Anniversary: 50 years of glucocorticoid treatment in rheumatoid arthritis

Philip Showalter Hench (Fig. 1) was awarded the only Nobel Prize in rheumatology for his work on glucocorticoids. The first patient he treated had rheumatoid arthritis (RA) and he administered Compound E (cortisone) on 21 September 1948 with almost miraculous effect [1]. The impact of this event has been captured [2] by dividing the history of rheumatology into 'BC' and 'AC' (before cortisol and after cortisol). The identification and use of glucocorticoid treatment can legitimately be seen as a major breakthrough in modern medicine. Since its discovery, cortisone and its equivalents have been shown to be life saving in a variety of diseases and conditions, including anaphylaxis, asthma, intracranial compression, systemic lupus erythematosus and vasculitis. However, even after half a century, the use and potential for misuse of glucocorticoids in RA remain the subject of vigorous debate [3–6].

The clues which set Hench to investigate the adrenal cortex were his own observations that pregnancy and jaundice ameliorate RA [7]. He hypothesized that in both conditions the improvement was caused by elevated corticosteroid levels, and this observation directed him to work with Kendall, Slocumb and Polley in trying to isolate compounds found in the adrenal cortex. It was supposed (and may yet, in a way, turn out to be the case [16]) that RA patients might have latent hypoadrenia, suggested by the clinical impression that RA patients were asthenic, weak, sometimes had low blood pressure and had low blood glucose levels. The results of the first treatment of the first patients were dramatic [1, 8, 9]. There is an original coloured file in which Hench and his colleagues documented the functional status of their first patients climbing stairs before and during treatment with Compound E. When the patients were switched to cholesterol treatment, serving as placebo, their functional status became worse [1]. This corresponded quite well with the theory that RA was a disease with adrenal insufficiency and did not cause concern. The new cortisone treatment of RA was applauded with great enthusiasm. Hench and Kendall (along with Reichstein from Switzerland) were honoured with the Nobel Prize only 2 yr later [8], in 1950. A few sceptical voices were raised. Russel Cecil's was one of them: '... hypoadrenalism is not the answer to the rheumatoid arthritis problem … Hench and Kendall have only given us two more drugs to fumble with' [9].

As time passed, it became more obvious that cortisone, and the derivatives subsequently developed, cause many side-effects when administered for long periods [3, 4, 10]. Although local and intra-articular use of glucocorticoids provide benefit for RA sufferers [11], systemic treatment was placed as 'third line' in the treatment pyramid, following unsuccessful treatment with specific anti-rheumatoid drugs [4]. In practice, however, glucocorticoids are widely used in RA [6]. This is so even though there are surprisingly few well-designed, controlled clin-

FIG. 1. Professor Philip Showalter Hench, drawn by Dr J. M. H. Moll [26]. Reprinted with permission.

ical trials of systemic glucocorticoids in RA, and even these provide conflicting results [4].

In recent years, much has been learned about the anti-inflammatory and immune-modulating actions of glucocorticoids [12–14]. Furthermore, the link between neuroendocrine control and the immune system has been firmly established. Inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) have an effect on the hypothalamic–adrenal–pituitary (HPA) axis, providing an anti-inflammatory feedback loop during inflammation [14]. This self-limiting control mechanism may be deficient in RA [15, 16], and thus a relative hypoadrenia may be unveiled in RA patients exposed to stress [17]. It also turns out that corticotrophin-releasing hormone (CRH) itself is pro-inflammatory and can be found in high concentration in the synovial fluid of RA patients [18]. Most recently, a CRH-promotor gene polymorphism has been discovered in which one allele seems to be protective against RA while the other promotes the disease [19].

The clinical use of chronic glucocorticoid treatment in RA is undergoing a period of re-examination. Fears about the toxicity of non-steroidal anti-inflammatory drugs lead some to suggest that glucocorticoid treatment is a rational choice for those with elderly-onset RA. Evidence for the erosion-preventing effect of low-dose glucocorticoid treatment in early RA is accumulating [20–22], and glucocorticoids are used for 'bridging' therapy in patients starting gold, methotrexate and other second-line drugs [3, 4]. New prednisolone derivatives are being investigated for beneficial effects with a better safety profile [23]. Other developments in glucocorticoid therapy will certainly follow, perhaps linking treatment more closely to the diurnal rhythm of the HPA axis [24, 25].

As Weiss has pointed out: 'No agents currently available are as effective as corticosteroids in alleviating the symptoms of rheumatoid arthritis' [4]. Glucocorticoid administration in one form or another is destined in its second half-century to find a better defined place in the treatment of RA.

Acknowledgement

The authors gratefully acknowledge Dr John M.H. Moll for providing his own drawing of Dr Hench.

J. R. KIRWAN[1], G. Bálint[2] and B. Szebenyi[1,2]

[1]*Rheumatology Unit, University of Bristol Division of Medicine, Bristol, UK and* [2]*National Institute of Rheumatology and Physiotherapy, Budapest, Hungary*
Correspondence to: J. R. Kirwan, Rheumatology Unit, University of Bristol, Bristol BS2 8HW, UK.

References

1. Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin 1949;24:181–97.
2. Kersley GD, Glyn J. A concise international history of rheumatology and rehabilitation. Friends and foes. London: Royal Society of Medicine Services Ltd, 1991:56–7 and 84–5.
3. Weisman MH. Corticosteroids in the treatment of rheumatologic diseases. Curr Opin Rheumatol 1995;7:183–90.
4. Weiss MM. Corticosteroids in rheumatoid arthritis. Semin Arthritis Rheum 1989;19:9–21.
5. Kirwan JR, Russell A. Systemic glucocorticoid treatment in rheumatoid arthritis—A debate. Scand J Rheumatol 1998;27:1–5.
6. Byron MA, Mowat AG. Corticosteroid prescribing in rheumatoid arthritis—the fiction and the fact. Br J Rheumatol 1985;24:164–6.
7. Hench PS. The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis and intermittent hydrarthrosis. Proc Staff Meet Mayo Clinic 1938;13:157–72.
8. Kasch J, Hetenyi G Jr. An historical review of rheumatoid arthritis treatment: 1948 to 1952. Semin Arthritis Rheum 1997;27:57–65.
9. Gutterbridge NM. Report on the American Medical Association Assembly June 11–15 1951. Lancet 1951;ii:33.
10. Saag KG, Koehnke RN, Caldwell JR *et al.* Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115–23.

11. Bird HA. Intra-articular and intralesional therapy. In: Klippel JH, Dieppe PA, eds. Rheumatology. London: Mosby, 1998:3.7.1–4.
12. Cutolo M. The role of the hypothalamus-pituitary-adrenocortical and gonadal axis in rheumatoid arthritis. Clin Exp Rheumatol 1998;16:3–6.
13. Baerwald CGO, Panayi GS. Neurohumoral mechanisms in rheumatoid arthritis. Scand J Rheumatol 1997;26:1–3.
14. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351–62.
15. Chowdrey HA, Lightman SL. Interaction between the neuroendocrine system and arthritis. Br J Rheumatol 1993;32:441–4.
16. Chikanza IC, Petrou P, Kingsley G, Chrousos G, Panayi GS. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis Rheum 1992;35:1281–8.
17. Gudbjörnsson B, Skogseid B, Öberg K, Wide L, Hällgren R. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis. Effect of glucocorticoids. J Rheumatol 1996;23:596–602.
18. Nishioka T, Karokawa H, Takao T *et al.* Differential changes of corticotropin releasing hormone (CRH) concentrations in plasma and synovial fluids of patients with rheumatoid arthritis (RA). Endocr J 1996;43:241–7.
19. Baerwald CGO, Panayi GS, Lanchbury JS. A new XmnI polymorphism in the regulatory region of the corticotropin releasing hormone gene. Hum Genet 1996;97:697–8.
20. Kirwan JR, ARC Low-Dose Glucocorticoid Study Group. The effect of glucocorticoid on joint destruction in rheumatoid arthritis. N Engl J Med 1995;333:142–6.
21. Hickling P, Jacoby RK, Kirwan JR, The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Br J Rheumatol 1998;37:930–7.
22. Boers M, Verhoeven AC, Markusse HM *et al.* Randomised comparison of combined step down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.
23. Gunnar N, Gudbjornsson B, Larsson A, Hallgren R. The timing of glucocorticoid administration in rheumatoid arthritis. Ann Rheum Dis 1997;56:27–31.
24. Markham A, Bryson HM. Deflazacort. A review of its pharmacological properties and therapeutic efficacy. Drugs 1995;50:317–33.
25. Masi AT, Chrousos GP. Dilemas of low dosage glucocorticoid treatment in rheumatoid arthritis: considerations of timing. Ann Rheum Dis 1997;56:1–4.
26. Moll JMH. The Heberden Society. History, portraits and biographies. London: Chapman and Hall, 1987:174.