BRITISH MEDICAL JOURNAL

LONDON SATURDAY 3 AUGUST 1968

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Developmental Heterotopias: Examples of unusual malformations described in Professor R. A. Willis's Roy Cameron Lecture (p. 267).

Penicillin Allergy: Use of passively sensitized human lung is described for detection of reaginic activity of sera, both for natural and drug allergies. Monkey lung is not an effective substitute (p. 272). Leader, p. 262.

Treating Cholera: Controlled comparison of furazolidone and tetracycline demonstrated that the latter remains antibiotic of choice, but furazolidone is useful for resistant strains (p. 277).

Intrauterine Transfusion: Two cases were studied post partum with reference to viability and fate of donor lymphocytes, and it is suggested that some immunological protective mechanism is developed by second half of gestation (p. 280).

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Depression and the Adrenals: Resistance to dexamethasone suppression in midnight test correlated with severity of depressive syndrome, and normal response was elicited on recovery (p. 285). Leader, p. 263.

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Sir Henry Dale

Born at the beginning of a period of unprecedented expansion in medical knowledge, Henry Dale made a contribution to it that was unique in its quality, its variety, and its relevance to therapeutics. His first period of great scientific discovery was between 1906 and 1914, when he brought the young plant of pharmacology out of a period in which growth was hesitant and uncertain into full bloom. This achievement was due in the first place to the combination of his profound physiological knowledge with an interest in chemical structure, unusual for a physiologist even today. Thus by 1914 he had built a bridge between chemistry and physiology, and pharmacology came to lie at the ends of this bridge.

But this achievement was due in the second place to the fact that this chemical interest was directed not to the products synthesized by the organic chemist, as was that of Ehrlich, but to the active substances present in the body, adrenaline, histamine, and choline. His first work on adrenaline, and the reversal of its motor action in smooth muscle by extracts of ergot, followed very easily on that of T. R. Elliott, to whom Dale referred again and again in the course of his life. Thus *Adventures in Physiology* is dedicated to Elliott, "who had so much to do with the beginnings of these adventures." We should remember that Dale's work on this reversal is the basis of the present use of phentolamine for the diagnosis of phaeochromocytomas.

Then with Barger to make the compounds there followed in 1910 the celebrated paper on sympathomimetic amines,[1] in which Dale examined the properties of substances related to adrenaline and so was able to indicate the important parts of its molecular structure. There is, however, a wealth of other information in this paper, which can be grasped only by those who give it close and repeated study. How many, for example, know the changes caused in these amines by quaternization?

The study of histamine, which began and was continued with Laidlaw, and rose to a climax with A. N. Richards, was a second example of Dale's interest in extracts of ergot. Barger and Dale had found that histamine was present in them. The intense stimulating action of histamine on the isolated guinea-pig uterus, as well as on other forms of smooth muscle, was difficult to understand in view of its powerful vasodilator action on the blood vessels of the cat, the monkey, and the fowl. A persistent study of these effects had three important results. It led to the demonstration that the vasodilator action was exerted on capillaries, and to the conception that the capillaries had a tone of their own. It led to the demonstration that a condition of shock could be produced by the effect of large doses of histamine in causing stagnation of blood in intestinal capillaries. Thirdly, part of the study was made at a time when Dale discovered the extreme sensitivity of the uterus of the anaphylactic guinea-pig to very small doses of the sensitizing antigen. When the sensitizing antigen was crystallized egg albumin, it had no effect at all on the uterus of a normal guinea-pig. This work eventually led to the conclusion that anaphylactic

shock in the guinea-pig was due to combination of antigen and antibody, not outside but inside the cells, with consequent liberation of histamine.

It is characteristic that in Dale's paper on "The anaphylactic reaction in the plain muscle of the guinea-pig," published in 1913,[2] he did not mention the liberation of histamine. He wrote in 1953, "I suspect that anybody reading this paper, in the light of what is now known and accepted, might detect an excess of caution, even an obstinate reluctance to indulge in the mildest flutter of mental enterprise, in my apparent avoidance of what is now a most obvious link between our own early observations on histamine, and those here recorded on the anaphylactic reaction."

Between so many important advances it is difficult to choose, but many will think that Dale's work on "The action of certain esters and ethers of choline"[3] was his most important contribution to physiological theory, calling attention as it did in cautious terms to "the biochemical similarity as shown by their common responsiveness to acetylcholine, between ganglion cells and nerve endings, voluntary motor as well as cranio-sacral involuntary." Here already expressed in 1914 was the possibility that one day acetylcholine might be shown to be the transmitter at all these points.

When Dale became director of the department of biochemistry and pharmacology at the National Institute for Medical Research in 1920, his most important service to medicine in the first five years was his work on biological standardization. Pituitary (posterior lobe) extract as sold in Great Britain varied in potency from 80 to 1 because there was no agreed standard. Neoarsphenamine made by British manufacturers was far less potent than that made in Germany. But, still more important, insulin was discovered by Banting and Best, and here the question of standardization was crucial. Without delay Dale took H. W. Dudley with him to Toronto in order to study both the extraction and preparation of insulin as well as the standardization. The main problem was the definition of a unit of insulin, and at first this was stated in terms of the amount required to cause convulsions in a fasting rabbit of a certain weight. Such a unit showed wide variation, because of the variation in rabbits. Dale's own view was that the method of standardization must be comparative, each preparation being tested in comparison with a standard preparation to determine the difference between them. Meanwhile H.P. Marks, working under Dale's direction, finally arrived at an expression of the hypoglycaemic effect of a given dose of insulin in a group of rabbits in terms of the mean effect in the group. The outcome was a conference in Geneva in 1925 arranged by the Health Organization of the League of Nations. Dale was the chairman. At this conference international standards were agreed upon by representatives of several countries for insulin, pituitary (posterior lobe) extract, neoarsphenamine, sulpharsphenamine, and digitalis. This was a great achievement, which was based on a careful organization of experimental work in different countries beforehand and led to close and friendly relations between all the workers concerned. It meant for insulin that a uniform system for measuring its potency was adopted throughout the world within four years of its discovery, and this was mainly due to Dale's skilful persuasion.

[1] Barger, G., and Dale, H. H., *J. Physiol. (Lond.)*, 1910, **41**, 19.
[2] Dale, H. H., *J. Pharmacol. exp. Ther.*, 1913, **4**, 167.
[3] Dale, H. H., *J. Pharmacol. exp. Ther.*, 1914, **6**, 147.

Just as Dale in 1910 did not consider the possibility that noradrenaline might be the transmitter of sympathetic impulses because at that time it had not been found in the body, so he did not consider the possibility of acetylcholine as the transmitter of other nerve impulses until 1929, when he together with Dudley identified it as being present in the spleen of the horse. In the following year Dale and Gaddum demonstrated that acetylcholine was liberated on stimulation of the chorda tympani nerve in the cat. They made use of the observation that skeletal muscles become highly sensitive to acetylcholine when the motor nerves to the muscles have degenerated, and showed that stimulation of the chorda tympani led to contracture of the tongue after the hypoglossal nerve had been cut and had degenerated. From their findings they concluded that "the evidence now available makes a very strong case for acetylcholine as the transmitter of parasympathetic effects." Dale with Feldberg in 1934 showed that the sympathetic nerves to the sweat glands in the cat liberated acetylcholine, and in 1936 with Feldberg and Vogt showed that the motor nerves to the skeletal muscles transmitted their impulses in the same way.

This work firmly established humoral transmission as a theory which has, since that time, had a great impact on neurology, on the treatment of myasthenia, and on the practice of anaesthesia. It introduced a new epoch in physiology and pharmacology in which we live today, when so much effort is expended in identifying the transmitter substances for the different pathways in the brain.

In the period up to 1914 Dale seemed a rather reserved person to his colleagues. After the first world war, when he was director of the departments of biochemistry and pharmacology at Hampstead, he was a more forceful figure, deeply concerned to see that the research carried out would be worth while and of a standard to be expected from a National Institute. By the time he reached the age of 60 he had become a commanding personality full of wisdom and with surprising agility of mind. From the beginning his published papers were unique. He was an artist in the preparation of figures to illustrate his results, and few scientists have equalled him in the writing of English prose. His papers are long and written with much care. The arguments are presented in measured sequence, in sonorous sentences, with a remarkable choice of the right words. He was a very great man.

Testing for Allergy

Measuring the circulating antibody responsible for the weal-flare skin reaction to common allergens presents many problems. Human reaginic antibody will not react in conventional precipitation, agglutination, or complement fixation tests. Its qualitative measurement in Prausnitz–Küstner tests, which entail injection of serum, is undesirable in view of the risk of serum hepatitis, and in-vitro tests[1 2] have not become established procedures. K. Ishizaka and T. Ishizaka[3] showed that reaginic activity is mainly confined to IgE immunoglobulin, and S. G. O. Johansson and colleagues[4] have now developed a radioimmunoassay method for the direct quantitative measurement of human reaginic antibody in serum.

Another approach to the problem of quantitative measurement of human reaginic antibody is the subject of a paper by Dr. E. S. K. Assem and Professor H. O. Schild, F.R.S.,