Brit. J. Pharmacol. (1949), **4**, 216.

THE EFFECT OF NEOANTERGAN AND OF BENADRYL ON SERUM-INDUCED MYOCARDITIS IN RABBITS

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(Received March 28, 1949)

Experimental tissue changes can be produced in various tissues of rabbits by the intravenous injection of horse serum. Ehrich *et al.* (1949) have recently reviewed the literature on this subject, adding the confirmatory results of their own investigations. Rich and Gregory (1943a) and McKeown (1947) were of the opinion that the myocardial and valvular lesions so produced were very similar to those found in human rheumatic fever. Other workers suggest that the allergic arteritis seen in the heart and other tissues more closely resembles that of human polyarteritis nodosa. The lesions probably arise from an antigen-antibody reaction in the surrounding tissues, as a result of anaphylactic hypersensitivity. All workers have noted a considerable variation in the incidence of vascular lesions in different experiments. Dammin and Bukantz (1949) observed an incidence of 85 per cent in one experiment and of only 10 per cent in another.

The release of histamine by the antigen-antibody reaction might play a part in producing these lesions, and it was reasonable to investigate whether histamine antagonists could influence their production or severity in serum-sensitized animals.

Kyser *et al.* (1947) recently reported that benadryl and another histamine antagonist (No. 1627) effectively prevented the appearance of rheumatic-like lesions in the myocardium of the serum-sensitized rabbit. In their experiments, complete protection was afforded to sensitized animals by benadryl, but all 11 survivors of a group of 12 sensitized animals not treated with an antihistamine substance developed moderate or severe lesions.

Dammin and Bukantz (1949) have recently reported that benadryl and neohetramine gave no effective protection against the lesions.

METHODS

Experimental hypersensitivity was produced by the original technique of Rich and Gregory (1943b). Twenty-two rabbits in all were given intravenous injections of sterile unpreserved horse serum in a dose of 10 ml. per kg. on the 1st and 20th day. The injection of 1 ml serum/kg. 2 days before the second injection of serum was omitted.

Twelve animals were given subcutaneous injections of an antihistamine substance twice daily; six received 5 mg. neoantergan/kg. and six received 10 mg. benadryl/kg. in each dose.

Of these twenty-two animals only one (from the control untreated group) died during the second serum injection. Several others showed marked weakness after this second injection, but all rapidly regained normal activity.

Electrocardiographic records were taken from the benadryl-treated rabbits and their controls by means of a Sanborn Viso-cardiette Electrocardiograph. Records were taken before the first injection and on the 28th day. All animals were killed on the 28th day and the excised hearts fixed in formol-saline for histological examination. The heart sections were stained in the usual way with haematoxylin and eosin, and examined for the lesions detailed below, particular attention being given to the extent and degree of perivascular damage.

RESULTS

In the control group of untreated, sensitized rabbits, 8 out of 10 showed moderate to severe damage characterized by patchy or generalized arteritis with medial necrosis and a periarterial reaction in the adventitia with polymorphonuclear and eosinophil infiltration. Small nodules closely resembling Aschoff bodies were occasionally found, often but not always in relation to vessels showing a severe arteritis. These nodules contained multinucleated giant cells, lymphocytes, eosinophils and large cells with clear cytoplasm like Anitschkow myocytes. Valvular and endocardial lesions were occasionally seen in some animals. Commonly there were also intermuscular collections of mononuclear cells with some oedema and necrotic collagen tissue near the severely affected vessels. The reaction appeared to be mainly a severe arteritis, the occasional endocardial and valvular lesions and Aschoff-like bodies being similar to the lesions of rheumatic carditis.

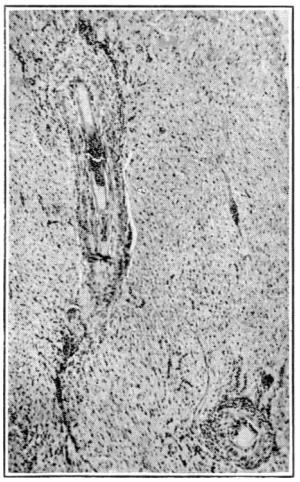

FIG. 1.—Myocardium of untreated serum-sensitized rabbit. L.P. (mag. × 60). Shows typical severe vascular and perivascular lesions.

Fig. 1 illustrates a typical severe periarterial lesion in a control animal which can be compared with the appearances of a normal rabbit myocardium shown in Fig. 2. An attempt was made to give some quantitative indication of the severity of the disease in each rabbit. A points system was devised, marks being awarded for intermuscular and perivascular infiltration, Aschoff-like bodies, muscle and collagen degeneration. Two observers assessed each animal independently. Normal rabbit sections were available for comparison.

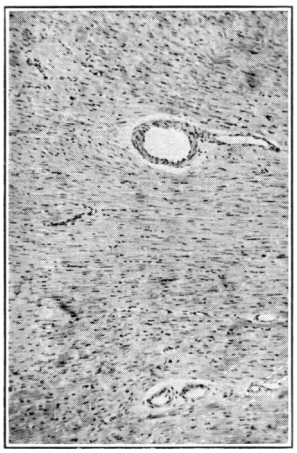

FIG. 2.—Myocardium of normal rabbit for comparison with Fig. 1 (same magnification).

This marking system was not absolutely necessary in the assessment of these results since there was not the slightest suggestion that any protection was given against the development of any of the observed lesions either by neoantergan or benadryl in the doses used.

Moderate or severe lesions were found in all 6 animals given neoantergan and in 5 of 6 animals given benadryl. The results are expressed in detail in the Table and Fig. 3.

TABLE

SEVERITY OF MYOCARDIAL LESIONS IN SERUM-SENSITIZED ANIMALS

Points were awarded for the presence of certain observed types of lesion. No protection is afforded by benadryl or neoantergan

Injections	No. of rabbits	Points	
		Total	Mean ± S.E.
Control serum only ..	10	26.5	2.65 ± 0.62
Serum plus Neoantergan, 5 mg./kg., s.c., b.d. ..	6	24	4.0 ± 0.86
Serum plus Benadryl, 10 mg./kg., s.c., b.d. ..	6	16.0	2.7 ± 0.64

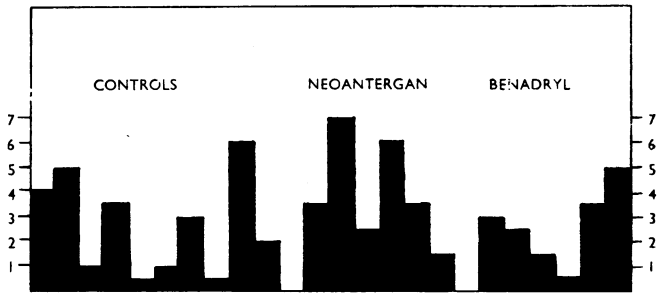

FIG. 3.—Showing the individual variation in the severity of the lesions produced in control and treated groups. Each column represents one animal and the ordinates are the points awarded to each rabbit (see text).

There was no alteration in the electrocardiographic pattern in either the control or treated group.

DISCUSSION

The histamine antagonists probably do not prevent the liberation of histamine during the antigen-antibody reaction (Bucher, 1948) but are able to antagonize the systemic effects of the liberated histamine. It is possible that antihistamine substances might prevent the pathological effects of serum disease and might consequently be of use in

treatment of diseases in which hypersensitivity is believed to play a part.

Some evidence has been reported that experimental nephritis in rabbits can be prevented by antihistamine substances (Reubi, 1946), and there have also been reports of the clinical usefulness of anthisan in human nephritis (Craig *et al.*, 1949) and of benadryl in polyarteritis nodosa (Sutherland, 1948). Examination of the kidneys of the animals used in the present experiments suggests that no significant protection against renal lesions due to hypersensitivity was afforded by the antihistamine substances.

The exact application of the above results in clinical practice is in doubt, but, in so far as the experimental lesions represent the nearest approach to the lesions of rheumatic fever, the results do not support the use of antihistamine substances in the treatment of human rheumatic fever; nor do they suggest that there is likely to be any benefit from their use in the treatment of polyarteritis nodosa. Hunter and Dunlop (1948) have reported that two cases of polyarteritis nodosa treated with antihistamine drugs were not improved.

Sodium salicylate is used routinely in rheumatic fever. Coburn (1943) has suggested that sufficiently large doses of salicylate, giving a blood concentration of about 35 mg./100 ml., may actually prevent the development of the cardiac lesions of acute rheumatism. Sodium salicylate has recently been shown to prevent the experimental cardiac lesions in rabbits subjected to serum sickness (Smull *et al.*, 1948; Ehrich *et al.*, 1949). Our preliminary experiments with sodium salicylate support this finding. Dammin and Bukantz (1949) suggest that administration of nitrogen mustards can provide protection against the development of the lesions.

Summary

1. Contrary to published findings, neoantergan and benadryl did not prevent the development of myocardial lesions in rabbits sensitized to horse serum.

2. The results do not support the therapeutic use of antihistamine substances in the treatment of rheumatic fever or of polyarteritis nodosa in man.

We wish to thank Professor E. J. Wayne for his help and encouragement in this work, Mr. E. Salvin for invaluable technical assistance including the histological preparations, and Mr. J. Kugler for the photomicrographs. The sterile horse serum used in these experiments was kindly supplied by Mr. G. J. Christie of Boots Pure Drug Co., Ltd. The expenses of this work were met by a grant from the University Research Fund.

References

Bucher, K. (1948). *Helv. physiol. pharmacol. Acta*, **6**, 299.
Coburn, A. F. (1943). *Bull. Johns Hopk. Hosp.*, **73**, 435.
Craig, J., Clark, N. S., and Chalmers, J. D. (1949). *Brit. med. J.*, **1**, 6.
Dammin, G. J., and Bukantz, S. C. (1949). *J. Amer. med. Ass.*, **139**, 358.
Ehrich, W. E., Seifter, J., and Forman, C. (1949). *J. exp. Med.*, **89**, 23.
Hunter, R. B., and Dunlop, D. M. (1948). *Quart. J. Med.* n.s., **17**, 271.
Kyser, F. A., McCarter, J. C., and Stengle, J. (1947). *J. Lab. clin. Med.*, **32**, 379.
McKeown, E. F. (1947). *J. Path. Bact.*, **59**, 547.
Reubi, F. (1946). *Helv. med. Acta*, **13**, suppl., 18, 1.
Rich, A. R., and Gregory, J. E. (1943a). *Bull. Johns Hopk. Hosp.*, **73**, 239.
Rich, A. R., and Gregory, J. E. (1943b). *Bull. Johns Hopk. Hosp.*, **72**, 65.
Smull, K., Wissler, R. W., and Waeter, J. M. (1948). *J. Lab. clin. Med.*, **33**, 936.
Sutherland, J. M. (1948). *Brit. med. J.*, **1**, 832.