An Historical Review of Rheumatoid Arthritis Treatment: 1948 to 1952

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Objectives: **The early responses by practicing physicians to the discovery of the effect of cortisone (compound E) and adrenocorticotropic hormone (ACTH) on acute rheumatoid arthritis in 1948 and their reactions to the drugs' scarcity have been reviewed.**
Methods: **Review of the relevant literature in American, British, and European medical journals and some newspapers.**
Results: **Whereas the effect of the compound E and ACTH was stunning, their scarcity made them unavailable to most physicians. Nevertheless, practicing physicians took a lively interest in the new therapy, as witnessed by the large number of letters with comments and questions to professional journals from all over the world. As expected, most of these were about attempts to find a substitute for cortisone or a way to release it endogenously to a sufficient degree. A few alternative therapies were suggested too, some quite unorthodox. A lively interest was shown by the general public.**
Conclusions: **No alternative therapy recommended to treat acute rheumatoid arthritis in lieu of cortisone proved to be effective. The era of scarcity was ended by the discovery of a more efficient method to manufacture cortisone.**
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WHENEVER a major discovery about the successful treatment of a frequent, painful, and potentially life-threatening disease is announced, the first reaction by the majority of the medical community is enthusiastic acceptance and a strong desire to apply the new discovery to the benefit of *their* own patients as soon as possible. The responses to the discovery of insulin or antibiotics among others offer examples. This enthusiastic acceptance runs parallel with the skepticism expressed by a minority of physicians and with the systematic objective clinical trials usually performed at large university-based centers. Ultimately it is the latter that lead to a consensus about the new therapy.

But what happens if the pathogenesis of the disease is as obscure as the rationale of the new therapy and the new drug so difficult to produce that it is practically unavailable to almost all physicians? This was the case with the discovery of the stunning effect of large doses of cortisone on acute rheumatoid arthritis (1).

We have reviewed the early history of the orthodox development of cortisone therapy (2). But beyond the traditional history of the systematic investigations into the effectiveness and indications of the new therapy, the paucity of cortisone led to other therapeutic avenues, some suggested and a few even tried, in the hope that if one unexpected result had been chanced on, another one may be just around the corner. Some of the approaches were rational; others were clearly not. At the end of the rainbow was a hoped-for therapy, as effective as cortisone, but readily available, less evanescent and with fewer undesirable side effects.

It is our purpose to review the practical, as well as the less orthodox responses by nonacademic physicians to cortisone therapy, very effective beyond doubt, but virtually unavailable to them and their patients. These reactions provide a human, often flawed dimension to a great discovery and are

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worthy of compilation because they enhance the story about the introduction of cortisone therapy.

EARLY PROFESSIONAL REACTIONS TO CORTISONE THERAPY

Newspapers, such as the *New York Times* and the (British) *Times,* were the first to inform physicians as well as the general public about the discovery made at the Mayo Clinic. The first news in professional journals, outside of the Proceedings of the Staff Meeting of the Mayo Clinic, were 22 appended lines to a special article entitled "Primer on Rheumatic Diseases," in the April 30, 1949 issue of the *Journal of the American Medical Association* (3). In Britain, the first mention in a professional journal, the *Lancet,* was April 23, a week before the *Journal of the American Medical Association* (4). Undoubtedly the news was spread also by the lectures presented by Hench in the United States and Britain, especially his presentation on May 30, 1949 at the International Congress of Rheumatic Diseases in New York. It is of interest to note that in his Heberden oration in London on the September 28, 1948—one week after the first patient had been treated successfully—he did not mention cortisone.

The early reactions to the good news are best reflected by the letters from physicians to professional journals and by reports of meetings, some organized by drug companies. These presented the opportunity to inform as well as to be informed by questioning the experts. The letters and the resumès of the meetings are documented, but the opinions, comments, and gossips voiced at rounds or in clubs or hospital staff rooms have been lost. Reminiscences, the few that are available, were published in retrospect years later (5-7). We do not know if or how they were altered in view of professional propriety or by the nature of the human mind, which tends to retain pleasant memories and forget unpleasant ones.

Most letters by doctors were predictably enthusiastic. Some were instigated by the news received from the public press or the radio. A few claimed that the writer had tried steroids (inevitably the wrong ones) before; others speculated on the mode of action of the new wonder drug. Questions about the new therapy were received from practicing physicians.

One enthusiastic letter to the *British Medical Journal* from Dr Cyriax (London) quoted from a letter of his friend who attended Hench's lecture in New York. He rated the discovery to be of equal importance with that of insulin, sulfonamides, and penicillin. The effect of compound E is "almost beyond comprehension." He opines that "the time is not far distant for rheumatoid arthritis to be wiped out" (8). Dr Forestier from Aix-les-Baines (France) visited the Mayo Clinic, took part in rounds, and even talked to patients. He too gave an enthusiastic but more balanced account of his experiences, noting that whereas the discovery is of the greatest significance, the mode of action of cortisone is entirely unknown (9).

Some believed that they had seen similar effects before. Dr Shirlaw from Wigan wrote that he treated a patient suffering from ankylosing spondylitis with a cortical extract (10). The condition of the patient, heretofore resistant to other therapy, improved. Dr Craig of Ormskirk, Lancashire, saw a case of tuberculous arthritis respond favorably to an extract from "whole suprarenal gland" (11). In contrast, Dr Schmidt (London) was skeptical. In his opinion, "the basal biochemical disturbance . . . is only a part of this complex disease . . . having seen during 30 years many new treatments to emerge triumphantly and then also to disappear unwanted and unwept." He believes that "much special knowledge and circumspection" is required before assessing the value of cortisone therapy (12). His views were soon vindicated.

At various meetings, most comments were also positive or even enthusiastic; only a few were cautious or worse, as the one by Professor Russell Cecil, who, after referring to cortisone (in this context) as "glorified aspirin," stated that: "hyperadrenalism is not the answer to the rheumatoid arthritis problem . . . Hench and Kendall have only given us two more drugs to fumble with" (13).

A course on the new therapy was organized. It was held in Paris; the registration fee was $10 (14).

SCARCITY OF CORTISONE AND ALTERNATIVE THERAPIES

From the very beginning, the virtual unavailability of cortisone was *the* major issue. It was even brought up in the British Parliament, where Mr Blackburn (Conservative) asked Mr Morrison, the Lord President of the Council: "what steps are being taken by the Medical Research Council or other bodies to ensure the production of this drug on a large scale at the earliest possible time?" (15). Certainly adrenocorticotropic hormone (ACTH),

first recognized by Hench to be the logical alternative, was also effective as shown by Hench et al (1) and later also by others. But ACTH too was in very short supply; moreover, not all preparations of ACTH were equally pure and therefore equally effective.

In view of the scarcity of compound E and ACTH, it was only natural to try other approaches. Some were indeed rational, for example, to implant pituitary tissue subcutaneously or to release ACTH and thus cortisone within the body in some way, such as by the injection of epinephrine. None of these attempts was successful, possibly because not enough ACTH could be released by any physiological stimulus to release the amount of cortisone needed to relieve the symptoms. Other steroids were tried or tried again, but only cortisone and hydrocortisone were effective (2).

Others returned to the early observation by Hench that acute rheumatoid arthritis improved during pregnancy and recommended the transfusion of blood from pregnant women (16) or of postpartum plasma (17). It was overlooked that acute rheumatoid arthritis might occur during pregnancy (18) and that the amount of any putative hormone in the 300 to 500 mL blood or plasma transfused is too small to have any biological effect. Not surprisingly, such transfusions were unsuccessful. Any transfusion, however, might have caused some temporary relief as a minor stress for some patients.

Attempts to convert desoxycorticosterone acetate (DOCA) to an active principle in the body by chemical reduction (19) were a priori doomed to failure; nevertheless, it was tried by many until it was finally laid to rest by properly designed trials and experimental evidence to the contrary (20).

Treatments with no or little rationale were asked about, recommended, or tried, often with reference to some anecdotal evidence. Many of these surfaced as Letters to Editors, or in the "Question/Answer" columns of various medical journals. As expected, none of them worked. The list shown on Table 1 was culled from American and European journals for the years 1946 to 1952. It reflects the hope, enterprise, and lack of judgment by many, and not only physicians. Comments, in alphabetical order, are listed below:

1. Antihistamines, often combined with Pyramidon: On the assumption that at least in some cases acute rheumatoid arthritis has an allergic component (21). The therapy was claimed to be moderately successful, with laboratory findings improved (22).
2. Adenosine-triphosphate: Originally recommended by two Swedish physicians, without any rationale other than a recognition of the role of the compound in "dextrose metabolism." When tested on 12 patients, it was shown to be useless (23).
3. Ascorbic acid: 2 to 3 oz. lemon juice three to four times daily to treat "rheumatic gout" was first recommended in 1849 by Doctor Owen Rees, "Physician to Guy's Hospital."

Table 1: Alternative Therapies Tried, Recommended, or Considered to Treat Acute Rheumatoid Arthritis in the Years 1946 to 1952

Drugs and chemical compounds:
Antihistamines (21, 22)
Adenosine triphosphate (ATP) (23)
Irgapyrine (38)
Nitrogen mustard (44)
Para-amino-benzoate (PABA) (45)
Sulfur (50)
Tetra-ethyl-amino-bromide (TEAB) (52)
Sodium thiosulfate (53)
Plant extracts, animal venoms:
Cafestol (25, 26)
Cobra venom (27)
Vitamins and nutritional factors:
Ascorbic acid (24)
Gelatin (30)
Iron (39)
Vitamin D (55, 56)
Hormones:
Desoxycorticosterone acetate (DOCA) (19, 20)
Growth hormone (31)
Insulin (34-37)
Steroids of other then adrenal origin (see in ref. 2)
Factors acting on the nervous system:
Electroshock (28)
Liquor pumping (40, 41)
Lobotomy (42, 43)
Surgery:
Splenectomy (49)
Drainage of long bones ("forage") (51)
Physical therapy:
Heat (32, 33)
Radar (48)
Fever (29)
Vaccines (54)

The clinical pattern of his patients corresponds with that of acute rheumatoid arthritis. It was claimed that a number of patients "became convalescent in 5 to 6 days." G.H. Barlow in his book *Manual of the Practice of Medicine,* published in 1856, refers to this treatment as "one of the most ingenuous methods" to treat rheumatic arthritis. Juhn suggested the effect to be attributable to the ascorbic acid in lemon juice. He noted that ascorbic acid "is in some physiological way active in the synthesis of adrenal cortical hormones" and that in many patients the plasma level of ascorbic acid is below normal (24).

4. Cafestol: An unsaponifiable fraction from coffee seeds, claimed by Italian workers to have some beneficial effect (25). More objectively, "relative lymphocytosis" and eosinophilia were noted. When tested in England on two patients, some improvement was indeed observed, but this was attributed to an analgesic effect of the drug (26).
5. Cobra venom was tried in 12 patients. There were no objective signs of improvement, but three patients experienced some subjective relief, likely because of its already recognized analgesic effect (27).
6. Electroshock: Recommended as an alternative to insulin shock and equally ineffective (28). Its use was strongly criticized (2).
7. Fever: A report on provoking fever to alleviate acute rheumatoid arthritis was published from a U.S. Naval Hospital. Fever was induced by "typhoid vaccine-autohemotherapy," which consisted of intravenously injected typhoid vaccine with the simultaneous intramuscular injection of the patient's own blood. The injections were administered twice a week over 3 weeks. Between the treatments, the patients were given nicotinic acid in doses sufficient to produce "peripheral flushing." This was supposed to improve circulation in the affected joints, which in turn was supposed to reduce arthritis. The three patients so treated showed "prompt remission." In 14 patients, fever therapy was combined with Speransky's liquor pumping (see below); again a favorable effect was claimed (29).
8. Gelatin: In response to a reader's question, it was noted that "gelatin has been given orally to patients with rheumatoid arthritis because of its nutritional value, however a specific benefit has not been demonstrated. . . . Nor does it serve better than other food sources with complete amino acids in the treatment of malnutrition which often accompanies rheumatoid arthritis" (30).
9. Growth hormone was tried on one patient, perhaps in the hope that if one pituitary hormone was unexpectedly effective, so may be another. It was not (31).
10. Heating the legs led to some relief when the knees or ankles were affected (32). This was attributed to an increased local blood supply to the inflamed joints. But lying in bed under an electric blanket immobilized the patient. Electrically heated trousers, however, would allow some degree of mobility and may be worn by patients at home (33).
11. Insulin had been tried in the 1930s because of its effect of increased appetite and "metabolism in general" (34). Now a different rationale emerged. Insulin-induced hypoglycemia was recognized to constitute "stress" and thus release ACTH. Kersley et al (34) injected insulin daily for 6 weeks to 72 patients to produce clinical signs of hypoglycemia: 82% of the patients "temporarily improved . . . 44% markedly so" (34). After 2 months 58% were considered still to be improved, and seven had complete regression 6 months later. However, 78% of the patients who received the same care and diet, but no insulin, also improved, 14% markedly. The small difference was attributed to a placebo effect elicited by a treatment of which the patients must have been very much aware (35). Nevertheless, others also reported favorable effects of repeated insulin-induced mild hypoglycemia. In one trial, seven of nine patients showed improvement, and a decrease of eosinophil leukocytes in the blood indicated the release of adrenaline, a hormone known to release ACTH (36). Another correspondent expressed hope that the effective dose of cortisone might be reduced if given together with insulin (37). (See Hetenyi and Karsh [2] for comments).

12. Irgapyrine was tried on a small number of patients. It was analgesic, but with no specific effect on arthritis (38).
13. Iron: In a letter to the *Lancet,* an intravenously injectable iron preparation was claimed to improve acute rheumatoid arthritis. Also, three patients observed for more than 1 year who took "iron regularly" felt subjectively better, but with no change in the erythrocyte sedimentation rate. Likely a placebo effect was observed (39).
14. Liquor pumping (40): This procedure, originally recommended by Speransky in 1935 (in the former USSR) consisted of taking about 10 mL cerebrospinal fluid from the spine into a syringe and re-injecting it. The procedure was repeated about 20 times in 40 minutes. The theoretical foundation of the maneuver was in the doctrine of "nervism," politically correct at its time and place. The basic tenet of nervism was the assumption that the nervous system plays an all-important part in the pathogenesis of many diseases, including arthritis. Liquor pumping was believed to increase the flow of antibodies from the blood to the subarachnoidal fluid, thus protecting the brain against toxins. Speransky claimed recovery in 70 of 100 patients with polyarthritis. The procedure was claimed to also be of value in the treatment of malaria and typhus. It was tried in South Africa and the United States and, in uncontrolled studies, beneficial effects were claimed in rheumatic fever, arthritis, and carditis. There were, however, most unpleasant side effects (especially headache) and one death caused by multiple cerebral hemorrhages (41). In seven of nine patients treated by Boucek and Lowman (29), liquor pumping was claimed to have had "immediately beneficial effects" (29).
15. Lobotomy: It was observed that lobotomy performed to alleviate intractable pain, or for some other reason, did not improve an existing arthritis, nor was pain suppressed (42). It was emphatically NOT recommended for the treatment of acute rheumatoid arthritis (43).
16. Nitrogen-mustard: Claimed to be effective in eight of nine patients. This appears to have been the first time an immunosuppressant was used in the treatment of acute rheumatoid arthritis, but the beneficial effect was attributed to an ACTH-like action of the compound (44).
17. Para-amino-benzoate (PABA): By competing for the enzymes involved in the breakdown of steroids by the liver, PABA was expected to delay the breakdown of cortisone and thus to prolong its effect. Given with 12 g/day PABA, 12 mg/day cortisone was claimed to be sufficient to produce remissions (45). PABA irradiated with ultraviolet light was alleged to be more potent (46).
18. Procaine: Given in daily intravenous infusion (0.4 mg/kg body weight over 20 minutes) over several days, procaine was claimed to improve 39 of 56 patients with acute rheumatoid arthritis. A number of these patients also received 500 mg vitamin C (ascorbic acid) injected intramuscularly. The treatment was found to be more effective in other types of arthritis (47).
19. Radar: The father of a teenage patient took a press clipping to the doctor claiming that treatment with radar may help his son. At the request of the physician, an expert responded that although heat relieves arthritis and radar might generate some heat, radar has no specific effect on acute rheumatoid arthritis (48).
20. Splenectomy: It was noted that there were no flare-ups of acute rheumatoid arthritis after splenectomy, but the operation was not explicitly recommended to alleviate symptoms of the disease. It was suggested, however, that an exploration of possible connections among the functions of the spleen, the bone marrow, and the adrenal cortex might lead to insights into the pathomechanism of the disease (49).
21. Sulfur: Answering an enquiry, an expert consulted by the *British Medical Journal* responded: "The suggestion that sulphur is of value is based on tenuous clinical impressions and not on scientific observation . . . [its use is] only sanctified by tradition" (50).
22. Surgery: A doctor asked the *Journal of the American Medical Association* whether surgical drainage of the long bones, called "forage," has any beneficial effect. The

question was answered in the negative by two experts. They noted that the procedure had been tried as early as 1890, with claims that 56% of the patients improved. They expressed "great skepticism regarding its value" (51), however.

23. Tetra-ethyl-ammonium-bromide (TEAB): Because the sympathetic nervous system innervates joints and ligaments, it was hypothesized that interrupting this innervation by the ganglionic blocker TEAB may improve arthritis or arthritic pain. In 45 of 55 patients, pain was relieved within 1 hour. In one patient after two injections it did not return for 5 months. TEAB has a mild analgesic action, which likely accounted for the acute response (52).
24. Thiosulfate: Originally proposed to convert DOCA into cortisone in the body (and quite useless in this respect) sodium-thiosulfate given together with salicylate was claimed to reduce pain in the affected joints more effectively than salicylate alone (53).
25. Vaccines have been used since the turn of the century to treat a specific disease of infective origin, such as furunculosis or tuberculosis (as tuberculin). These vaccines were proved useless. According to a correspondent, vaccines are still being used to treat acute rheumatoid arthritis, without any rationale, because there is no known immediate specific cause of acute rheumatoid arthritis. To quote: ". . . many hundred pounds . . . and many hours of time . . . are wasted. . . . Never been proven to be of more value than boiled tap water" (54).
26. Vitamin D: The treatment of acute rheumatoid arthritis with large doses of vitamin D was reported in 1947 to be fatal in a 63-year-old woman who took large doses (50,000 U.S.P.) for over 18 months on the advice of "her private physician" (55). Nevertheless, a child was treated with high doses of vitamin D over 5½ years with disastrous effects, fortunately reversed by the discontinuation of the "therapy" in 1950 (56).

The success of, and the reservations about, steroid therapy did not entirely displace arguments about the value of other, moderately successful treatments of acute rheumatoid arthritis, such as the use of gold salts (chrysotherapy) or salicylate. Rather, the benefits of these therapies were attributed to a potential endogenous release of cortisone. It was assumed that salicylate, especially in larger doses, exerted its anti-rheumatic effect by stimulating ACTH or cortisone secretion (57, 58). Resorcylate, a compound with some chemical similarity to salicylate, was particularly effective (59). In France, gentisate, another derivative of salicylate, was tried with some success (60). Although salicylate and particularly resorcylate caused fluid retention, negative N-balance, and puffiness of the face, no convincing laboratory basis for the stimulation of the pituitary-adrenocortical axis was ever presented.

The beneficial effect of spas (61) and the importance of general nursing care were emphasized. In a letter to the *Lancet,* Col. Stoddard-Scott, MD, Member of Parliament and Chairman of the Rheumatic Society, asked whether retired nurses would be interested in taking a "rheumatic sufferer" as a lodger, either permanently or for a holiday season. Most applicants for such care are expected to be in the "lower income group" and could pay something like 3 pounds 3 shillings to 4 pounds 4 shillings a week (62). We do not know whether there were any takers.

It was already recognized by Hench et al (1) that evaluation of the effectiveness of any therapy of acute rheumatoid arthritis was complicated by frequent spontaneous, if temporary, remissions. This cast doubt on all claims based on inadequately controlled studies on a small number of patients. Possible placebo effects were rarely considered. When they were, they were surprising. In one early study, 82% of the patients treated with myochrisine (a gold compound) said that they felt better after treatment, but 72% of the patients on placebo said so too (63).

But how to assess the success of any therapy objectively? Quinn et al (64) attempted to use objective measures, such as grading joint tenderness, measuring the strength of grip, and the walking distance without pain (64). Measuring blood flow in the inflamed knee by plethysmography was also applied (65). Others pointed out that some of these tests are not entirely objective and suggested the use of measurable parameters, such as joint swelling and skin thermometry over the inflamed joint (66). An apparatus to measure the extent of digital swelling was designed (67).

EARLY THEORIES ABOUT THE EFFICACY OF CORTISONE THERAPY

Theories to explain the stunning effects of cortisone were forthcoming (2). None of these came from any of the centers in which systematic clinical trials were performed with cortisone or ACTH. All of the offered explanations were within the framework of some doctrine or theory in vogue at its time and place. In the West, some saw it as a manifestation of the general adaptation syndrome (68) or tried to integrate it with allergy (21, 69, 70) or psychosomatic medicine (71). In the East, Speransky's proposed liquor-pumping procedure was based on the doctrine of "nervism." The most truthful statement was given by Professor McNee: "No one knows how cortisone acts (72).

PUBLIC RESPONSE TO CORTISONE THERAPY

Pressure on physicians undoubtedly came from the public informed by the newspapers and the radio. Patients who had received the news demanded that their doctors treat them with the new drug. Salespersons from drug companies might have been another source of persuasion. The relationship between academic physicians and scientists and their colleagues at pharmaceutical houses was largely cordial and certainly very fruitful in developing cortisone therapy. The contact between practitioners and the commercial aspects of the industry seem to have been equivocal. There are no records available about the conversations in the doctors' offices, and in all likelihood most were ethically unimpeachable. Nevertheless, a physician wrote to the *Journal of the American Medical Association:* "Some of us recently have been subjected to pressure from medical detail men as to use adrenal cortical extracts and DOCA. These men sometimes have less scientific knowledge, than the ability to sell. We physicians have to be extremely careful during a new trend of therapy, that we do not succumb to excessive enthusiasm" (73). Kendall mentions in his reminiscences that the sales figures of vitamin E were substantially increased after the reports of the effects of compound E became known (7). He added, perhaps as a joke, that it was because of this that the Mayo team had decided to use the name cortisone rather than compound E.

DISCUSSION AND CONCLUSIONS

How did this historical period end? It ended simply by the discovery of a better, much more efficient way to synthesize cortisone on a much larger scale. Murray and Peterson working in the laboratories of the Upjohn Company (74) discovered that the mold *Rhizopus nigricans* converts progesterone (a relatively more easily available steroid) to cortisone with close to 100% efficiency. Cortisone became widely available. Efforts to find a substitute for cortisone became obsolete.

The introduction of corticosteroids in the late 1940s is regarded among the most significant scientific events in the field of rheumatology. Coinciding with the description of the LE cell phenomenon in 1948 by Hargraves and his associates, also at the Mayo Clinic, the diagnostic and therapeutic foundations of rheumatology were established (75). As corticosteroids became more readily available, it prompted their application to other diseases, where, as in rheumatoid arthritis, they often changed the course of disease and the patient's prognosis for the better. Unfortunately, the antiinflammatory mechanisms of action of corticosteroids remained elusive, inhibiting further therapeutic advances, and the side effects of corticosteroids became a dominant issue. At the extremes of the reaction, corticosteroids were damned by some, whereas others embraced their use in ways that were clear quackery.

The 1990s see somewhat of a rehabilitation of corticosteroids in rheumatoid arthritis. In addition to the obvious clinical improvement reported by many patients (76), corticosteroids are potent inhibitors of intrasynovial mononuclear inflammatory cells, an effect associated with decreased disease progression (77). It is the additional insights into basic disease mechanisms and explanations of the benefits of corticosteroids that add excitement in this new era of the use of corticosteroids.

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