

THE DESIGN OF ANTI-INFLAMMATORY DRUGS: SOME CONSIDERATIONS BASED ON PESSIMISM, MOLECULAR PHARMACOLOGY AND CELLULAR PATHOLOGY

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THE IMPORTANCE OF A SATISFACTORY 'LEAD' AND PHARMACOLOGICAL ASSAY

Professor Ariens in another context¹ (and elsewhere in this Symposium) has drawn attention to the possibilities of molecular pharmacology serving as a guide to the development of new drugs. In pursuit of this theme, I should like to examine with you later in this lecture some of the biological and molecular characteristics of the principal non-steroid anti-inflammatory drugs known to us today, in order to discover which various properties ought to be associated with a particular chemical compound if it is to predictably manifest anti-inflammatory activity in animals and hopefully, anti-arthritic activity in man. This is what might be called the multi-analytical approach to drug research since it may be summarized as in *Figure 1*.

This familiar, widely employed and apparently rational approach, given a suitable lead, was brilliantly illustrated by the development of the quinine antimalarials and the benzoate esters used as local anaesthetics following the labours of devoted and inquisitive medicinal chemists who wanted quite simply to know why quinine and cocaine respectively manifested their well-known pharmacological activities. This analytical-cum-synthetic approach was deservedly successful in disclosing new chemical species with pharmacological characteristics which were qualitatively similar to, but quantitatively and therapeutically superior to, those of the two particular alkaloids which provided the appropriate lead (both chemically and

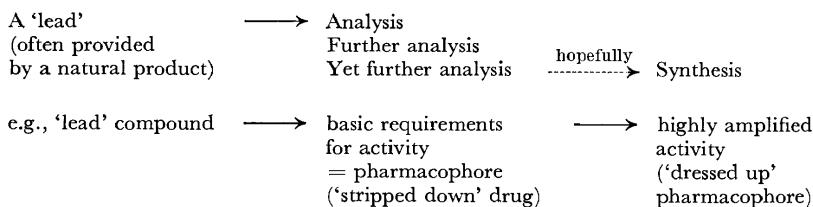


Figure 1. Multianalytical approach to drug research.

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pharmacologically) for an antimalarial and an anaesthetic pharmacophore respectively.

I am not at all sure that this same pattern of analysis and intelligent chemical manipulation will necessarily lead to the superior anti-arthritic drugs of the future, which are certainly needed and whose discovery we hope may be hastened by the deliberations of this meeting. I have these doubts about the value of such a multianalytical approach in this particular area of drug research because of some profound misgivings about the nature of the 'leads' available, particularly those apparently provided by nature herself. Almost instinctively, some of us tend to venerate unduly those 'leads' provided by natural products and this I think is a mistake. In some respects, we are all prisoners of our past and it would seem that drug designers are no exception to this rule. Believing that the mere repetition of a past formula for success may yet once again lead to a repetition of former successes, there is always the temptation to seize upon any lead—even a distinctly poor 'lead'—in the belief that the medicinal chemist will always come up with a chemically simplified and/or pharmacologically superior substitute for the lead compound. This confidence in the chemist's contribution is on the whole quite justified by past experience, but if the 'lead' itself is faulty or conceptually dubious, then clearly little real progress may be achieved unless serendipity intervenes.

In admittedly becoming wise only after the event, I wonder if the sorry lack of progress towards a satisfactory anti-arthritic drug is not simply a reflection of the fact that the two rational 'leads' which have spawned so much of the research in this area—namely the salicylates from the plant kingdom and cortisol (hydrocortisone) from the animal kingdom—are in fact poor inhibitors of degenerative disease, and by this I mean simply that they are not very efficient in 'switching off' the ongoing disease process(es). There is no doubt that these particular natural products and the whole host of conceptually derived non-steroidal aromatic acids and chemically derived steroids, which we term anti-inflammatory drugs, *do* suppress the overt signs of many disorders residing in the connective tissues, particularly the inflammatory and proliferative symptoms, and *do* render these dysfunctions in man more tolerable by induction of analgesia or euphoria. Nevertheless, it is also true that none of these particular drugs has curative, as opposed to palliative, properties and all too frequently the true course of a chronic inflammatory disease may proceed unchecked even though the symptoms may respond to these drugs. For example, many clinicians have repeatedly commented on the fact that the pain and swelling of an affected human joint may subside in response to the steroids and indomethacin and the mobility of the joint may be largely restored but the underlying joint erosion may still continue and might even be accelerated. (On theoretical and practical grounds, using these drugs for the treatment of certain dermatological disorders is perhaps more satisfactory and it should be recognized that the strictures applied to using these drugs in degenerative arthritis may not be valid in the context of suppressing an acute inflammatory state in the skin or elsewhere.)

It is perhaps unfortunate that this rather fundamental shortcoming in our lead compounds is not always recognized by those who design new drugs,

nor is it easily ascertained by the experimental pharmacologist who is principally concerned with applying some preliminary screens to detect potential pharmacological activity amidst the prolific output of his colleagues engaged in synthetic organic chemistry. To keep abreast of this tide of compounds, the pharmacologist has had to lean rather too heavily in the past on 'rapid results' assays with the emphasis being necessarily on the detection of drugs which suppress the acute (erythemic, oedemic) phase of an experimentally-induced inflammation or the early proliferative (granulomatous) response to an injury in small animals. It is not surprising that salicylates, cortisol and their derivatives are effective in these *acute* animal assays for the usual test that such an assay is satisfactory is simply the fact that it should detect these particular chemical species. It should, therefore, hardly be any surprise if the main realization of all this combined effort of the chemists and pharmacologists should simply be to duplicate the lead compound in nearly all respects except potency, which has been notably enhanced but not always in the true therapeutic sense (other properties such as ulcerogenicity have also been favoured in many instances). The one really desirable property from the viewpoint of what is most needed in the clinic—that of being able to prevent tissue destruction or malfunction accompanying a *chronic* inflammatory state—has normally been the one least intensively studied in the laboratory.

I should like to propose that for a reasonable trial period, both the steroids and the 'standard' anti-inflammatory acids such as phenylbutazone and indomethacin be removed from the pharmacology laboratories where drug testing is conducted, in order to hasten the development and introduction of new pharmacological assays which will assess the potential anti-arthritic activity of a compound by some parameter other than mere pharmacological similarity to the master compound, be it a steroid or supersalicylate. Progress might be very slow, but at least we would be spared the establishment of a branch of pharmacology with unsound foundations like that house in the parable which was built upon the sand².

Looking on the bright side, it is apparent that whatever else the battery of currently popular *in vivo* tests for anti-inflammatory activity may or may not disclose, they do indicate whether or not an orally or parenterally administered compound actually distributes into the connective tissues, the site of inflammation. This fact is not always predictable from other considerations of the physicochemical and biochemical properties of the compound under investigation. There are at present no generally useful shortcuts to obtaining the structure-action relationship for a compound to reach the joints, skin and other connective tissue and this fact alone wholly justifies the 'sweat and toil' approach to pharmacology through *in vivo* studies with the intact animal. Conversely, any drug-screening procedures carried out *in vitro*, apart from the whole animal, are almost certain to turn up a large number of false-positive compounds which fail to exhibit anti-inflammatory activity *in vivo* because these particular compounds either fail to build up in the plasma or fail to partition therefrom into the connective tissue space. This makes it very difficult to evaluate objectively the predictive value of such biochemical or pharmacological assays conducted outside the intact animal^{3, 4}.

MOLECULAR PROPERTIES OF NON-STEROID ACIDIC DRUGS

The importance of certain physicochemical properties in determining drug potency has been clearly indicated by a number of *in vitro* and *in vivo* studies^{3, 5}. Two of these properties, the acid ionization constant and ability to partition into or across lipid-rich membranes and subcellular particles, are also reflected by the avidity of binding of these drugs to erythrocytes^{6, 7} and to serum proteins, as determined by chemical^{8, 9}, enzymatic^{10, 11} or physical methods¹²⁻¹⁴. It will be very interesting to see if the Hansch-Fujita theorem (Eq. 1)¹⁵, which mathematically relates the potency of individual members of a chemically related series of acidic drugs determined in rather simple test systems, to their partition coefficients between *n*-octanol and water and σ , the appropriate Hammett substituent constant (computed for substituted benzene derivatives), can also successfully predict the relative potencies of anti-inflammatory acids.

$$\begin{aligned} \text{Log (Biological response in rate terms)} &= \log 1/[D] \\ &= -k\pi^2 + k'\pi + \rho\sigma + k'' \quad (1) \end{aligned}$$

where $[D]$ is the concentration in molar units of related compounds (drugs); π is a free energy related constant for a substituent, related to the partition coefficient (P) = $\log (P_x/P_H)$; σ is the Hammett function, a measure of the way a substituent modifies the electron density; ρ = reaction constant and k, k', k'' are appropriate constants obtained by regression analysis.

Equation (1) would certainly need to be extended by the inclusion of further terms which would, among other factors, reflect differences in the half-lives *in vivo* of the individual compounds under consideration. While we cannot yet mathematically compute drug potencies *in vivo* from first principles with any real confidence, nonetheless we should not neglect the qualitative implications of the relationships between potency, pK_a and lipophilic character, even though today we cannot yet satisfactorily harness the relationship to predict drug potencies in quantitative terms. In any series of acids exhibiting some anti-inflammatory activity and amenable to investigation *in vitro* such as through the related property of selectively inhibiting mitochondrial ATP synthesis (uncoupling oxidative phosphorylation)⁵ or binding to specific sites on a protein⁹, optimal activity *in vitro* is associated with a certain degree of lipophilic character and a particular pK_a range (usually 4.5 to 6.0). This generalization might be represented rather empirically by the solid curve in *Figure 2*, which can be analysed as the sum of the two dotted curves *A* and *B*. One of these (*A*) would represent the relative affinity of an anion-binding site for the drug anions, where the association is primarily ionic in character (and perhaps including the induction of dipoles at the receptor). The other curve (*B*) would represent the probability of the drug anions escaping from an extracellular aqueous environment and concentrating at a hydrophobic site. If the binding of the drug to its receptor(s) also involved some hydrophobic binding in addition to ionic association, then it is not difficult to see why both the pK_a and a degree of lipophilic character should appear to determine drug potency.

These simple physicochemical considerations have so far completely neglected the appropriate fit of the drug to the hypothetical receptors.

Shen³ has described how the D and L enantiomorphs of the α -methyl derivative of 3-chloro-4-cyclohexylphenylacetic acid and indomethacin (and some of its analogues) display quite different activities with the (+) isomer (having the sinister absolute configuration) being powerful anti-inflammatory drugs. The other isomers presumably fail to fit or are preferentially metabolized to inactive products or otherwise bound at sites of loss. Somewhat related to this, Dr. Witiak and I have observed distinct differences in the binding of the 2 enantiomorphous α -methyl-4-chlorophenoxyacetic acids to rat and bovine serum albumens.

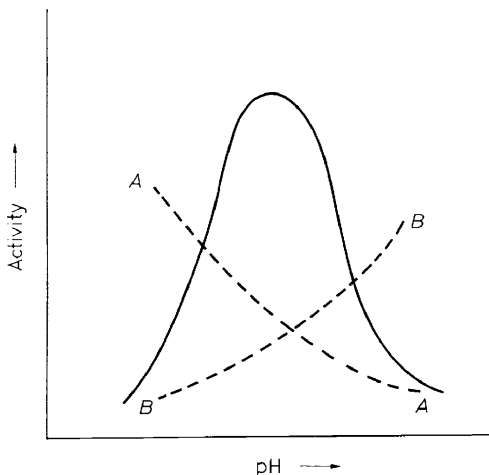


Figure 2. An empirical relationship between anti-inflammatory activity and pH [for an explanation of the curves see text].

These considerations suggest that one important molecular property of the anti-inflammatory (and other) acidic drugs may be quite simply to fit onto and bind to cationic sites on hydrophobic surfaces or within hydrophobic phases. One consequence is that where this site is the lysyl ϵ -amino group of a protein intimately participating in key biochemical events such as binding a coenzyme (e.g., pyridoxal phosphate)⁹ or directing an enzyme reaction, then this one pattern of association of drug with its receptor might nevertheless be able to affect numerous individual biochemical activities⁵, both within cells and in the plasma and other extra-cellular spaces (but occurring at hydrophobic surfaces including those of soluble macromolecules). For example, many acidic drugs, including some anti-inflammatory acids¹⁰, which inhibit tryptic digestion of serum albumen by binding to protein lysyl amino groups in competition with the enzyme, are also powerful inhibitors of mitochondrial phosphorylation^{5, 11} suggesting that within the mitochondria they might associate similarly with, and thereby block, a key amino group normally engaged in energy conservation (i.e., ATP biosynthesis).

We might now enquire if at the molecular level there are any features in common between the postulated cationic receptor(s) for the acidic drugs and the complementary surfaces which bind the anti-inflammatory steroids such as cortisol (hydrocortisone). Cortisol cannot ionize under physiological conditions to form an anion, but could perhaps combine with an amino group serving as a cationic receptor site if the steroid 21-hydroxy group were either oxidized to the aldehyde and formed an aldimine complex with the receptor ammonium ion (assuming it would readily lose its proton, i.e., had a low pK_a) or if the aldehyde was further oxidized to yield the α -keto acid. There is very little evidence to support either conjecture. Furthermore, several non-steroid anti-inflammatory drugs have now been described which are not appreciably acidic—perhaps the best known examples at present are amidopyrine and indoxole¹⁶.

This means that we should perhaps look for other molecular properties shared by different classes of anti-inflammatory drugs besides acidic character, whether manifest or latent. One of the most obvious molecular properties we might consider is the disposition in these drugs of the individual atoms capable of forming extramolecular bonds. For this, we will need to know the preferred conformation of the molecule where several possible conformations are possible. This data is sometimes obtainable from studies of the crystalline state but can also be obtained by calculating the energy of the whole molecule in each of several possible conformations using well-tried approximations. Dr. Kier of the Battelle Memorial Institute in Columbus has used such molecular orbital (M.O.) calculations to deduce that the distance between the oxygen atom at C-20 and the 11 β -hydroxyl group of cortisol (in its energetically preferred stable conformation) is 4.8 ± 0.5 Å while the separation between the C-11 hydroxyl and C-3 oxygen is 6.0 ± 0.5 Å¹⁷. From similar calculations, he has deduced that the distance between the two nitrogen atoms of serotonin is 5.84 Å in its one preferred conformation¹⁸, while the inter-nitrogen distance in one of the two preferred conformations of histamine is 4.55 Å¹⁹. Dr. Kier has therefore suggested that two of the three oxygen atoms of cortisol may bind to complementary sites on the receptors which normally bind the nitrogen atoms of serotonin and histamine respectively (see *Figure 3*).

Now, I am well aware that we are not here to talk about steroids, but if cortisol does owe some of its activity as an anti-inflammatory agent to its ability to antagonize the interaction of these two inflammatory amines, histamine and serotonin, with their inflammagenic receptor sites, we should look further to see if any of the effective non-steroid anti-inflammatory drugs could also spread themselves over these amine receptors and thereby perhaps mimic cortisol. Dr. Kier and I have now carried out some of the appropriate M.O. calculations and measurements of molecular models to deduce the distances between certain atoms in indomethacin, flufenamic acid and some compounds related to phenylbutazone.

In animals, but not so in man, indomethacin is deacylated to give 5-methoxy-2-methylindol-3-yl acetic acid. The acetic acid side chain of this compound is not completely free to rotate about the methylene-carboxyl bond and the molecule assumes one of two possible conformations, in each of which the plane of the carboxyl group is perpendicular to the

indole nucleus. The distances between the carboxyl-H and the imino N are either 6.17 or 5.05 Å, so that this molecule could not at all readily fit a histamine receptor (inter-N distance = 4.55 Å) but would fit a serotonin receptor. This may explain why indomethacin is so very potent in the rat, compared with phenylbutazone for example, but not so in other species—because the rat is uniquely sensitive to serotonin as an inflammatory mediator.

In flufenamic acid and other *N*-aryl-anthranilates ('fenamates'), there is a possibility of H bonding between the N and one of the carboxyl O atoms. If the molecule is locked in this configuration, the separation between

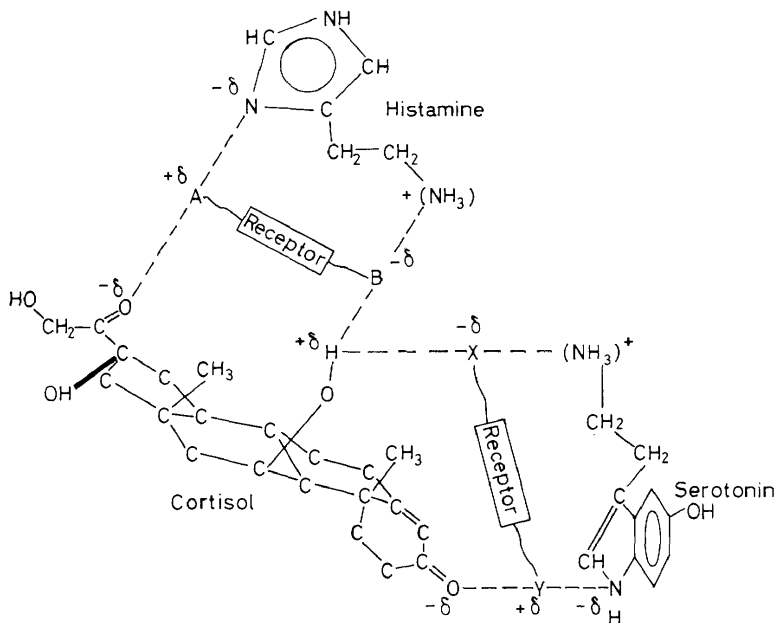


Figure 3. A pictorial representation of Kiers's hypothesis¹⁷, viz. that the cortisol molecule can perhaps bind to both a histamine and a serotonin receptor.

the N and the carboxyl-H is 4.65 Å. Similarly in the unionised salicylic acid molecule, the separation between the phenolic-O and the carboxyl-H (assuming the other carboxyl O engages in intramolecular H bonding) is 4.60 Å. These are astonishingly close to the inter-N distances in histamine.

Phenylbutazone is metabolised in man yielding 2 hydroxylated derivatives. In one of these, the γ carbon of the *n*-butyl side chain is hydroxylated. A further possible metabolite is the γ -keto derivative (3'-oxobutylphenylbutazone) which is a useful anti-inflammatory drug²⁰ and extensively used as an antirheumatic drug in Czechoslovakia under the name Ketazon. This drug is much less potent *in vitro* than phenylbutazone in biochemical test systems²¹ which principally measure drug association with cationic receptors, suggesting it has other pharmacological activities contributing to its anti-rheumatic efficacy. The separation of the 3'-oxo group and the enolic-H

in this molecule can be either 4.4 or 6.0 Å depending on whether the enolic-OH is *cisoid* or *transoid* to the oxobutyl side chain. We might infer that this one molecule, like cortisol, could spread over both a histamine and a serotonin receptor. The distances between a ring carbonyl group and the side chain secondary alcoholic group in one of the phenylbutazone metabolites would presumably be somewhat similar (approximately 4.4 or 6.0 Å).

If we assume (i) that histamine and serotonin bind to non-cationic receptors—a reasonable assumption in view of the fact that these amines are normally cations at physiological pH; and (ii) because of their fairly high pK_a 's, these acidic drugs could be protonated when adsorbed to those compartments of the biophase with low polarity, then the OH function of these steroid and non-steroid drugs (carboxyl, enol, alcohol) might well mimic the amine NH_3^+ in associating with that site on the amine receptors which binds the amine agonist (and we might speculate, also binds these anti-inflammatory drugs) through a hydrogen bond—the micromolecule (agonist, drug) donating the H bond to the receptor macromolecule. This amine-binding site need not necessarily be that which responds to the inflammatory amines in the microcirculation to give hyperemia, oedema, etc. It could be a regulatory site—assuming that amine biogenesis is subject to autoregulation, either through classical end-product inhibition or, more subtly, through an allosteric control mechanism. In either case, these anti-inflammatory drugs might then act as 'false' feedback inhibitors.

The need for some molecular rigidity implied in these discussions may explain why so far, there are as yet no clinically useful aliphatic non-steroid anti-inflammatory drugs apart from sodium aurothiomalate.

Now I would like to discuss just one biological effect of the non-steroid drugs which I find quite paradoxical. We tend to consider the non-steroids only as inhibitors of metabolism. It is well known that the effective steroids such as cortisol may initiate certain metabolic reactions such as liver gluconeogenesis from non-carbohydrate precursors. Dr. Houck and his colleagues^{22, 23} at the Children's Hospital in Washington have found that non-steroids such as indomethacin and oxyphenbutazone (3 mg/kg) and cortisol may 'switch on' enzyme synthesis in rat skin fibroblasts and mouse 'L' cells (fibroblasts) in tissue culture.

These drugs induce the fibroblasts to produce a collagenase (active at pH 5) and some neutral proteases, one of which resembles chymotrypsin and so could destroy kinins. Previous studies have shown that both cortisol²⁴ and these non-steroids²⁵ will inhibit mucopolysaccharide biosynthesis in fibroblasts. The same drug molecule may therefore hasten connective tissue dissolution by both *shutting off* the synthesis of one type of macromolecule and *switching on* the synthesis of another, the catabolic enzymes, to bring about tissue lysis. Obviously a drug which interacts with the cell nucleus to initiate the synthesis of new messenger RNA need only be administered in small quantities since a biological scale-up occurs with one molecule of RNA directing the synthesis of many protein molecules, each of which if they are enzymes, may metabolize many substrate molecules. This is probably why steroid drugs are so effective when compared on a mole/mole basis with many other pharmacodynamic agents. I am amazed but fascinated by

Dr. Houck's discovery that perhaps the unnatural non-steroids may also interact in a positive sense with the nuclear control mechanisms of the gene. This emphasises the need to study possible drug binding to the basic histones and other nuclear proteins which may lose their repressor functions²⁶ on combination with the drugs.

DRUG ACTION AND THE CELLULAR AND EXTRACELLULAR EVENTS IN INFLAMMATION

An analysis of the molecular properties of some current anti-inflammatory drugs should give some insight into the possible mechanism of action of these drugs in suppressing the symptoms, if not the underlying disease processes, associated with stiffness, joint degeneration and loss of mobility in arthritis. However, such insights may not be of much help in finding the new drugs that are still needed—those which may act fairly selectively upon some critical pacemaker event in the maintenance, rather than the establishment, of a chronic inflammatory state with its attendant tissue destruction. *Figure 4* shows some of the postulated sequence of events involving a variety of cell types and some extracellular systems, which may initiate and establish the inflammatory and reparative responses. This diagram shows that there are at least 3 possible cycles enumerated I, II and III which may hinder the spontaneous remission of inflammation and so confer an element of 'chronicity'.

Cycle I is concerned with the sustained release of leukocyte and tissue proteases, resembling trypsin, which degrade kininogen(s) to form the pro-inflammatory kinins.

Cycle II is concerned with the establishment of an 'autoimmune' (more correctly, an auto-intolerant) state wherein the body fails to recognize tissue degradation products and regards them as foreign material, i.e. antigens.

Cycle III is the elevation of circulating globulins, including perhaps kininogen(s) and fibrinogen (which are precursors of the pro-inflammatory kinins and fibrin) as the liver attempts to manufacture more glycoproteins which neutralize circulating proteases.

I am sure other cyclic events may be found, for example controlling mast cell degranulation or cellular proliferation, in which there is a positive feedback of some key chemical stimuli.

We should consider for a moment just how many different types of cells and extracellular systems may contribute to these events shown in *Figure 4*, since they are all potential targets for drug action. An incomplete listing would certainly include the following.

- (i) Lymphocytes and macrophages which may initiate an immune response.
- (ii) Other lymphocytes which, having become sensitized, may initiate tissue destruction²⁷.
- (iii) Phagocytic leukocytes, attracted by chemotaxis which may die and release intracellular (lysosomal) kinin-forming and tissue-destroying hydrolases.
- (iv) Mast cells which may release inflammatory amines and at least one proteolytic enzyme, chymase, closely resembling chymotrypsin²⁸.
- (v) Fibroblasts and epithelial cells which proliferate and initiate wound repair.

- (vi) α -globulin synthesizing cells in the liver.
- (vii) γ -globulin synthesizing cells (plasma cells) in the lymph nodes, chronic granuloma and other sites of injury (e.g., inflamed synovial membrane).
- (viii) The blood platelets which aggregate at the site of injury to cause haemostasis but may fail to aggregate after giving aspirin²⁹ and phenylbutazone³⁰ *in vivo*.

Important extracellular events would certainly include:

- (a) Kinin formation from kininogen which has escaped from the circulation.
- (b) The interaction of the first 7 components of complement³¹ leading to the formation of chemotactic factors which bring neutrophils (polymorphonuclear leukocytes) to the injured area and anaphylotoxin which releases histamine from mast cells.
- (c) The further contributions of the last 2 components of complement which cause cell lysis.
- (d) The transmission of the, as yet, unknown chemical stimuli which cause the connective tissue and lymph node cells to proliferate.
- (e) The production of factors stimulating glycoprotein synthesis in the liver.
- (f) Intravascular clotting which is possibly shortened in duration through activation of fibrinolysis by high concentrations of acidic anti-inflammatory drugs^{20, 32}.

Many of these different cell types and extracellular reactions are sensitive to both steroids and non-steroid drugs and these drugs are therefore effective over a wide front. It would be worth exploring the possibility of evolving some more specific drugs, acting on only one or two cell types or a particular extracellular phenomenon and then seeing how such a drug might influence a chronic inflammatory state. A hopeful pointer in this direction is provided by numerous recent reports that certain immunosuppressive agents, useful in treating lymphoma, may also benefit arthritic patients who have become resistant to the conventional anti-inflammatory drugs. These immunosuppressors have little effect on an acute inflammation but very effectively 'desensitize' the lymphoid apparatus, rather as the steroids may do so, by inhibiting lymphocyte proliferation and possibly even leukopoiesis.

For discussion, I would suggest that it may be profitable to search for at least three new types of drugs.

1. Molecules, perhaps macromolecules, able to 'blindfold' or 'anaesthetize' motile cells so that they would fail to respond to chemotactic and proliferative stimuli and whatever the stimulus is that causes sensitized cells to initiate tissue destruction (e.g., graft rejection). A conceptual and experimental prototype is provided by anti-lymphocyte serum which suppresses rat adjuvant arthritis³³. A small molecule might be equally effective as a cell depressant. For example, the adrenocorticosteroids dramatically inhibit fibroblasts³⁴ and lymphocytes³⁵.

2. Specific inhibitors of proteolytic enzymes and other hydrolases that might be either small molecules which are substrate-related antimetabolites, for example the anti-trypsin drug α ,*N*-tosyl-lysyl-chloro-ketone³⁶ or, paradoxically, the very enzymes whose activity it is desired to inhibit. If these were, for example, proteases obtained from an exogenous source it might be possible to boost the formation of anti-protease glycoproteins by the liver after injecting the exogenous protease. This may be one of the reasons why trypsin and chymotrypsin have proved to be moderately useful anti-inflammatory agents.

3. Antagonists of the chemical factors used in communication between the cells. Such a family of drugs might be patterned after the anti-histamines which are useful in interrupting the pathogenic responses associated with the anaphylactic release of histamine at one site and its uptake at another.

It is clear that a search for any of these three classes of drugs will have to be conducted on a rather more rational basis than the manner in which the pharmacology of rheumatoid disease has been practiced in the past. The chemist might usefully spend less time scrutinizing the patent literature and more time studying the natural factors which promote chronic inflammation and other factors which normally lead to remission of the inflammatory state (for example, those acting at sites A, B and C in *Figure 4*). As 'leads', these are undoubtedly superior to those I discussed earlier in this talk. I only hope that synthetic and natural products chemists will rise to the challenge they present before we have another IUPAC symposium devoted to this subject.

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