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Nonspecific Anti-Inflammatory Agents

Some Notes on Their Practical Application, Especially in Rheumatic Disorders

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• A number of acute and chronic inflammatory disorders are amenable to varying degrees of therapeutic control with the administration of nonspecific anti-inflammatory drugs. An evaluation of these suppressive agents in the field of rheumatic diseases and practical suggestions regarding their administration are presented.

Eight synthetically modified corticosteroid compounds are available commercially. Each of them exhibits qualitative differences in one or several physiologic actions, each has certain advantages and disadvantages in therapy, and each shares the major deterrent features of corticosteroids. Prednisone, prednisolone, methylprednisolone, fluprednisolone and paramethasone have similar therapeutic indices, and there is little choice between them for the usual rheumatoid patient requiring steroid therapy. Conversely, the therapeutic indices of dexamethasone, betamethasone and triamcinolone are lower than that of prednisolone; they are less desirable for routine use and should be reserved for specially selected cases.

Salicylates are preferred to adrenocortical steroids in the treatment of the ordinary patient with acute rheumatic fever. Steroid therapy should be reserved for resistant cases and for those with significant carditis. Salicylates are mainstays for pain relief in rheumatoid arthritis, but with the analgesic doses usually employed their anti-inflammatory action is slight.

Phenylbutazone is a highly useful anti-inflammatory agent, especially in management of acute gouty arthritis and ankylosing (rheumatoid) spondylitis; its metabolite, oxyphenylbutazone, does not exhibit clear-cut advantages.

Colchicine specifically suppresses acute gouty arthritis. Its analogues, desacetylcolchicine and desacetylthiocolchicine, produce fewer unpleasant gastrointestinal symptoms, but may promote agranulocytosis and alopecia.

A number of indole preparations with anti-inflammatory activity have been tested clinically. One of them, indomethacin, has received extensive therapeutic trial; with dosages that can be tolerated the drug is fairly effective in the symptomatic control of ankylosing (rheumatoid) spondylitis but it is of questionable value in peripheral rheumatoid arthritis.

MANY DISEASES of obscure cause are characterized by acute or chronic inflammation reactions, and therapeutic control of them is dependent on the administration of certain hormonal and nonhormonal agents that have the capacity to suppress inflammation in a nonspecific fashion. Among the anti-inflammatory drugs now available to the physician may be listed hydrocortisone and cortisone and their synthetic derivatives, corticotropin, phenylbutazone and its analogues, as well as salicylates and colchicine. Ad-

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ditionally, several indole preparations have anti-inflammatory properties and are under clinical investigation. An attempt will be made herein to review certain general considerations pertaining to the therapeutic application of these compounds, especially in the field of rheumatic diseases.

ADRENOCORTICAL STEROIDS AND THEIR SYNTHETIC ANALOGUES

The adrenocortical steroids and their synthetic analogues are, of course, the most potent antiphlogistic agents now available. An enormous amount of basic research has been accomplished with them during the past 14 years, yet the physiologic mechanisms by which they suppress inflammatory processes are not fully understood. It would appear that the collagen disorders and a number of other conditions responsive to steroids may represent hypersensitivity reactions of connective tissue and that the steroids or their metabolites operating at the tissue level inhibit such excessive reactivity. Whether their influence is exerted by interfering with antigen-antibody mechanisms, by blocking tissue enzyme systems, by interrupting histamine metabolism, by modifying cellular permeability, or by counteracting a "mineralo-corticoid" type of response remain a matter of theoretical consideration.

Irrespective of theoretical speculations, a number of practical considerations are germane in the therapeutic application of anti-inflammatory steroids: (1) Their influence is not specific against any one disease or group of diseases. Any specificity they possess is against some yet unidentified factor common to a number of disease states. (2) They do not destroy pathogenic organisms or directly antagonize toxins, allergens or other noxious agents. Rather, their benefits seem to depend on an ability to modify tissue reactions to adverse stimuli. (3) Their action is not curative, but in responsive self-limited conditions they may restrain pathologic processes while the disease runs its course or undergoes remission. (4) Most of their effects, favorable and unfavorable, are temporary. In chronic diseases such as rheumatoid arthritis, for example, therapeutic benefits depend, therefore, on more or less continuous administration. (5) Even with continued treatment, successful control of chronic inflammatory or allergic manifestations may not be preserved indefinitely because some patients become relatively refractory to the drugs after they have been used for extended periods. (6) Steroid therapy frequently fails to halt progression of the disease process itself even while symptomatic relief and increased functional capacity are being maintained. (7) Each of the available anti-inflammatory steroids promotes, in addition to its antirheumatic effect, a variety of other physiologic actions. Many of these are undesirable, producing unwanted reactions, sometimes dangerous complications, which serve as obstacles to successful management. (8) A number of pathologic conditions may be aggravated by steroid administration, and when these coexist they set up relative or absolute contraindications for treatment. (9) Protracted use of them causes functional depression of the patient's adrenal cortices—and, although reversible, this creates a potential hazard that requires the application of special protective measures during periods of extraordinary stress.

Thus, it is obvious that the adrenal cortical hormones have many shortcomings as suppressive agents for chronic inflammatory diseases. But they also have distinct attributes and constitute the only therapeutic weapons now available that have the capacity to inhibit rapidly the signs and symptoms of certain inflammatory disorders. When properly prescribed, they allow rehabilitation for useful occupation in a high proportion of patients with rheumatoid arthritis and related collagen diseases; and in many such patients successful control cannot be accomplished by other existing means.

The principles that govern systemic steroid administration vary with the nature and severity of the disease concerned. In acute, self-limited conditions such as rheumatic fever, for example, large doses are necessary for the suppression of the inflammatory process; but the hazards are not great because treatment is for a relatively short period. Again, during crises of disseminated lupus erythematosus, massive doses may be required; but these may be life-saving and the risks from the drug may be distinctly less than the risk of uncontrolled disease. The many ramifications of steroid therapy cannot be discussed in this short communication, so my remarks will be confined to prolonged uninterrupted therapy in chronic disorders such as rheumatoid arthritis.

The basic policy should be to promote and sustain a degree of disease suppression which is optimal for the individual patient—that is, to provide improvement with dosages that are consistent with the avoidance of significant hormonal complications. A number of lessons gained from experience and which may serve as helpful guides may be enumerated as follows:

1. Satisfactory improvement cannot be expected for all patients. The dosage requirements for adequate control are often larger than can be tolerated, especially when the disease is severe or very active. In such circumstances patients must settle for results which, although worthwhile, are less than desired.

2. Complete inhibition of the disease should not be sought—rather, both the patient and the physi-

cian must be satisfied with the improvement which can be obtained with so-called safe dosage levels.

3. Initial doses should not be too large or continued too long. The achievement of rheumatic control in a leisurely fashion, with dosages close to the estimated maintenance level, will often prevent unwanted reactions from the beginning. It is better to avoid the drama from early "overcharging" than to struggle with complications thereafter.

4. Reductions from initial suppressive to smaller maintenance doses should be made slowly, and by small decrements. Sudden reductions in dosage often result in loss of clinical control.

5. Dosage should be determined principally on the basis of clinical improvement and the occurrence of undesirable side-effects. The erythrocyte sedimentation rate and other laboratory tests are not reliable gauges.

6. Maintenance doses, once established, should be considered as relative, not fixed. Disease activity may wax and wane, and dosages must be altered accordingly. Adjustments of dosage should be made by small changes, not by large or erratic swings in dosage.

7. Maintenance requirements vary in individual cases, but the amounts needed depend more on the activity of the process and on the physical or emotional stress to which the patient is subjected than on other factors. Successful management may depend as much on proper regulation of the patient's activities as on proper manipulation of medication.

8. Steroids should be prescribed in divided doses because available preparations are absorbed quickly and the effects dissipated rapidly. Proper division of dosage such as two to four times a day (following meals and at bedtime) provides more even control and minimizes the total daily requirement.

9. Some patients who have been well controlled for prolonged periods may eventually become relatively refractory; improvement may deteriorate despite increasing and finally prohibitive amounts of steroid. In such instances responsiveness may return if the drug is gradually withdrawn and a treatment-free period of two or three months is allowed.

10. When, for any reason, steroid therapy is discontinued, the dosage should be tapered off slowly to prevent withdrawal symptoms (such as weakness, fatigue, lowered resistance to stress, sudden flare-up of joint inflammation, etc.). Generally it is best to gradually wean the patient from treatment over a period of two to three months.

The results of hydrocortisone therapy in a group of 150 rheumatoid patients treated continuously for two years or more were compiled in 1954.[1] Although far better than in the presteroid era, the overall results left much to be desired. Less than 60 per cent of cases were considered adequately controlled at the end of two years, and the proportion decreased to approximately 50 per cent at the end of three years. As might be expected, results were poorest among patients with more severe disease whose dosage requirements for good control were greater than could be tolerated, and statistically the improvement status tended to deteriorate as treatment was prolonged. The major deterrent to more successful management was the development of unwanted side-effects from the hormone, the appearance of which necessitated dosage restriction to suboptimally effective levels.

The obvious limitations of hydrocortisone and cortisone as treatment agents led chemists and clinicians to search for more efficient antiphlogistic drugs. Since 1953, the molecular structure of the natural hormones has been modified in many ways with the hope of fabricating artificial steroids which would possess higher therapeutic indices. That steroids with superior effectiveness might be synthesized was suggested by the knowledge that various modifications in chemical structure were capable of altering anti-inflammatory potency of cortisone and hydrocortisone and, more importantly, that certain chemical changes could selectively amplify or attenuate one or more of those accessory biologic properties that create unwanted and impeding side-effects.

Some of the ingenious chemical changes that have been made and which have led to the development of compounds of direct or indirect therapeutic interest are shown in Figure 1. They are: Fluorination at C-9 and at C-6; dehydrogenation at C-1—C-2 and at C-6—C-7; methylation at C-2, at C-6, and C-16, and C-21; dehydrogenation at C-21; hydroxylation at C-16; and desoxygenation at C-21. Many analogues have been fashioned by making one or more of these changes. We have tested the effectiveness of 33 different steroid compounds during the past ten years, and eight of these compounds have been made avail-

TABLE 1.—*Analogues of Hydrocortisone and Cortisone Available Commercially*

	Potency Times Prednisolone (Av.)	Prudent Dosage Range (MG Per Day)
Prednisone (Meticorten)	1.0	2.5-10.0
Prednisolone (Meticortelone)	1.0	2.5-10.0
Methylprednisolone (Medrol)	1.2	2.0- 8.0
Triamcinolone (Aristocort: Kenacort)	1.2	2.0- 8.0
Dexamethasone (Decadron: Deronil)	7.0	0.5- 1.5
Betamethasone (Celestone)	7.0	0.5- 1.5
Fluprednisolone (Alphadrol)	2.5	2.5- 5.0
Paramethasone (Haldrone)	2.5	2.0- 5.0

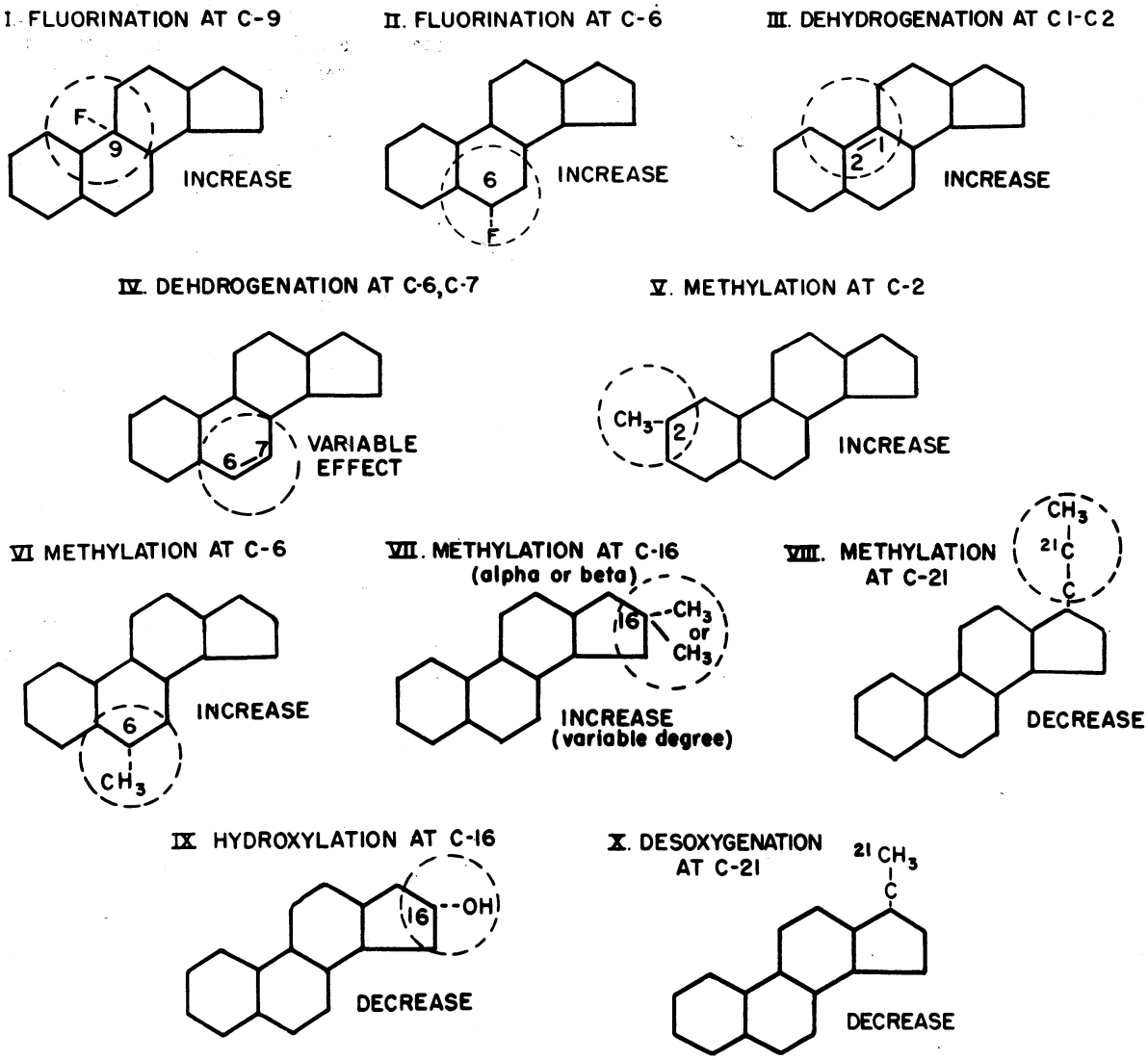


Figure 1.—Influence of certain individual structural alterations on antirheumatic potency (general).

able commercially. In general, each of them promotes a similar pattern of improvement when given in doses of comparable antirheumatic potency. They differ in antirheumatic activity, and they display qualitative differences in one or several physiologic properties. But no one preparation exhibits consistent advantages, and none is divested of the major inherent limitations of corticosteroid therapy. (See Figure 2.)

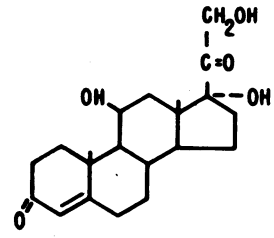
The compounds which have been marketed and their relative antirheumatic strengths per milligram are shown in Table 1. The potencies of prednisone and prednisolone are similar and, on average, are approximately four times greater than hydrocortisone. Methylprednisolone and triamcinolone are approximately 20 per cent more potent than prednisolone, and the strengths of dexamethasone and betamethasone are about seven times greater. Fluprednisolone and paramethasone occupy intermediate positions, having potencies that are roughly two and one half times greater than that of prednisolone.[2]

But antirheumatic potency is not synonymous with therapeutic efficiency. This depends on the maintenance of adequate improvement in relation to the development of undesirable effects and complications, not on the number of milligrams required per day. Hence a word is in order regarding the relative merits of each of these steroids, based on long-term treatment studies.[3]

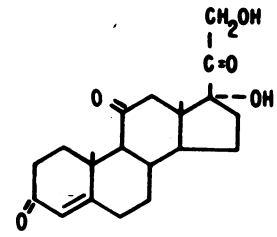
Prednisolone and Prednisone: These analogues differ from hydrocortisone and cortisone, respectively, by the presence of a double bond between the first and second carbon positions. This change enhances anti-inflammatory potency and glycogen deposition without causing a corresponding increase in electrolyte activity. Of interest is the fact that each

synthetic analogue that has been marketed has contained this modification.

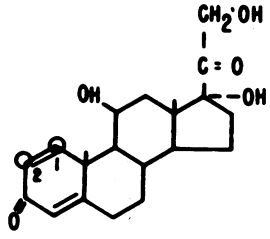
Our observations with prednisone and prednisolone in a series of 400 rheumatoid patients treated over a five-year period indicate that their therapeutic indices are greater than those of the parent compounds. Their antirheumatic potency per milligram is approximately four times greater than that of hy-



HYDROCORTISONE

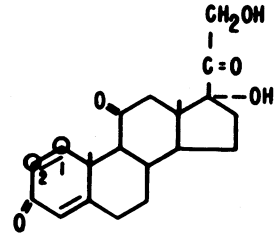


CORTISONE



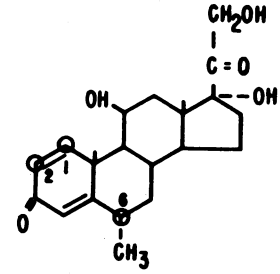
PREDNISOLONE

(Δ¹-hydrocortisone)



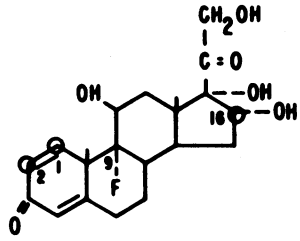
PREDNISONE

(Δ¹-cortisone)



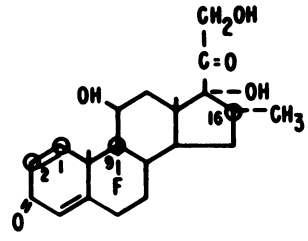
METHYL PREDNISOLONE

(6α-methylprednisolone)



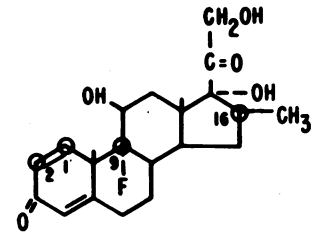
TRIAMCINOLONE

(16α-hydroxy, 9α fluoroprednisolone)



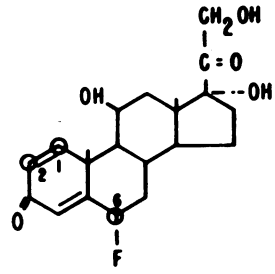
DEXAMETHASONE

(16α-methyl, 9α fluoroprednisolone)



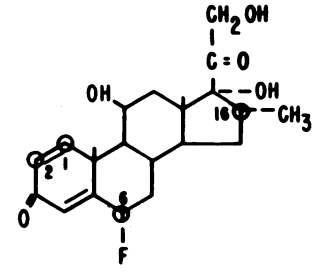
BETAMETHASONE

(16β-methyl, 9α fluoroprednisolone)



FLUPREDNISOLONE

(6α-fluoroprednisolone)



PARAMETHASONE

(16α-methyl, 6α fluoroprednisolone)

Figure 2.—Chemically modified adrenocortical steroids of therapeutic interest for systemic administration.

drocortisone, and, accordingly, substantially smaller milligram dosages are required. It has been clearly demonstrated that prednisone and prednisolone are capable of maintaining satisfactory response among patients who are amenable to hydrocortisone therapy. Furthermore, a substantial number of patients in whom improvement had deteriorated during hydrocortisone therapy regained and maintained adequate improvement status after a switch was made to prednisolone. The attainment of higher levels of improvement with the analogues can be attributed in many, but not all patients, to the fact that an absence of salt and water retention permits the use of more effective doses.

Prednisone and prednisolone differ from hydrocortisone in their proclivity for individual unwanted effects. The incidence of salt and water retention and raised blood pressure are distinctly less. Conversely, digestive complaints, peptic ulcers, vasomotor symptoms, and cutaneous ecchymoses develop more frequently. Other undesirable reactions, such as facial mooning, fat pads, nervous excitation, hypertrichosis, acne, skin tags, disturbances in glucose tolerance and osteoporosis, seem to appear with similar frequency when comparable antirheumatic doses are prescribed. It has been shown that the incidence of digestive complaints and of roentgenographically identified ulcers is substantially reduced when nonabsorbable antacids are taken with each dose of the drugs, and with combined administration the incidences are then no greater than during hydrocortisone administration.

Like most investigators, we prefer prednisone or prednisolone to hydrocortisone and cortisone for rheumatoid patients requiring steroid therapy. The reasons for this choice are their lower tendency to produce salt and water retention and potassium loss, their ability to restore improvement in a significant percentage of patients after improvement from hydrocortisone has deteriorated, and the better statistical results on long-term administration.

Methylprednisolone: In 1955 a series of steroids containing a methyl grouping at the sixth carbon atom were synthesized. The substitution was found to potentiate anti-inflammatory activity as measured by the granuloma pouch technique and without increasing electrolyte activity. One of these compounds, 6-methylprednisolone, was subsequently introduced commercially. Its structure differs from prednisolone only by the presence of a methyl radical at C-6.

During 1956 and 1957, in collaboration with Doctor Grant Liddle of Vanderbilt University, we appraised the metabolic and antirheumatic effects of methylprednisolone. Our conclusions were that the analogue was a satisfactory antirheumatic agent, but that it did not exhibit clear-cut advantages or disadvantages over prednisolone. Its antirheumatic potency is approximately 20 per cent greater than that of prednisolone, and therefore proportionately smaller milligram doses are required. However, when equivalently potent doses of the two drugs are given, clinical improvement is upheld equally well on long-term administration, and the unwanted reductions that intrude are similar in kind and degree.

Triamcinolone: In 1956 another series of compounds were introduced, and these contained a hydroxyl group at the sixteenth carbon position. This modification lessened anti-inflammatory potency but reduced electrolyte activity much more drastically. Importantly, it eliminated the severe sodium retention that results from adding a fluorine atom at C-9 and allowed 9-fluorinated compounds to be used therapeutically for the first time. Triamcinolone is a complex steroid which differs chemically from prednisolone in two details: the addition of an hydroxyl radical at C-16 and of a fluorine atom at C-9.

On a weight for weight basis, the antirheumatic potency of triamcinolone is somewhat greater (about 20 per cent, on average) than the potency of prednisolone, and is about equal to that of methylprednisolone. At dosage levels up to 12 mg a day, the compound does not cause sodium retention—in fact, it may induce sodium and water diuresis. Edema of even a slight degree is rarely seen—and the drug does not tend to produce or aggravate arterial hypertension. It has less tendency than other steroid preparations to appetite stimulation, and it frequently causes anorexia and loss of weight.

In our experience, the proportion of patients who are maintained satisfactorily for long periods on triamcinolone is distinctly smaller than with prednisolone and methylprednisolone. This is due principally to the fact that troublesome side-effects peculiar to the drug frequently intrude during the course of treatment and make the transfer to another steroid necessary or prudent. Actually it was found advisable to discontinue triamcinolone in approximately 25 per cent of our patients who received the drug as initial treatment and in over 30 per cent of those who were switched to it from prednisolone. Among the unique unwanted effects of triamcinolone are anorexia, loss of weight (sometimes with notable wasting of subcutaneous and muscle tissue), muscle weakness, leg cramps, nausea, cutaneous erythema, dryness and burning sensations, generalized fatigue, and dizziness. The occurrence rates for some of these have been considerable: Anorexia in 10 per cent, muscle weakness in 16 per cent, and pronounced loss of weight in 18 per cent. These peculiar effects have been troublesome enough to discourage routine use of triamcinolone for rheumatoid patients

requiring steroid therapy. In our opinion, the drug may be employed to best advantage as a "special purpose" steroid. It should be reserved for selected situations, such as when salt and water retention develops from other steroids or from cardiac decompensation, or when excessive appetite and weight gain are problems in management.

Dexamethasone and Betamethasone: In 1958 a family of analogues containing in common a methyl grouping at C-16 was synthesized. This substitution, like 16-hydroxylation, decidedly reduces the salt retaining property of 9-fluorinated compounds; but, unlike 16-hydroxylation, the methyl substitution does not reduce anti-inflammatory potency. Dexamethasone differs from prednisolone by the presence of a methyl group at C-16 and a fluorine at C-9. The methyl group is attached at the alpha position of C-16; a point is made of this because subsequently another steroid, betamethasone, was introduced which has the grouping placed at the beta position. Despite claims to the contrary, betamethasone does not, in our clinical experience, differ significantly in any respect from dexamethasone.

Dexamethasone is approximately seven times as potent as prednisolone in anti-inflammatory activity and is effective in remarkably small milligram doses —amounts ranging from 0.5 to 1.5 mg a day.

The overall incidence of adverse reactions from the drug is considerably higher than from prednisolone, and certain unwanted effects are frequent and troublesome. The drug is more inclined than prednisolone to cause excessive appetite, excessive gain in weight, increased abdominal girth, abdominal bloating and distention, ecchymotic skin lesions and thinning of the skin. These unwanted effects were sufficiently pronounced to warrant switching to another steroid in over one-third of our patients.

Although dexamethasone has greater biologic potency than prednisolone, our observations made during the past five years have led us to the conclusion that its general therapeutic efficiency is distinctly less than that of prednisolone and methylprednisolone. We do not employ it as a general purpose steroid, but, instead, restrict its use to a very few special situations—as when refractoriness may prompt a change of medication to another steroid or when appetite stimulation and weight gain are desired and cannot be obtained with other compounds.

Fluprednisolone: In 1958 a number of compounds containing 6-fluoro substitutions were synthesized. This modification intensifies anti-inflammatory activity, but unlike 9-fluorination it does not disturb electrolyte metabolism. One of these compounds, fluprednisolone, has antirheumatic activity which is approximately two and a half times greater than that of prednisolone. With maintenance dosages ranging from 2 to 5 mg a day, the steroid has proved to be a satisfactory antirheumatic agent. Its therapeutic index is at least equal to that of prednisolone: It appears to have even less proclivity for salt and water retention, and perhaps has slightly less tendency to promote appetite stimulation, weight gain and abnormal fat deposition.

Paramethasone: Paramethasone is the last synthetic analogue that has been marketed. It differs chemically from fluprednisolone only by the addition of a methyl radical at C-16. Paramethasone is slightly more potent than fluprednisolone, but otherwise its effects are similar. In our experience it appears to have a slightly greater tendency than fluprednisolone or prednisolone to bring about weight gain and abnormal fat deposition.

In summary, our experience with the eight antirheumatic modified corticosteroid analogues now available would indicate that none of them satisfies the criteria for an ideal suppressive agent for rheumatoid arthritis and other steroid-responsive conditions. Some of the compounds exhibit qualitative differences in one or another physiological action, but the major deterrent features of corticosteroids are shared by each of them. Prednisone, prednisolone, methylprednisolone, fluprednisolone, and paramethasone seem to have similar therapeutic indices; and there appears to be little to choose between them for the ordinary patient who requires steroid therapy. Conversely, because they produce unique reactions of their own and because they have greater proclivity to promote certain troublesome hormonal side-effects, the therapeutic indices of dexamethasone, betamethasone, and triamcinolone are lower than that of prednisolone; they are less desirable for routine use and are best employed for selected cases as "special purpose" steroids.

Most adverse reactions (weight gain, abnormal fat deposits, hypertrichosis, and the like) are avoided or kept to within acceptable degrees by using minimally effective dosages, and in rheumatoid arthritis we rarely exceed 5.0 mg of prednisolone a day in moderate cases, 7.5 mg in moderately severe cases or 10.0 mg in severe cases. The appearance of edema is usually readily controlled by dietary sodium restriction or administration of chlorothiazide. Digestive complications usually can be avoided by giving the drugs after meals and combined with nonabsorbable alkalis. Symptoms of hypokalemia (weakness, fatigue, mental aberrations) are rarely encountered and may be combated by the administration of potassium salts in dosages of 3 to 5 gm a day. Shock resulting from adrenal insufficiency during periods of stress, such as a major surgical procedure or acute infection, may

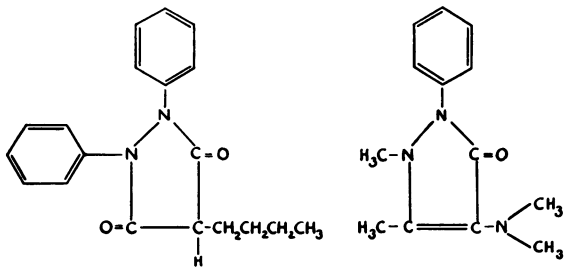


Figure 3.—Chemical structure of phenylbutazone and aminopyrine.

be avoided by fortifying the patient with extra steroid medication. It is our custom, for example, to administer 100 mg of cortisone acetate intramuscularly 24 hours before and again on the day of the surgical operation to all patients who are on steroid therapy. With such a schedule we have had no deaths due to adrenal insufficiency in over 70 patients subjected to major surgical procedures.

Among our rheumatoid patients who have received steroid therapy continuously for years, the most troublesome complications have consisted of osteoporosis and pathologic fractures (especially of the spine), increased capillary fragility and ecchymotic lesions, thinning and friability of the skin, and delayed wound healing. We have found no satisfactory way of combating these complications of cellular catabolism other than withdrawing steroids or reducing the dosage. High protein diets, complemental calcium, and the administration of anabolic sex hormones may be of value, but the effects of these measures are most difficult to measure. Rarely has vasculitis or peripheral neuropathy developed in patients we were treating, which is fortunate because these complications are serious and particularly refractory to treatment.

SALICYLATES

Salicylates, and particularly acetylsalicylic acid or aspirin, are the most commonly employed analgesic and antipyretic drugs in medicine. For the past 75 years they have been universally employed for the relief of the pain, aching and stiffness that characterize many rheumatic disorders. It has been amply demonstrated that salicylates administered in large doses have anti-inflammatory activity but not so much as adrenocortical hormones and their analogues, corticotropin and phenylbutazone. In animals acetylsalicylic acid will delay the erythema induced by ultra-violet light, will inhibit the exudative reaction of turpentine-induced pleurisy, and will lessen the capillary permeability that is ordinarily provoked by a variety of irritants. The mechanisms by which salicylates exert anti-inflammatory action are not entirely known, but presumably they involve the inhibition of certain enzyme systems and the suppression of vascular reactivity.

A number of authorities still prefer salicylates to adrenocortical steroids in the treatment of the ordinary patient with rheumatic fever. Steroid therapy is reserved by them for patients whose articular and febrile reactions cannot be symptomatically controlled by full doses of salicylates and for patients with clinical evidence of significant carditis. Ninety per cent of patients without signs of carditis during the acute attack recover without having clinical evidence of rheumatic heart disease. These are patients whose predominant manifestations are acute polyarthritis and they usually respond adequately to large oral doses of salicylates. Initial doses of 10 gm (150 grains) of acetylsalicylic acid per day are recommended for patients weighing 70 kilograms (150 pounds) or more, and proportionately smaller doses for patients weighing less. It is important that the total daily amount be divided into six doses given every four hours in order to maintain adequate blood levels of salicylate. Large doses should be continued until there is complete relief from the arthritis and until the temperature has returned to normal; dosage should then be reduced gradually over a period of days or weeks. Toxic symptoms (tinnitus, coloring of vision, nausea, impaired hearing, mental confusion) are not uncommon with high dosage and may force reduction in dosage before the desired response has occurred. In such circumstances the substitution or the addition of adrenocortical steroid therapy is in order.

Salicylates are the mainstays for the relief of pain in patients with rheumatoid arthritis. Aspirin or sodium salicylate is usually prescribed in doses of 0.3 to 0.6 gm (5 to 10 grains) four to six times a day. In these amounts it is probable that the anti-inflammatory effect is slight, but larger doses are not recommended for prolonged continuous use in a chronic disease such as rheumatoid arthritis. The concomitant ingestion of nonabsorbable antacids and the taking of the drug after meals or with milk reduces the incidence of gastritis and activation of peptic ulcers. There is no good evidence that various combinations with antacids increase the effectiveness or rate of absorption of salicylates.

PHENYLBUTAZONE AND OXYPHENYLBUTAZONE

Since its clinical introduction in 1951, phenylbutazone has established itself as a successful anti-inflammatory and analgesic agent in several conditions affecting the musculoskeletal system, especially

acute gouty arthritis and ankylosing (rheumatoid) spondylitis. The drug, better known as Butazolidin,® is a pyrazol and is related to aminopyrine (Figure 3). Actually it was first employed as a solubolizing agent for aminopyrine and only later was found to have inherent therapeutic effects of its own. Like other pyrazole compounds it exerts several biologic effects. The anti-inflammatory quality of phenylbutazone has been amply demonstrated in laboratory animals: it delays or inhibits the erythema that follows exposure to ultraviolet light, and it inhibits the edema which normally follows the injection of formalin or egg albumin into the paw of a rat. The drug is also capable of causing sodium retention and it exerts uricosuric action in both normal and gouty subjects.[4]

The anti-inflammatory action of phenylbutazone is best exemplified in acute gouty arthritis, and during the past few years it has made a fair bid to replace colchicine in treatment of an acute episode. Given early in an attack and in adequate dosage, it causes the pain of acute gouty arthritis to subside dramatically within a few hours (within 24 hours in 95 per cent of early cases), and the signs of inflammation usually resolve within 24 to 72 hours. In well established attacks, when the synovitis has existed for several days, the response is slower and may not be complete for seven to fourteen days.

Our usual program for administering phenylbutazone orally in acute gouty arthritis is to prescribe a large initial dose of 400 to 600 mg, followed by 200 mg every two hours for two or three doses, so that a total of 1,000 mg is given during the first 24-hour period. Beginning on the second day and continuing until the inflammation has subsided, 100 mg is prescribed two to four times a day, depending on the severity of the attack and the response to the drug. Noxious side effects (diarrhea, nausea and vomiting) which occur so commonly with full therapeutic doses of colchicine, are not a problem with phenylbutazone. An occasional patient experiences gastric irritation from large initial doses, and in such circumstances the drug may be administered intramuscularly. The intragluteal injection of 500 to 1,000 mg early in an attack dramatically aborts or suppresses the inflammatory reaction. Given infrequently and for short periods, such as for an acute gouty attack, phenylbutazone rarely produces toxic reactions.

The drug has proved to be very useful in the symptomatic control of ankylosing (rheumatoid) spondylitis, and here again it appears to exert anti-inflammatory action. It is much more effective in spondylitis than in peripheral rheumatoid arthritis, and may even afford worthwhile relief in advanced cases in which ankylosis is present. Patients who respond well during the first six months of administration usually continue to do so over long periods. In our experience the results in peripheral rheumatoid arthritis from the small doses (100 to 200 mg a day) of phenylbutazone that can be tolerated on continued administration are unimpressive; rarely is a true anti-inflammatory response noted, and the degree of analgesia that results is usually not sufficient to warrant the risks involved.

With long-term phenylbutazone therapy, total daily doses should not exceed 200 to 300 mg, as the incidence of toxic reactions is decidedly greater when higher dosage is used. Some spondylitic patients respond symptomatically to doses of 100 mg a day. If larger amounts (400 to 800 mg a day) are required to quell a temporary exacerbation, they should be employed for only a few days at a time. The physician must be thoroughly familiar with the drug's potential toxic effects and be ready to discontinue its administration or to lower the dosage if they appear. He must be particularly vigilant for such reactions as skin rash, indigestion and symptoms of peptic ulcer (including bleeding), fluid retention, suppression of hemopoiesis (agranulocytosis, aplastic anemia) and hepatitis. Blood cell examination should be done routinely each month during continuous therapy, and nonabsorbable alkalis should be ingested with each dose of the drug.

Favorable anti-inflammatory action from phenylbutazone has been reported in acute rheumatic fever and in superficial thrombophlebitis, but we have had no personal experience with the drug in the first and very limited experience in the second condition.

During the past four years, oxyphenylbutazone, a metabolite of phenylbutazone, has been introduced commercially under the trade name of Tandearil.® It was hoped that fewer unwanted side-effects would be produced by the derivative, but the results of carefully controlled studies indicate that phenylbutazone and oxyphenylbutazone do not differ significantly in either their ameliorating effects or toxicity.

COLCHICINE

Colchicum is perhaps the oldest anti-inflammatory drug in medicine, having been used by Byzantine physicians as early as the fifth century. Its alkaloid, colchicine, acts specifically in suppressing the inflammatory reaction of acute gouty arthritis, and the drug does not antagonize any other form of inflammation. The mechanism of its action in acute gouty arthritis is unknown: it exerts no effect on the production or excretion of uric acid; it does not influence the solubility of sodium urate in the plasma; it has no effect on adrenocortical function;

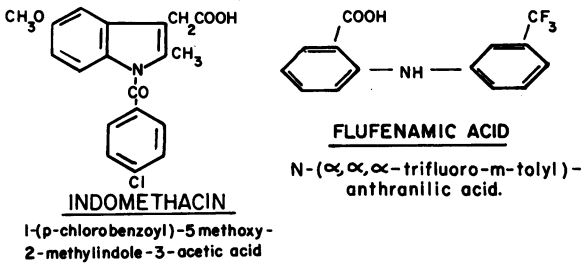


Figure 4.—Chemical structure of indomethacin and flufenamic acid.

and, insofar as can be determined, its anti-gout activity is unrelated to its antimytotic properties.

The response of acute gouty arthritis is usually dramatic if the drug is given early and in proper dosage. The specificity of its action makes colchicine of value both diagnostically and therapeutically. Joint pain, tenderness, redness and swelling usually begin to subside within 12 hours after therapy is begun, and in most instances pain is completely relieved after 24 to 72 hours. Acute bouts are considerably diminished in 80 or 85 per cent of cases by a single course of the drug, but the response rate is considerably less if treatment is delayed for several days after an attack has been established. Today authorities are divided in their preference of colchicine or phenylbutazone for treatment of the acute attack. Suffice it to say that phenylbutazone has successfully rivaled colchicine as the drug of choice in recent years, and phenylbutazone is usually effective in those cases that do not respond to colchicine.

For an acute attack we usually advise that 0.65 mg (1/100 grain) of colchicine be given orally every hour for 8 to 12 doses or until the occurrence of nausea, vomiting or diarrhea. Many patients learn by experience the optimum number of tablets necessary to relieve an attack, and by taking one or two tablets short of toxic effects they avoid undesirable gastrointestinal symptoms.

For patients who, for one reason or another, cannot take the drug orally, colchicine may be given intravenously. If the dosage by this route does not exceed 3 mg, gastrointestinal symptoms are usually obviated. It is our custom to give a second intravenous dose of 3 or 2 mg after 12 or 24 hours.

During the past few years a number of colchicine analogues have been prepared and evaluated. Of these, desacetylmethylcolchicine and desacetylthiocolchicine are effective for acute gouty episodes and have considerably less gastrointestinal toxicity. These drugs should not be considered as satisfactory alternative agents, however, because they have much greater tendency than colchicine to produce agranulocytosis and loss of hair.

EXPERIMENTAL NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

During the past five years a number of nonsteroidal compounds with anti-inflammatory activity, as demonstrated by animal testing, have been tried clinically in patients with rheumatic disease. The most promising of these has been a series of indole preparations, one of which, known as indomethacin (MK-615), has been investigated extensively in many centers. Another family of compounds which is now being assessed for anti-inflammatory, analgesic and antipyretic properties is represented by flufenamic acid (Figure 4).

Indomethacin has shown anti-inflammatory activity in rats by the cotton-pellet granuloma-inhibition test and by its capacity to suppress the edema that usually results from the subplantar injection of irritating agents. The level of its activity may be compared with that of phenylbutazone, and toxic effects from oral administration to animals have consisted of gastrointestinal irritation for the most part. Chemically, indomethacin is 1-(p-chlorobenzoyl) -5-methoxy-2-methylindol-3-acetic acid (Figure 4).

Our clinical experience with indomethacin embraces a total of 119 patients with various types of rheumatic disease who were treated for varying periods (from 1 to 18 months) and with oral dosage ranging from 50 to 200 mg a day. Among patients with osteoarthritis, chronic tendinitis and bursitis, the results have been disappointing, and the majority so afflicted have noticed no difference when placebos were given. Among 51 patients with active peripheral rheumatoid arthritis, most of whom received 100 to 200 mg per day, the influence of the drug on subjective complaints as well as on lessening of the measurable objective manifestations of the disease has been inconclusive. An occasional patient with mild or moderate disease activity has responded well, but even among these less severe cases objective evidences of significant antirheumatic action have been witnessed irregularly and unpredictably. Among corticosteroid-treated patients the concomitant administration of indomethacin has only occasionally allowed reduction of maintenance dosage of the steroid. Conversely, indomethacin in dosages of 100 to 200 mg a day has proved to be quite effective in reducing the subjective complaints of ankylosing (rheumatoid) spondylitis, and its ameliorating influence might eventually prove comparable to that of phenylbutazone in this condition.

In the experience of some investigators, attacks of acute gouty arthritis respond rapidly to indomethacin given in dosages of 400 to 600 mg during the first 24 hours. Reportedly, the benefits derived compare favorably with those observed from phenylbutazone and colchicine. We have had no experience with the drug in acute gouty arthritis because

we have been unwilling to risk dosages that exceed 200 mg a day.

Adverse effects from indomethacin are frequent, and their occurrence limits the usefulness of the drug. With daily dosages of 100 to 200 mg a day, headaches, dizziness or drowsiness have been the most common side effects noticed.[5] Gastric irritation has been common, and in five of our patients roentgenographically demonstrable gastric ulcers developed. Four of the five were treated simultaneously with oral adrenocortical steroids while one patient with a severe hemorrhagic ulcer received indomethacin only.

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