Middle Articles

Histamine and Sir Henry Dale

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Histamine is a name well known to the physiologist, pharmacologist, and pathologist. This account of the histamine story over the past 50 years is compiled largely in the words of Sir Henry Dale, in honour of his ninetieth birthday and to commemorate his own extensive contributions in this field.

Sir Henry (1950b) says: "It was in August, 1907, while watching a demonstration at an International Physiological Congress at Heidelberg, that I first became conscious of the existence, in certain extracts of ergot, of a potent substance different from any of those which we had hitherto encountered in that drug. Kehrer (1908), an obstetrician of Heidelberg, had been working in the Department of Professor Magnus there and had found that Magnus's method of studying the reactions of surviving loops of intestine, suspended in a saline solution, was applicable to the horn of a cat's uterus. He had tested a number of substances for their action on this, including, as was most natural, a series of preparations of ergot. Of these he had found one to be pre-eminent in its prompt and powerful stimulant effect, of which he gave a striking demonstration. This was the so-called *Ergotinum dialysatum* of Wernich. Knowing something already by that time of the occurrence in ergot extracts of bases recognized elsewhere as products of bacterial decomposition, and finding, on inquiry, that Wernich's method of preparing his extract by dialysis was such as to provide optimal conditions for an active putrefaction, I was not inclined to accept Kehrer's conclusion.

"Meanwhile, in 1907, it was clear that Kehrer's test had revealed the presence, in a particular ergot extract, of something with an intense and immediate stimulant action on the tone of isolated uterine plain muscle, and different from any of the substances which had then been found in ergot. It seemed likely, on previous experience, to be an amine produced by putrefaction from some amino-acid. This news I carried back from Heidelberg to London and to my late friend, George Barger. We had a batch of the *Ergotinum dialysatum* prepared for us. Our colleagues at the factory confirmed, with some emphasis, the suspicion that the process would be attended with extensive putrefaction. From it, with the guidance of my physiological tests, Barger isolated histamine (Barger and Dale, 1910). Just as we had obtained it, and before we had quite completed its identification, Ackermann (1910), of Würzburg, published an account of his preparation of histamine from histidine by deliberate putrefaction.

"In any case, histamine was not a new substance. Windaus and Vogt had already prepared it by synthesis in 1907, though they had no suspicion of its physiological activity or of its potential interest. The matters of real interest were: the nature of the action of histamine itself as it came into view, when my late friend, Laidlaw, and I (Dale and Laidlaw, 1910, 1911) began to work on it in detail: later, its demonstrable presence in the body, apparently as a natural constituent of most living cells, but in widely different proportions in those of different tissues; and, lastly, the conditions of its release from these, in a form enabling it to produce its intense and characteristic actions on such cells as are sensitive to its effects, particularly on the cells of plain muscle and endothelia."

In the few years that remained before the first world war Dale and his colleagues continued their investigations on the nature of the action of histamine. Recently we have come to know more of the cellular location of histamine and the mechanism of its release. For the moment let us turn aside and consider the phenomenon of anaphylaxis.

Biological Significance of Anaphylaxis

At the turn of the century two French workers, Portier and Richet (1902), described the curious state of hypersensitivity that may be revealed when an animal receives a second injection of a foreign protein. They had injected dogs with an extract prepared from the poisonous tentacles of sea-anemones, expecting, no doubt, that dogs which had recovered from a first injection would have acquired some degree of immunity to a second. Instead, they were more sensitive. On receiving a second injection, after an interval of about two weeks, the animals collapsed in a state of shock and their blood was found to have become incoagulable. Soon, Theobald Smith, in the United States, and Otto, in Ehrlich's Institute, were able to show that the guinea-pig can likewise be made hypersensitive and that the primary injection need not of itself be toxic. The term "anaphylaxis" was coined for the hypersensitive state to emphasize its complete contrast to the immunity ("phylaxis") which more commonly accrues from repeated injections of a foreign protein.

Two main hypotheses of the mechanism of anaphylaxis were proposed: the humoral hypothesis, which postulated the production of an "anaphylatoxin" in the blood by a reaction of the antigen with a circulating antibody, and the cellular hypothesis supported by Dale, which regarded anaphylaxis as due to the fixation in or on the surface of the living and reactive tissue-cells of an antibody which is protective when it circulates in excess. Dale's opinions were based largely on his work on isolated plain-muscle preparations *in vitro*. Richard Weil, of New York, had reached similar conclusions from experiments on intact guinea-pigs. Sir Henry writes: "Weil and I had a most pleasant and interesting meeting at the International Congress of Medicine in London in 1913, when we found ourselves propounding the same theory, in the same programme of the Congress, with the support of different experimental methods, and were accordingly able to make a friendly play into one another's hands, with a resulting economy of the time available to both of us in the programme. Weil most unfortunately, acting as a Medical Officer to camps of American recruits towards the end of the ensuing first world war, caught from his patients the deadly influenzal pneumonia then rampant, and died before we could meet again."

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After the war, in 1919, Sir Henry was able to arrange his thoughts on anaphylaxis into his classic Croonian Lecture (Dale, 1920). "In the limits of its specific discrimination, anaphylaxis shows a remarkable and suggestive similarity to the well-known type of immunity dedpendent on the so-called 'precipitin' reaction." However, "the serum of the anaphylactic guinea-pig contains no demonstrable precipitin ; that is to say, it forms no visible precipitate when mixed with the sensitizing antigen. On the other hand, the animal in which, as the result of repeated injections, a strong precipitating quality has been acquired by the serum, is not anaphylactic but immune."

Much of the evidence then available had been obtained from the guinea-pig. "I may remind you that the most characteristic feature of the anaphylactic shock in the guinea-pig is the contraction of the plain muscle surrounding the bronchioles, causing asphyxiation. I found that, if the lungs of the anaphylactic guinea-pig were removed from the body and their blood-vessels perfused clear of blood by Ringer's saline solution, while the lungs were rhythmically inflated by a pump, addition of a trace of the specific antigen to the perfused fluid caused an immediate constriction of the bronchioles, so intense that air could not be forced past the obstruction. The effect was perfectly specific, and it seemed clear that the action of the antigen on the plain muscle of the bronchioles was direct, and independent of other organs and of the presence of the blood. Using the horn of the uterus of a young virgin guinea-pig as an easily isolated and reactive sample of plain muscle, I was able to demonstrate practically all the characteristic phenomena of active and passive anaphylaxis."

Meanwhile, Schultz, in Washington, had independently discovered the phenomenon, and in their joint observations the Schultz-Dale test was devised, to be repeated times without number in pharmacological laboratories throughout the world. This, then, is the mechanism of anaphylaxis. What of its biological significance in relation to immunity? "We have seen that there is good reason for regarding anaphylaxis as a phase in the production of the type of immunity associated with the precipitin reaction. This represents a mechanism of defence against the incorporation into the tissues of proteins differing in type from those characteristic of the species." Needless to say, "the sudden introduction of a foreign protein into the general circulation is not a natural event. An animal may be highly immune to infection with a micro-organism through natural channels, and yet anaphylactic to the proteins of that organism introduced by artificial means. A generalised anaphylactic reaction, the anaphylactic shock, is a creation of the injection needle. A localised anaphylactic reaction, on the other hand, defends the system from invasion at the expense of the tissues immediately affected. Anaphylaxis, as we see it in the laboratory, is not the opposite of immunity, it is the physiological response, of an animal in a certain phase of immunity, to the artificial test which we impose" (Dale, 1920).

Histamine and Anaphylaxis

Shortly afterwards Dale and Kellaway (1923) again confirmed, with "diagrammatic simplicity," that whereas "a precipitating antibody, when so firmly attached to the plain muscle that it cannot be removed by prolonged perfusion, renders the muscle specifically sensitive to the antigen, the same antibody present in excess in the fluid bathing the sensitive muscle protects it." At the same time they critically examined the various preparations which were supposed to contain the "anaphylatoxin." Some lengthened the clotting-time of the blood, others shortened it. None caused so intense a bronchial spasm as that seen in the anaphylactic reaction of the guinea-pig ; nothing in fact was then known to produce such spasm, except, perhaps, histamine.

In 1926 Sir Thomas Lewis (1927) gave his Croonian Lectures on the blood-vessels of the human skin. This work on the H-substance in man had been running parallel to that of histamine in the laboratory animal. The two lines now converged. In a lecture given in 1929 Sir Henry regards it "as highly probable that the substance, recognized by Lewis, as liberated from irritated or injured cells of the human skin, and as evoking the vasodilator complex in their neighbourhood, is either histamine itself or some loose combination owing its action to histamine." The antigen-antibody reaction behaves "like any other injurious stimulus, by releasing the pre-formed H-substance."

Yet histamine, as Barger and Dale (1910) had long ago observed, does not influence the clotting-time of dog's blood, though capable of producing a spasm of the suprahepatic veins as in anaphylactic shock in the dog. Clearly anaphylaxis is more than a simple release of histamine. Nevertheless, as later workers were to show, histamine does occupy a central position in the pharmacology of anaphylaxis in certain species (Feldberg, 1941). Its release can be demonstrated both *in vivo* and *in vitro* (Gebauer-Fuelnegg, Dragstedt, and Mullenix, 1932 ; Bartosch, Feldberg, and Nagel, 1933).

In 1937 the first of the antihistamine drugs was introduced (see Gaddum, 1948, 1951). Consideration of their actions led Sir Henry (1950a) to suggest that histamine in the tissues may be of two types, extrinsic and intrinsic. Extrinsic histamine diffuses some distance before it produces an effect: intrinsic histamine acts at the site of its release, possibly even in the same cell. Thus, "wide differences may be encountered between effects which are otherwise closely similar, according to whether a pharmacodynamic agent reaches the responsive cell by diffusion from without or by liberation in intimate relation to, perhaps actually within, its limiting membrane" (Dale, 1950b). Around this time MacIntosh and Paton (1949) discovered the histamine-liberators, substances which specifically release histamine from its links in the tissues. Not only could the histamine content of a tissue now be measured, but histamine could be released or antagonized at will. The problem was: in which cells does histamine reside ?

Mast-cell and Non-mast-cell Histamine

The discovery that histamine is normally held, pre-formed, in the basophilic granules of the mast cells helped to fill the gap. A fluorescent histamine-liberator was traced to its site of action in the mast cells of the rat (Riley, 1953), and subsequent pharmacological investigations fully confirmed the mast cell as the source of the histamine (Riley and West, 1953 ; Riley, 1959). Mast-cell tumours from dogs and the skin lesions of urticaria pigmentosa in man, composed of mast cells, may contain milligrams of histamine per gramme of tissue. In some species, including man, even the mast cells of the blood, the basophils, are rich in histamine (Graham, Wheelwright, Parish, Marks, and Lowry, 1952). The eosinophil cell now seems to be concerned more with disposal of histamine than with its elaboration, and to be attracted secondarily to sites where histamine is being released (Riley, 1956 ; Archer, 1963).

Living mast cells can be isolated and studied *in vitro*: histamine-liberators and the antihistamine drugs can be observed at work. Mast cells isolated from a sensitized animal respond to the specific antigen by releasing histamine into the surrounding medium (Humphrey, Austen, and Rapp, 1963 ; Keller, 1963). A strip of non-sensitized plain muscle in such a medium contracts, as it does to the addition of synthetic histamine. And for the first time many of the apparently unrelated events of anaphylaxis can be tied to a single phenomenon, a specific injury to the mast cell. Outstanding, perhaps, is the dual release of histamine and heparin from the liver of the shocked dog (Riley, 1964).

Yet it would be foolish to claim that the participation of the mast cell answers all, or even most, of the puzzles of anaphylaxis: this is but "a small area of a very large field." At the

same time, it is not without its fascination to recall that the histamine on which Sir Henry Dale has spent so much of his working life should eventually be located in a cell discovered by his former teacher, Paul Ehrlich.

One brief chapter remains as yet incompletely written. Mast-cell histamine is virtually static, waiting for trauma to release it. There is now well recognized a second source of tissue histamine, formed as a response to stress (Schayer, 1961) and often associated with tissue growth (Kahlson, 1960). The histamine in mast cells is a measure of the tissue content: "nascent histamine" implies a newly aroused capacity of a tissue to form histamine, whether stored or not—a dynamic event. This new concept was under discussion in a Symposium during the International Congress of Physiology at Leyden in 1963, to which, in the words of its Chairman, Sir John Gaddum, the "two grandfathers" of histamine, Professor Ackermann and Sir Henry Dale, had been invited. Sir Henry was unable to be present on that occasion, although his message of greeting was read out. During the present year yet another large volume on histamine will be published under the editorship of Dr. Rocha e Silva (1965). Most fittingly the foreword is by Sir Henry Dale.

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IMPRESSIONS OF HEALTH CENTRES

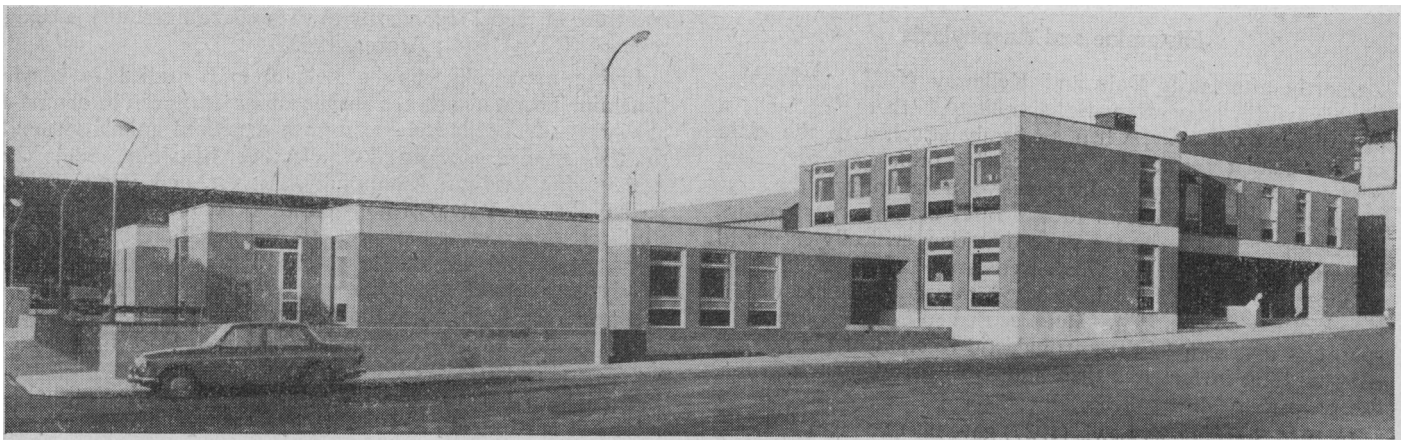
2. Centres for a County—Cleckheaton and After

[FROM A SPECIAL CORRESPONDENT]

The West Riding of Yorkshire has a long tradition of co-operation between family doctors and the county public health authorities. Shortly after the National Health Service Act of 1948 a liaison committee of four general practitioners (elected by the executive council) and four public health doctors was formed. This meets four times a year, and after its recommendations have been discussed by the local medical committee they go to the executive council and in their turn to the family doctor. Though this sequence seems cumbersome, it works well and to-day there is probably more integration of community health services in the West Riding than anywhere else in Britain. For their part the county authorities base this on three principles: firstly, to provide surgeries for family doctors, whether in clinics or health centres; secondly, to provide them with room for their own clinics, whether antenatal, post-natal, or infant-welfare; and, thirdly, the attachment of staff. The last has been on a strikingly large scale, so that by 1 April 1965, 78 health visitors were attached to 88 practices, 36 home nurses to 56 practices, and 20 midwives to 38 practices—the practices involving 205, 123, and 70 family doctors, respectively, out of a total of 1,400 in the West Riding. On their side the general practitioners do rather more than a third of all the local health authority antenatal and infant-welfare clinics, and are paid for this by the county council.

So far five clinics are used part-time by family doctors for their surgeries and at least another thirty are planned. Furthermore, doctors are encouraged to hold antenatal and infant-welfare sessions on their own patients at the premises used as county clinics. The help of midwives or health visitors is usually available, and no rent is charged for the use of the building.

Such a comprehensive programme would obviously eventually entail the building of health centres, and the West Riding claims to be the first authority to provide a purpose-built centre



The Cleckheaton Centre.