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A "shocking" ten years at the Square—mechanisms of experimental shock

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During the period 1955 to 1965, more than 150 research papers concerned with the problem of shock were published from the Department of Pharmacology at the School of Pharmacy. This state of affairs would not have been possible but for the fantastic efforts of some 15 colleagues of mine, most of whom were in the process of obtaining higher degrees. The present paper provides a unique opportunity of thanking them all for combining into such an excellent team. As certain aspects of the work are re-lived, only some will be named but all in some way enabled the most important paper of all the ten years to be published, that on a new approach to the medical interpretation of shock (Starr & West, 1970).

The story begins in 1955 at the Royal Veterinary College, Camden Town where part of the Department of Pharmacology (in fact most of those members of staff teaching the final undergraduate year) was temporarily stationed whilst the building at Brunswick Square was being completed. The remainder of the Department was still located in Bloomsbury Square, also awaiting the move to Brunswick Square. The location of most of the histamine in the body having been identified as the tissue mast cells where heparin is also concentrated, it was a natural step forward to study other components of these cells, particularly as the actions of the materials released from these cells were not totally inhibited by the popular antihistamine drugs. Parratt spent 3 years on this problem, first proving that some of the body 5-hydroxytryptamine (5-HT) resides with histamine in these mast cells in the rat and mouse (Parratt & West, 1957) and then showing that both amines can be released when shock and oedema occur (Parratt & West, 1960). This fundamental observation provided an explanation for the inability of the antihistamine drugs to be effective in all types of shock and oedema in man. In fact, 5-HT was shown to be about 100 times more effective than histamine as a drug increasing vascular permeability in the rat, though the reverse was found to be true in the guinea-pig. Such release of histamine and 5-HT occurs during anaphylactic shock in sensitized rats and the two amines are also released during anaphylactoid reactions in non-sensitized rats (Sanyal & West, 1958). Furthermore, their release can be considerably reduced by administration of adrenal cortical hormones (Hicks & West, 1958), suggesting that human allergy may be explained on the basis of reduced adrenal cortical output. However, 5-HT is not present in human skin mast cells and so ideas concerning histamine and 5-HT involvement in human allergic reactions had to be revised. Whilst these studies were proceeding, Shirley Price was looking at 5-HT and other tryptamines in the brain of mammals of different ages and also in edible fruits such as tomatoes and pineapples (Price & West, 1960). As these fruits ripen, so hydroxylation of the tryptamine and tryptophan occurs, but for what purpose? Just as the physiological role of 5-HT in the mammalian body had not been clearly identified, so also the role of 5-HT in the botanical field has also not been clarified. Even today, the importance of 5-HT to the body has not been established, though there is no doubt that its presence in the central nervous system and the gut signifies some regulatory activity on nervous and muscular tissues.

When the move to Brunswick Square came, new faces appeared and enormous progress in the histamine field was made. It was particularly important to have a look at the rate of formation of the amine in relation to growth, development and repair. In particular, the formation and excretion of histamine in pregnancy was studied. Rat foetal liver was found to be a potent source of the specific histidine decarboxylase and the quantities of free histamine in the maternal urine during the latter half of pregnancy were shown to reach relatively huge amounts. Interference with the foetal enzyme activity interrupted pregnancy so that resorption of the foetus occurred (Kameswaran & West, 1962). However, the growth of tumours (both induced and transplanted) did not require increased activity of the histidine decarboxy-

lase in the rat except in one or two cases (Kameswaran & West, 1961), and the same was true for the process of repair, when tested after partial hepatectomy in rats. It seemed that the involvement of histamine in rat pregnancy was a special case, particularly as there was little increase in histidine decarboxylase activity in pregnancy in other species of animal tested.

Meanwhile, the anaphylactoid reaction produced in rats by the intraperitoneal injection of clinical dextran or native egg-white, whereby the first and all subsequent doses produce gross oedema of the extremities and severe systemic shock (so reminiscent of human allergy), was being earnestly studied. Pretreatment of the animals with thyroxine or insulin greatly potentiated the reaction (Spencer & West, 1964) whilst injections of adrenal cortical hormones greatly reduced its intensity (Telford & West, 1960). All of these findings (summarized in Table 1) formed the basis of a significant review article in Clinical Pharmacology under the heading of 'A Pharmacological Approach to Allergy' (West, 1963).

About this time, the eagle eye of John Harris had picked out the important fact that not all rats respond to dextran, an observation which proved to be a milestone for some of the later work. An autosomal recessive gene was found in these resistant (or non-reactor) rats and a new sphere of activity opened up. The gene was transferable from albino Wistar rats into coloured rats of other strains and a resistant rat could be produced when required by suitable meetings based on family histories (Harris & West, 1963). After only a year and a half on the problem, the work was submitted to the New York Academy of Sciences and an A. Cressy Morrison Award in Natural Sciences for the year 1963 (framed certificate and valuable cheque) was won (Harris & West, 1964). Telephone calls from New York announced the good tidings!

Table 1. *The anaphylactoid reaction produced by intraperitoneal dextran in rats.*

Non-effective dose (30 mg kg^{-1})	Effective dose (180 mg kg^{-1})
Made effective by pretreatment with	Made non-effective by pretreatment with
(a) thyroxine	(a) anti-thyroid drugs
(b) insulin	(b) glucose
(c) *B. pertussis* vaccine or after adrenalectomy	(c) vitamin C
	(d) adrenal cortical hormones

The years 1963 to 1966 were also of significance to one group working on shock for the following reasons. First, a grant from the Egg Marketing Authority enabled a study to be made of the mechanism of action of drugs inhibiting the anaphylactoid reaction produced in rats by fresh egg white (Ankier & West, 1968)—such a study again having the clinical connection with egg-white allergy. Then the proof that yet another chemical mediator (this time, bradykinin) was involved in the anaphylactic reaction (Dawson, Starr & West, 1965) was reported although surprisingly enough it was not found to be important in the anaphylactoid reaction. However, with the assistance of these resistant (or non-reactor) rats, two colleagues from Hungary showed that in traumatic and tourniquet shock the rate of formation of bradykinin and its release were deciding factors as to whether the shock was severe enough to result in death. Rats resistant to dextran and egg white were significantly slower in forming kinins and had higher thresholds so that they very seldom died in these two types of shock (Gecse, Karady & West, 1965). The work was later extended to heat shock in which one paw of an anaesthetized rat was kept in warm water (46·5°) for 30 min to develop heat oedema shock, and again the resistant rats withstood higher temperatures and were slow producers of bradykinin (Starr & West, 1967). We now know these rats have a higher threshold than sensitive rats to most forms of shock and they cannot make and release kinins from α_2-globulin at the same rate.

Poyser introduced the yeast mannan anaphylactoid reaction to the shock study and had great success with simple inhibitors of the reaction. Yeast mannan is a polymer of monosaccharides (in this case, only mannose) so it was expected to reproduce effects like dextran, a polymer of only glucose. In fact, mannan was many times more active than dextran in increasing vascular permeability in rat skin, and, as expected, mannan was ineffective in rats resistant to dextran. Glucose inhibited the mannan and dextran reactions in reactor rats but galactose did not and with the aid of about 50 other simple carbohydrates it was possible to establish the stereospecificity of the dextran receptor (Poyser & West, 1968). Monosaccharides most active as inhibitors of the dextran or mannan reaction contained the D-threo type of chemical structure in their cyclic forms, a structure conferring maximum affinity for the receptor site.

Environmental factors influencing these anaphylactoid reactions were studied by yet another worker from Hungary, rats being heated or cooled before being tested with egg-white, dextran, mannan or

synthetic chemical mediators. Cooling the animal to 25° before testing delayed the reaction and raising the body temperature to 40° prevented its development in the parts of the body subjected to heat (Csaba & West, 1966), and an explanation was found why certain reactions occur better at one time of the year (summer versus winter). Although rats do not require Vitamin C in their diet, as they make their own, the anaphylactoid reaction produced by dextran was shown to be inhibited by injections of the vitamin, and furthermore Vitamin C greatly potentiated the action of antihistamine drugs in the rat (Dawson, Starr & West, 1966). This work followed from studies in guinea-pigs (which require dietary Vitamin C) where treatment with the vitamin markedly inhibited anaphylactic shock.

An interesting outcome of the combined results at this stage in the study was the fact that animals resistant to dextran, egg-white or mannan also were found to be resistant to injury produced by a wide range of stimuli (Ankier, Starr & West, 1967). The types of shock studied included anaphylaxis in the presence of insulin to increase the severity of the reaction, heat shock at temperatures well above 45°, tourniquet shock where the tourniquets were maintained round the limbs for more than 4 h, and traumatic shock using a revolving drum for more than 600 revolutions. In all of these states, the resistant or non-reactor rats formed less kinin from the blood globulin, released more adrenaline from the adrenal glands, and exhibited less degranulation of tissue mast cells. As many human allergies are inherited, it was considered that the non-reactor rats respond like non-allergic man whereas the reactor rats behaved like allergic patients. Subsequent work over the next 10 years has not in any way resulted in a change of this view and important advances in allergy and shock may still be made when the cause of non-reactivity in rats has been determined.

The final effort in this study was, as mentioned earlier, the plunge into the medical interpretation of shock where the suggestion was made that shock could best be treated with a compound antagonizing the actions of bradykinin (Starr & West, 1970). At present, dibenzyline (an α-receptor blocker) is used but sodium phenylbutazone appears to be worthy of trial.

Very small doses of some histamine releasers result in giant urticaria and angio-oedema in some patients and most of these releasers produce erythema, pruritus and oedema in sensitive rats. Angio-oedema reactions in man are not infrequently evoked by exposure to other agents such as foreign serum, different foodstuffs, and animal poisons. If this reactivity is inherited, there may be some advantage in having the character, otherwise the polymorphism would never have persisted. The situation also applies to sensitivity to shock states where it may simply be that the concentration of a particular enzyme is much lower than in control individuals so that a much smaller dose of active material is effective. Many genetic polymorphisms are the result of biochemical differences (even taste thresholds) and this may be why some rats are resistant to different forms of shock.

The hereditary defect in hereditary angio-oedema in man is the defective function or even absence of serum esterase (Cla) inhibitor which inhibits kallikrein, the enzyme activating kinin formation from kininogen. Rats may be normally deficient in this inhibitor and so respond to dextran, except for those which are resistant and which may have excess of the inhibitor in their serum.

Later studies carried out elsewhere have shown that non-reactor rats do not develop arthritis when injected with adjuvant whereas those which respond to dextran show the joint involvement so reminiscent of the human rheumatoid arthritis. This further raises the possibility that non-reactivity may be in some way linked to resistance to shock (Eisen, Freeman & others, 1973). In fact, isolated peritoneal mast cells from non-reactor rats do not release their histamine when challenged with dextran (Hanahoe, Tanner & West, 1973) so it may well be only a matter of cell membrane reactivity or possibly the type of heparin present. Differences in heparin prepared from different animal species are known and modern methods allow measurements of heparin specifically when it is present in a mixture of mucopolysaccharides.

Although non-reactor rats have a higher blood polymorphonuclear neutrophil count than do reactor rats, the transfer of white blood cells and lymphocytes from spleen, thymus and lymph nodes of reactors failed to break down the resistance of non-reactors to dextran (West, 1974). Insulin likewise did not render non-reactor rats sensitive to dextran although it markedly potentiated the reaction in reactors. If new protein synthesis induced by insulin is involved in this potentiation, then non-reactors may lack the ability to synthesize this protein in the presence of insulin. This possibility is well worth testing. Another study worth following is why Wistar rats selectively bred for non-reactivity to dextran produce few reaginic antibodies to allergens such as ovalbumin or horse serum (West, 1975).

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