
History of the development of corticosteroid therapy

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ABSTRACT

The first clinical evidence that an extract of animal adrenocortical tissue could counteract human adrenal failure was demonstrated in 1930. As chemical analyses of cortical extracts proceeded, mainly in the laboratories of Kendall at the Mayo Clinic and Reichstein in Zurich, it became evident that there is not one cortical hormone, but that all are steroids. By 1940 it was understood that there are two categories: those that cause sodium and fluid retention and those that counteract shock and inflammation. Structurally the presence or lack of oxygenation at C₁₁ on the steroid skeleton was critical. In 1948 the first patient with rheumatoid arthritis was treated with cortisone and soon thereafter other rheumatologic patients received cortisone or, to stimulate native cortisone production, ACTH. Oral and intra-articular administration of cortisone and hydrocortisone began in 1950-51. Several lines of research to produce cortisone semi-synthetically showed some success by 1952. Between 1954 and 1958 six synthetic steroids were introduced for systemic anti-inflammatory therapy. By 1960 all of the toxic effects of chronic corticosteroid administration had been described, as well as protocols to withdraw such drugs while minimising symptoms of cortical insufficiency. To enable use of lower corticosteroid dosages, companion use of non-steroidal anti-inflammatory drugs began in the late 1950s, with phenylbutazone the first. In the 1970s the introduction of methotrexate and other anti-metabolites further circumscribed the dosages and indications for corticosteroids in the rheumatic diseases.

Antecedents of medicinal cortisone

According to the 1920 (9th) edition of *The Principles and Practice of Medicine*:

“The relation of Addison’s disease to the adrenals is not the same as that of

myxoedema to the thyroid gland, in which the insufficiency is promptly relieved by the administration of thyroid preparations” (1). However, efforts were soon to be undertaken to extract what was presumed to be “the hormone” the deficiency of which causes the symptoms of Addison’s disease. In 1930 Wilbur W. Swingle (1891-1975) and Joseph J. Pfiffner (1903-1975), biochemists at Princeton University, succeeded in preparing enough of an adreno-cortical substance for clinical trials. The adrenals of two steers had to be extracted to obtain one cc. of injectable hormone. The trials were conducted at the Mayo Clinic by Leonard G. Rowntree (1883-1959). Twenty cases of Addison’s disease and 20 other (non-rheumatologic) patients were treated. The usual regimen was 40-60 cc. by intravenous infusion in 4-10 days in increments of up to 20 cc. Replacement therapy in the cases of adrenal failure usually was transiently successful (2). The extraction process devised by Swingle and Pfiffner also was adopted by other investigators (3). It began with 3-4 kilos of whole cattle adrenals that were frozen in the slaughter house for shipment to the laboratory. The mass was finely chopped while frozen and then immediately transferred to the first of a series of solvents, beginning with ethanol or acetone. The most difficult part of the separation was the elimination of epinephrine. The final product was believed to be “the adrenal cortical hormone” called “cortin” (F.A. Hartman, 1928). Research headed by Edward C. Kendall (1886-1972) (4) at the Mayo Clinic, and in Zurich, headed by Tadeus Reichstein (1897-1996) (5) proceeded.

“In December 1933 a crystalline organic substance was first obtained from an extract of the [adrenal] gland.... [the] crystalline material possessed physiologic activity similar to the extract from which it had been separated. Subsequent investi-

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gation has shown that the problem is much more complex than at first realised." (Mason *et al.*, 1936) (6).

Kendall labelled compounds alphabetically, while Reichstein used his own alphabetical nomenclature. "[Compound E] has now (1936) assumed a position of importance, since it possesses, as far as can be determined, the same qualitative physiologic activity as cortin.... A study of Compound E will also reveal the essential nature of cortin" (7). The initially proposed structure for Compound E was corrected in 1938 (8). Oskar Wintersteiner (1898-1971) and Pfiffner had also isolated Compound E, but believed it to be inactive (9). By 1939 Reichstein had isolated 22 adrenocortical steroids, while Kendall, by somewhat different methods, had isolated 11 compounds. The total soon grew to 28 of which, however, only six demonstrated physiologic effects (10). Kendall's group of biochemists focused their research on compounds they designated A, B, E and F, that affect carbohydrate metabolism, while Reichstein's research emphasised compounds that affect electrolyte homeostasis (11). According to reviews by Kendall in 1941, experiments on adrenalectomised rats and some dogs had shown that substitutions at C₁₁ and/or C₁₇ on the steroid skeleton are responsible for different physiologic effects. There are two principal categories: compounds lacking an oxygen on C₁₁ affect electrolytes and those with an oxygen at that position, such as "compound E", affect gluconeogenesis (11, 12).

According to Kendall in 1942, 1000 pounds of cattle adrenals yielded 340 mg. of compound E and less than 100 mg. of compound F (Fa and M in Reichstein's nomenclature). However, these values were not to be considered to represent physiologic proportions. On a smaller scale, 75 gm. of tissue were used to prepare 1 cc. of extract that contained 0.05 mg. of compound E (10).

Toward clinical use of corticosteroids

A shift in thinking about rheumatoid arthritis (RA) away from an infectious etiology was indicated in 1943 by Ralph Pemberton (1877-1949) and C.S. Scull (Philadelphia):

[Several clinical] "...facts may be correlated by considering the symptoms of rheumatic diseases, at least rheumatoid and osteo-arthritis as, primarily, direct consequences of disturbance in the several functions of the neuro-endocrine system as a whole and especially those of the pituitary gland.... It appears unlikely that any single factor is responsible for producing the full pattern in any case.... These considerations, addition to their theoretical interest in accounting for the symmetrical distribution of lesions and certain systemic dysfunctions, bear suggestive therapeutic corollaries which have not yet been fully explored and invite clinical as well as experimental exploitation" (13).

Desoxycorticosterone acetate (DOCA), synthesised by Reichstein from desoxycholic acid in 1937 (14) and from cortex extracts in 1938 (10, 15, 16), was the first crystalline cortical substance to be produced in potentially therapeutic quantities. The acetate is more effective than the free form (12). The first clinical study, by George W. Thorn (1906-2004) *et al.* (1940, Boston) on 30 cases of Addison's disease, showed that DOCA did not alter the characteristic hypoglycemia, but did normalise electrolyte balance (17). A double-blind study of DOCA with five cases of RA in 1950 showed it to lack anti-inflammatory efficacy (18).

Even if compound E might have therapeutic value, there was no method whereby to produce it in sufficient quantity for clinical trials. In 1944 a method for the synthesis of compound A was developed in Kendall's laboratory (19). However, in the following year compound A disappointingly was found not to be effective hormonal replacement in a case of Addison's disease (20). In 1949 three Mayo Clinic RA patients were administered compound A to compare it with cortisone, and confirmed it to be an ineffective anti-inflammatory agent (21).

Both Kendall at the Mayo Clinic and Lewis H. Sarett (1917-1999) at Merck Laboratories sought to produce compound E in larger quantity, and Sarett in 1947 developed the first practical proc-

ess, proceeding from Kendall's synthesis of Compound A (22). By early 1948 400 mg. of compound E acetate had been produced. However, it was believed that the acetate would be absorbed by tissue too slowly to be therapeutically effective. A procedure to obtain free compound E was devised in that September. Awaiting this development is the reason that the first clinical trial did not take place sooner (23).

The clinical introduction of cortisone

The first clinical use of cortisone was announced in the *Proceedings of the Staff Meetings of the Mayo Clinic* on April 13, 1949 (24). Philip S. Hench (1896-1965), chief of the Rheumatology Section (25), had selected the first patient, a 29 year old married woman who was in her 4th year of RA. It was determined to use the same dosage of compound E as had been administered in the Compound A trial. The patient had initially been seen at the Mayo Clinic in Feb. 1948 and had received various medications on several occasions before Sept. 21, 1948, when she received the first twice daily IM injections of 50 mg. cortisone (26). Subjective improvement was described after the second injection. On day 9 the dose was reduced to 50 mg. per day, then to 25 mg., but by day 17 she began to complain of increasing skeletal symptoms. Resuming twice daily 50 mg. injections resulted in improvement, but by day 23 facial puffiness was apparent and by day 60 there was facial hirsutism and acne. While cortisone dosage oscillated between 50 mg and 100 mg/day, increasingly depressive and hostile ideation developed, although rheumatoid symptoms were "50% improved". There are no comments about withdrawal symptoms following her discharge in May.

The medical director of the Merck Corp. came to observe the initial response to cortisone of the next two patients. In April 1949 compound F, extracted from hog adrenals, was administered to one other RA patient. It was deemed a little less effective than compound E (23).

Of the first 33 corticosteroid treated patients 23 carried the diagnosis of RA

or ankylosing spondylitis, 8 acute rheumatic fever, one each psoriatic arthritis and systemic lupus erythematosus (27). Hench proposed "cortisone" for compound E as an acronym for corticosterone (23). Only seven of these patients had received any free cortisone during their treatment, while nearly all received cortisone acetate, even though the acetate had initially been anticipated to be less effective than the free substance (27). One RA patient received cortisone acetate for 30 days, cortisone for 100 days, compound F and ACTH for 12 days each. The evaluation of these agents clearly was governed by the availability of each. A subsequent more detailed article, a year after cortisone became clinically available, concludes with the plea: "The use of these hormones should be considered an investigative procedure, not a treatment" (28).

In 1952 Joseph J. Bunim (1906-1964) *et al.* (National Institute for Arthritis and Metabolic Diseases) confirmed the findings in acute rheumatic fever and added "juvenile rheumatoid arthritis" to the diagnoses with acutely favourable responses, but warned that cortisone should only be used in cases of "severe, rapidly progressive forms of disease" and not as the only therapeutic measure (29).

The Merck Corp. during the war was awarded a federal subsidy for corticosteroid research. Despite its frustrating results, the Research Department decided to continue these investigations and at least \$13 million had been invested by 1949 (23, 30). Since the initial clinical success of cortisone was expected to cause demand to rapidly exceed its availability, the National Academy of Sciences in cooperation with the Merck Corp. established a seven member committee to allocate the drug, analogous to the procedure that had been established in 1944 for penicillin. It became operative in June 1949, but lacking a rheumatologist, it at once came into conflict with the Arthritis Foundation (31). As early as August, the committee was being bypassed, and it soon was disbanded.

According to the recollection of Richard H. Freyberg (1904-1999) in 1998, in February 1949 he and four

other rheumatologists were invited by Hench to observe the acute effect of cortisone in RA. Two patients who "were wonderful volunteers who loved Dr. Hench" were injected with 300 mg. of cortisone and "during the course of 2 days we saw them miraculously improve" (32). This may have been a sales maneuver by Merck, because each of the visitors was provided with enough cortisone with instructions "to treat different forms of arthritis".

In 1949 Howard F. Polley (1913-2001) and Harold L. Mason administered "twelve steroid substances other than cortisone and four adrenal extracts in 22 trials on 11 patients who had RA and/or ankylosing spondylitis" (21). Some of these were the same individuals as were cited previously. In ten of these experiments comparisons with response to cortisone and/or ACTH were made. Only cortisone, hydrocortisone and, more weakly, adrenal extracts, demonstrated anti-rheumatic activity. Hench was alluding to such experiments when he reiterated in his Nobel Prize Lecture (Dec. 11, 1950): "These hormones still belong to the physiologist and to the clinical investigator as much as, if not more than, to the practicing physician" (32).

In 1950 Freyberg *et al.* (New York) found that cortisone administered orally was as effective in the same dosage as intra-muscularly (33). However, dosage was arbitrary and generally larger than subsequent experience indicated. Jerome W. Conn (1907-1994) *et al.* (Ann Arbor, MI, 1951) concluded that compound F (hydrocortisone) and not compound E (cortisone) is the actual product of the normal adrenal cortex. This was based on experiments with one young woman who was administered the large dose of 400 mg. of hydrocortisone per day and within four days demonstrated the same clinical and metabolic effects as elicited by ACTH (34). Furthermore, administration of ACTH resulted in increased secretion of hydrocortisone rather than cortisone.

The search for a semi-synthetic process

The production of sufficient cortisone to meet the growing clinical demands

required a method not dependent on extracting animal tissue. As semi-synthetic manufacturing processes were being developed the price of cortisone decreased between July 1949 and November 1950 from \$200 to \$35 per gram, and continued to decrease (30). By 1952 cortisone was available in a 20 cc. vial containing 40 mg. per cc (36). A botanical raw material would be preferable to having to depend on desoxycholic acid from bile as the initial compound. The most difficult problem was to obtain hydroxylation at C₁₁ of the steroid skeleton, which was considered essential for anti-inflammatory effectiveness. In about 1940 a method to produce progesterone in just five steps from stigmaterol, a steroid that is present in Mexican species of yam, had been discovered. The concentration of progesterone increases during pregnancy, when symptoms of RA tend to diminish, and it also is in part produced by the adrenal cortex. Thus progesterone was hypothesised to be a precursor that could be modified into cortisone, perhaps by microbial enzymes. Durey Peterson, a chemist at the Upjohn Co., attempted this synthesis with a *Rhizopus* mold, and indeed, this added an OH at C₁₁. Then reducing the OH to =H resulted in semi-synthetic cortisone. This product became available in late 1952 (36).

Another botanical source that was explored involved the seeds of a common West-African vine, *Strophanthus sarmentosus*. Seeds of some varieties contain *sarmentogenin*, a steroid that has the advantage of being hydroxylated at C₁₁. Several expeditions to Africa obtained a range of varieties of the vine (38). The botanical problem turned out to be inability to differentiate seeds that contained the desired compound (38). However, these seeds for about two years also became a source of semi-synthetic cortisone.

Adrenocorticotropin (ACTH)

ACTH was extracted from sheep pituitary glands by C.H. Li (1913-1987), *et al.* (Berkeley, CA) in 1943 (39) and by George Sayers (1914-?) *et al.* (Salt Lake City, UT) from hog pituitaries (40). It was found to be a protein with a mo-

molecular weight of about 22,000. Subsequently it was extracted commercially from hog pituitaries. The early preparations obtained from Armour & Co. were contaminated with varying amounts of oxytocin. In 1948 Li *et al.* reported that a polypeptide of this protein with molecular weight of 1,200 retained its adrenal stimulating effect (42). The structure became recognised as a 39 amino acid polypeptide which has the same physiologic effects in humans despite species-specific substitutions at two or three loci. Potency is retained by a peptide of 20 of the 39 amino acids (42). Early in 1949 Hench administered ACTH to two RA patients and observed the same ameliorating effects as were being obtained with cortisone (24). Some trials were made to treat only with ACTH, on the hypothesis that the release of several anti-inflammatory substances might thereby be elicited and that therefore ACTH therapy may be more potent than exogenous cortisone. This was disproved (27).

Corticosteroid analogues useful in systemic therapy

In the decade following the demonstration of the anti-inflammatory effects of cortisone it was discovered that various small alterations at any of eight positions on the steroid skeleton modify its anti-inflammatory and/or sodium retaining effects. The first analogues of cortisone and hydrocortisone to be tried clinically were metacortandracin and metacortandrolone, beginning in 1954 (43). They differed from the naturally occurring hormones only in having a double bond between C₁=C₂. Their commercial names, originated by the Schering Corp., became *prednisone* and *prednisolone*. By weight their anti-inflammatory effects were 4-5 times as great as those of the natural hormones, and they exhibited the tremendous advantage of minimal sodium retention or oedema formation. Abraham Cohen *et al.* (Philadelphia) confirmed these findings with 132 patients (44). Facial rounding developed in half of these individuals, but there was "a lack of sodium retention, absence of increased potassium excretion, and the unlikelihood of the production of hypertension".

Adding a fluorine atom at C₉ of hydrocortisone or prednisolone further increased the anti-inflammatory effect, but increased fluid retention much more. However, then also adding a hydroxyl radical at C₁₆ blocked the sodium retention and obtained a slight further increase in the anti-inflammatory efficacy. This compound became called *triamcinolone* (45). Per milligram, *dexamethasone*, which differs from triamcinolone by having a methyl radical rather than hydroxyl at C₁₆, is the most potent anti-inflammatory and cortical atrophying steroid, but because of toxicity after several months administration, it has come into only short-term systemic use (46, 47).

In practice, prednisone and prednisolone have become the basic drugs in systemic corticosteroid therapy. Methyl-prednisolone became used as short-term intravenous therapy, dexamethasone particularly in neurologic emergencies, fluorocortisone, triamcinolone and numerous later synthetics in topical dermatologic management. Dwight J. Ingle (1907-1978, Chicago) had shown in 1938 that administration to rats of the crude adrenocortical extracts then available caused atrophy of their adrenals (48). W.M. O'Donnell *et al.* studied the adrenal glands of terminally ill patients who had received either ACTH or cortisone until death. Similar adrenocortical atrophy was demonstrated, while in patients for whom such therapy had been discontinued a few weeks before death there was some recovery (49). Thomas A. Good *et al.* (Salt Lake City, UT) described symptoms of steroid withdrawal in four cases of juvenile polyarthritis (50). Evan Calkins *et al.* (Buffalo, NY, 1960) studied abrupt cessation after more than two years administration and found that hypofunction persisted after symptomatic recovery from withdrawal symptoms (51).

It was at first assumed that intermittent administration of ACTH will permit smaller dosages of corticosteroids and will facilitate withdrawal of corticosteroid therapy. Based on the evidence of hormone suppression, once sufficient cortisone became available for prolonged therapy, two questions came

Table I. First clinical use of corticosteroids.

Cortisone 1948
Hydrocortisone 1950
Prednisone 1954
Prednisolone 1954
Fluorocortisone 1954
Triamcinolone 1956
Methyl-prednisolone 1957
Dexamethasone 1958

under discussion: 1. Can anticipated adrenocortical atrophy be minimised during cortisone administration by also administering ACTH? and 2. Can withdrawal symptoms when discontinuing prolonged cortisone therapy be ameliorated by then administering ACTH? Pituitary function appeared to recover more rapidly after cessation of ACTH therapy than adrenocortical function did after the cessation of corticosteroid administration, which may remain subnormal for months (52). Polley already in 1956 believed that ACTH "has not seemed to facilitate recovery of both adrenocortical and pituitary function sufficiently to be a routinely useful adjunct" (53). Bunim in the 1960 edition of *Arthritis and Allied Conditions* stated flatly: "Corticotropin is not effective in combating withdrawal symptoms" (54). Whether ACTH administration should be used for a few weeks after corticosteroid dosage has nearly or fully been stopped was debated into the late 1960s. In 1966 Bacon *et al.* (London) reported that symptomatic exacerbation upon corticosteroid withdrawal could not be counteracted by administration of ACTH (55), while Thorn at the same time recommended the administration of ACTH once or twice per week for two or three months in this circumstance (56).

Intra-articular injections

Joseph L. Hollander (1910-2000) and colleagues (Philadelphia) pioneered intra-articular steroid therapy, beginning in 1951 (57). They found that the injection of 25 mg. of cortisone acetate into a rheumatoid inflamed knee was ineffective and that 50 mg. only resulted in irritation. However 25 mg. of hydrocortisone acetate usually resulted in symptomatic relief within 24 hours. For some severely inflamed

knees a dose of 37.5 mg. was effective. No difference was found between the effect of hydrocortisone acetate and the free substance. However, the average duration of improvement was only eight days. In osteoarthritic knees the average benefit lasted three weeks. Curiously, the authors commented “the advisability of using these agents is doubtful because of expense and possible dangers, particularly in persons past middle age – the very group suffering from osteoarthritis.”

After experience with more than eight thousand injections, Hollander reported that temporary unpredictable local exacerbation occurred after 1.8% of injections and in two instances the joint became infected (58). Osteoarthritic joints, except for hips, responded as well as rheumatoid joints. 68% of the injections were into knees, and these had the highest success rate, 94%. Success was defined as objective local improvement that persisted for at least three days. Hollander made no recommendation about the number of joints to inject at one time, or the frequency with which a joint may be injected, although mentioning that he has injected one joint 47 times. Hydrocortisone acetate was presumed to be more effective than hydrocortisone because of its lesser solubility and systemic absorption. Consistent with this, Frank Austen (Boston) and Evan Calkins (Buffalo) also found hydrocortisone acetate to more effectively normalise synovial fluid (59). However, Freyberg *et al.* (1958) found triamcinolone effective by intra-articular injection whether its di-acetate or alcohol compound was used (45).

Corticosteroid toxicity

The Mayo Clinic physicians suggested in 1950 that “such terms as “side effects” or “toxic reactions” not be applied to physiologic alterations induced by cortisone and ACTH which do not have favourable therapeutic implications, for these designations do not indicate a broad appreciation of the biologic significance of these important substances” (27). After knowledge of these physiologic alterations had accumulated for a decade, Bunim advised: “The patient should be informed at the

outset that corticosteroid withdrawal after prolonged administration may be difficult, that risks of considerable magnitude are involved in prolonged administration and that it will be necessary to remain under a physician’s care throughout the period of therapy” (60). Some symptoms of corticosteroid toxicity were easily recognised because they were known from the pathological corticosteroid overproduction of Cushing’s syndrome.

Charles A. Ragan (1910-1976, New York) compared the frequency of findings in Cushing’s syndrome with those of long-term cortisone and ACTH administration. With the single exception of ankle oedema, they were equally common or more frequent in Cushing’s syndrome (61). However, it took about a decade for all of the toxic effects of prolonged and/or excessive dosages of corticosteroids to be recognised.

Hench *et al.* in early 1950 concluded that when cortisone or ACTH are given for a few weeks to a few months “... side effects will probably not present an important problem”. Based on his experience with 23 patients, among whom only two “rebound relapses” occurred, they favoured abrupt withdrawal rather than tapering of cortisone or ACTH dosage (28). However, in another publication three months earlier they speculated: “The possibility should be borne in mind that function of the adrenal cortex might be inadequate under conditions of stress, such as fever or trauma, in a patient who had recently received cortisone” (27). During apparently successful chronic corticosteroid therapy it is uncertain to what extent symptomatic improvement is attributable to suppression of inflammatory symptoms or spontaneous remission. However, there soon was general agreement that tapering of dosages is preferable, the only argument being how fast this should be achieved. Thorn (1966), for example, suggested 5% per month, but the dosage from which withdrawal was to be begun, as well as personal variables had to be considered (56).

The first fairly large survey of untoward effects of cortisone therapy was published by Freyberg *et al.* in 1951 (62). It reviewed 44 RA patients who

had been treated for at least 100 days. Concurrent medications are not cited. “In many patients a good partial remission could be maintained with 50 to 75 mg. daily”. “The longer the treatment was continued, the greater was the chance for trouble!” Most frequent untoward effects were oedema, rounded facies, tachycardia, hypertension, and insomnia. Symptomatic relapse was recognised in some cases when dosage was reduced below 50 mg/day, and improvement rarely persisted 60 days after cessation. After 18 months experience the authors questioned whether “...treatment with cortisone will be worth while for this patient? What will happen not only during its use but also after the hormone is discontinued?”

William S. Clark (1914–1996 *et al.*, New York) (63) reviewed their experience with 52 RA patients in 1953. The majority relapsed within ten days after either cortisone or ACTH was discontinued. The most frequently observed side effects were euphoria, moon facies, and depression.

David S. Howell and Ragan (1954) (64) divided toxic effects into six categories: Cardiovascular & electrolyte, gastrointestinal, decreased resistance to infection, metabolic, cutaneous, and psychiatric. Among 75 cases of RA treated at Columbia-Presbyterian Medical Center (New York) during 1949-1954 39 different findings were attributed to corticosteroid toxicity. Three had not yet been recognised: “Steroid pseudorheumatism”, aseptic bone necrosis, and posterior sub-capsular cataracts.

All of the reviewed side effect surveys emphasised the frequency of psychiatric alterations of various kinds, most frequently insomnia and/or depression. Paul Goolker and Joseph Schein (New York, 1953) made a psychiatric diagnosis in 46% of 80 patients who were being treated for various ailments (10% RA) (65). Of greatest interest are the investigators’ conclusions that psychiatric reactions to steroid therapy were not related to the patients’ pre-morbid psychic state and that therefore psychiatric abnormalities did not preclude corticosteroid therapy; disturbances tended to reverse with drug withdrawal.

The prevalence of gastro-duodenal ul-

cers in rheumatic diseases or with corticosteroid therapy was uncertain because only symptomatic patients usually underwent radiologic examinations. Robert H. Freiburger *et al.* (New York) routinely performed upper gastrointestinal radiography on 114 RA patients who had received corticosteroids for at least six months (68). Radiographically 31% had an ulcer compared to 9% of RA patients who had not received such medications. Ulcers were relatable to the corticosteroid dosage, but not to the duration of RA. 28% (10/35) were asymptomatic; only 5/35 ulcers were duodenal and the majority of gastric ulcers were located in the antrum, both findings being unusual in the absence of corticosteroid therapy.

Paul H. Curtiss *et al.* (Cleveland) in 1954 reported the occurrence of osteoporotic compression fractures in three men with RA and a boy with juvenile polyarthritis (69). Contrary to earlier reports of such findings, they did not consider the cause in these cases to be anything other than prolonged corticosteroid therapy. More impressively, Howell and Ragan's cohort of 75 cases of RA included eleven with "severe osteoporosis and six with vertebral compression fractures (64). The complexity of corticosteroid induced osteoporosis was reviewed extensively by Barbara Lukert and Lawrence Raisz in 1990 (72).

The association of aseptic (avascular) bone necrosis with corticosteroid therapy was described in 1960 in four patients with non-rheumatologic diseases. The authors emphasised the large doses of ACTH, cortisone and prednisone they had received (73). As of 1963, 62 corticosteroid treated cases, predominantly affecting femoral heads, had been reported, one half of the patients having RA. The occurrence of aseptic necrosis was not well correlated with the corticosteroid dosages (74). Of 169 cases examined at the Johns Hopkins Hospital (1974-1982) only 52% had received corticosteroid therapy (72). Thus, the relative importance of the therapy, the underlying disease and other factors is uncertain.

Roger L. Black *et al.* (NIH) in 1960 described the development of posterior subcapsular cataracts as a complication

of corticosteroid therapy in RA (71). In 11 months they detected this ocular lesion in 17 of 44 steroid treated patients and in none of 19 RA patients who had only received other medications. The finding was correlated with dosage and duration of therapy, but not with any one glucocorticoid. The cataracts were not so dense as to severely interfere with vision.

Most confusing was the "pseudo-rheumatism" mentioned briefly as a "pan-mesenchymal reaction" by Charles H. Slocumb in 1953 (67), and described by Jerome Rotstein and Robert A. Good (1922-2003, Minneapolis) in 1957 (75). There is increased tenderness of muscles and myalgia, rather than an increase in articular symptoms; there may also be peripheral paresthesias and dysesthesias, emotional lability and fatigue. In these circumstances corticosteroid dosage should be decreased rather than increased.

Bunim advised in 1960:

1. Systemic corticosteroids *should never be the initial agent* used in the treatment of rheumatoid arthritis.
2. *Should be given only after a conscientious and unhurried trial of conservative measures* fails to achieve satisfactory results.
3. *Should not constitute the only measure* in the treatment...
4. *Should not be given until a careful survey* for the presence of *contraindications* and *infections* has been completed (75).

In 1972 Evelyn V. Hess and John A. Goldman (Cincinnati) used the same wording (76). In his textbook, Warren A. Katz (Philadelphia) in 1988 begins his presentation of corticosteroid therapy with the exclamation "Corticosteroids are hazardous!" (77). Hence, one of the main indications for the use of "non-steroidal anti-inflammatory drugs" (NSAIDs) was to facilitate the use of lower dosages of corticosteroids.

Non-steroidal anti-inflammatory drugs

Freyberg suggested in 1958 "It may be that administration of a mixture of steroids, each contributing separate advantages in some patients, may be preferable to the use of only one" (45).

Table II. Chronology of recognition of side effects of corticosteroid therapy.

1950 (27)	Facial rounding Acne Hirsutism Cutaneous striae Muscular weakening Oedema Increased appetite Abnormal menses Euphoria Depression
1951 (63)	Hypertension Hyperglycemia Purpura Telangiectasias
1953	Infections (64) Pseudorheumatism (68)
1954 (65)	Peptic ulcer Osteoporosis Compression fractures
1960	Aseptic necrosis of bone (74) Posterior subcapsular cataracts (73)

Rather than this, additive non-steroidal drugs came into practice. The first to be considered superior to aspirin was phenylbutazone, introduced in 1949. In a small comparative study in RA patients, only one of ten exhibited a better response to cortisone than to phenylbutazone (78). The drug was phased out clinically in the 1970s, mainly because of cases of bone marrow failure, but remains important in equine medicine.

Next, beginning in 1961, came indomethacin, which eventually replaced phenylbutazone, mainly because it lacked bone marrow toxicity. Charley J. Smyth (1901-1997 (Denver) found that adding indomethacin to a steroid (preparation not specified) causes a greater anti-inflammatory effect than either drug alone, but the findings were equivocal (79).

Although the former two drugs also are "non-steroidal anti-inflammatory agents," this term was first generally applied to ibuprofen, which was introduced in England in 1967, but in the U.S. not until 1974. In 1979 it was considered "a mild but effective anti-inflammatory and analgesic drug whose salient clinical property is reduced symptoms of gastric irritation (compared to aspi-

rin).... The drug is probably not as immediately anti-inflammatory as aspirin or corticosteroids” (80). Naproxen likewise became available first in England (81). The flood of competing NSAIDs opened in the United States in 1976 with the introduction of fenoprofen, naproxen and tolmetin (82). All act by inhibiting cyclo-oxygenase. In the 1970s, after the introduction of anti-metabolite therapy, especially with methotrexate, azathioprine, and cyclophosphamide, systemic treatment of RA with an oral corticosteroid, most often, prednisone, became much more a secondary therapy (83). The clinical circumstances under which low dosage chronic corticosteroid therapy should be initiated remain in dispute, but their continued employment appears likely (84).

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