Suppression of an "adjuvant arthritis" in alloxan-diabetic rats

SIR,—Several reports suggest a relationship between carbohydrate metabolism, inflammation and allergy. In general, hyperglycaemia reduces, and hypoglycaemia increases, inflammatory and allergic phenomena. Alloxan-diabetic rats are more resistant to anaphylactoid reactions (Goth, Nash, Nagler & Holman, 1957), and produce less granulation tissue around subcutaneously-implanted foreign bodies than do normal animals (Nagy, Redei & Karady, 1961). Diabetogenic doses of alloxan, or high doses of glucose, greatly reduce the anaphylactic reaction in rats sensitised to horse serum (Thompson, 1961). Similarly, resistance to sensitisation with *Bordetella pertussis* is increased in alloxan-diabetic mice (Ganley, 1962).

The pathogenesis of rheumatoid arthritis has been the subject of controversy for many years, and many experimental models have been suggested and, on the whole, rejected (see Gardner, 1960). The possible involvement of an auto-immune response in this disease is now being widely considered, and an experimental model in rats which resembles in some respects, the human disease, is also being investigated (Pearson, 1964). This model, a so-called "adjuvant arthritis" is produced by injecting Freund's adjuvant, or a variety of acid fast bacilli, into rats. About 14 days after this injection a polyarthritis develops that affects the peripheral joints, ears and tail.

In the present study we have investigated the development of a polyarthritis in alloxan-diabetic rats. Female rats (130–150 g) were given 150 mg/kg of alloxan intraperitoneally and those that had blood sugar levels of over 350 mg% one week later, were used. Groups of normal and alloxan-diabetic rats were given a subcutaneous injection of 0·05 ml of a 2·5 mg/ml suspension of dead tubercle bacilli in liquid paraffin into the plantar surface of the left hind paw. The bacilli were derived from human stains PN, DT and C. The diameter of the foot originally injected was measured before and at intervals after injection, using the method described by Newbould (1963). The rats were carefully observed for the development of secondary lesions of the paws, ears and tail. The blood sugar levels of the alloxan-diabetic rats were checked weekly. The result of 28 days observation are summarised in Table 1.

In the alloxan-diabetic rats, when compared with normal animals, there was a significant reduction in the primary inflammatory response to injection of dead bacilli into the paw. The appearance of secondary lesions was delayed in the

TABLE 1. SUPPRESSION OF AN "ADJUVANT ARTHRITIS" IN ALLOXAN-DIABETIC RATS

	Normal					Alloxan-diabetic			
Days after adjuvant injection	Mean increase in foot thickness mm ± s.e.	Distribution of secondary lesions Foot	Tail	Ear	Mean number of secondary lesions/rat	Mean increase in foot thickness mm ± s.e.	Distribution of secondary lesions Foot	Tail (Ear, nil)	Mean number of secondary lesions/rat
3	4·46 ± 0·12	0	0	0	0 (18)	2·59 ± 0·21	0	0	0 (12)
5	5·02 ± 0·14	0	0	0	0 (18)	3·22 ± 0·33	0	0	0 (12)
7	5·20 ± 0·17	0	0	0	0 (18)	3·04 ± 0·27	0	0	0 (11)
10	5·10 ± 0·24	3	0	0	0·17 (18)	2·69 ± 0·23	0	0	0 (11)
12	5·12 ± 0·24	3	0	0	0·18 (17)	2·29 ± 0·18	0	0	0 (11)
14	5·07 ± 0·21	11	4	0	0·88 (17)	2·68 ± 0·18	1	0	0·09 (11)
17	5·42 ± 0·21	19	4	6	1·70 (17)	3·70 ± 0·17	3	1	0·36 (11)
19	4·93 ± 0·18	20	8	6	2·00 (17)	3·58 ± 0·22	3	6	0·82 (11)
21	4·96 ● 0·22	20	8	6	2·00 (17)	3·50 ± 0·23	3	7	0·91 (11)
24	4·95 ± 0·21	20	8	6	2·00 (17)	4·00 ± 0·28	3	7	0·91 (11)
26	4·72 ± 0·16	20	8	6	2·00 (17)	3·80 ± 0·23	2	6	0·73 (11)
28	4·77 ± 0·18	20	8	6	2·00 (17)	3·78 ± 0·25	2	6	0·73 (11)

Figures in parentheses indicate number of animals.

hyperglycaemic rats and the average number of new lesions produced was reduced from 2·0 to 0·91 per rat. The distribution of the new lesions appeared to be different in the two groups. In normal animals the feet were predominantly affected and in hyperglycaemic animals the tails.

The mechanism of this suppressive effect of hyperglycaemia in allergic and inflammatory conditions is unknown. It has been suggested that hyperglycaemia inhibits, and hypoglycaemia potentiates the antigen-antibody reaction if this reaction involves a carbohydrate moiety (Adamkiewicz, 1963). An example is the tuberculin reaction which high blood sugar levels decrease and low levels increase (Cornforth & Long, 1953). Polysaccharide antigens are known to be involved in this reaction. However, this hypothesis does not take account of how hyperglycaemia inhibits anaphylactoid reactions and suppresses the formation of granulation tissue, processes which do not involve antigen-antibody combination.

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Validity of ptosis as a measure of the central depressant action of reserpine

SIR,—Ptosis is a characteristic feature of the action of reserpine in many animal species and has been used for the bioassay of reserpine-like alkaloids (Rubin, Malone, Waugh & Burke, 1957). It is usually regarded as a sign of the central action of reserpine, and the ability of drugs to prevent reserpine-induced ptosis has been proposed as a test for antidepressants (Chen, 1964). However, ptosis is also produced by adrenergic-neurone blocking agents of the quaternary ammonium or guanidine types (Costa, Kuntzman, Gessa & Brodie, 1962; Fielden & Green, 1965), which do not enter the brain in significant amounts (Boura, Copp, Duncombe, Green & McCoubrey, 1960). Since reserpine causes profound noradrenaline depletion in peripheral adrenergically-innervated tissues, with consequent loss of sympathetic function (Carlsson, Rosengren, Bertler & Nilsson, 1957), it is pertinent to inquire whether reserpine-induced ptosis may not also occur as a result of peripheral sympathetic blockade.

In Table 1, the extent of ptosis, scored on a 0–8 scale (Rubin & others, 1957), is compared with the depletion of heart and brain noradrenaline, or brain 5-hydroxytryptamine (5-HT) 4 hr after subcutaneous injection of various doses of