NONSTEROID ANTI-INFLAMMATORY AGENTS

By Charles A. Winter
Merck Institute for Therapeutic Research, West Point, Pennsylvania

The treatment of rheumatic diseases by anti-inflammatory drugs is a recent development, except for the use of salicylates. The use of cortisone and of phenylbutazone dates from about the same time (93, 233), with the first publications in 1949. For more than a decade thereafter, attention in the anti-inflammatory field was focused mostly upon steroids. Some of the newer synthetic steroids, such as prednisolone, dexamethasone, and many others, are far more potent than any of those occurring naturally.

A similar increase in potency among nonsteroid anti-inflammatory compounds has not appeared until recently. During the 1960's, interest in this field has increased at an accelerating pace. Several new compounds have appeared in clinical trial, and a few of them have reached the market. The literature is growing at such a pace that any review is bound to be out of date by the time it reaches print. The present review selects some of the papers which came to this reviewer's attention up to the end of June 1965. A longer and more detailed discussion by the present author is in press (246). A review covering in detail the biochemical aspects of anti-inflammatory drug action has recently appeared (230). The latter was prepared by Dr. Whitehouse, of Oxford University, and deserves careful reading by anyone attempting to work in this field. A brief survey of certain very limited aspects of the subject has also recently been published (192).

Possible Sites of Action

The dynamic process which manifests itself as a succession of changes occurring in irritated or damaged tissue offers a number of points of attack for the pharmacologist seeking to inhibit the inflammation. This has led to a multiplicity of methods of testing for anti-inflammatory activity, and it is rather remarkable that drugs useful in the amelioration of rheumatic symptoms have been developed from such a wide variety of testing methods. Some of the possible mechanisms of action of anti-inflammatory drugs may be listed.

Blood vessel walls.—A compound might stabilize the walls of the small blood vessels, preventing the increase in permeability which occurs early in inflammation. This action alone probably would not provide a generally useful anti-inflammatory drug; Halpern (86) has shown that promethazine was quite active in this respect, yet it has not found a place in the anti-rheumatic therapy.

Mediators of inflammation.—A similar effect might be obtained by antagonizing chemical substances which, when released, act as mediators in increasing permeability of the small vessels. In general, antagonists to

these substances have not made an impression as anti-inflammatory drugs of more than special application. An inhibitor of the histidine decarboxylase system postulated by Schayer (172, 173) might have a similarly limited usefulness.

Rocha e Silva (164) suggested that the problem of anti-inflammatory therapy might be solved by finding a very potent antibradykinin agent. Inhibitory effects on "45° thermic edema" were correlated with antibradykinin activity in a number of compounds, but none of them came under the category commonly called "anti-inflammatory" drugs. If thermic edema is due to bradykinin release, as seems apparent from Rocha e Silva's data, such correlation would be expected. Certain anti-inflammatory drugs antagonize some of the actions of bradykinin (55, 56, 57, 125), but Lewis (126) argued that bradykinin is probably not involved in inflammation, since aspirin and related compounds do not antagonize those actions of bradykinin that it would if bradykinin were involved.

Catecholamines (or more specifically epinephrine) are regarded by some as endogenous anti-inflammatory substances; the evidence in favor of this view has been summarized by Spector & Willoughby (188-191, 236, 237). Some of Northover's findings may be regarded as favorable to this view (148, 150), but some other findings, in the same papers, seem not to support it. Möller's direct measurement of catecholamines during inflammation (142) provided no evidence that the amines either promoted or inhibited inflammation. Evidence that epinephrine may be pro-inflammatory rather than anti-inflammatory has been summarized by Zweifach (259, 260). Rocha e Silva (164) suggested that the amines may play a role in inflammation as part of the process releasing bradykinin. Strom & Coffman (196) found the reactivity of small vessels in human subjects to epinephrine to be attenuated by aspirin. Smyth & Staub (186) found no evidence that changes in reactivity to catecholamines play a role in the pathogenesis of rheumatoid arthritis.

On the whole, the study of possible mediators in the inflammatory process has not led to drugs of general anti-inflammatory usefulness.

Leukocyte emigration.—Limiting the migration of leukocytes, or decreasing their phagocytic activity, might inhibit part of the inflammatory process. Leukocytic emigration may be inhibited by anti-inflammatory steroids (71). An evaluation of the ability of a compound to inhibit this effect has been proposed as a screening technique for antiphlogistic agents (101). Saxena (171) found cellular migration to be affected not only by anti-inflammatory agents but by a variety of other drugs as well. He expressed the view that the effect of a compound on cellular infiltration can be useful only as a supplement to other methods for anti-inflammatory testing.

According to Page (153), inhibitors of protein synthesis (actinomycin D, 6-mercaptopurine, and puromycin) block lymphocyte emigration into the inflammatory site, but these can scarcely be considered examples of anti-inflammatory drugs.

In gout, the leukocytes may actually play a part in exacerbating an inflammatory process. Seegmiller & Howell (176) envisage gouty inflammation as being due to the precipitation of microcrystals of sodium urate; leukocytes ingest the crystals; their metabolic activity becomes increased, with greater production of lactic acid, decrease in local pH, leading to further urate crystallization, thus completing a vicious cycle. Anti-inflammatory drugs diminish the inflammatory response to injected crystals in human volunteers (131). McCarty (133) has made similar observations and recently discussed in detail the significance of this research. The therapeutic response of acute gout to colchicine has been postulated to be due to interference by the drug of the metabolic processes of the leukocyte, probably interfering with the phagocytosis of the crystals, and thus interrupting the cycle (131).

Drugs discovered by testing their effects on capillary permeability might be different from those affecting the emigration or activity of leukocytes, since the two phenomena have been shown, under appropriate circumstances, to be different both in space and in time course (60).

Proteolytic enzymes.—Drugs might also act by limiting the release of proteolytic enzymes or by inhibiting their activity. A great deal has been written about the role of such enzymes in inflammation, and some about the effect of anti-inflammatory steroids upon them, but little about non-steroids in this respect. Fessel & Chrisman (74) obtained enzymes from human articular cartilage capable of degrading chondromucoprotein *in vitro* and suggested that the initial changes in osteoarthritis might be enzymatic rather than mechanical, and that the possibility of reversing these changes by chemical means should be investigated. This kind of approach would be a departure from screening for purely "anti-inflammatory" effect. Some sort of biochemical approach to the discovery of more effective anti-rheumatic drugs may well prove in the future to be more fruitful than merely looking for more and more potent drugs by the anti-inflammatory methods currently available, as we now have available compounds with satisfactorily high potencies according to present techniques.

Many authors recently have emphasized enzymal release when cells are disrupted or when they are subjected to various stimuli. Of especial interest is the lysosomal hypothesis. The existence of lysosomes as cytoplasmic organelles was postulated by de Duve (64) in 1955; various studies have indicated that they are disrupted during tissue injury or inflammation, with the release of injurious enzymes. Hypotheses suggesting that this is an important factor in the etiology of connective tissue disease have been elaborated by Dingle (66), Weissmann (226), Zvaifler (258), and others.

Reviews of the lysosomal hypothesis have appeared, with attempts to relate the observations to the various biochemical events in connective tissue disease (88, 120, 225). Local application of protein material extracted from lysosomes produces inflammation (105), and a nonantigenic material, streptolysin S, said to disrupt lysosomes more readily than other organelles,

was found to produce either acute or chronic arthritis when injected intra-articularly in rabbits (228). There is much to suggest that lysosomal injury may produce tissue damage; anti-inflammatory steroids are known to stabilize the lysosomes [references in (225)], with the site of action perhaps within the lysosomal membrane (224), and lysosomal stabilization has been suggested as a possible mechanism of action of adrenocortical steroids (66, 227). This postulated mechanism cannot be extended to include action of the nonsteroid anti-inflammatory agents; the only such agent that has been shown to stabilize lysosomes seems to be chloroquine (225), which is certainly not a typical anti-inflammatory drug (230). If the etiology of chronic inflammatory disease were simply a matter of disrupted lysosomes, the pharmacologist could screen compounds for their stabilizing properties. Unfortunately, there is no proof that this approach would yield useful drugs. Weiss & Dingle (224) wisely commented: "Considerable caution must be exercised when considering the results of these experiments in relation to the possible role of lysosomal enzymes in disease processes."

Quite different is the hypothesis suggested by Houck & Patel (103) that anti-inflammatory steroids may release a proteolytic enzyme from the extracellular compartment (not from lysosomes), and that this action may be related to the fibrinolysis of the thrombi which contribute to the microcirculatory insufficiency of inflamed wounds.

It may be worthy of comment that these hypotheses (sketchily presented) refer only to the mechanism of action of steroids. Steroids have many biochemical actions which the nonsteroids do not share; the actions of corticosteroids upon protein metabolism, for example, give us relatively little information from which to deduce the mechanism of action of nonsteroid compounds. A process which would be equally affected by both steroids and nonsteroids might yield valuable information about the inflammatory process, and perhaps be a better guide to the search for more effective compounds than would a process affected only by certain compounds.

Antigen-antibody reactions.—Drugs which inhibited the production of antibody, or prevented antigen-antibody union, or prevented the biological effects of antigen-antibody complexes might have potent antirheumatic activities. The notion that connective tissue disease, and specifically rheumatoid arthritis, may be of immune or autoimmune origin is widely held. The subject is far too complex for treatment within the space available here, and the reader is referred to the many excellent reviews and discussions that have appeared elsewhere (37, 52, 81, 137, 215, 256). Weissmann (226) has sought to relate the lysosomal hypothesis to autoimmunity by pointing out that proteins denatured by degradative enzymes released from lysosomes could well act as antigens which might induce antibodies directed against not only these antigens but related normal tissues. A not very dissimilar suggestion was elaborated by Zvaifler (258).

These suggestions are in accordance with the hypothesis of Hollander

and associates (98). Hollander supposes that the release of lysosomal enzymes is the result of an antigen-antibody reaction; i.e., a reaction between a rheumatoid factor and 7S gamma globulin. The resulting complex precipitates as a 22S particulate which is phagocytized by leukocytes; the lysosomes then are disrupted in the degenerating leukocytes, and tissue damage follows from the degradative action of the released enzymes. Particulate matter consistent with the hypothesis was said to have been identified in synovial fluid leukocytes of arthritic patients (159), and an acute inflammatory response was induced by injection of autologous purified 7S gamma globulin into the knees of patients known to harbor the rheumatoid factor (160).

If these are important factors in the etiology of joint disease, it is conceivable that one might attack the disease by finding a drug which would prevent the antigen-antibody union, and thus forestall the appearance of inflammation, rendering the use of an anti-inflammatory drug unnecessary.

Oxidative phosphorylation.—All the above supposed mechanisms for antirheumatic or anti-inflammatory activity might be combined into a single approach if one could find a good, single, unifying biochemical concept of connective tissue disease or of the action of antirheumatic drugs. In his recent review, Whitehouse (230) has discussed this at some length. He has advanced the hypothesis that the ability of antirheumatic compounds to uncouple oxidative phosphorylation may be such a unifying biochemical concept. The attacks that have been made on this view and Whitehouse's defense of his position are so thoroughly discussed in his review that we need do no more here than call attention to their existence. Whitehouse has indicated that this class of drugs might well come to be considered as "oxidative phosphorylation uncouplers" instead of "anti-inflammatory" or "antirheumatic" drugs, in the same way as the psychopharmacologists refer to "monoamine oxidase inhibitors." Unfortunately for this analogy, there are many compounds which share the psychopharmacological effects of monoamine oxidase inhibitors without being monoamine oxidase inhibitor compounds, and to the present author it seems equally tenuous to suppose that one can equate oxidative phosphorylation inhibition with anti-inflammatory activity until much more evidence is available.

Testing Methods

Locally induced edema.—New methods of testing for anti-inflammatory activity or modification of existing methods have appeared with increasing frequency within the past few years. Most attention has been paid to those early changes in acute inflammation which lead to a loss of fluid or leakage of protein.

The various substances used to produce local edema work by different mechanisms and give varying responses to drugs (245). To say that a compound inhibits "edema produced by an irritant" is, therefore, meaningless

for characterizing the overall anti-inflammatory effect of the drug, unless the irritant is specified and some comparison can be made with a compound of known activity. Increases in amino acid concentration following injection of various irritants are said to follow different time courses (111). The composition of edema fluid after topical application of xylene is said to change with time (9, 122, 200). The curves of swelling of the foot of the rat with respect to time differ after intraplantar injection of various edema-producing agents (245).

Several workers have proposed that the leakage of fluid and of plasma proteins are two separate mechanisms (61, 83); for example, Brown & Robson (34) observed a differentiation in the effect of diverse anti-inflammatory drugs on the coloring due to accumulation of injected dye in the inflamed ear of the mouse and the inhibition of swelling in the same ears. Studies of the extravasation of protein during local inflammation have usually involved labeling of plasma proteins; not all of these studies have involved the examination of the effects of drugs. Fluorescent labeling has been employed (251), as well as radioactive iodine (9, 115, 212, 223).

A more common method of labeling the plasma protein is to inject an animal intravenously with a dye which is bound to the protein (e.g., trypan blue, pontamine blue). Accumulation of dye in a locally inflamed area is used as an estimate of the degree of inflammation. This may be estimated subjectively (147, 148), or by extracting the dye and reading it colorimetrically (96, 109). In several recent papers, Northover (149–151) has produced an intraperitoneal irritation in animals previously injected with dye. The amount of dye that could be recovered from the peritoneal cavity in an hour was taken as a measure of "peritoneal permeability." Northover studied a large number of compounds and calculated values for "ED_{50}," i.e., the dose of drug reducing the optical extinction (dye concentration) by 50 per cent. The ED_{50} values listed for such compounds as aspirin, phenylbutazone, mefenamic acid, and flufenamic acid all seem to have been about the same. The inability to distinguish between compounds of differing potencies (according to other tests) may be a serious drawback to this technique as a screening method. In addition, the method is entirely insensitive to steroids. This may not seem an important consideration in looking for nonsteroid compounds, but it indicates that the method does not respond to some types of well established anti-inflammatory agents, and hence there might be a good chance of missing potentially useful compounds. Whittle's application of this technique (232) yielded an unrealistically high ED_{50} for phenylbutazone—200 mg/kg, which is within the grossly toxic range—and sodium acetylsalicylate was said to be twice as potent as phenylbutazone. These findings indicate a lack of applicability of this method for anti-inflammatory testing.

The method of Ungar, Kobrin & Sezesny (210), involving the weighing of a circle of skin after intradermal injection of "inflammatory-producing substances," and also used by Tommasini et al. (204) and by Jaquet (107),

has not been widely adopted, possibly because foot edema in the rat can be more easily and accurately measured. Many methods have been used in an attempt to measure edema induced in the rat's foot by injection of phlogistic substances; some of these have been listed by Domenjoz (69) and by Winder, Wax & Been (239). Some variety of plethysmometer (40, 69, 95, 239) seems to have been most widely used. The adaptation of the plethysmometer described by Winter, Risley & Nuss (248) was especially time-saving and objective. An electrical method employed by Kemper & Ameln (117) and by Niemegeers, Verbruggen & Janssen (143) also seems to be rapid and accurate, but has not been widely adopted.

Methods involving the inhibition of foot edema in rats have suffered from the tendency of a number of investigators to draw conclusions by results obtained when grossly toxic doses of drugs were injected intraperitoneally. Several authors have described nonspecific inhibition of foot edema or of granuloma formation when irritating substances are injected intraperitoneally (20, 35, 36, 62, 76), yielding misleading results with respect to the activities of compounds. Similar artifacts in analgesic testing have also been pointed out when the intraperitoneal route is employed (247).

Dextran, egg white, and formalin have been widely used to induce edema in the feet of rats; edema produced by these agents can be inhibited by anti-inflammatory steroids, by antihistaminic or antiserotonin compounds (69, 87, 113, 245), or by a variety of other agents which are not specifically anti-inflammatory (239), but not by nontoxic doses of phenylbutazone, indomethacin, or flufenamic acid (129, 197, 239, 245). Since the last three compounds are unquestionably active anti-inflammatory and antirheumatic agents, the phlogistic materials listed above may be considered to be unsuitable for screening for such compounds (129, 245).

Phlogistic agents that have been described as producing edema which can be inhibited by moderate doses of known anti-inflammatory agents include mustard powder (198, 245), kaolin (54, 95, 129, 213), and a finely powdered glass known as "aerosil" (214). Several laboratories have recently used carrageenan, a polysaccharide derived from *Chondrus,* Irish sea moss. The use of this substance to induce foot edema was introduced by Winter, Risley & Nuss (248); others have used it for stimulating the growth of connective tissue (10, 17, 45, 77, 94, 134, 136). Atkinson et al. (10) pointed out that not all samples of carrageenan are active phlogistic agents; active samples contain a type of galactan designated as λ-carrageenan (135, 136). The results obtained by Winter, Risley & Nuss (248) have been confirmed by others (7, 8, 143). Niemegeers, Verbruggen & Janssen (143) commented that all clinically active antirheumatic drugs seem to possess anticarrageenan activity. Edema produced by carrageenan is inhibited equally well by steroid and nonsteroid compounds, whether the phlogistic agent is injected into the foot (248) or the back (17). Numerous other substances have been used for local production of edema (6, 32, 99,

106, 119, 124, 193, 244), but data on the effects of anti-inflammatory drugs are not available for some of them. Pulmonary edema in mice also is said to respond to anti-inflammatory drugs (138a).

Erythema.—Erythema is another manifestation of inflammation which has been used for drug testing. Tetrahydrofurfuryl nicotinate when applied to the skin produces erythema in man or the guinea pig. In man, this erythema is highly sensitive to aspirin, but apparently not reliably so to other known antirheumatic drugs (5); in guinea pigs it responds to sodium salicylate or phenylbutazone (85). Most of the studies on erythema and its modification by anti-inflammatory drugs have used ultraviolet light as the irritant. Introduced by Schikoor (174) and applied to guinea pigs by Wilhelmi (233, 234), this method has been studied by a number of investigators (2, 3, 4, 33, 110, 240). Winder (240) made a particularly thorough analysis of the method, and achieved results with doses of phenylbutazone comparable to those effective in foot edema induced by kaolin or carrageenan. There are, however, some inconsistencies in the method. Anti-inflammatory drugs do not prevent the appearance of the erythema; they merely delay its appearance. Recent data (241, 242) indicate that the assay may be markedly affected by feeding or fasting the animals, or by the physical form of the administered drugs. Whitehouse (230) has pointed out a number of inconsistencies in the test, including the inactivity of steroids and of oxyphenbutazone. Certain metabolic enzyme inhibitors are highly active in the erythema test, with an apparent correlation between inhibition of erythema and inhibition of glycolysis and oxidation according to Görög & Szporny (82); the latter authors did not study known anti-inflammatory drugs, however. Salicylates are potent inhibitors of several enzymes of importance in intermediary metabolism (185, 229) and are also active against ultraviolet erythema (240).

Granuloma.—Inhibition of granuloma has also been widely used for anti-inflammatory testing. Granuloma growth may be stimulated by subcutaneous injection of an irritant such as carrageenan or turpentine (10, 205), by the well known granuloma pouch technique (162, 177), or by implantation of a pellet of cotton (138). The granuloma pouch technique, used mainly for testing steroids, has also been applied to nonsteroids (30, 123, 257). Granuloma growth may be inhibited by most of the antirheumatic drugs; chloroquine was active in the granuloma pouch but not against granuloma induced by the cotton pellet, according to Van Cauwenberge (211), but the data did not convincingly demonstrate inhibition in either test. The claim (1) that chloroquine inhibited granuloma in bacterially contaminated but not in sterile cotton pellets seems to have little relevance to anti-inflammatory testing. The introduction of an infection, either accidental or deliberate, adds a variable which is not controllable by merely an anti-inflammatory action.

Technical differences in the performance of the cotton pellet test in various laboratories have led to diverse figures, but in general there is agree-

ment that both steroids and nonsteroids inhibit granuloma in this test. The precision of the assay varies widely; Bush & Alexander (39) claimed a value for λ as low as 0.14 for steroids; for nonsteroids, values obtained have been 1.885 (201), 1.32 (241), and 0.46 (250). When comparisons are made between steroids and nonsteroids, some laboratories obtain nonparallel lines for regression of effect on log dose (241–243), while others find the regression lines to be parallel (18, 19, 245, 250).

A modification of the granuloma test introduced by Rudas (168) consists of removing a circle of skin from the back of a rat, preventing regrowth of skin over the wound by means of a plastic ring, and weighing the granulation tissue covering the wound after a week. This granulation tissue can be used for chemical analysis (169), and can be inhibited by either steroidal or nonsteroidal anti-inflammatory agents (128, 168). Rudas' results have been confirmed by Jørgensen (108) and by Garn, Newmann & Kramer (79), but the method has not been widely adopted for screening purposes.

The inhibitory effects of anti-inflammatory drugs upon granuloma formation have not received a satisfactory explanation in biochemical terms; indeed, the cotton pellet has been almost ignored by those studying the biochemistry of granuloma tissue formation. The biochemical studies have been made on granulation tissue formed after the implant of polyvinyl sponges (15, 26–29, 31, 252). The cotton pellet has been used for drug studies largely because it produces marked tissue reactions, while the polyvinyl material used in the sponges was originally selected for surgical prosthesis (84) because of its relative freedom from tissue reactions. One cannot be sure that the granulation tissue formed by the two stimuli would be identical, or that the responses to drugs would be the same; no direct study seems to have been made, but certain differences may be inferred from some scattered results (14, 23, 127, 170). Some differences between steroids and nonsteroids in their biochemical effects upon granuloma induced by turpentine or by cotton pellets soaked with carrageenan have been described (205–207). Some of these observations probably should be repeated at different dose levels of drugs. No biochemical changes were seen to be induced by either steroids or nonsteroids in granulation tissue produced by the Rudas method (108, 169); the only change was in the total weight of the granuloma.

One may conclude that the effects of nonsteroid anti-inflammatory agents upon chemical composition of granuloma tissue constitute a largely unexplored field.

Experimental arthritis.—Experimental arthritis has been produced in animals by a large number of procedures (78), but recent increased interest in this field has been the result of the ease with which arthritis can be induced in rats by the injection of heat-killed *Mycobacteria* in oil—resulting in "adjuvant arthritis." Starting with the observations of Stoerk et al. (194) and studied intensively by Pearson (155–158), Ward (221, 222),

Waksman (179, 216, 217), Newbould (145, 146), Formanek (75), and Kalliomäki (112), adjuvant arthritis has recently been shown to respond to treatment by various nonsteroid anti-inflammatory drugs (80, 144, 152, 203, 220). Whether this system will prove to be more relevant to the problem of treating arthritis in man than the methods involving inflammation induced by other means remains to be seen. There is some hope that it may be, since it does involve a chronic condition and the arthritis is a secondary event which most workers have thought to be a form of delayed hypersensitivity reaction (75, 112, 158, 179, 216).

Compounds Recently Described

Anti-inflammatory activity has recently been described for an increasing number and variety of compounds. These range all the way from uncharacterized extracts of inflammatory tissues or exudates (67, 68, 94, 140, 161, 163) or plant extracts (50, 51, 96, 97) to complex synthetic organic chemicals. A substance of plant origin prepared from lignin in wood, dimethyl sulfoxide (DMSO), has attracted considerable attention, especially in the lay press. When applied externally, DMSO is said to relieve swelling, stiffness, and pain in a variety of inflammatory conditions (165, 166). The compound is relatively nontoxic (11, 16, 46, 48, 72, 73, 167, 187, 238). No teratogenic effects were seen with relatively large doses in mice, rats, or rabbits, but could be obtained in chick embryos (48). Pulmonary constriction has been described in the isolated lung of the guinea pig (47). There is some evidence that dimethyl sulfoxide may promote percutaneous absorption of certain drugs (195), though Horita & Weber (102) did not obtain clear evidence of such activity. There seems to be little additional information available on the pharmacological activities of this potentially interesting compound.

Oxyphenbutazone.—Of the many chemical relatives of phenylbutazone which have been studied, oxyphenbutazone seems to be of special interest from the standpoint of the present discussion. Although it is a metabolite of phenylbutazone (38, 175, 255), its therapeutic properties are essentially the same as those of the parent compound, as are the incidence and severity of side effects (53). There are some pharmacological differences, as oxyphenbutazone is said to have slight antiserotonin activity (70) and to be inactive in the ultraviolet erythema test for anti-inflammatory activity, though more active than phenylbutazone on the granuloma pouch. Statistically controlled studies, with responses related to log dose, are lacking in much of the published work on phenylbutazone and related compounds, although they can be as easily obtained with these compounds, employing doses below the grossly toxic range (129, 240, 245, 250), as with other classes of pharmacologically active agents. A wide variety of toxic reactions to phenylbutazone have been observed, as could be expected with an active drug so widely used; these have recently been reviewed (132).

Ibufenac.—Compounds derived from phenylacetic, phenoxyacetic, and

related acids have received considerable attention. A number of them have been tested for anti-inflammatory or analgesic activity, or both (139, 147, 149–151, 178, 208). The most thoroughly studied of these compounds is 4-isobutylphenylacetic acid (3), which received clinical trial under the name of "Ibufenac" (49), and was said to be as effective as aspirin but with fewer side effects, especially less fecal blood loss (209). Evidences of liver dysfunction have been described in patients receiving this compound (202), but some have thought that this effect was not sufficiently serious to preclude further study of the compound (92).

Indomethacin.—Indole compounds with acid side-chains at position-3 have attracted considerable attention recently. Northover (151) studied several such compounds, but chief attention has been focused upon indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (180). The anti-inflammatory, antipyretic, and analgesic effects of this compound in animals have been studied in some detail (21, 245, 247, 249, 250). This drug is remarkable for its high potency in these tests, and also for the fact that its metabolism in man is different from that in other species (89, 104). Its clinical activity as an active antirheumatic drug seems to be well established (12, 13, 24, 43, 59, 63, 90, 91, 100, 116, 154, 199, 218, 219, 253). Most authors have found headache to be the most troublesome side effect; the headache responds to methysergide (22). Sicuteri (181–183) has developed a hypothesis that the headache is due to reactive intracranial vasodilatation following drug-induced vasoconstriction. Sicuteri (184) reported an action of indomethacin on migraine similar to that of ergotamine. Gastrointestinal intolerance is said to be a serious problem by some (114, 130), but not by others (12, 24, 90, 116). The formulation of the compound seems to have influenced the blood levels, therapeutic results, and incidence or severity of side effects, with a more favorable outcome in every respect when tablets were replaced by capsules (12, 13, 25, 42, 154, 218, 219); one worker reported no detectable difference between tablets and capsules (59). Apparently, tablets containing indomethacin harden on storage, have a variable dissolution rate, and produce erratic blood levels.

Anthranilic acids.—Derivatives of anthranilic acid that have been found to be active include N-(2,3-xylyl)-anthranilic acid (mefenamic acid), N-(α,α,α-trifluoro-*m*-tolyl)-anthranilic acid (flufenamic acid), and N-(2,6-dichloro-*m*-tolyl)-anthranilic acid (CI-583). The last of these was the subject of a pharmacological paper (243), but the other two have been more extensively studied. They are active in Northover's "peritoneal permeability" test (151); they uncouple oxidative phosphorylation (231); they stabilize plasma proteins against heat coagulation (141). In antigranuloma and ultraviolet erythema tests, flufenamic acid is more potent than mefenamic acid (241, 242). It has been claimed the mefenamic acid exhibited analgesic activity of a different sort (presumably central) from that exhibited by other anti-inflammatory agents (241), but the present author has taken exception to this view (247). Analgesic activity comparable to that of as-

pirin has been described in human subjects (44, 235). Clinical antirheumatic activity has been reported for these compounds (41, 58, 65, 118, 254). These studies are not as numerous or as detailed as those listed above for indomethacin. So far, side effects seem not to be unduly troublesome; diarrhea and other gastrointestinal complications seem to be the most common unwanted effects. Blood in the stools may be less of a problem than with aspirin (121).

Conclusion

Anti-inflammatory activity has been described for a large number of other compounds. Space does not permit discussion of these, but lists of them, together with literature references, are to be found in the reviews by Whitehouse (230) and Winter (246). Some additional compounds not listed in either of these reviews are discussed in the volume *Non-steroidal Anti-inflammatory Drugs* (Excerpta Medica Foundation, International Congress Series No. 82), the proceedings of an international symposium held in Milan, Italy, 8–10 September 1964.

The advances that are being made in testing of compounds for antirheumatic activity, and the rapid rate at which new and promising candidates for therapeutic use are being discovered, give us reason to anticipate that the lot of the rheumatic sufferer may soon become an easier one. The ideal therapy will emerge, though, only when we learn to treat the disease itself and not just its symptoms.

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