensibilisation. J. suisse Méd. **90**, 258–265 (1960).

Dixon, F. J.: Experimental serum sickness. In: Immunological diseases, p. 161 (M. Sameter, ed.). Boston: E. Little, Brown & Co. 1965.

Dodge, W. F., Pravis, L. B., Daeschner, C. W.: Anaphylactoid purpura, polyarteritis nodosa and purpura fulminans. Pediat. Clin. N. Amer. **10**, 879–987 (1963).

Doerr, W.: Allgemeine Pathologie der Organe des Kreislaufs. In: Handbuch der allgemeinen Pathologie, Bd. III, part 4, S. 633. Berlin-Heidelberg-New York: Springer 1970.

Fitzsimmons, J. S.: Uncommon complication of anaphylactoid purpura. Brit. med. J. **4** 431–432 (1968).

French, A. J.: Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy. Amer. J. Path. **22**, 679–687 (1946).

Gairdner, D.: The Schönlein-Henoch syndrome (anaphylactoid purpura). Quart. J. Med. **17**, 95–122 (1948).

Girard, J. P.: Allergic reactions to antibiotics. Helv. med. Acta **36**, 3–22 (1972).

Habib, R., Levy, M.: Les néphropathies du purpura rhumatoïde chez l'enfant. Arch. franç. Pédiat. **29**, 305–324 (1972).

Kinlwa, B., McCune, W.: Severe reaction to sulfadimethoxine (Madribon). Clin. J. med. Sci. **242**, 30–31 (1961).

Lichtenstein, L., Fox, L.: Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole. Amer. J. Path. **22**, 679–687 (1946).

McCombs, R. P.: Systemic allergic vasculitis: clinical and pathological relationships. J. Amer. med. Ass. **194**, 157–162 (1965).

Meadow, S. R., Glasgow, E. F., White, R. H., Moncrieff, M. W., Cameron, J. S., Ogg, C. S.: Schönlein-Henoch nephritis. Quart. J. Med. **41**, 241–260 (1972).

Sherlock, S., White, J. C.: A fatal case of purpura after sulphapyridine. Brit. med. J. **23**, 401–403 (1944).

Starky, G., Thileu, A.: A study on the onset and prognosis of acute vascular purpura (the Schönlein-Henoch syndrome in children). Acta pediat. **49**, 217–229 (1960).

Vernier, R. L., Whorten, H. G., Petersen, R. D., Colle, E., Good, R. A.: Anaphylactoid purpura: pathology of the skin and frequency of streptococcal infection. Pediatrics **27**, 181–191 (1961).

Whitsed, H. M., Penny, R.: IgA/IgG cryoglobulinemia with vasculitis. Clin. exp. Immunol. **9**, 183–193 (1971).

Zeek, P. M.: Periarteritis nodosa and other forms of necrotizing angiitis. New Engl. J. Med. **248**, 764–772 (1953).

Dr. J. N. Cox
Department of Pathology
40, Boulevard de la Cluse
CH-1211 Geneva/Switzerland