THE CHEMISTRY OF NON-Steroidal ANTI-INFLAMMATORY AGENTS

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It is not possible to discuss immediately the chemistry of, and the therapeutic response to, anti-inflammatory agents which do not possess the steroidal skeleton without properly defining the terms. It is even more fundamental, but entirely in order, to make some introductory remarks concerning those small molecules, normally dubbed 'drugs', which are designed to combat diseases of major importance and those diseases normally lumped together under the catch-all phrase 'inflammatory'. At this time it must be recognized that the drugs to be discussed should not be listed under such headings as 'non-narcotic analgesics', 'antipyretics', etc. Even the term 'anti-inflammatory' must be applied with caution since, if properly defined, it reflects only one requirement for a useful drug.

The diseases which we wish to combat adversely affect the joints, bones, ligaments and connective tissues in many parts of the human body. Further, they are of poor prognosis and their exact etiology is still uncertain. Much human suffering is associated with these diseases since they are deforming and crippling. Consequently, they are of great economic importance since a substantial part of the population is afflicted. In other words, we are not very much concerned with sun burns, but with arthritis and rheumatism to name a few. Although it is true that the etiology of these diseases is still uncertain, nevertheless the combined efforts of chemists, biochemists, and pharmacologists have resulted in the emergence of a reasonable pattern which will hopefully prove rational enough to influence research positively and decisively. This pattern is both illuminating and challenging and shows clearly the multiplicity of factors involved. Figure 1 shows that the acute phase is triggered off by the effect of an irritant which causes an insult to tissues. The irritant may be chemical or physical, or an infective agent. In every case increased vascular permeability results as documented by the appearance of the typical signs 'reddening', 'heat', 'swelling' and 'pain' at the site of the injury. The factors which account for the increase in vascular permeability have been discussed at length previously by Whitehouse and others and include the pharmacologically active amines, histamine and serotonin; the kinins formed by proteolysis of serum proteins, proteolytic enzymes such as plasmin and kallikrein. An ill-known globulin factor, sometimes called 'rheumatic factor' has also been described.

If we look now at this very rudimentary scheme it becomes apparent that one should define drugs which combat any part of the normal inflammatory response as truly 'anti-inflammatory'. However, those substances which interfere with the secondary and highly undesirable processes which
induce the self-perpetuating chronic diseases should, more properly, be called ‘anti-rheumatic’ or ‘anti-arthritic’.

It follows logically that anti-inflammatory drugs as defined can hardly be expected to provide more than symptomatic therapy. In order to make them truly useful ‘anti-rheumatic’ agents they should show a multiplicity of other effects such as, for instance, stabilization of lysosomal membranes, restoration of proper cellular energy transfer and balance, inhibition of proteolytic enzymes or possibly even immuno-suppressant activity. Lacking, but most important, is the characterization of the true etiological agent or agents which then, in turn, would permit an all-out effort towards the discovery of truly curative anti-rheumatic drugs.

**Figure 1.** A series of events triggered off by the effect of an irritant to the tissues.

Having considered briefly the impressive difficulties in rationale, attention must now be directed to the complexities which confront us if we set out to find an anti-inflammatory and anti-rheumatic agent. Unfortunately, most experimental animals do not suffer from connective tissue diseases and pharmacologists are thus forced to employ models, hoping that their findings in experimental animals inflicted with various conditions simulating certain phases of the inflammatory process and response may become applicable to man. A whole battery of tests both acute and chronic is normally employed to evaluate potential drugs. Some of the screens are described below:


(B) Chronic tests: Non-established and established adjuvant arthritis test in rats. Carrageenin granuloma test in rats.

Biochemically, simultaneous studies are carried out to collect information on the following parameters:

(a) *In vitro*—inhibition of complex-formation between 2,4,6-trinitrobenzaldehyde and bovine plasma albumin, indicative of the ability of a drug to bind to protein lysyl-ε-amino groups.
In addition the following classical tests are performed:

(a) Hot plate test
   (Acetic acid stretch test) Analgesia
(b) Antipyresis (yeast)
(c) Ulcerogenicity

Having thus set the stage properly, I can now turn to the major topic of this review. A study of the literature may easily lead the novice in this complex field to the erroneous conclusion that active anti-inflammatory agents and effective anti-rheumatic drugs are available in abundance. The reality is grim. Since the introduction of salicyclic acid in 1876 the research efforts in the entire world over more than 90 years (including the ever escalating efforts in this area over the past 20 years) have not yielded more than a few drugs which have proven themselves clinically in the management of rheumatic disease (cf. Figure 2). From this enumeration it already becomes apparent that anti-rheumatic drugs can be very roughly classified into two major categories: acidic and basic. While knowledge accumulates on acidic agents and possible receptor sites are even discussed, very little is known about the basic compounds. And although chloroquine has highly undesirable toxic manifestations, in particular, the unfortunate retinopathic effect, it nevertheless is anti-rheumatic in man.

It would be preposterous to rehash all the chemical aspects of these five agents. Their chemistry and pharmacology has been amply discussed in the literature. As far as phenylbutazone is concerned, the comprehensive review by von Rechenberg is unsurpassed. I am, therefore, only going to mention a few of the less well-known facts about these drugs.
1. The urinary metabolites of Aspirin® in man have been identified: they are salicyluric, gentisic and salicylic acids (Figure 3). Only a minute quantity of acetylsalicylic acid is excreted unchanged. Varying amounts of glucuronides accompany these metabolites. Of the metabolites only salicylic acid has anti-rheumatic effects in high doses.

2. The well known syntheses of phenylbutazone and oxyphenbutazone.

Figure 3. Urinary metabolites of Aspirin® in man.

Figure 4. Metabolism of phenylbutazone in man.
and the success of these compounds have naturally led to a widespread interest in alternative processes and pathways\textsuperscript{6–9}.

The metabolism by pyrazolidine-3,5-dione derivatives in man and in other species has been worked out in a collaborative effort between scientists at Geigy and various other scientific centres, notably by Haefliger and Pfister\textsuperscript{5}, Hermann and Pulver\textsuperscript{10, 17}, Burns and Brodie\textsuperscript{11–14} and Dayton\textsuperscript{18}, to name a few\textsuperscript{15, 16}. Figure 4 gives a short summary of these findings.

The extraordinary differences in the half-life of these drugs in blood plasma in various species are very interesting. Data are given in Table 1 which also shows how difficult extrapolation from experimental animals to man can be.

Intensive structure–activity relationships in the series of pyrazolidin-3,5-diones have been published, for instance, by Schonhofer and Ojurmah\textsuperscript{19} and by Dayton\textsuperscript{18}. In passing it is noteworthy that there exists a definite relationship in man between \( pK_a \) and anti-rheumatic activity. In general, it has been found that those derivatives of higher acidity than \( pK_a \) 4.0 are no longer anti-rheumatic but uricosuric. The result of this research is the uricosuric agent Sulfinpyrazone or Anturane\textsuperscript{®} \((pK_a 2.8)\) which is shown below together with another drug specific for the treatment of gout.

\[
\begin{align*}
\text{Sulfinpyrazone} & \quad \text{Anturane}^\text{®} \\
\text{Allopurinol} & \quad \text{Zyloprim}^\text{®} \\
\text{(Burroughs Wellcome)} & \\
\text{JAMA 187, 220 (1964)} & 
\end{align*}
\]

Although among the oldest non-steroidal anti-rheumatic drugs, phenylbutazone and oxyphenbutazone are by no means obsolete. The scientific
and patent literature shows clearly the continued interest in this class. Some of the examples of this class of drugs are given below.

Wallace and Tiernan  
U.S. Pat. 3 135 764 (1964)

Siegfried  
French Pat. 1 393 596 (1965)

Görgö and Szporny  
*Arzneimittel Forschung* 16, 1211 (1966)

We can now turn our attention to one of the latest additions to the list of useful anti-rheumatic agents, namely indomethacin or Indocin®. The discovery of this agent has been adequately described by Tsung-Ying Shen20 in the excerpts of the International Symposium on Non-steroidal Anti-inflammatory Drugs. The first synthesis was published by the Merck group in 196321 and already at the time of publication more than 350 compounds had been synthesized. Various alternative syntheses have been described in the patent literature22. In general, mono- or di-substituted hydrazines are condensed with suitably substituted γ-ketoacids and the hydrazones subjected to the Fischer indole cyclization (*Figure 5*).

Alternatively, 3-indolylacetic esters were acylated using sodium hydride in dimethylformamide (see, e.g. *Figure 6*). The utilization of the t-butyl ester, easily removable by heating, is especially advantageous in view of the lability of the N-acyl groups in the indole series under mildly alkaline or acidic conditions.

In addition to the syntheses by the Merck group also other approaches have become known. In 1965 Makato Takahashi23 reported the synthesis of 2-methyl-5-methoxy-3-indolylacetic acid via quinoline intermediates (*Figure 7*).

*Figure 5.* General synthesis of substituted indoles.

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In 1966, Kowa Ltd.\textsuperscript{24} in Japan claimed in a patent the synthesis of indomethacin by cyclization of 3-(2'-p-chlorobenzoylamino-5'-methoxyphenyl)levulinic acid (Figure 8). The study of a wide variety of indomethacin-analogues has yielded surprisingly few equipotent substances. As a matter of fact, it appears that the structure is fairly specific and rather sensitive in the negative sense to molecular manipulations. Only the corresponding p-chlorobenzyl analogue shows a pharmacodynamic profile similar in nature to that of indomethacin. As Sarett and Shen\textsuperscript{25} disclosed [at the International Symposium on Inflammation held in Freiburg (Germany)] the compounds shown in Figure 9 are all less active, including the isosteric 'reversed indomethacin'.

Recently, however, the Merck group has prepared the indene analogue of indomethacin and has shown that the cis-form has about one half the activity of the latter. The trans-form is about one tenth as active. The synthesis of the indene analogue and its \(\alpha\)-methyl derivative is shown in Figure 10\textsuperscript{22b, 26}. A careful investigation of the optically active forms of the \(\alpha\)-methylindene derivative, as well as of \(\alpha\)-methylindomethacin had clearly shown that the biological activity is solely due to the dextro-rotatory isomer. The results of crystallographic and rotatory dispersion studies indicate clearly the (S)-configuration for these (+)-compounds. For indomethacin

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\text{Figure 6. Alternative synthesis of 3-indolyacetic acid.}
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\[
\text{Figure 7. Synthesis of 2-methyl-5-methoxy-3-indolyacetic acid.}
\]
itself and its $\alpha$-methyl analogue the correct representation is that given in Figure 11. Based on these results a speculative receptor site has been postulated\(^{29}\) the biological importance of which may be considerable (cf. Figure 12).

The metabolism of indomethacin in various species including man has been studied and clarified\(^{27-29}\). In rats, dogs and other laboratory animals, indomethacin is largely metabolized to its deacylated and demethylated derivatives, excreted as such or as their glucuronide conjugates. In man, the major urinary metabolite is the unchanged drug or its glucuronide. These metabolites have been synthesized\(^{28}\) and have been found to be inactive (cf. Figure 13).

Let us turn now our attention to chloroquine. This compound has found extensive use as an anti-malarial agent. However, during World War II it was observed that this agent showed definite anti-rheumatic properties upon prolonged and chronic administration although the onset of action
seemed to be unusually delayed. These initial findings have been confirmed. The mechanism of action is unclear. Matters are complicated by the fact that it is very difficult to investigate chloroquine in pharmacological tests since it is practically inactive in all. Even in the adjuvant arthritis test only marginal response to the development of secondary lesions can be seen. What is known thus far of the metabolism of the drug has failed to shed light on this puzzle. The well-known investigations of Kuroda and McChesney make it clear that the major route of metabolism in man involves oxidation of the side-chain. However, most of the drug is eliminated as such. Major metabolites are the des-ethyl derivative (I) and the bis-desethyl compound (II). Minor metabolites (III), (IV) and (V) are formed in tiny amounts (cf. Figure 14).

M. W. Whitehouse has advanced the speculation that the simultaneous oxidative metabolism involving both the quinoline nitrogen and the terminal side-chain nitrogen followed by degradation of the side chain 'would almost certainly lead to products which would inhibit ATP formation to some degree by inhibiting electron transport in mitochondria'. Since only a small fraction of the administered drug would be expected to undergo this complex sequence, considerable time would elapse before effective levels
Figure 12. Hypothetical receptor-site for indomethacin.

Figure 13. Urinary metabolites of indomethacin.
of this hypothetical metabolite would be formed. It must be said that there is no evidence in the literature which supports this speculation. Further, one would have to assume that the accumulation of this species would not be interfered with by other enzyme systems.

In view of all the difficulties guidance is sought from biochemistry and immunology. Immuno-suppressive activity of anti-malarial agents in the treatment of systemic lupus erythematosus and allergic diseases is recorded in the literature. Biochemical investigations have failed to demonstrate an appreciable effect on the uncoupling of oxidative phosphorylation and incorporation of $^{35}$S in the synthesis of mucopolysaccharides.

In this respect, metabolites (I) and (V) fare better. Schoenhoefer has shown that chloroquine exerts only moderate inhibitory effects on L-glutamine-D-fructose-6-phosphate aminotransferases. Kurnick and Radcliffe have demonstrated the formation of a DNA-Chloroquine complex in a stoichiometric ratio of 1:10. This complex apparently inactivates deoxyribonuclease inhibitors. As far as clinical side effects are concerned reversible and irreversible eye damage is best known. In summary, chloroquine presents a puzzle but also a challenge. The suspicion is aroused that this compound may be acting on the molecular level and influences the rheumatic process in a much more profound manner than most other anti-rheumatic agents with which the degenerative process progresses under cover of treatment. Therefore, the development of a less toxic and more active, basic anti-rheumatic agent with rapid onset of action is a desirable and potentially rewarding task for research.
The brief outlines on the well documented anti-rheumatic drugs in clinical use will undoubtedly have helped to demonstrate some of the main difficulties and complexities encountered in their screening, development and evaluation. This helps us, however, to exercise the necessary caution in the following discussion on compounds presently in various phases of clinical trial and particularly on those substances which may become drugs of the future.

In Figure 15 are given the structures of those substances which are presently under clinical trial or which have even already been marketed in a limited number of countries. However, the true value of these drugs has not yet been fully ascertained. Mefenamic acid has been marketed as Ponstan® and Ponstel® but so far is mainly claimed effective as an analgesic against inflammatory pain. Flufenamic and meclofenamic acids are apparently more potent—their clinical trial is in progress. A variety of syntheses have been reported in the patent literature and elsewhere. The syntheses of some of these compounds are outlined in Figures 16–19. Alkali salts of o-halobenzoic acids are condensed with substituted anilines in the presence of cupric ion and base or alkali salts of o-aminobenzoic acids are reacted with analogous substituted halobenzenes under the same conditions (see, e.g. Figure 16). Another route involves an interesting rearrangement of arylxybenzylimines (see, e.g. Figure 17). Still other pathways leading to mefenamic acids involve the synthesis of aryl-substituted quinazolinediones, dibenzodiazocinediones and the like followed by alkaline hydrolysis (Figure 18). The synthesis of the starting materials employs the same aryl-rearrangement as mentioned before (see, e.g. Figure 19).

The metabolism of mefenamic and flufenamic acids has been reported. The urinary metabolites of mefenamic acid in man are the 3'-alcohol and
carboxylic acid (cf. Figure 20). The urinary metabolites of flufenamic acid in man are hydroxylated derivatives which are either excreted as such or in the form of glucuronides. The latter are labile towards alkali (Figure 21). A receptor site very similar to that proposed for indomethacin has been put forth for the fenamic acids. The biological significance of this hypothesis is uncertain.

Structure–activity relationships in the series have been discussed by the Parke-Davis group. In order to optimize activity the N-aryl group should
Figure 18. Alternative synthesis of fenamic acids.

Figure 19. The synthesis of key intermediates.
not be coplanar. The replacement of nitrogen by oxygen, sulphur and methylene leads to a reduction of activity. The substitution of nitrogen by various groups causes loss of activity.

The pharmacological properties of flufenamic acids have been described by Winder\textsuperscript{45, 46} and Boris and Stevenson\textsuperscript{47}. All position isomers of N-fluorophenyl-anthranilic acid have been prepared and tested\textsuperscript{48}.

As indicated earlier a number of fenamic acids analogues have been prepared (Figure 22). Glaphenine, marketed in Europe as an analgesic against inflammatory pain deserves some further comments. The hybridization of the fenamic acid principle with the nucleus of chloroquine has resulted in a product which fits the fenamates only on paper, if at all. For one thing, the free acid hardly displays activity in the standard pharmacological tests. The esters are active. The free acid has been demonstrated to be the urinary metabolite in man\textsuperscript{54}. The anti-rheumatic efficacy of glaphenine in the clinical practice requires further clarification\textsuperscript{55}.

Extensive studies on structure-activity relationship have been published\textsuperscript{56-57}. It appears that monosubstitution of the benzene ring in the quinoline moiety by halogen, alkoxy and trifluoromethyl in the 7-position provides the most active compounds. The position of the ester function is important. The ortho isomer is at least four times more active than the meta or para analogues in the edema test used by the French workers\textsuperscript{58}. Loss or reduction of activity is seen when the ester is converted to the free acid, amide, methylketone or hydrazide. The synthesis of these substances offers no new chemistry and is amply documented in the patent literature\textsuperscript{59a-i}.

The developments in the series of arylcarboxylic acids have led to similar studies in the area of arylacetic acids. Some of these agents, shown in Figure 23, have reached the clinical stage. Others have yielded very interesting pharmacological results. 4-Cyclohexyl-3-chloro-α-methyl-phenylacetic acid
Figure 22. Fenamic acid analogues and related compounds.

Figure 23. Some of the arylacetic acids which are in use in the clinical practice.
and particularly the dextro-rotatory form has been described by Shen and collaborators at Merck. The compound is apparently most active in the carrageenin edema essay, having an ED\textsubscript{50} of 0.3 mg/kg p.o. It is of interest to note that the active (+)-form also has the (S)-configuration possessed by indomethacin. The synthesis of the new agent and many of its analogues has appeared in two patents and proceeds via substituted acetophenones according to the scheme outlined in Figure 24. No toxicological and clinical data have so far been presented.

Ibufenac, 4-isobutyl-phenylacetic acid, was first reported by Adams and coworkers to have 'anti-inflammatory properties'. Its synthesis was described in the patent literature. Clinical trials indicated initial efficacy in arthritic patients at one half the dose of Aspirin\textsuperscript{®}. Caution was indicated after it was found that the drug induced hepatotoxic effects upon chronic administration as well as an elevation of serum transaminases in 20–30 per cent of all cases.

The corresponding α-methyl-isobutyl-phenylacetic acid has been described recently. The substance has been named 'Ibuprofen' and is approximately 10 times more active than ibufenac and 20 times more potent than Aspirin\textsuperscript{®} in the u.v. erythema essay. Its optical resolution has been effected and, interestingly enough, no difference in activity has been noted between the pure enantiomers. This contrasts sharply with the findings by the Merck group on other aryl-α-methyl-acetic acids. The urinary metabolites of ibuprofen in man have been characterized and are found to be both the dextro-rotatory enantiomers (Figure 25).

The first clinical report concerning 20 patients with rheumatoid arthritis has appeared. Ibuprofen, in this double-blind study with doses up to 900 mg daily for 7–14 days proved to be ineffective.
Detailed pharmacological and toxicological data on Naphthypramide and \( \alpha \)-methyl-\( \alpha \)-2-piperidinoethyl-1-naphthylacetic acid, shown in Figure 23 have appeared in the literature\textsuperscript{70–73}. No clinical evaluation is available. To complete this series, the following structures represent the various related agents.

\[\begin{align*}
\text{(Rhone-Poulenc)} & \\
\text{(Rhone-Poulenc 16 091)} & \\
\text{(C.P 1044 J3)} & \\
\text{(Mead Johnson MJ 1983)} & \\
\text{Namoxylrate (Warner-Lambert)} & 
\end{align*}\]

\( \rho \)-Anilino-phenylacetic acid\textsuperscript{74} has shown high activity in both the carrageenin and u.v. edema tests. The substance is also active in the adjuvant
arthritis test. R.P. 16·09175, 76 has been found active in the carrageenin granuloma, carrageenin edema and u.v. erythema tests. It also has analgesic and anti-pyretic properties and in three-month toxicity studies in dogs and rats, a 'no-effect safe level' was seen at 60 mg/kg/day.

*p*-Butoxyphenylacethydroxamic acid (C.P. 1044 3) has been studied and the pharmacological and toxicological results have been published77, 78. Clinical data is not available. Mead Johnson's 4-biphenylyl-3-hydroxybutyric acid (M.J. 1983) is claimed to have four times the activity of indomethacin in the u.v. erythema test79.

Namoxyrate, a salt of 2-(4-biphenylyl)butyric acid with dimethylaminoethanol has been repeatedly reported as a clinically effective anti-rheumatic agent80, 81, 83. Its metabolism in the rat has been described82.

Mention should also be made of two benzoxazines (A 350 and A 302) which, in a way, can be considered as derivatives of salicylamide. A 302 has shown some activity in standard anti-inflammatory tests84. The pharmacology of A 350 was already reported at the International Symposium on Non-steroidal Anti-inflammatory Drugs in Milan (1964)89. The compound is known to be active in edema essays and to exert a mild CNS-depressant action. No new developments have taken place since.

I would now like to describe a number of compounds possessing structures unrelated to those previously discussed. Short mention should first be made of benzydamine. This agent was extensively discussed at the International Symposium in Milan in 196485. Since then the chemistry of benzydamine has been published86, and its absorption and elimination in mice, rats, dogs and man has been studied87. It appears that benzydamine, upon oral administration to man, leads to prolonged blood plasma levels at the dose
of 70 mg/patient. Fifty per cent of the drug was recovered from the urine in unchanged form. The chemical nature of the metabolites has not yet been determined. During a subchronic toxicity study in rats and dogs the possible anthelminthic activity of benzydamine was noted. The synthesis of benzydamine is straightforward and proceeds as described in Figure 26. Further reports evaluating this agent as an anti-arthritic in man are awaited with interest.

Workers at Upjohn have reported interesting anti-inflammatory data on 2,3-bis(p-methoxyphenyl)indole or ‘Indoxole’. The synthesis of this compound has been described in a number of patents and in a recent publication by Smuszkovicz and coworkers. It proceeds normally by the application of the Fischer indole synthesis to the phenylhydrazone of deoxyanisoin. Alternative routes involve the condensation of aniline with p-anisoin. The pharmacology of the drug has been published. The oral potency is apparently very much dependent upon the vehicle employed. The intrinsic activity in animals is reflected by efficacy in the adjuvant treated animals as well as in the carrageenin-induced edema. No clinical
studies evaluating the anti-arthritic activity of Indoxole have so far been published. The suppressive effects of the agent in crystal-induced synovitis in man has been the subject of a study and it has been shown that a large dose of $3 \times 800 \text{ mg/13 hours}$ produces measurable levels of Indoxole in serum and synovial fluids of patients.

Another agent reported to be effective in the clinic is Armour's 5-amino-1-phenyl-1-(H)-tetrazole (Fenamole). The activity of Fenamole has been related to the copper chelating properties of this species. Its pharmacology has been recorded by Bobalik and coworkers. They have shown that the drug is practically equipotent to phenylbutazone in the inhibition of adjuvant induced arthritis. The clinical efficacy, if further confirmed, would immediately call for in-depth studies of the mechanism of action. Very recently, 5-n-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (Paramidin®) has been claimed as a new anti-arthritic agent. Its synthesis has been described and proceeds as outlined in Figure 27. Pharmacological studies have shown that the drug apparently inhibits capillary permeability, rat paw edema induced by carrageenin and adjuvant arthritis. No anti-spasmodic, local irritation and sodium or potassium retention-properties were observed. Clinical studies have not yet been reported.

Into the category of experimental drugs belong also derivatives of imidazoles on which we at Geigy Ardsley have worked for some time. GPA 878

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\text{Fenamole (Armour)}
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\text{Paramidin® (Takeda)}
\]

\[ \text{Figure 27. Synthesis of Paramidin®.} \]
or metazamide may be mentioned here. This compound is active in standard pharmacological anti-inflammatory tests. The synthesis of compounds of this class can be accomplished in a number of ways. Chemically most interesting is the route outlined in Figure 28.

Various patents relating to pyrazolo-pyridinones have recently appeared and one of the agents of this class has been claimed to be very active in the...
granuloma pouch test. Most prominent in this respect appears to be SU 15 335. The utilization of a p-fluorophenyl-substituted pyrazole as part of an anti-arthritic molecule is not new. Some of the most potent cortisone analogues display this feature as shown in the above structure. It will indeed be very interesting to learn more about SU 15 335.

Another CIBA-development is ‘Glyvenol’ (CIBA 21401-Ba). This substance antagonizes in vitro the smooth-muscle action of a large number of biogenic amines such as histamine and serotonin and polypeptides such as bradykinin. Also antagonized is the accelerated migration of leucocytes induced by endotoxin and the Schultz-Dale antigen/antibody phenomenon. In vivo, anti-allergic properties against systemic anaphylaxis and activity in the dextran-induced edema test were seen. The future fate of this agent is of interest in the light of its unusual structure and its interesting biochemical pattern.

Finally, I should like to mention that immuno-suppressive agents and their potential anti-rheumatic properties receive increasing attention. This is based upon the suggestion that rheumatoid arthritis may conceivably result from a disturbance of endogenous immune mechanisms. The availability of the adjuvant arthritis test has made it possible to screen immuno-suppressives relatively simply. In this way some of the interesting substances described above were discovered. I.C.I. 43 823 prevents secondary lesions in the rat, but is not effective against the primary lesions. I.C.I. 47 776 inhibits the development of polyarthritic lesions and auto-immune syndromes in the rat. Unfortunately, no clinical reports on these substances have so far appeared.

Figure 29. Immunosuppressive agents.
It is to be hoped that the development which started with Aspirin®, and led to a variety of drugs with definite beneficial clinical effects such as phenylbutazone and indomethacin, will eventually result in the discovery of truly curative and causal agents.

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