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Experimental Necrotizing Arteriolitis Induced by a Protein Cleavage Product.

RALPH R. MELLON, MARGARET R. BAKER, AND ALICE P. McILROY.

From the Western Pennsylvania Hospital, Institute of Pathology, Pittsburgh.

With K. F. Semsroth, formerly of this Institute, one of us (Mellon) initiated experiments that have been substantially amplified and extended through the assistance of the above collaborators. The few original experiments were the outgrowth of unpublished studies by one of us (Mellon), attempting to correlate the antiseptic action of iodine with its wound healing power—the inference appearing justified that it might be partially accounted for by its neutralization of certain toxic products of protein decomposition, originating perhaps from the tissues or from microorganisms. In support of this point of view Eppinger,[1] found that iodine neutralized the toxicity of putrifying meat pulp. He inferred from his experiments that the toxicity was due to certain unsaturated protein cleavage products, of which allylamine is a type. From our standpoint, the pertinent pathological effect of allylamine as shown by him is a marked increase of endothelial permeability.

It was, therefore, natural to see whether allylamine applied to wounds would delay their healing, and to observe whether the effect on the endothelium was reflected in detectable morphologic alterations in the vessel walls. Both effects were observed, the latter being of a noteworthy character, consisting in their close similarity to the experimental arteriolitis of Klinge[2] as shown in his hyperergic vascular lesions, and to the necrotizing arteriolitis and malignant nephrosclerosis of Fahr.[3]

Twenty-one rabbits were employed. The allylamine was applied to small areas denuded of skin, as well as given intradermically. Control administration of NH_4OH was employed. Each type of solution, the allylamine and the NH_4OH, was used in both buffered and unbuffered form. All buffered solutions had a pH of 7. The doses of allylamine ranged from 0.2 cc. to 0.5 cc. (intradermically) of solutions varying in concentration from 1% up to one to one million (10^{-6}). Vascular changes were discernible in concentrations as low as 10^{-5}, although they were more characteristic at 10^{-3} and 10^{-4}.

1 Eppinger, H., *Klin. Woch.*, 1935, **13**, 1105.

2 Klinge, *Ergebn. d. Allg. Pathol.*, 1933, **27**.

3 Fahr, Th., Henke-Lubarsch, Handbuch. d. spec. pathol. Anat., Vol. VI.

This was the case for even the buffered solutions, none of which caused macroscopic lesions in dilutions of more than 1:100. Although the unbuffered NH_4OH controls caused local sloughing, especially in higher concentrations, in only an insignificant percentage of lesions was a vascular effect detected—unless employed on the same animal as the test substance. For example, when histamine was employed as an additional control, the unbuffered NH_4OH yielded at times an appreciable percentage of lesions.

The histamine dosage ranged from 10^{-2} to 10^{-5} cc., 0.2 cc. of each dilution being employed. Both buffered (pH 7) and unbuffered solutions were used. Vascular effects were absent in *all dilutions of the buffered material;* but with the unbuffered, the characteristic microscopic effects were observed in solutions no more dilute, however, than in $1x10^{-3}$. Macroscopic effects were also noticeable in the unbuffered, but not in the buffered solutions. In this connection it is of interest that histamine has in its molecule the allylamine linkage. Moreover, control observations with allylformate and allylalcohol indicated the paramount importance of the amine group.

In its earlier stages an outstanding feature of this arteriolar disease is first: hemorrhage into the wall; and second, a loss of its structure accompanied by the presence of a homogeneous, highly eosinophilic material. (Fig. 1.) In its later stages a definite proliferative endarteritis is often seen, even to obliteration of the ves-

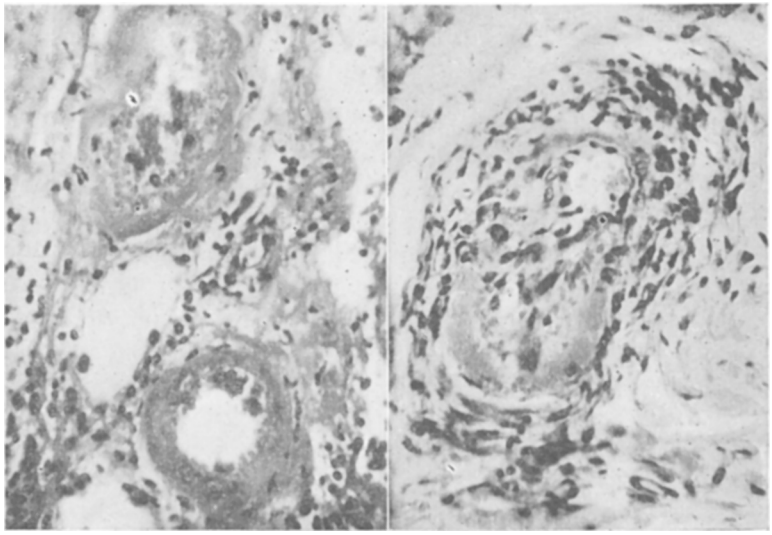

FIG. 1 FIG. 2.

sel's lumen. Perivascular changes consist of mononuclear infiltration of tissue polyblasts (Fig. 2), as well as the formation of a nodular periarteritis (Figs. 3 and 4). Fig. 3 represents a nodule

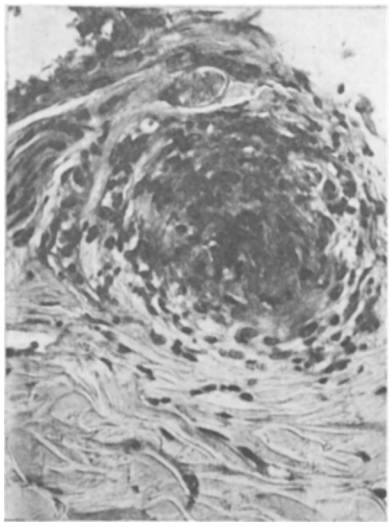

FIG. 3.

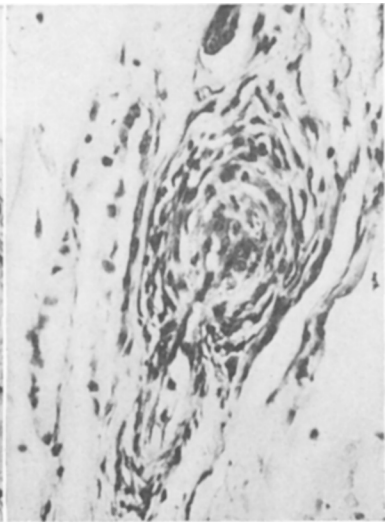

FIG. 4.

whose continuity with the adventitia of the occluded vessels seen in Fig. 4 was traced by serial section. Thus the process recalls a periarteritis nodosa. Note also in Fig. 2 that the lower segment of the vessel shows the intramural change, while in the upper portion the perivascular infiltration of mononuclear cells dominates.

Endarteritic, as well as periarteritic, processes are *suggestively sequelae* of the appearance within the vessel wall of the homogeneous eosinophilic material described above. The coincidence of the latter with endothelial necrosis and intramural hemorrhage in early, rather than late, stages, the absence of nuclear fragmentation within the homogeneous matter in the early stages, its extension beyond the arteriolar walls, suggest that this intramural homogeneous material is composed of coagulated blood plasma. Weigert's fibrin stain, silver stains, and Mallory's anilin blue support this impression that the substance is fibrin or fibrin-like. Its presence in the arteriolar wall obscures and probably partially destroys the normal mural structures.

Summary. From these results it appears justifiable to draw tentatively the following inference: the intracutaneous injection of allylamine in rabbits leads to a necrotizing arteriolitis strikingly

similar to that conventionally present in certain human infections (the streptococcoses especially) which have prominently in their background the phenomena of hypersensitiveness. In the pathogenesis of the latter a primary endothelial damage making for increased permeability appears to be of significance.

Histamine, the substance par excellence from which one might expect such effects, produces it only in relatively high concentrations; and only in the unbuffered form. As far as we are aware such vascular changes have not been described for protein cleavage products of relatively simple constitution; particularly in rather high dilution and of a neutral pH. In a physiological sense the allylamine is to be looked on as histamine-like, at least in its vascular effects. But it is decidedly more active in this respect, even under pH conditions prevailing in the host where histamine has exhibited no effect as far as the studies have progressed.

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A Sex Difference in Gonad-Stimulating Potency of Young Gonadectomized Rats.

KATHRYN F. STEIN. (Introduced by A. E. Adams.)

From the Zoology Department, Mount Holyoke College.

Clark[1] recently reported that in rats gonadectomized at 1 or 2 days of age and assayed 16 to 18 days later the gonad-stimulating potency of the pituitaries was approximately the same in both sexes. Since in normal control animals of that age (17 to 20 days) the sex-stimulating potency of the female pituitary exceeds that of the male, she concluded that castration at 1 or 2 days produced a relatively greater increase in gonadotropic potency than spaying. The following series of preliminary experiments indicates that if gonadectomy is delayed for a week the pituitary of the castrated male does not gain as much in gonadotropic potency as that of the spayed female in the same period of time.

Littermate male and female rats 7 to 9 days of age were gonadectomized and after 17 to 19 days their pituitaries were injected into immature female rats 23 to 26 days of age. Normal males and females, littermates of the gonadectomized series, served as control donors. A host series consisted of 4 littermate females. Three

[1] Clark, H. M., *Anat. Rec.*, 1935, **61**, 193.