The discovery and early use of cortisone

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PERSONAL PAPER

On 21 September 1948, at the Mayo Clinic, cortisone was injected for the first time ever into a patient with rheumatoid arthritis. 1998 therefore marks the fiftieth anniversary of a milestone not only in rheumatology but also in a large section of general medicine. The story mainly relates to the imaginative convictions of one man, Philip Showalter Hench, and his friendship and association with Edward Kendall. What follows is partly a personal account, because in my early days as a research worker Hench became a friend as well as a colleague.

HENCH'S EARLY RESEARCH

It all started in 1929 when Hench observed an excellent remission in one of his intractable rheumatoid arthritic patients who developed an intercurrent attack of jaundice. Unlike previous observers such as Garrod[1], who had witnessed and recorded rheumatoid remissions but had regarded them as being part of the natural history of the disease and therefore of no particular significance, Hench refused to accept the observation as fortuitous. Instead, he judged that the early inflammatory pathology of rheumatoid disease, far from being relentlessly progressive, as was usually taught, was strikingly reversible[2]. He argued that, if one could learn to control this inflammation, one should be able to prevent the joint contractures and deformity patterns that so often resulted in crippling and major disability. He further argued that if jaundice is capable of suppressing rheumatoid inflammation there must be an 'anti rheumatic substance X' which is responsible. Over the next nineteen years he made it his mission to confirm his observation by studying other rheumatoid patients who developed intercurrent jaundice.

He collected several other patients with this uncommon combination of diseases and, although the observations were by no means consistent, he recorded some impressive remissions whilst the patients remained jaundiced, with relapse when the jaundice disappeared[3]. He also incidentally noted that haemolytic forms of jaundice were never associated with remissions.

He then systematically tried to identify the antidote responsible for the remission by performing a series of intrepid clinical trials in which both liver metabolites and liver toxins were administered to reproduce jaundice iatrogenically. A few years later his team made similar efforts to identify a female sex hormone which might be responsible for remissions of rheumatoid arthritis in pregnancy[4]. Hench's recognition of pregnancy remissions was astute not only because the prevailing view was that pregnancy was strongly contraindicated in rheumatoid arthritis patients but also because, as with the jaundice remissions, pregnancy remissions were by no means constant; indeed, I have seen patients in whom the onset of rheumatoid disease coincided with the start of their pregnancies. Experimental attempts to mimic pregnancy remissions artificially were as unsuccessful as those aimed at producing remissions by inducing jaundice. In retrospect, the ethical licence with which these trials were blessed is extraordinary.

Another reason for beginning the story in 1929 is that, by chance, it coincided with a decision by Edward Kendall to transfer his research activities from the hormones of the thyroid gland to the largely unexplored territory of the adrenal cortex[5]. In the same year a Ukrainian refugee by the name of Tadeusz Reichstein, whose early scientific endeavours had been concerned with the nature of the aroma of coffee, was appointed to the State Technical College in Zurich and shortly afterwards became professor of pharmaceutical chemistry in Basle.

Reichstein had earlier been concerned with the isolation and constitution of aldosterone but he soon developed a more eclectic interest in adrenocortical hormones. His research ran parallel to Kendall's and in 1950 he shared the Nobel Prize in Medicine and Physiology with Hench and Kendall. Both these laboratories were extracting hormones from the adrenal cortices of cattle and sheep. It was a profoundly slow and tedious technique. Reichstein recorded in his Nobel Oration that from 1000 kg of cattle adrenal glands he managed to obtain but 1 kg of dry yield. Of this 1 kg, the concentrate that he had used for identification and characterization was no more than 25 g[6].

In fact cortisone had been isolated and identified both by Kendall and by Reichstein as long ago as 1935. This was one amongst twenty-eight different isolates from the adrenal cortex and, even had they known which of these extracts might have had therapeutic properties, the amounts

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available would have been too small for realistic clinical trials[7].

In due course the pharmaceutical firm of Merck Sharp and Dohme attempted a semisynthesis of corticosteroids. Their starting point was desoxycholic acid, which they derived from the bile of sheep and cattle. Again production was on a laboratory rather than a commercial scale, and cortisone was initially marketed at $1000 per g. Part of this inflated price related to the astronomical rise in the price demanded by farmers for the gallbladders of their livestock.

One of my jobs when I joined the first UK cortisone research unit was to visit several eminent British biochemists to enquire whether they thought cortisone could ever be made in commercial quantities and at a reasonable price. Their answers were uniformly pessimistic. The only justification, at that time, for attempting large-scale production was the hope of producing an adrenocortical extract which would be more effective in the treatment of Addison's disease than the relatively ineffective desoxycorticosterone acetate (DOCA).

The main obstacle to synthesis of cortisone related to two radicals that needed to be part of the corticosteroid nucleus—a ketone radical at the 11 position and a hydroxyl radical at the 17 position (Figure 1). It is noteworthy that, in the subsequent fifty years, no therapeutically active corticosteroid has been produced that does not possess these two radicals. Within three years the problem had been largely solved by the use of plant sources such as sisal and the Mexican yam as the starting-point for semisynthesis.

Hench appreciated that, since jaundice remissions were seen in both sexes, any hormone which might be relevant to rheumatoid remissions must be present in both sexes. It was this thought that initially led him to extend his researches to the adrenal cortex. As long ago as 1925 he had been struck by certain features such as listlessness and hypotension which are common to Addison's disease and chronic rheumatoid arthritis. He had also arranged post mortem examinations of the adrenal glands of some of his patients; but, finding no evidence of structural disease, he had abandoned this particular approach.

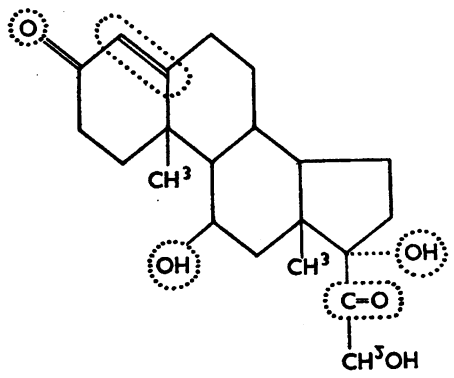

Figure 1 **Structure of cortisone**

Apart from his friendship with and working proximity to Edward Kendall, there were other factors that might have led Hench to concentrate on the adrenal cortex in his continuing search for 'Nature's dramatic antidote'. First, throughout the 1940s there had been a growing appreciation of the metabolic significance of the hypothalamic-pituitary-adrenal (HPA) axis in health and disease. For example, Hans Selye had published from McGill University in Montreal a series of elegant rat experiments demonstrating an association between various types of stress reaction and the HPA axis. Selye did not identify the individual adrenocortical hormones involved but he was able to distinguish two broad groups that he labelled glucocorticoids and mineralocorticoids. It was the glucocorticoids that seemed to be related to stress, and cortisone falls within this group[8]. At the same time, rheumatologists were beginning to appreciate the non-specificity of the treatments which they were routinely recommending. For example, the search for and eradication of suspected 'septic foci' was widely practised. Gradually, it became apparent not only that the resulting improvement was short-lived and non-specific in terms of the infecting agent, but also that virtually any surgery seemed to result in temporary improvement. Even the giving of an anaesthetic alone, or the induction of artificial hyperpyrexia, could result in temporary remissions. These observations fitted well with the concept of non-specific stress reactions which, according to Selye's experimental observations, were capable of increasing secretion of glucocorticoids. Such a mechanism was in due course confirmed when it became possible to measure accurately the output of urinary corticosteroids.

A final reason for transferring attention to the adrenal cortex may have been a wartime rumour to the effect that the Germans were experimenting with a 'wonder drug' that greatly increased the endurance and physical tolerance of their bomber pilots and submariners. This substance was believed to be obtained from the adrenal cortex. There was, incidentally, an associated rumour that German submarines were ploughing the South Atlantic to Buenos Aires in order to buy large consignments of cattle adrenal glands from which to extract this substance. True or not, it is a fact that the American Government Department of Health did summon a national conference featuring adrenocortical secretions in 1941. I do not know the exact purpose or details of this conference but there is no doubt that by 1941 the hormones of the adrenal cortex had become a central focus of medical interest and this may well have influenced Hench in his search for Nature's antidote.

Philip Hench (Figure 2) was a charismatic, enthusiastic and generous character who had a wide range of interests outside of medicine. A severe cleft palate deformity made his speech loud and difficult to understand, and probably for

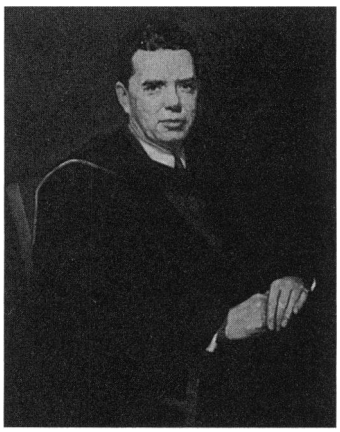

Figure 2 **Philip Hench**

this reason teachers advised him to enter a specialty in which communication with patients was of secondary importance. He did in fact study pathology at Freiburg University under Aschoff and also for a time at the Von Müller Clinic in Munich. However, Hench was not the sort of man to be deterred by such a disability: he was appointed as a clinician to the permanent staff of the Mayo Clinic in 1926 and soon became head of the Section of Rheumatic Diseases.

FIRST USE OF CORTISONE IN RHEUMATOID ARTHRITIS

By 1948 Merck were able to distribute only 9 g of cortisone for clinical trials. Hench put in his bid, which was actively contested by his Mayo Clinic colleague Randal Sprague, who considered Hench's rheumatological claims to be frivolous compared with his own planned scientific investigations[9]. However, it was Hench's close colleagues (Figure 3) Charles Slocumb and Howard Polley who, on that day in September, injected 100 mg of 'compound E' (cortisone) into a rheumatoid patient who had proved refractory to many previous therapeutic experiments and who had refused to go home until he had been used as a 'guineapig' for yet another trial. The results were spectacular. The pain relief and functional benefits were of a different dimension from those achieved in previous trials. Equally spectacular results were obtained on three other specially selected patients in the same ward. A triumphant atmosphere pervaded the initially cautious Mayo Clinic team. Extraordinary events occurred; thus one of their totally bedridden patients was able to get out of bed and attempt to dance, another took seven baths in one day to compensate for the baths she had missed. Ironically, Hench nearly missed all the excitement because he was busy preparing for a European lecture tour. Sadly, when the supplies ran out a week later all the patients relapsed completely; but Slocumb and Polley were convinced that they were on to an important breakthrough.

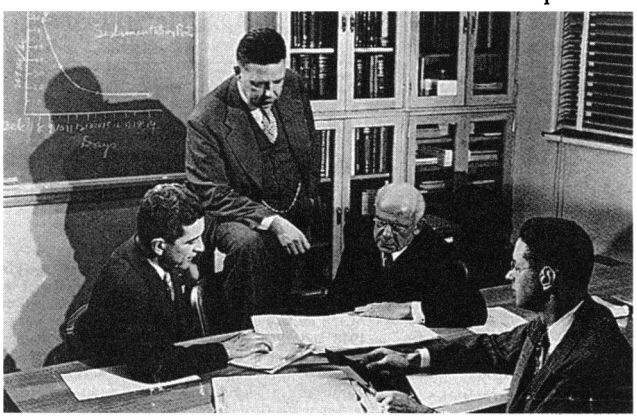

Figure 3 **Hench's team at the Mayo Clinic**

In 1949 the first official announcement of their success was made at the Seventh International Congress on Rheumatic Diseases, in New York, and after the Congress Hench invited a group of his friends, many of whom were British, to visit him at the Mayo Clinic. Their enthusiasm resulted in the setting up of the Clinical Research Unit in London to which I had the privilege of being appointed research registrar. In 1950, little more than a year after the official announcement of their achievement, Hench, Kendall and Reichstein were jointly awarded the Nobel Prize for Medicine and Physiology in recognition of their work.

No one has ever explained to me why they decided to use the pharmacological dosage of 100 mg for initial injections. This corresponds to at least ten times the dose of DOCA then recommended for treatment of Addison's disease. Had they used the smaller dose, the anti-inflammatory potential of corticosteroids might have taken much longer to emerge, Merck might have abandoned the costly quest for commercial synthesis and the progress of corticosteroid research might have been much delayed. They were also lucky in the size of the crystals which they used. Had the crystals been larger they would probably have formed depots at the injection sites, with inadequate absorption (to say nothing of the fact that depot residues of injected steroids can cause horrific abscesses).

CONTRASTING CLINICAL USE IN THE USA AND THE UK

In the UK the Medical Research Council advised a strict import and distribution policy for any supplies of cortisone that might become available. These were to be distributed exclusively to recognized research units that had submitted suitable research protocols. By contrast in the United States a free market developed in which cortisone was initially sold for $1000 per gram. Patients tended to take the law into their own hands, and many had the dangerous belief that, if the prescribed dose provided partial relief, a supplementary dose might eliminate the symptoms entirely. Cases of steroid dependence became common as did cases which were indistinguishable from true addiction. Many

patients were forced onto the black market to obtain their supplies. Some were threatened with bankruptcy. In 1952 cortisone was still being officially marketed at about $250 per gram; and to obtain further supplies such victims had to submit themselves to the mercies of a city-subsidized hospital clinic such as the Bellevue Hospital in New York, to which I was attached in 1952 in the course of my fellowship with the New York University Rheumatism Research Group. Here they could obtain excellent medical attention, but in truly squalid surroundings. Such patients were regarded as research material and no exclusions were offered to them should they be required as 'guineapigs', sometimes for quite unpleasant and invasive experiments.

In 1952 the Nuffield Committee of the Medical Research Council sponsored a trial in which cortisone was to be compared with old-fashioned aspirin for treatment of rheumatoid arthritis. The trial protocol, and in particular the dosage schedule, was in my opinion rigid and unrealistic in several ways. Final assessments were made after one year, which was many months after all active treatment had ended; in other words, the trial was based on the incorrect premise that cortisone was a 'cure' for the disease rather than a treatment. The statistician responsible for the protocol was Professor Austin Bradford Hill. The widely publicized conclusion of the committee was that there was 'little to choose between aspirin and cortisone in the treatment of rheumatoid arthritis', a finding that was trumpeted by the tabloid press immediately after its publication in the *British Medical Journal*[10]. In my capacity as a field worker who made some of the assessments, I felt that this was an incorrect conclusion, and I expressed these dissenting views in a letter to the *British Medical Journal*[11]. My letter brought a dismissive reply from Bradford Hill[12], and my seniors advised me not to continue the correspondence—if only to protect my career. Many years later, however, I had the satisfaction of meeting Bradford Hill. He remembered our correspondence and was generous enough to give me a huge wink as he conceded that 'I had a point'.

MAKING AND LOSING FRIENDS

About a month later I received a totally unexpected letter from Philip Hench. He had apparently been fuming ever since the publication of the Nuffield Committee report which he felt condemned most of his claims. He was all the more upset since he regarded most of the signatories as being amongst his closest British friends, and he was a great anglophile.

His letter told me that he had been invited to deliver various lectures in the UK and that he was happy to do so if there was no risk that he would be heckled or otherwise insulted—what did I advise? It was an astounding letter for someone in my position to receive. My advice was positive and he came over not only for that visit but on many subsequent occasions. He remained deeply offended by his old friends and was even heard to refer to them as traitors. He refused to meet or even to talk to them, much to their mystification and distress. At that time I had been commissioned to transform my MD thesis, which covered much of the ground discussed above, into a book suitable for general practitioners. This was in anticipation of cortisone becoming generally available in the UK in 1955[13]. Hench agreed to advise me and for this reason I saw much of him over the next year or so. I also visited him in the Mayo Clinic in 1953.

Despite the disparity in our age and experience we became very friendly; indeed he was in our home the day before our daughter was born and at his insistence she bears the female version of his first name (it was only by skilful diplomacy that we avoided his original suggestion that we should call her Cortisona).

Despite the cautious and modest attitude which he originally adopted towards his discovery (he insisted on referring to cortisone as an 'investigative' as opposed to a 'therapeutic' weapon) he later seemed to find it extremely difficult to accept that cortisone was not the ultimate solution to the treatment of rheumatoid arthritis. He argued that the side effects of cortisone therapy were not 'inevitable', indeed that they were the result of failing to tailor the dose accurately to the patient's requirements. Towards the end of his life he fell out not only with his British friends but also with many American colleagues. Howard Polley and Charles Slocumb, who were his close collaborators to the end of his life, were loyal but eventually concluded that he suffered a profound personality change in the 1950s (Polley HF, personal communication). Certainly he lost a huge amount of weight and he also developed severe diabetes. He seems in fact to have tragically become a victim of his own fame and he certainly achieved less happiness from his brilliant labours than he deserved. He died in 1965 at the age of sixty-nine, on a trip to Jamaica.

Philip Showalter Hench was the most remarkable man I have ever met.

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