
The origins, results and consequences of the 1995 Arthritis Research Campaign Low-dose Glucocorticoid Study

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ABSTRACT

The discovery and subsequent therapeutic use of glucocorticoids, which took 30 years, was stimulated by clinical observation and achieved by persistent investigation. Early reports of the potential of glucocorticoids to modify the underlying course of rheumatoid arthritis (RA) were overshadowed by pharmaceutical innovations with symptom relieving non-steroidal anti-inflammatory drugs (NSAIDs), and it was not until 1995 that clear-cut evidence of a powerful glucocorticoid disease-modifying action was published as the Arthritis Research Campaign Low-dose Glucocorticoid Study. This review reports how the study came to be designed and implemented, adds some additional information from the study not previously published, and considers the subsequent impact of the 1995 paper. Eighty years after Hench and colleagues made their first suggestion of benefit the UK National Health Service suggested all patients newly diagnosed with RA should have early access to glucocorticoid treatment.

In their seminal report announcing the therapeutic use of glucocorticoids for the first time (1), Hench, Kendall, Slocumb and Polley recalled that it was 1929 when Hench first noted the beneficial effects of pregnancy and jaundice on rheumatoid arthritis (RA). It was this observation that started the hunt for an underlying agent. In 1938, lecithin from adrenal glands was tried but failed. In 1941 it was suggested that Compound E, extracted from the adrenals, might help but it was not until 1948 that sufficient Compound E was available to test in an RA patient. The symptomatic benefit was astounding (1, 2).

The first suggestion that glucocorticoids might also be able to halt the underlying progression of destructive erosions in RA was in the study published

by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials in 1959 (3). Further hints about this possibility followed (4-6) but the first definitive evidence came with the publication of the ARC low-dose glucocorticoid study in 1995, for which I was the principal investigator (7). Here I describe how the 1995 study originated, reveal some findings not included in the original reports, and consider how the results may be interpreted in retrospect.

The paper by West (6) had produced the strongest evidence so far that x-ray progression could be slowed by glucocorticoids, but it was published in an obscure journal with a title that held little indication of its contents. It was effectively unread. In 1983, 24 years after the MRC study, Harris published another suggestive but inconclusive report (8) and, soon after, a survey showed that, while the use of glucocorticoids was generally condemned it was widely practiced (9). This practice continues today, as shown by a study in which 66% of 4363 patients at 48 clinical sites in 15 countries were taking glucocorticoids (9a). Dr John Decker, one of the fathers of Rheumatology in the USA, had encouraged me to try and clarify the role of glucocorticoid therapy, and these issues were considered at a weekend postgraduate training meeting of UK Senior Registrars (consultant trainees), who felt the Rheumatology community should surely, by now, have resolved the point. It was on the train journey going home from that meeting that Dr Margaret Byron and I drew up the first draft of a proposal for a properly designed randomised controlled trial to settle the issue. In a departure from traditional practice, but in line with current thinking about clinical trials and trial registries (10), the study design was published as a stand alone paper some time before the study it-

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self was undertaken (11). In 1987 the ARC Low-dose Glucocorticoid Study Group formed itself around the ideas published in that paper and was awarded £46,000 (\$86,000) by the Arthritis Research Campaign (now Arthritis Research UK) to carry out the trial. The study began with the first patient in April 1989. Most of the clinical work of the trial was undertaken by the study authors personally, often in their lunch breaks seeing the trial patients outside their usual clinics. The last patient had their last (2 year) visit in April 1993.

The results showed that in early active RA, adding 7.5mg prednisolone daily to a standard disease-modifying anti-rheumatoid drug (DMARD) resulted in a quicker resolution of symptoms compared to DMARD alone, and to the almost abolition of radiographic erosion progression. The analysis had been done blind, and various results and charts drawn up with the labels 'Group 1' and 'Group 2'. Several of the investigator team gathered to review these, and the code was broken by a telephone call to the pharmacy once we had agreed that the result was definitive. The clear message – that at last we knew for sure that it was possible to stop the joint damage of RA – was celebrated with a champagne toast! (Fig. 1).

Submission of the results to the *New England Journal of Medicine* (NEJM) resulted in an opinion favourable to publication, but requests to present a different statistical analysis and to draw a new figure which showed every patient as a specific point on a chart. (The original and subsequent figures are shown in Figs. 2a and 2b). The revised statistical analysis drew identical conclusions, but a resubmitted and appropriately revised paper resulted in a request for a further analysis, using yet a third statistical method. Once more, the conclusions were unchanged, and it was this last analysis that was published.

Our paper was met with a barrage of congratulations and condemnations. The ARC asked us to pre-circulate information on the results to general practitioners (family doctors, GPs) a week before publication so they would know about the study and its implications. We were subsequently rebuked for doing this by

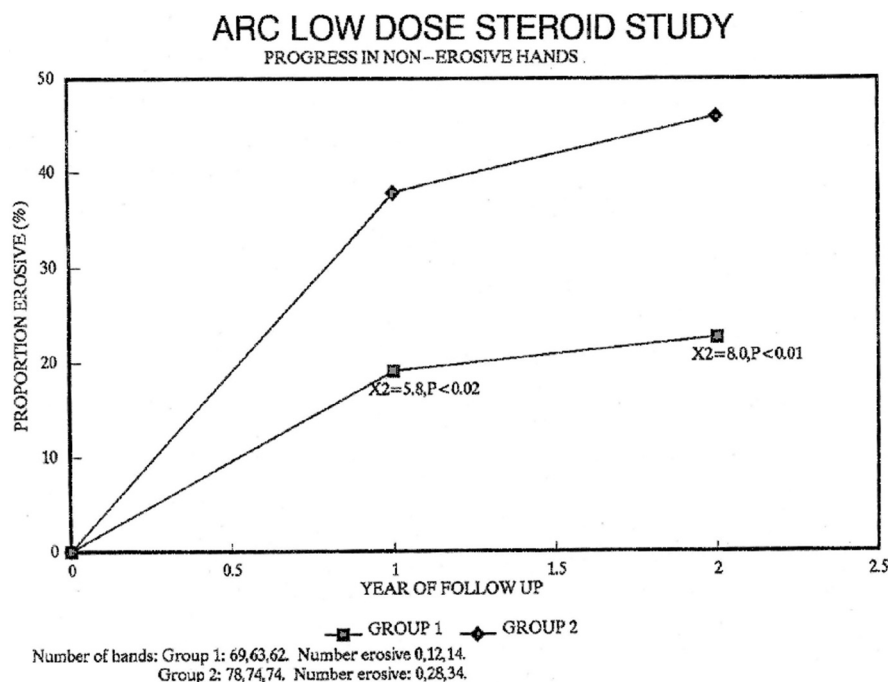


Fig. 1a. The unblinded results charts being held by the author in Figure 1b.



Fig. 1b. Doctors E. George, J. Kirwan and I. Watt celebrating the news that it was Group 1 that had been treated with low-dose prednisolone.

some of our peers (12-14). Perhaps it was a relatively slow news week, but with the publicity generated by ARC we made it to UK national TV on the BBC, and were then quickly picked up by news programmes and newspapers from around the world. For two days I did nothing but telephone interviews with journalists, live radio chat programme interviews and photoshots for local and national TV. Many GPs were therefore very grateful to have had the information available to answer patients' questions.

A string of invited presentations at various international and local post-graduate conferences and meetings followed over the next year or two. At one, in Monash University in Australia, when the audience was invited to ask questions, an enraged local physician jumped to her feet and, using the forthright language for which some Australians have a reputation, loudly condemned our publication. She felt it was a scandalous throw-back to an unacceptable treatment that rheumatology had been trying to curtail for 20 years.

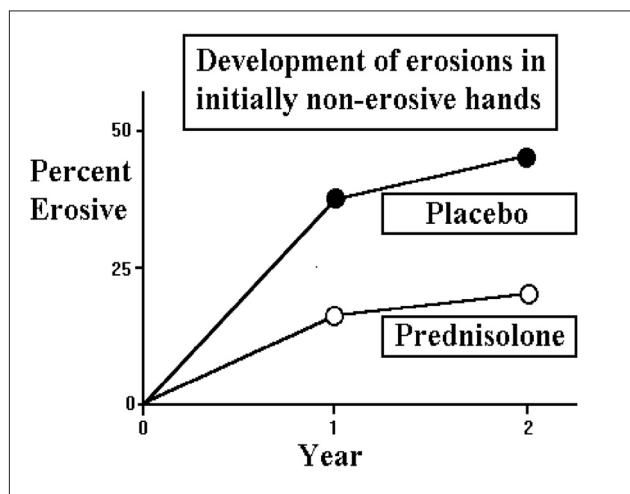


Fig. 2a. Original figure considered for the study report.

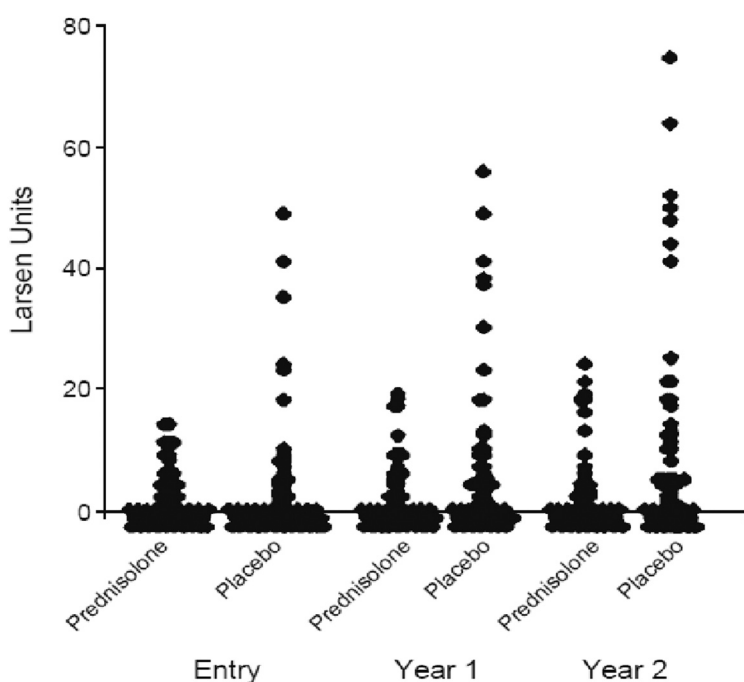


Fig. 2b. Figure included in the published study report.

Our paper would result in thousands of patients suffering the adverse effects of long-term high-dose glucocorticoids. In her opinion it would have been best if our publication team had never taken an interest in rheumatology at all. While representing an extreme example, this concern was reflected to some degree by a small minority of colleagues wherever we went. Several Letters to the NEJM Editor, and several additional letters to me as the corresponding author, complained that we had undertaken the wrong statistical analysis, or incorrectly interpreted our results. In accordance with my own

belief that full data from published studies should be made widely available (15, 16), we placed all the (anonymised) trial results on a memory disc and sent them to anyone who indicated that they thought an alternative analysis would give a different result. Only one person replied, to say he had tried his alternative analysis and had arrived at the same conclusion as we had published. However, he declined to write back to the NEJM to say so in their correspondence columns. We asked a senior independent statistician (Professor Doug Altman) to look at the results. He placed his thumbs over the non-

erosive patient dots in Figure 2b, held up the page to view at arms length, and said, "You don't need a statistician to show this treatment works, only to tell you by how much". One letter I particularly valued was from Professor West himself (6), now long retired, writing in a shaky hand to say how pleased he was to see this work taken forward.

We kept patients and clinicians blind to the original treatment allocations while we undertook a 1 year clinical and x-ray follow-up. In effect, we were putting low-dose prednisolone through a second trial. Would the x-rays now progress rapidly and the situation at the end of a further year be just as bad (or even worse) than in those who never took prednisolone? Or would progression re-start as the same rate as in those who had not received the prednisolone? Or even, could it possibly be that the prednisolone had a permanent effect and the x-ray progression never re-started? As it turned out, it was the middle option that proved the case – or almost so (Fig. 3) (17).

There were some observations we made from the data that have never been published, so here they are now:

Some patients go into remission within six months: If we define remission as an articular index of <4% of the maximum plus pain <30% of the maximum plus a normal acute phase response, then 10.3% of patients treated with standard DMARDs alone were in remission at 6 months while 19.6% of those also treated with prednisolone were in remission. The difference between the groups was not significant, but the combined proportion of patients entering remission (15%) was significant.

About 5-6% of RA patients may need glucocorticoids to suppress their clinical symptoms: There was no difficulty in stopping prednisolone after 7.5mg daily for two years. This was done by (blindly) switching to alternate day treatment for 2 weeks then every third day treatment for 2 weeks then stopping. No investigator reported any patient who suffered any kind of glucocorticoid withdrawal problems, but, although on average symptoms did not deteriorate after glucocorticoid withdrawal (17), some patients did suffer

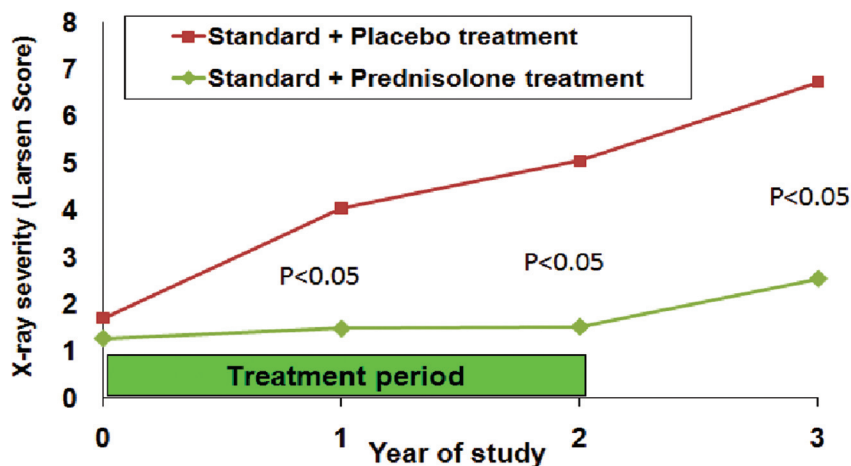


Fig. 3. post-study follow-up.

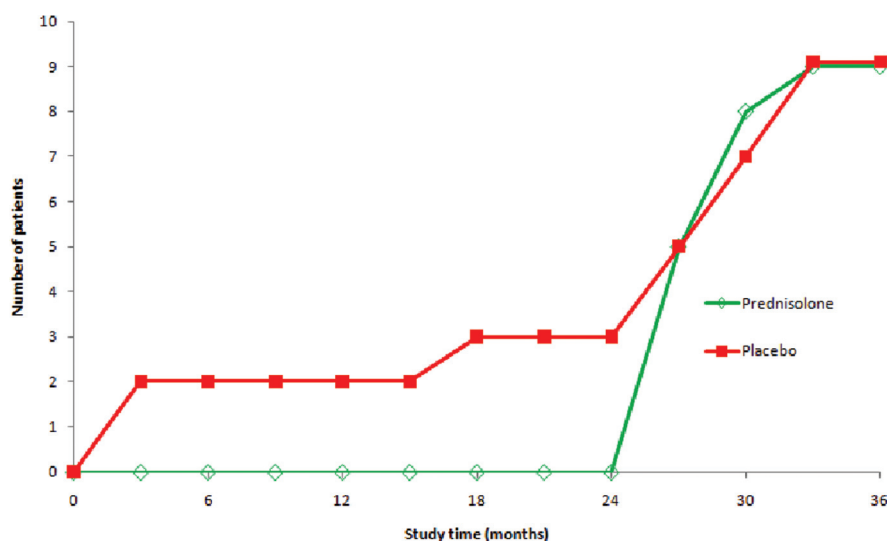


Fig. 4. Patients started on glucocorticoids during and after the treatment period

an exacerbation of their symptoms. During the study 3 patients had been withdrawn by their managing physi-

cian specifically because it was felt the patients need glucocorticoid treatment. All three turned out to be in the placebo

Table I. Continuing GC requirement for a minority.

Centre	Number of patients given glucocorticoids			Number of patients entered	Proportion (%) given glucocorticoids
	During study treatment	After study treatment	Total		
C1	0	0	0	2	0
C3	0	0	0	7	0
C4	1	3	4	38	11
C5	1	0	1	7	14
C6	0	2	2	13	15
C7	1	2	3	19	16
C8	0	4	4	18	22
C9	0	3	3	12	25
C10	0	1	1	2	50
Combined	3	15	18	128	14

arm. This suggests that about 5–6% of RA patients may need glucocorticoids to suppress their clinical symptoms. However, after the end of the study treatment, when there was no longer any blinding about current therapy, twice as many patients were started on glucocorticoids by their rheumatologist (Fig. 4). This suggests that some rheumatologists had a lower threshold for glucocorticoid therapy, but were holding back during the study. Indeed, there were considerable differences between the proportions of patients eventually treated with prednisolone in different participating centres (Table I).

“Glucocorticoid adverse effects”: For blood pressure, the proportion of glucocorticoid treated patients in whom there was an increase of 10% or more in systolic or diastolic blood pressure was no greater than placebo (it was non-significantly less). (Fig. 5). Weight gain occurred in both groups of patients as they started treatment, presumably because their RA was better controlled. Weight gain was faster in the prednisolone treated patients (as was clinical improvement), but there was a significant difference at the end of 2 years (Fig. 6). This was quickly lost as soon as the prednisolone tablets were discontinued. Nobody developed glycosuria. There was another conclusion, related to the observation that, against the background of DMARD therapy, glucocorticoids did not continue to add a clinical benefit for most patients after about a year but did continue to suppress

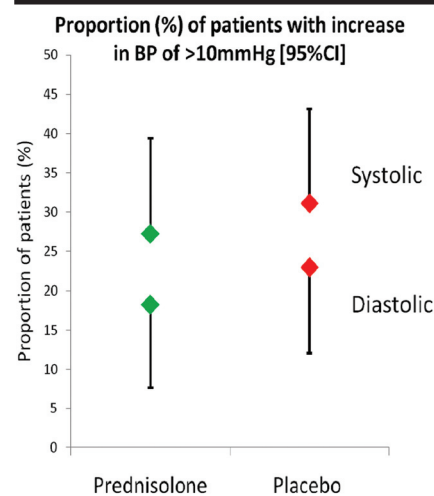


Fig. 5. Changes in blood pressure.

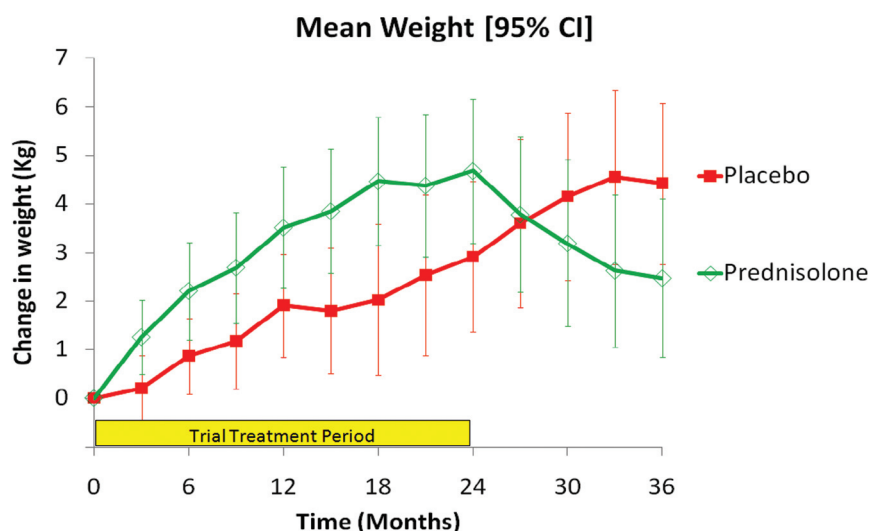


Fig. 6. Changes in weight.

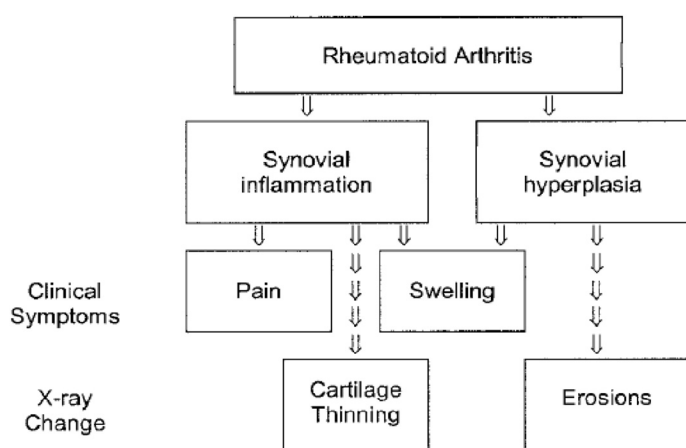


Fig. 7. Model of rheumatoid arthritis consistent with currently available data.

x-ray progression. We hypothesised (17) that this was the result of two parallel (though linked) processes as first suggested in 1983 (18) and illustrated in Figure 7. In another surprising (and disquieting) aggressive response to our results, when this suggestion was made during a presentation at the American College of Rheumatology Annual Scientific meeting it was greeted by one senior academic member of the audience with the comment that, "Everyone knows that joint inflammation causes all the damage in RA and we don't need to waste time on new explanations". Our hypothesis, as expounded in a subsequent editorial (19), would explain why NSAIDs can reduce the signs of inflammation and not prevent erosion progression, and why some animal experiments gave the results they did. We tested and seemed to confirm the

hypothesis by re-reading some of the x-rays from the original study and also by re-analysing the individual patient records of clinical joint involvement (20). Although not fully supported by all the studies that have addressed the issue, and in spite of the opinion of the aggressive professor, the notion that inflammation and erosions might be suppressed by different interventions has been gaining ground (21).

In our clinical centre we have continued since 1995 to treat patients who meet the entry criteria for the original study with low-dose prednisolone and methotrexate. More recently we have become convinced that the COBRA regimen (22) offers a better treatment choice for those patients who meet the (more severe) criteria for entry to that study. We feel it is worth the extra effort required to explain the COBRA treat-

ment to patients and to support them as they get started. We were in the process of finalising our new RA patient pathway, including these treatments, when the UK National Institute for Health and Clinical Excellence (NICE) made a recommendation to have such a pathway available, and to incorporate within it the opportunity for combination therapy including glucocorticoids as first line treatment (23). We initiated our pathway only 2 months later: patients with severe disease who meet the COBRA entry criteria are offered the COBRA regimen; those with less active disease but who meet the ARC low-dose glucocorticoid study entry criteria are offered prednisolone 7.5mg daily and methotrexate weekly; those with relatively mild disease are supported with regular NSAIDs and analgesics, and appropriate physiotherapy etc., but will be offered stronger treatment if their disease becomes more active.

We have come a long way since the initial idea to undertake the ARC low-dose glucocorticoid study. While we were in our recruitment phase, Moeser summarised the then (1991) current, widely held position dismissing any substantive role in for glucocorticoids in long-term disease suppression. He wrote, "For articular disease, these drugs must be targeted to short-term goals, such as symptom relief" (24). In contrast, in 2009 when the UK National Institute for Health and Clinical Excellence (NICE) published their guidelines for the treatment of people with newly diagnosed RA (23), they made the following recommendation on treatment, "... offer a combination of disease-modifying anti-rheumatic drugs (DMARDs) ... plus ... glucocorticoids, as first line treatment as soon as possible..." Sometimes the progress from ideas to implementation can be slow. Hench and colleagues spent about 20 years from an initial observation in 1929 to first treatment in 1948 (Fig. 8). Though not in the same league as that momentous discovery, the work showing how low-dose glucocorticoids are our strongest DMARD has been spread over a further 60 years, and I am pleased that we were able to make a useful contribution to this process about half way through.

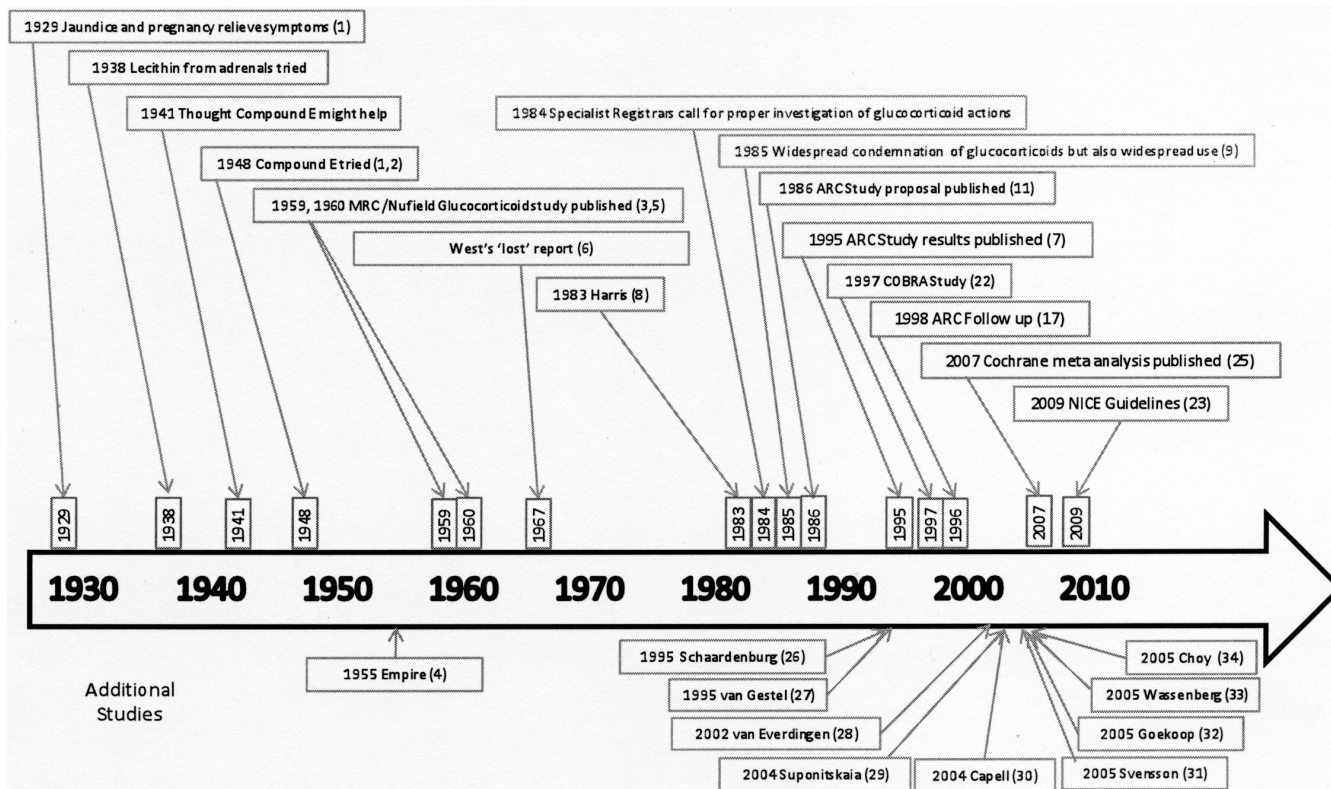


Fig. 8. Glucocorticoid timeline 1929 to 2009: From Philip Hensch's idea to a treatment recommendation by NICE in 80 years.

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