LETTERS TO THE EDITORS

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Anaphylactoid Response in Guinea Pigs to the Parenteral Administration of Sulphate Esters of High Molecular Weight of Dextran

DURING an investigation of the biological activity of the synthetic heparinoid anticoagulant, dextran sulphate, it was noted that the parenteral administration of certain samples gave rise to a peculiar transitory reaction in guinea pigs[1]. This reaction was anaphylactoid in type, being characterized by jactitating convulsions followed by acute circulatory collapse. Although superficially resembling true anaphylaxis, it differed from the latter in that (*a*) it occurred in animals which had not been exposed previously to dextran sulphate; (*b*) it was not accompanied by severe respiratory embarrassment. No coughing, wheezing or sneezing occurred, and animals killed during attacks showed no evidence of bronchiolar constriction or pulmonary emphysema; (*c*) the reaction could not be prevented or inhibited by large doses of the antihistamine compounds which inhibit anaphylaxis[2]. Equivalent doses of the compounds producing this effect in the guinea pig did not produce similar reactions in the mouse, rat, rabbit, dog or baboon.

Investigation of the molecular characteristics of the compounds giving rise to this anaphylactoid response showed that: (1) the molecular weight of the dextran sulphate must exceed a certain critical level and that, above this, equivalent doses by weight of compounds of increasing molecular size caused reactions of increasing intensity; (2) at the critical level of molecular size a certain sulphur content must be exceeded to produce the reaction. Dextran sulphates with average molecular weights greater than 20,000 invariably produced anaphylactoid responses. Similar responses only occurred with occasional samples of smaller average molecular weight. Such samples were suspected to be unusually polydisperse. Ethanol fractionation[3] of one such sample gave a series of fractions of decreasing molecular weight (as shown by decline of their intrinsic viscosities) and demonstrated more precisely the relationship between molecular weight and capacity to produce the response (see table).

The parent neutral dextrans, regardless of their molecular size, failed to produce reactions. With dextran sulphates of molecular weights greater than 20,000, it was shown that a sulphur content of at least 10 per cent was necessary to evoke the response. On the other hand, the sulphur content of homogeneous samples with average molecular weights of 7,000–10,000 could be increased to 20 per cent without producing the reaction.

	Intrinsic viscosity	Sulphur in sodium salt (per cent)	Fibrinogen precipitation	Deposition of material in reticulo-endothelial cells	Anaphylactoid response
Original sample	0·044	17·9	+	+	+
Fraction 1	0·070	19·4	+++	+	+
,, 2	0·058	19·3	++	+	+
,, 3	0·054	20·6	++	+	+
,, 4	0·044	19·4	+	+	0
,, 5	0·035	19·6	0	0	0
,, 6	0·026	19·3	0	0	0
,, 7	—	14·9	0	0	0

It has previously been reported that dextran sulphates with molecular weights greater than 20,000 form insoluble complexes with fibrinogen and possibly other macromolecular proteins under physiological conditions[4]. This behaviour has been shown to be accompanied by alteration of the suspension stability of the blood, with resultant agglutination of the blood-cells and especially the platelets[5]. In intact rats and rabbits, the insoluble particulate precipitates so formed were shown to be phagocytosed by reticulo-endothelial cells[1] or deposited on the vascular endothelium as thrombi or emboli. Such deposits were found to be demonstrable histologically by the metachromatic reaction given by the dextran sulphate – protein complex on staining with toluidine blue. The association between these phenomena and the occurrence of the anaphylactoid response in guinea pigs is shown in the accompanying table.

Two other synthetic anticoagulants, a sulphuric ester of xylan, and a sample of sodium polyanethol sulphonate ('Liquoid') which caused similar precipitation of fibrinogen and agglutination of blood-cells, were found to evoke anaphylactoid responses of similar character in guinea pigs.

These associated phenomena have been regarded as rendering such compounds unsuitable for therapeutic use. The sensitivity of the guinea pig in producing an anaphylactoid response to samples of dextran sulphate of low average molecular weight 'contaminated' with the large molecules responsible for the phenomena has suggested this as an empirical screening-test in investigating the suitability of batches for subsequent clinical appraisal.

KENNETH W. WALTON
Department of Experimental Pathology,
University of Birmingham.
COLIN R. RICKETTS
Medical Research Council
Industrial Injuries and Burns Research Unit,
Birmingham Accident Hospital,
Birmingham 15.

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Kinetic Evidence for New Participants in the Hill Reaction

A SIMPLE method for obtaining non-stationary kinetic data from photo-reactions is to use periodic illumination. The photosynthetic process of *Chlorella* and other algæ has been extensively studied in this way. The results have been confusing in that different relationships between the photosynthetic yield per flash and the interval between flashes (t_d) have been observed. They can be divided into two categories depending upon whether the period of illumination was short (10 μsec. per flash) or long (1 m.sec. per flash or greater). Under conditions of short flashes, the yield per flash reached a maximum value when t_d was about 0·03 sec.; further increase of t_d did not change the yield, nor was the maximum yield altered by variation of temperature[1–3]. With long flashes at high light intensities, greater values of t_d were required to secure greater maximum yields per flash