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Prologue

Some deconstructed dogmas ☆

Thank you for your kind invitation to the beautiful city of Montpellier, and to this workshop held to mark the retirement of my former graduate student and dear colleague, Denis Noble. I have greatly enjoyed these days: historical surroundings, good company, exciting new work, splendid nourishment for mind and body alike.

Standing here in front of you, I should declare that I have nothing new to present. Nor do I have profound insights to offer. Long years, you see, are not directly correlated with insight. With long-sight—yes. With hindsight—most certainly. But—not with insight, and still less with foresight!

So why then have I accepted the kind invitation by the organisers to speak? Well, in order to set a precedent. You see, right now most of you are still in harness. But sooner or later you also will (have to) retire. And then, I hope, each of you will invite Denis to your retirement symposium as your scientific progenitor. That will keep Denis occupied, I hope, for many years to come. Denis will of course always contrive to conjure up something original. But I dare say, that by the time, *Deo volente*, Denis turns octogenarian—as I have now done—even he will be tempted to indulge in a little retrospection. So do let me start by telling you how I became 'hooked on physiology'.

In 1942, on leaving school with 'Science Highers', I entered employment at the Wellcome Physiological Research Laboratory, on a job that was considered essential war work. The first Director of the Wellcome Laboratories had been Sir Henry Dale, and in the laboratory in which I worked one could still find little brown jars of Ergot extracts, their labels signed H.H.D. So, when Sir Henry Dale gave a course of lectures on 'Chemical Transmission in the Nervous System' at the Royal Institution in 1943, I was curious to attend.

And what an experience those lectures were for a 19-year old lad! You have to realise that this was in the middle of the war. University College was evacuated to Leatherhead. The only Physiology lectures in London were given in the evenings at Chelsea Poly by the young Richard Gregory, who came up from Leatherhead and did us proud. But to

☆ This is the manuscript of the Plenary Lecture, given at the Integrative Physiology Workshop in Montpellier, 3–5 August 2004, held on the occasion of the retirement of Professor Denis Noble, CBE, FRS, FRCP (Hon.) from his British Heart Foundation Chair at the University of Oxford. It gives a unique personal account of the development of the ideas underlying chemical transmission, which started to emerge just over one century ago. The editors felt that this text would be of interest to many more than those who were able to attend the workshop, and we are thankful to Professor Otto Hutter for allowing us to print his talk here in full.

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hear an eminence like Sir Henry Dale, even just to sit in that sumptuous lecture theatre at the Royal Institution, was an experience of a quite different order. Dale had a wonderfully modulated, sonorous voice. But to tell the truth, in 1943 I understood little of what he said. Fortunately for me, Dale repeated those lectures in the subsequent 3 years. So I returned to Albemarle Street to hear him again in 1944, and in 1945, and yet again in 1946. By that last time, I was already at University College, and I went once more just to hear the anecdotes with which Dale laced his lectures.[1]

In retrospect, Dale's message was a seductively simple one. In the peripheral nervous system, nerve-endings were either cholinergic or adrenergic. Receptors were postsynaptic, as John Langley (1907) had shown. Autonomic ganglia were relay stations, the rate of transmitter release being set centrally. Regarding the central nervous system, Dale pointed to the axon reflex. And he suggested that if only the vasodilator substance released by sensory nerve endings in the skin could be identified, it would prove to be also the transmitter at the central terminals of the sensory nerve (Dale, 1935). Dale based this suggestion on the metabolic unity of the neurone, and it became known as Dale's Principle (Eccles, 1957).

Dale's colleague, William Feldberg, was an even more ardent advocate of central chemical transmission, and in his 1945 review—which I mugged up for my finals—Feldberg made a strong case for acetylcholine as a central transmitter. The open question then remaining was, to quote Feldberg (1945): "Must we assume also other transmitter substances in the central nervous system, or that some excitation is effected by the circulating current from the presynaptic terminals?".

That question settled itself, as you know, with John Eccles' conversion to chemical transmission (Brock et al., 1952).[2] And once Eccles had shown acetylcholine to be released from motor neurone collaterals—as a first step in recurrent inhibition—he embraced Dale's Principle with all the

[1]Of course, Dale told us about Otto Loewi, and about his claim to have conceived the idea for his famous experiment in a dream. I think Dale was a little incredulous. But in 1954 Otto Loewi told me something that convinced me his story was really true. Loewi and his wife were spending that summer at Woods Hole and I was duly introduced to him by Stephen Kuffler. Loewi, by then in his 70s, spoke mishmash of English and German, and once he discovered that I could actually understand him, I was frequently summoned to keep him company after lunch. I had then done some work on how sodium, calcium and magnesium affect the release of acetylcholine from the perfused superior cervical ganglion. That prompted Loewi to tell me about his experiments on the effects of ions on the heart. In particular, he described how when a frog ventricle on a Straub cannula is treated with a calcium deficient solution, contractions are at first abolished; but after a while gradually returns. And he attributed that recovery to the release of calcium from stores in the ventricle into the small volume of fluid within the suspended ventricle. Now Loewi himself made no connection between that finding and the design of his famous 1921 experiment. At the time I also did not spot the connection. But later, when I looked up the work to which Loewi had referred (Lieb and Loewi, 1919) I noticed that it just preceded his classical experiment testing whether any chemical transmitter released by the N. vagus might accumulate within a heart containing only a few drops of fluid. So here we have a wonderful example of Peter Medawar's dictum that "the spontaneity of an idea signifies nothing more than our unawareness of what precedes its eruption into conscious thought", or in this case into an awakening dream.

[2]At the Royal Society Symposium in 1952, when after long opposition Eccles first came round to chemical transmission—on the grounds that he could not account for the inhibitory postsynaptic hyperpolarisation in any other way—Sir Henry Dale thundered: "Had I and my colleagues proposed chemical transmission in the peripheral nervous system on grounds such as Dr Eccles now advances for the central nervous system, the he would have been right to disbelieve us!"