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NONSTEROID ANTI-INFLAMMATORY AGENTS[1]

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The study of mechanisms of inflammation and of anti inflammatory agents accelerated greatly following initial reports of the remarkable clinical effects of cortisone, in 1949 (89), and of phenylbutazone, in 1952 (42, 108). Several comprehensive publications describing the basic concepts of inflammation and the immunological disorders have now appeared (127, 150, 176, 180, 188, 214, 221, 242). As a result of the enormously increased interest in the immunological disorders, anti-inflammatory agents, and phenomena of inflammation, together with increases in public funds available for research, detailed reviews have recently described important advances in development and evaluation of anti-inflammatory agents (50, 133, 203, 206, 210, 228, 232, 237, 238). Those written by Whitehouse (232) and Domenjoz (50) will be most helpful to those seeking orientation in this field.

The purpose of this review of nonsteroid anti-inflammatory agents is to present some of the typical studies published principally in the two years since the previous review in this series (238). With a few noteworthy exceptions involving papers presented and now in press, the subject matter of this review does not go beyond the end of June 1967.

The *First Symposium of The International Inflammation Club* brought together outstanding workers in the field of inflammation in 1967 at Augusta, Michigan. The proceedings will appear in a supplement to *Biochemical Pharmacology* early in 1968 and later in book form by the Pergamon Press. Several of the participants have kindly made some of the pre-publication manuscripts available to this reviewer for current consideration (57, 74, 147, 192, 233).

Semantics

The terms anti-inflammatory and antirheumatic which are employed, sometimes interchangeably, deserve some comment and an attempt at definition.

"The present designation of a drug as 'anti-inflammatory' is really too comprehensive, too vague in fact, to be of much use in delineating its properties other than it might be of some potential value for the management of one or several ill-assorted physical complaints of mankind, varying from the almost total physical incapacity of advanced arthritis to a highly localized ectopic dermatitis. By its very nature of being a 'catch-all' description, the current use of the term 'anti-inflammatory' loses any element of

[1] The survey of the literature pertaining to this review was concluded in June 1967.

being an exact description as to what the anti-inflammatory compound really does or how it does it" (232).

Anti-inflammatory.—Anti-inflammatory, used clinically, designates an agent which will lessen or prevent one or more of the various recognized components of the inflammatory reaction. Clinically it is, of course, understood that such agents may effectively be employed at dosage levels which are unaccompanied by frequent untoward side effects of medication. In the experimental laboratory, however, the term is used more broadly to designate agents preventing or diminishing manifestations of inflammation in ranges of dosage which often transcend those conceivably employable in man.

Antirheumatic.—Antirheumatic generally is understood to describe agents which clinically alleviate manifestations of the various rheumatic disorders. Relief of pain by analgesics, which do not also diminish inflammatory reactions involving joints, tendon sheaths, muscles, and serous spaces, does not qualify them for inclusion in this group. In the experimental laboratory, confusion often arises since agents which diminish inflammation in and around joints of small laboratory animals are sometimes designated antirheumatic when, at best, their action is simply anti-inflammatory within the confines of the criteria of the experimental model employed and may be without relevance to human disorders.

Since rheumatic disorders in man are multiple and of diverse etiology, the use of the term antirheumatic may be too general. Some drugs which alter clinical manifestations of rheumatoid arthritis, i.e. gold preparations, are without effect in other recognized rheumatic disorders. The pyrazolidines (phenylbutazone and oxyphenbutazone) and indomethacin are more effective in acute gouty arthritis and in ankylosing spondylitis than in rheumatoid arthritis, where their use is common but less effective. Osteoarthritis, the most prevalent rheumatic disorder, is usually mild and its symptoms are relieved by salicylates, pyrazolidines, indomethacin, mefenamic acid, and flufenamic acid but certainly not by gold or anti-malarials. One might devote considerable time to a recitation of the variability in effectiveness of so-called antirheumatic agents when employed in juvenile rheumatoid arthritis, systemic lupus erythematosus, Reiter's syndrome, rheumatic fever, psoriatic arthropathy, intermittent hydrarthrosis, the fibrositis syndrome, acute and chronic gouty arthritis, polymyositis, scleroderma, and traumatic arthritis–to mention a few–but the vagaries of their present treatment are well outlined in the rheumatology texts edited by Hollander (91) and Copeman (33). Here, it is sufficient to emphasize that the etiology of most rheumatic diseases is obscure, despite the vast compilation of clinical and laboratory data concerning them.

The exact mode of action of these agents is not completely documented, and their use in the treatment of patients with rheumatic disorders of undetermined etiology can be condoned only because it affords patients a greater range of functional activity–in most instances without amelioration of the

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underlying disease process. Apart from the rheumatic disorders, the usefulness of anti-inflammatory agents in dermatology, ophthalmology, vascular disorders, and incident to transplantation of organs is prevalent for similar reasons even though thoroughly satisfactory descriptions of the inflammatory processes involved are yet to be forthcoming.

Among the many problems encountered in this field are the clinical difficulties often encountered in correctly diagnosing early cases of rheumatic disorders, as well as the frequent occurrence of more than one disorder in a single patient. Thus, evaluation of treatment may be clouded by the lack of universal criteria for diagnosis and response to therapy. Comparison of one drug with another presents additional difficulties related to the variable biological half-life of drugs previously administered, the use of other drugs concurrently (often surreptitiously), as well as the natural tendency toward remission in some of these disorders. When patients, previously treated with glucocorticoids, are to be evaluated on nonsteroid anti-inflammatory agents, one must first reduce carefully the daily ration of steroid to the least amount sufficient to maintain clinical control of the disorder. Otherwise, compilation of clinical data describing effective substitution of nonsteroid agents in withdrawal or diminution of steroid requirements is not only misleading but nonsensical.

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Testing Methods

Species differences.—Koppanyi & Avery have reviewed information available on effects of drugs and poisons of different strains of the same species and on different species of animals to compare differences in rate of turnover and metabolic degradation of drugs (106). Such differences may be measured by methods of essential elimination as well as by biochemical techniques. They attempted to suggest ways to minimize difficulties presently encountered in extrapolation of results from small animal studies to man. They emphasized the importance of comparing drugs on the basis of plasma levels instead of on a w/w basis. They also emphasized that species differences are largely understandable on the basis of enzyme activities. The mechanism of metabolic degradation and the final metabolite may vary from species to species, thus it is important to find animal species or strains which can metabolize or excrete a drug at a rate similar to that of man and in which the mechanisms of detoxification are identical. This is of particular importance in toxicity studies since enzyme activation or *de novo* enzyme synthesis in response to drugs is so subject to species variation. Koppanyi & Avery indicated four areas where animal studies are not applicable and where *Phase I* clinical trial in necessary: "(a) adverse effects, particularly toxic psychoses, skin lesions, and allergenic reactions; (b) optimum therapeutic benefits in a given disease in cases where there are no exact counterparts of a human disease in one or more laboratory animals; (c) dose-response curves, maximum tolerated doses, and pathways of metabolic degredation; (d) essential elimination of a remedial agent which must be measured in humans and compared with that determined in animals" (106).

Chick embryo.—D'Arcy & Howard have described a novel method of placing filter paper discs on the chorio-allantoic membrane of an eight-day chick embryo, incubating at 37° C for four days, and measuring the inflammatory reaction on the adjacent membrane. Impregnation of the discs with test substances revealed significant reduction of inflammatory response using betamethasone (0.063 μg), hydrocortisone (0.63 μg), chloroquine (0.025 mg), phenylbutazone (0.1 mg), indomethacin (2.5 mg) or sodium salicylate (5 mg). Response was graded according to the quantity of drug employed. Additionally, various effects of drugs on the embryos were described. Since this method is economical of time, materials, and space, it may prove suitable in initial screening for anti-inflammatory effectiveness and comparative dosage relationships (43).

Pleural effusion.—Sancilio & Rodriguez measured the volume of rat pleural fluid following intra-pleural injection of Evans Blue. Anti-inflammatory drugs were administered orally and reduction of pleural fluid volume determined at various time intervals. Acetylsalicylic acid, phenylbutazone, and indomethacin were effective at 17 hrs, but flufenamic acid was only effective at six hrs. While this method offers a different parameter in drug evaluation, their description of using a single oral dose without regard to variation in biological half-life suggests that correction for this factor would enhance the applicability of the method (182).

Monkeys.—Lucherini & Porzio (119) have described an interesting experimental arthritis produced in rhesus monkeys by intradermal and subcutaneous injections of human fibrin emulsified with Freund's adjuvant (Difco). A polyarticular arthritis appeared, and all of the six test animals died 93 to 102 days after its appearance. One monkey showed a positive Waaler-Rose test, and histologically, the arthritis resembled rheumatoid arthritis in man. This method may provide an experimental arthritis for evaluating agents for treatment of rheumatoid arthritis.

Pigeons.—A method employing measurement of delay in beginning of one-leg standing in pigeons following intra-tarsal injection of a talc suspension has been suggested as a measurement of anti-inflammatory drug activity (14). The greater effectiveness of indomethacin than of other drugs in this test indicates the different nature of this procedure. The local injury produced appeared to be unrelated to the release of serotonin but suggested that histamine may play a role.

Swine.—An experimental arthritis in swine may be produced with Erysipelothrix insidiosa (195). This polyarthritis, which is characterized by pannus formation and ankylosis similar to that of human rheumatoid arthritis, shows moderately low titers to the rheumatoid arthritis latex agglutination test. Studies of the synovial fluid do not differ markedly from rheumatoid arthritis (38). This experimental arthritis could be employed for drug evaluation, and the care of the animals would probably be no more troublesome than the care of hospital patients.

Mice.—F1 hybrids of NZB and NZW mice have shown a uniquely high

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incidence of kidney disease with a general resemblance to human systemic lupus erythematosus nephritis (23, 31, 49, 235). Antilymphocyte serum given to young B/W mice in amounts sufficient to inhibit circulating antibody response failed to suppress the subsequent onset of renal disease (47). Lymphoid follicles evolve in the perivascular connective tissue of many organs, including the thymus, in NZB/B1 mice with hemolytic anemia (194). Transplantation of spleen cells from old NZB/B1 mice with renal disease induced both the structural and functional changes of membranous glomerulonephritis in young NZB/B1 mice within a few weeks and well in advance of its usual spontaneous appearance (124). These unusual disorders of NZB mice may serve as experimental models for testing agents of possible usefulness in systemic lupus erythematosus.

Osteoarthritis develops in mice of strain C57BL Jax 6 when they are kept on a lard-enriched ration lacking unsaturated fatty acids. The addition of a dietary enrichment of 3 per cent linoleic acid partly reversed the tendency to develop osteoarthritic changes (196).

When mice are injected with rabbit anti-mouse macrophage serum, previously injected nonvirulent hemolytic streptococci are not eliminated and produce local lesions in the tail (45/300), the wrist and ankle joints (17/300), and the heart (9/300). The incidence of lesions depends upon the strength of the antimacrophage serum. This is the first reported instance of the development of arthritis and carditis by streptococci in experimental animals (30).

Rats.—Various antirheumatic agents given to rats toward the end of a sensitization period to horse serum will diminish production of histamine from mast cell suspensions subjected to horse serum (143). No correlation was found between the clinical potency of the drugs tested and their ability to inhibit histamine release.

Adjuvant-induced arthritis in rats has been the subject of many experimental studies. Young rats (one to seven days old) were resistant to the adjuvant. Thymectomy, splenectomy, bileduct ligation, castration, and pregnancy did not alter the course of the disorder. Stress reduced the incidence of arthritis. Local trauma to joints increased their involvement. Reactions to carrageenin and egg albumin were not altered by the ajduvant, and there was no evidence of an anamnestic response following a second injection of adjuvant (75, 76). Serum complement levels were elevated in arthritic rats. Serums from arthritic rats showed depression of serum albumin, glycoproteins, mucoproteins, and α-2 globulins. Since similar changes were observed in sera of rats with granuloma pouches, the changes were considered to be reflections of nonspecific inflammation (77). Puromycin, 5-fluorouracil, 6-mercaptopurine, actinomycin D, and cyclophosphoramide inhibited the incidence of the arthritis but were less efficient than hydrocortisone acetate. Nonsteroid anti-inflammatory agents produced inhibitory effects on the arthritis and alterations of the serum, but at dosages which produced signs of animal toxicosis (72). Plasma inflammation units (proteins precipitable at 56° C) are objective indices for the study of experi-

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mental inflammation and its inhibition by anti-inflammatory drugs (77). Determination of plasma or serum concentrations of α-2-GP is essentially a simple immunologic procedure utilizing a monospecific antiserum reagent in the agar-gel double diffusion technique of Ouchterlony. The use of the α-2-GP parameter is favored in assessment of drug therapy when one considers the factors of specificity, sensitivity, and a wide range of response between high and low values necessary for quantitation (20).

The follow-up study of untreated adjuvant arthritis of rats indicates that it is a chronic self-sustaining disease with patterns of evolution resembling to some extent those of rheumatoid arthritis in man (110). Thymectomy, in another study, induced decreased incidence and a diminution in severity of adjuvant arthritis (120). Treatment of the rats with methopyranone prior to adjuvant injection tends to favor development of the arthritis (223). A lysosome-protecting

after the arthritis became fully developed and was not detectable when the arthritis subsided (153). The activities of two lysosomal enzymes, acid phosphatase and β-glucuronidase, released from organelles in the presence of a 1:10 dilution of arthritis serum were diminished to 47 and 41 per cent of control values, respectively.

Twenty-eight days after injection of adjuvant, there was depletion of neurosecretory material in the hypothalamo-hypophyseal tract and in the infundibular process and the nuclear area of the neurons in the supraoptic nuclei increased, suggesting increased activity of the hypothalamic neurosecretion in rats with adjuvant disease (97). In most instances, the endogenous heparin value became labile and sometimes increased indicating an interaction between the serum heparin level and the severity of the arthritis (117). Using rat adjuvant arthritis as a test screen for anti-inflammatory agents, it was noted that results often varied from one laboratory to another. Indomethacin was described as without effect (59) and also as effective (82, 239). Phenylbutazone was effective, while chloroquine and hydroxychloroquine were ineffective (229). Aurothiomalate was effective (140). Inhibition of both components of the autonomic nervous system diminished with statistical significance the severity and extent of adjuvant disease. Vagal preponderance tends to intensify the arthritis, while sympathetic stimulation tends to diminish it (179). Another phenomenon of considerable interest is the failure of adjuvant arthritis to develop in the affected limb when femur fracture or sciatic nerve section is present (36).

The use of antilymphocyte heterologous serum prepared in rabbits from thymus, spleen, and lymph nodes of rats prevented adjuvant arthritis, suppressed antibody response to sheep red blood cells, but did not prevent the appearance of antibody to the injected rabbit globulin (41). It is interesting to recall the profound lympholytic effect of cortisone (29), and in mice the graft-versus-host syndrome has been prevented by the use of rabbit anti-mouse lymphocyte serum (18).

Using the carrageenin-induced edema of the rat hind paw as an assay

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of anti-inflammatory effect, the potency ratios obtained for acetylsalicylic acid, phenylbutazone, and hydrocortisone were fairly close to the ratios of their respective daily dosage in treatment of rheumatic diseases. A potent anti-histaminic-antiserotonin compound, cyoroheptadine, was without effect on carrageenin-induced edema (240). Irritants injected subcutaneously at a site distant from the carrageenin-induced abscess caused diminution in abscess weight, but when mixed with the carrageenin, produced increase in abscess weight. Anti-inflammatory compounds, when mixed with carrageenin, reduced abscess weight. This comparative effect is offered as a test method to distinguish between nonspecific irritants and anti-inflammatory agents (79). Carminati reported that many substances (alcohols, spasmolytics, antihistamines, stimulants and depressants of the CNS, local anesthetics, anti-malarials, succinyl-choline, cysteamine, and cystine) caused diminution of granulomas in rats produced by carrageenin, formalin, and yeasts. These substances were thought to act at the neurovascular-cellular level in altering inflammation (27). Bacterial contamination of injections of kaolin or carrageenin causes a great increase in the edema of rat hind paws suggesting that such suspensions should be handled with aseptic precautions (85). Another type of experimental arthritis in rats has been produced by injection of fluid from granuloma pouches under the skin of the feet (60). Rats subjected to sound stress or avoidance learning stress showed highly significant decrease in their ability to produce foreign body granulomas against implantation of cotton pellets (68).

Crystal-induced synovitis.—Intraarticular injection of microcrystalline sodium urate into normal human knees was used to test the anti-inflammatory effect of a new drug, 2,3-bis (*p*-methoxy-phenyl)-indole, versus a placebo. Separation of drug and placebo results was possible in each trial on the basis of an inflammatory index derived from objective measurements of knee joint swelling, tenderness, skin temperature, and the volume of fluid aspirated from the joint at the end of the experiment. Joint swelling and tenderness were less with the test drug (212). Single injections of bradykinin into such joints caused rapid increase in swelling, but carboxypeptidase-B did not suppress the increased intensity of the reaction suggesting that bradykinin is not a mediator of the acute inflammatory response induced by sodium urate (157). Oral administration of phenylbutazone and indomethacin prevented or reversed a similar urate-induced acute synovitis in dogs. Acetylsalicylic acid, codeine, promazine, chlorpromazine, topical counter-irritants, and intravenous hydrocortisone were inactive (171). Apparently, the polymorphonuclear leukocyte was necessary to the inflammation induced by the urate crystals because of the invariable migration of these cells into the synovial fluid, suppression of the synovitis by depletion of the leukocytes in animals treated with vinblastine, dependence of the degree of suppression on the degree of leukocyte mobilization into the joint, and finally by restoration of the inflammatory response in a leukopenic animal by perfusion with normal blood (156). The beneficial effect of colchicine on gouty

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inflammation may result from its inhibiting the phagocytosis of sodium urate microcrystals by leukocytes (67, 78, 230). This is particularly interesting since in human pseudo-gout due to crystals of calcium pyrophosphate, the use of colchicine is ineffective.

Carbon tetrachloride (CCl_4) induced granuloma.—In rats 24 hours after subcutaneous injections of CCl_4 granulomas appeared. These reactions were inhibited by orally administered streptokinase plasminogen or trypsin; and epsilon-aminocaproic acid blocked the granuloma inhibiting effects of trypsin or streptokinase plasminogen suggesting that the effect of these substances is due to their enzymatic activity (93).

Bilirubin conjugation.—Ibufenac (4-isobutyl-phenylacetic acid) inhibits *o*-aminophenol and bilirubin conjugation in *in vitro* conjugating systems suggesting that glucuronyl transferase can be inhibited even at therapeutic concentrations (86).

Paw temperature changes.—A radiometric method for measuring paw temperature on unanesthetized rats has been described (160). This method may be used as a supplement to other methods for the evaluation of anti-inflammatory activity. The paw temperature profile following subplantar injection of yeast in rats shows two peaks, an initial rise followed by a more pronounced rise (160).

Protein coagulation.—Mizushima & Nakagawa showed that the effect of drug action on heat coagulation of Cohn's fraction IV-4 correlated with anti-inflammatory activity. The correlation was reconfirmed by an extensive experiment using 65 compounds. Sixteen new anti-inflammatory agents were found by measuring their action on coagulation of Cohn's fraction IV-4 (131, 133). Phenylbutazone, oxyphenbutazone, salicylate, flufenamic acid, indomethacin, ibufenac, and dodecyl sulfate stabilize serum albumin intensively both at pH 5.2 and 6.9. Antipyretic-analgetic drugs other than antirheumatics showed very weak action or no action on coagulation (131). A modification of the Mizushima technique involves testing the blood of rats given various drugs 3 hrs prior to cardiac puncture. This modification of the test permits testing the effect of metabolic products rather than of the drugs per se. In addition, serum turbidity changes are employed in the assessment of anti-inflammatory agents in adjuvant arthritis (158). Neither trinitroplenyl-albumin nor N-acetyl-albumin could be protected from heat denaturation in this way, and furthermore, neither of these modified proteins reacted with trinitrobenzaldehyde. Mizushima's method may measure the protein complexing, or more specifically the lysine-binding, ability of compounds tested. Measuring aldehyde binding in the presence of potential anti-inflammatory drugs affords another quantifiable index of potency in association with protein (lysyl) epsilon-amino-groups (202).

Platelet adhesiveness.—Mustard and his associates have described a number of compounds which inhibit platelet aggregation and the release of platelet constituents by enzymes and surface stimuli (147). Cortisone, acetylsalicylic acid, phenylbutazone, sulfinpyrazone, salicylaldoxime, and

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phosphatidyl serine are effective. They have described the inhibition of release of platelet nucleotides, serotonin, and the platelet permeability factor by sulfinpyrazone and phenylbutazone. These drugs impair the adherence of platelets to surfaces and diminish platelet turnover (208). Acetylsalicylic acid affects platelet function similarly (58). Platelets react with particulate stimuli, such as antigen-antibody complexes, viruses and bacteria, surface stimuli, such as collagen, and enzymes, such as thrombin. "There is little doubt, however, that the reaction can lead to the formation of large platelet aggregates and the release of ADP and other constituents from the platelets which affect the surrounding tissues, particularly the vessel wall" (147). Further study of the metabolism of platelets may afford an additional screening method for anti-inflammatory agents.

Grant & Becker have produced micro-burns on the luminal side of the endothelial wall of small vessels in the rabbit ear (81, 83, 84). This injury results in formation of a thrombus in the vessel wall without apparent intervention of perivascular or extravascular factors. The material which causes attachment of the white thrombus represents altered platelets or leukocytes on their products. Such studies suggest an important role for the vascular endothelium in inflammation. Stasis thrombi and marked shortening of the whole blood clotting time were produced in rabbits by injection of eluates of collagen which contained Factors XI and XII (142). Chloroquine inhibited agglutination, both of leukocytes and platelets in experiments with sera containing isoantibodies or autoantibodies against leukocytes and platelets (213).

Serum complement was increased in ankylosing spondylitis, rheumatoid arthritis, psoriatic arthropathy, and Reiter's disease. The synovial fluid complement level, however, was increased in all inflammatory diseases of the joints except rheumatoid arthritis and systemic lupus erythematosus in which at least C'_2 and C'_4 were decreased, while C'_3 was increased (152). While serum complement fluctuated significantly during the active stage of rheumatoid arthritis (6, 185), the presence of an anti-complementary substance could not be demonstrated in the synovial fluid. Synovial tissue obtained by needle biopsy revealed a different pattern of localization for rheumatoid factor and tissue-bound complement (170). In the rat, however, rheumatoid factor inhibited the serum complement lowering effect of intraperitoneally injected aggregated human immunoglobulin-G (IgG) (81). Rheumatoid sera were also shown to contain an inhibitor of complement-fixation in the 19S globulin fraction, which failed to agglutinate sensitized cells or latex particles coated with human immunoglobulin G (87).

In acute gouty arthritis, the inflammatory reaction to sodium monourate crystals is explained either by direct cellular injury (157, 212), by activation of the Hageman factor (Factor XII) with generation of kinin activity (99), or by the production of anaphylatoxin, a C'_3 complement fraction, which increases vascular permeability. Incubation of urate crystals with rat plasma resulted in an anaphylatoxin-like activity. Urate crystals

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also depleted complement from serum lacking Hageman factor—suggesting that its activation is not important in complement depletion. Pre-kallikrein contained in the γ-globulins isolated from guinea-pig serum can be converted to active kallikrein by brief shaking with glass beads or collagen previously treated with guinea-pig or human serum or plasma and then washed. This suggests that Hageman factor is implicated in the activation of pre-kallikrein (46, 51, 125, 138).

Serum levels of complement and its fractions are related to the progress of the disease in rheumatic fever (218). In ulcerative colitis, marked elevations of serum complement were thought to represent a nonspecific expression of inflammation (65).

In rheumatoid arthritis, the intravascular and interstitial fibrinogen and the transcapillary transfer rate of fibrinogen, as well as its catabolic and synthetic rates, are greatly increased. These increases are secondary to the increase in the rate of synthesis of fibrinogen, the degree of which is roughly proportional to severity of the disease process (219). Two studies demonstrated marked inhibition of fibrinolysis with an increase in antiplasmin activity (4, 211a). In the fibrinolytic system of synovial fluid, fibrinogen was usually absent, but there was a heightened activity of Factors XI and XII (contact factor), of factors VII, VIII, IX and XIII (fibrin stabilizing factor), and of immediate and progressive antithrombin (211b), Fearnley & Chakrabarti treated 20 rheumatoid arthritics with a combination of fibrinolytic drugs (phenformin plus ethyl-estrenol) and 12 of them showed considerable improvement followed by relapse with cessation of therapy (62). A group of pyrazolidines possessing anti-inflammatory activity were subjected to the von Kaulla test for fibrinolytic activity. Phenylbutazone, ketophenylbutazone, and benzopyrazone showed marked fibrinolytic activity suggesting that parallelism between antiinflammatory and fibrinolytic activity may be of importance in screening of nonsteroid anti-inflammatory agents (177).

Considering the biochemical properties of drugs currently used in treatment of rheumatic and chronic inflammatory diseases, Whitehouse (233) notes that: "(*1*) They are polyvalent, i.e. able to inhibit several diverse enzyme reactions (37). (*2*) At the molecular level, the steroid drugs may act in a rather different manner to the acidic drugs (phenylbutazone, indomethacin, fenamic acids) though the net result of steroid interaction with key events in inflammation may resemble the effects of the acidic drugs in many respects (112, 204). (*3*) They can suppress the formation of inflammatory mediators, notably histamine, 5-hydroxytryptamine (and perhaps the kinins) and moderate the action of inflammatory proteases (203). (*4*) They can deprive inflamed tissue of essential metabolic energy, in the form of adenosine triphosphate (ATP), needed to promote the inflammatory response. (*5*) The acidic drugs, steroids, and indoxole may affect protein and RNA synthesis in circulating lymphocytes—cells which mediate the immune response and play a role in the pathogenesis of certain chronic

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inflammatory (and auto-immune?) states, e.g. graft rejection, adjuvant arthritis in rats" (233).

Glenn feels that the large number of molecular mediators studied in relation to the inflammatory reaction may simply reflect primary changes in the integrity of cells membranes (74). Erdös studied the effects of nonsteroid anti-inflammatory drugs on endotoxin shock in dogs and described a beneficial effect which might be explained by their diminution of capillary permeability in the second phase of shock. His hypothesis was based on the considerations that these drugs abolish some of the actions of bradykinin and inhibit kallikrein and because these two substances are among the liberated vasoactive materials in shock (57). Selye has described "pluricausal diseases," in which identical nonspecific lesions can be elicited by several combinations of in-themselves inactive, essentially different pathogens: "(*1*) Sensitizers which induce a latent predisposition for a specific reaction form (e.g., inflammation, necrosis, calcification, thrombosis, and hemorrhage; (*2*) 'Challengers' which unmask this predisposition by making the disease manifest and determining its location" (136, 186–190–193). These interesting experimental innovations present new avenues of approach for study of the complexities of inflammation.

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Therapeutic Observations

Gold.—Gold (particularly thiomalate and thio-glucose) is widely used in treatment of rheumatoid arthritis of adults (123). A world survey of 107 rheumatologists revealed that all but four of them used gold (132). Gold is now being used effectively in juvenile rheumatoid arthritis (92, 141). In addition, pulmonary involvement due to rheumatoid disease has responded to gold therapy (167). Intra-articular use of gold has been particularly effective when used alone (115) and in combination with triamcinolone and lidocaine (107). One author indicates that the combined use of gold and chloroquine is more effective than the use of either substance alone (186). Gold inhibits lysosomal hydrolases, and the inhibition of lysosomal acid phosphatase, β-glucuronidase, and cathepsin is reversed by sulfhydryl compounds (56, 154). The use of DL-penicillamine in rats decreased the gold content of spleen and lung but caused an increased deposition in liver and kidney during mobilization of predeposited gold (178). Plasma gold determinations showed no relationship between the average plasma gold levels and appearance of muco-cutaneous lesions of gold toxicity (175). Colloidal Au^{198} has been used intra-articularly as a means of applying radiation directly to the synovial cavity (61, 234). Gold-induced thrombocytopenia occurred seven months after a 50 mg gold dose and responded to dimercaprol therapy (184). Pancytopenia, three months after the last of a series of gold injections responded also to dimercaprol therapy (69).

Pyrazolidines.—A ten-year follow-up study of 36 patients with ankylosing spondylitis, who were treated with phenylbutazone, reported that progression of the disease was arrested in about half of the cases (114). A double-

blind comparison of the clinical effects of phenylbutazone and monophenylbutazone showed a similarity of therapeutic effect and a lesser incidence of side effects for monophenylbutazone (222). Potentiation of anticoagulant therapy by oxyphenbutazone (90) is due to competition for binding sites on the albumin molecule by the drug and the anticoagulant (1). A survey showed no relationship of oxyphenbutazone to leukemia (55). There were two reports of transient anuria after intramuscular administration of phenylbutazone (16, 17). In dogs developing peptic ulcers while receiving phenylbutazone, the serum showed a diminished histamine binding power, while those without ulcers were normal in that respect (44). Human peptic ulceration is also accompanied by diminished serum histamine binding power (44). Concurrent use of methylandrostenolone caused elevation of oxyphenbutazone plasma levels in man due to alteration in its distribution between plasma and tissues (231).

Salicylates.—Eighteen of 27 rheumatoid arthritics experienced less morning-stiffness following a high nocturnal dose of polyoxoalbumin salicylate (103). Acetylsalicylic acid (ASA) stabilized rat liver lysosomes ***in vitro*** (129), and on a molar concentration basis, slightly more effectively than hydrocortisone and chloroquine. Sera from patients with rheumatoid arthritis have a greater affinity for low concentrations of I^{131}-labeled sodium acetrizoate than do normal sera (88). Normal human serum albumin (HSA) is altered following ***in vitro*** exposure to ASA, as evidenced by an increased capacity to bind I^{131}-labeled sodium acetrizoate. Specific antibodies with capacity to bind ASA-HSA were present in the immunoglobulin-G (IgG) fractions. Sera occasionally also contained ASA-HSA binding in IgA and IgM, but no anti-HSA was detected (130).

The simultaneous administration of corticosteroids and salicylate resulted in a blood salicylate concentration lower than expected possibly because the corticosteroids increase glomerular filtration rate and diminish tubular reabsorption of water (105). Study of human gastrectomy specimens obtained after administration of repeated doses of ASA showed erosions. More than 70 per cent of 226 patients receiving ASA showed blood loss of more than 2 ml daily. In atrophic gastritis, a high turnover of gastric epithelial cells may prevent formation of erosions (39). Among 533 rheumatoid patients there was a tendency, in the early years of the disease, to dyspepsia not solely due to therapy (40, 70). Patients dyspeptic prior to development of arthritis showed more frequent peptic ulceration (61.5 per cent) than those becoming dyspeptic afterwards (23 per cent) (70). Study of gastrointestinal clearance of Cr^{51} albumin showed that salicylates increase the loss of serum protein (13). Erythrocyte survival time in rabbits is reduced by salicylates in relation to the duration of medication (121), and salicylates hasten the transference of iron from plasma to erythrocytes (162).

Pancytopenia, observed in five women, was related to prolonged medication with acetylsalicylic acid (236). Two instances of ASA hypersensitivity with presence of circulating antibodies were described (126). Quick (165)

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developed an ASA-tolerance test which postulated that prolongation of bleeding time is consequent to depression of a plasma factor which controls bleeding from small vessels and which depends upon the acetyl linkage.

Antimalarials.—Several long-term evaluations of chloroquine in rheumatoid arthritis indicate a place for such therapy in selected cases (102, 140, 146). The effect of chloroquine on complement dependent antigen-antibody reactions may be responsible for its therapeutic effect in certain connective tissue disorders (139). Affinity of dermal melanin for chloroquine was demonstrated in mice using ultraviolet light (181). The pentose cycle in discoid lupus erythematosus appeared to be enhanced by chloroquine (15). Antimalarial drugs may conceivably act by interference with complement activity at local tissue levels in both systemic and discoid lupus erythematosus and in polymorphous light eruptions (113). Corneal opacity and retinopathy have been attributed to chloroquine usage in numerous reports. Retinopathy is related to dosage and duration but may appear long after cessation of therapy—a most worrisome clinical observation (8, 24, 144, 174, 183, 227). Chloroquine keratopathy produced in rats was characterized by epithelial edema, epithelial and superficial stromal deposits of yellow or reddish-brown color and newly formed capillaries in the subepithelial stroma (66). Chloroquine-induced neuromyopathy has been reported with subsequent recovery (25, 35, 54). Dihydroxy-propoxy-4-phenylamino-7-chloroquinoline was found to have good analgesic action in 46 rheumatic patients and no side-effects were reported (155). Both chloroquine and hydroxychloroquine have severely exacerbated skin manifestations in psoriasis and keratoderma blenorrhagicum (7).

Indomethacin.—Clinical observations describing prolonged use of indomethacin in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gouty arthritis indicate that the most outstanding antirheumatic effects are observed in ankylosing spondylitis and acute gouty arthritis (5, 98, 104, 128, 151, 161, 169, 172, 173, 241). In a highly controversial cooperative clinical trial (11 cooperating clinics) the effects of indomethacin for three months were compared with those of a placebo on a double-blind basis. Results revealed that test and placebo groups showed the same therapeutic response, although patients were permitted to take salicylates *ad libitum* (3). Another controlled study showed indomethacin to be effective in rheumatoid arthritis (48). A study comparing indomethacin (100 mg/day) with phenylbutazone (400 mg/day) declared phenylbutazone "slightly superior but produced slightly more side-effects" (168). Indomethacin was found less effective than paramethasone, and its maximum therapeutic effect required two to four months (207). A double-blind study comparing indomethacin with ASA revealed no therapeutic superiority; headache was more common with indomethacin, and auditory symptoms more common with ASA (159). A more rigid double-blind crossover clinical trial reported no antirheumatic effect of indomethacin (52). Thus, presently available reports are confusing, indicating everything from no response to

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good symptomatic relief in rheumatoid arthritis. An evaluation of side-effects of medication showed that on low-dosage, 75 per cent of these consisted of mild "transient giddiness or muzziness." On higher dosage, side-effects were more common and severe—headaches the dominant complaint. Patients with a previous history of pyrazole intolerance experienced more dyspepsia (19). Side-effects were found in 37.1 per cent of patients on low-dosage (1.1 mg/kg/day) and in 61.7 per cent on high-dosage (2.9 mg/kg/day). Among more severe side-effects were isolated reports of activation of latent infection (209), sudden death in children (94), and bronchial asthma (226).

Flufenamic and mefenamic acid.—In a trial on rheumatoid patients, flufenamic and mefenamic acid appeared to be satisfactory substitutes for either ASA or phenylbutazone (9). Flufenamic acid compared favorably with ASA in a crossover trial. Two of 23 patients experienced diarrhea from flufenamic acid (198). Prednisone (7.5 mg/day) was more effective than flufenamic acid (600 mg/day) (63). One controlled clinical trial failed to reveal any difference between flufenamic acid, phenylbutazone, and ASA (166), while flufenamic acid was more effective than a placebo in another double-blind trial (216). Neither flufenamic or mefenamic acid altered levels of serum uric acid (111), and fecal loss of blood with mefenamic acid was clearly less than with ASA (205).

Griseofulvin.—Both acute gouty arthritis and Raynaud's phenomenon were relieved by griseofulvin. Side-effects included headache, vertigo, pyrosis, and diarrhea (71). No improvement was noted in treatment of rheumatoid arthritis (225). Another report described effective use of griseofulvin in the shoulder-hand syndrome, cervico-brachial neuralgia, shoulder periarthritis, and sympathetic dystrophy (95). The anti-inflammatory effects of this anti-fungal agent have yet to be explained (224).

Immuno-suppressive agents.—Forty rheumatoid patients, previously unresponsive to conventional therapy, were treated with chlorambucil. Eleven had "excellent" results, and 13, "moderately good" results (22). Many preliminary reports describe the use of various immuno-suppressive agents in rheumatoid arthritis and systemic lupus erythematosus (12, 21, 26, 32, 34, 116, 134, 137). Too few patients have thus far been treated to permit firm conclusions regarding the possible role of these toxic agents in treatment of rheumatic disorders.

Natural products.—Recent studies of the anti-inflammatory activity of indigenous drugs include: P. Lancelolata in granuloma pouch and formalin arthritis in rats (164); Gandha Prasarini, Bala, Rasna, and Nirgundi (200); Dalbergia Lanceolaria (201), and the glucoside of Vanda roxburghii (163) were also effective in formalin arthritis.

New drugs.—Catalase produced favorable symptomatic relief in two studies of osteoarthritis (101, 135, 199). Methyl glycyrrhetic acid and glycyrrhetic acid diacetate showed similar, though less pronounced activity than hydrocortisone in formalin arthritis of rats (220). The following list of

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compounds have been the subject of preliminary animal experimentation in which anti-inflammatory effects have been claimed: benzdiamine (197), 2,3-bis(*p*-methoxyphenyl) and related compounds (73, 96, 217); imidazo (1,2-α)pyrimidines, and other bi- and tricyclic imidazo derivatives (2); hamycin, a heptaene antifungal antibiotic (45); succinic semi-aldehyde (109); acids and amides of phloroglucinol (122); hexadimethrine bromide (100); 1-substituted 3-dimethylamino-alkoxy-1H-indazoles (149); acetyl-epsilon-aminohexanoic acid (64); ethylbutyl-malonic acid di(*m*-amino)-anilide (80); 3-phenylcinnoline-4-carboxylic acids (118, 215); *p*-butoxy-phenylacethydroxamic acid (25); a series of *l*-aryl-2-pyrrolidinone derivatives (145); a series of N-amino-N substituted guanidines (53); and α-substituted 1-naphthyl-acetic acids (28, 148).

Conclusion

Some of the numerous recent studies on the mechanisms of inflammation and the activity of nonsteroid anti-inflammatory agents have been reviewed. Despite prodigious work in this field, we have in prospect much further research before the ideal anti-inflammatory agent is described. It may well be that because of the complexity of the inflammatory process, the clinical use of combinations of agents will be more rewarding than the use of such agents alone, Factors such as placebo responsiveness and persistence of response to prior use of medications should be carefully weighed in all future clinical trials (10, 11).

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