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COMMENTARY

ENDOGENOUS ANTI-INFLAMMATORY PROTEINS

D. A. LEWIS

Pharmacological Laboratories, Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET, United Kingdom

Inflammation is characteristic of the rheumatic diseases and when it persists it is accompanied by destruction of connective tissue. An essential part of the modern treatment of the rheumatic diseases is the use of anti-inflammatory drugs. Unfortunately these drugs have side-effects and since the nature of the disease often demands long term drug therapy the problem of side-effects is a major one particularly when steroids are employed in treatment. Much effort has been devoted to developing new drugs, particularly non-steroidal ones, that are less toxic to the patient. However despite the efforts of medicinal chemists it appears unlikely, in the near future at least, that a major breakthrough will be made in this field of synthetic chemistry. The development of new anti-inflammatory drugs suffers from the disadvantages that no satisfactory animal model for the rheumatic diseases exists and the etiology of the human diseases is largely unknown. Consequently research leading to the production of new anti-inflammatory drugs must be largely empirical in approach.

This approach has produced drugs that are undoubtedly beneficial to the patient but the biochemical action of these drugs is poorly understood. Although drugs may relieve the pain and inflammation in arthritic joints it is by no means certain that they inhibit the crippling erosions of connective tissue in such serious diseases as rheumatoid arthritis. It is well documented that natural remissions occur in the rheumatic diseases. Certain specific conditions (e.g. pregnancy [1], viral hepatitis [2]) often result in the remission of the disease. Furthermore sometimes spontaneous remissions occur but the patients have a greater risk than normal of rheumatoid disease reoccurring.

The biochemical events in these remissions is unknown but the fact that such remissions occur has stimulated efforts to elucidate the molecular mechanisms involved. This commentary is concerned primarily with the role of endogenous anti-inflammatory proteins which, for the purposes of this commentary, are defined as proteins which can mediate against biochemical mechanisms induced by inflammation. Due to the heterogeneous nature of inflammatory mediators the possibility exists that other molecular species may also have anti-inflammatory properties.

It is known that inflammatory exudates contain substances with anti-inflammatory properties [3] which inhibit a range of features associated with inflammation in animals such as the deposition of granulation tissue [4], the oedema induced by carrageenin [5] and delayed hypersensitivity [6]. It is likely that some, or all, of these substances are proteins.

Anti-inflammatory proteins

It has been shown that the implantation of irritant substances at one site has an anti-inflammatory effect at other sites in the animal [7]. There are various explanations for this phenomenon. It is possible that anti-inflammatory substances are produced at one site and transported in the circulation to the other, or that in response to local inflammation, anti-inflammatory substances are synthesised at a central site (e.g. liver) and enter the circulation. A third possibility is that a 'counter-irritant' action would lead to competition between inflammatory stimuli for mediators or for their precursors [8]. The implantation in animals of irritants such as polyester sponge caused inflammatory exudates which contained substances with both irritant [9] and anti-inflammatory properties [5]. This anti-inflammatory substance was separated from the irritant substance by Sephadex G150 gel filtration followed by preparative polyacrylamide gel electrophoresis [10]. The anti-inflammatory activity was associated with a protein fraction that migrated electrophoretically between the α-glycoproteins and transferrin. The final product represented a 75-fold purification on a weight basis over the freeze dried crude inflammatory exudate and its anti-inflammatory activity was measured against the carrageenin rat model. At a dose of 8 mg kg^{-1} (s.c.) the oedema was suppressed by 55 per cent. In this animal model the effectiveness of this protein fraction is of the same order as that of many established non-steroidal drugs [11]. It has been suggested that the liver is the site of the synthesis of anti-inflammatory proteins, since in animals injured by sponge implantation proteins with anti-inflammatory activity have been isolated from the plasma and have been detected in perfusates of livers [12]. The synthesis of the anti-inflammatory proteins was blocked by treating the rats with actinomycin D. Although these experiments show that inflammatory injury induces the synthesis of anti-inflammatory substances, there is evidence that substances may be present in plasma of normal rats, although in much lower concentration. In other work it was found that the plasma from adrenalectomised Wistar rats had anti-inflammatory activity in the carrageenin rat model [8]. An anti-inflammatory activity of a high molecular weight protein fraction isolated from normal Wistar rat plasma has been shown in the carrageenin and arthritic rat models [13].

The stimulating action of inflammation on the biosynthesis of anti-inflammatory proteins by the liver

is not an immediate one for appreciable amounts of the proteins were only found in plasma and exudates 3–4 days after the original injury [14]. This delay in the response of the liver to injury was found in other work [15] when the liver toxin dimethylnitrosamine was administered to rats with induced adjuvant arthritis. The anti-inflammatory action induced by the toxin was only evident 3 days after its administration. Furthermore saline extracts of livers taken from rats treated with dimethylnitrosamine had anti-inflammatory activity when injected (i.p.) into rats with adjuvant induced arthritis. It was noted that the activity was only present in extracts from livers taken from rats that had been treated 3 days previously with the toxin. This delay of 3 days eliminated the possibility that the toxin itself was anti-inflammatory since dimethylnitrosamine, like other alkylating agents, is rapidly metabolised by the liver. The possibility that endogenous corticosteroids contributed to the anti-inflammatory properties of the inflammatory exudates was eliminated by the use of adrenalectomised rats or by monitoring corticosteroid concentrations [5]. However the anti-inflammatory action of inflammatory exudates may be explained in part by their ability to stimulate corticosteroid production. In a recent experiment [16] the exudate produced by carrageenin in rat plantar tissue contained a factor of unknown identity that elevated corticosteroids in other rats when the exudate was administered by injection (i.p.). This factor appeared at an early stage in the exudates whereas proteins with anti-inflammatory activity appeared later. It is possible that the corticosteroid stimulating factor was itself an irritant because the irritant action of inflammatory exudates has been correlated with the appearance of anti-inflammatory activity [17] and it is known that the corticosteroid levels rise in the circulation after inflammatory stimuli [18]. The nature of the irritant fraction in inflammatory exudates is not known but it may contain enzymes, or their products, and products of cell and tissue damage arising from the inflammation.

It is likely that other factors with anti-inflammatory activity in addition to proteins or hormones are present in human blood. A substance active in the carrageenin rat model and which can also inhibit the release of chemotactic and anaphylatoxic factors from rat and guinea pig serum has been described. The active substance has a mol. wt below 500 daltons and is resistant to acid and to proteolytic hydrolysis [19, 20].

The methods employed in the examination of plasma and of other fluids for substances with anti-inflammatory activity are very similar to those employed in testing synthetic compounds in conventional screening programmes. Consequently very little information is gained of the biochemical mode of action of the substance under test. An alternative approach has been taken by other workers who examined both normal and diseased mammalian tissues, such as blood, connective tissue, synovial fluid and inflammatory exudates for substances with biochemical properties that suggest that they may have a retarding action on inflammatory disease. This approach has an advantage in the fractionation of protein mixtures because a single protein can be identified with a specific biochemical property.

Lysosomal membrane stabilising proteins

The central role of lysosomes and of lysosomal enzymes in inflammation is well established. Lysosomal enzymes have been associated with both the inflammation and the destruction of connective tissue in rheumatoid disease. Leucocyte destruction and the release of their granule contents (the granules are similar to lysosomes) have been associated with vasodilation, oedema, tissue disintegration and the chemotactic accumulation of leucocytes, all of which would perpetuate and extend the inflammatory reaction [21, 22]. Anti-inflammatory drugs have proved to be useful tools in probing the role of the lysosome in inflammatory disease and the discovery that steroids [23] and some non-steroidal drugs [24] can inhibit the release of enzymes from lysosomes has encouraged some workers to examine endogenous substances for similar properties. The release of lysosomal enzymes into the blood [25], and into inflammatory exudates, in parallel with the inflammation in rats with adjuvant induced arthritis has been reported [26]. The inflammation associated with this model induces the appearance in the blood of a substance with charge properties similar to that of an α_2-globulin [27]. The molecular weight of the protein was found to be greater than 170,000 daltons on the basis of Sephadex G200 gel filtration. It reacted with the membranes of both normal washed rat erythrocytes and isolated rat liver large granules and it was responsible for the stabilising action of arthritic rat sera on rat liver lysosomes *in vitro*. The possibility that the stabilising action of the sera was due to circulating corticosteroids or antibodies was eliminated. The tentative suggestion was made that the protein was an 'acute-phase' protein. However other work [28] has shown that dialysed plasma from normal rats has the ability to inhibit Triton X-100 induced lysis of granules of rabbit polymorphonuclear leucocytes. In these experiments it was found that the stabilising action of the plasma decreased during adjuvant induced arthritis. This finding may indicate species differences in the adjuvant rat model since the persistence of inflammatory symptoms in this series of experiments [28] was different from that in the strain of rats employed in the earlier work [27]. Human sera also has the ability to stabilise rabbit polymorphonuclear leucocytes against lysis [29] by Triton X-100, and this property is sharply elevated during the last 3 months of pregnancy, a period when rheumatoid arthritis often regresses in patients. Although the factor in 6–9 month human pregnancy sera has not been identified the possibility that the stabilising action of the sera was due to increased corticosteroid levels was eliminated. Synovial fluid aspirated from patients with rheumatoid disease can also stabilise rat liver lysosomes *in vitro* [30]. This stabilising action of the fluid was abolished by pre-treatment of the fluid with trypsin. In these experiments it was shown that proteins in the synovial fluid were responsible for its stabilising action on the lysosomes. Rat liver lysosomes were incubated with freshly aspirated human rheumatoid synovial fluid and after lysis and washing, the isolated rat liver lysosomal membranes were used to raise anti-sera in rabbits. The anti-sera was used in immunoelectrophoresis studies on human rheumatoid synovial fluid and two precipitin lines

were obtained in the α/β globulin region. Recent work (unpublished) in our laboratory has shown that these proteins bound by rat liver lysosomes react with commercial anti-sera against human plasma proteins but not with commercial anti-sera against human α_2-macroglobulin. When the rheumatoid synovial fluid was fractionated by Sephadex G200 gel filtration both of the proteins were detected in the higher molecular weight α/β globulin fraction and not in the immunoglobulin (150,000 daltons) fraction. In our experiments it seems likely that the proteins present in the synovial fluid, that can stabilise rat liver lysosomes, are normal plasma proteins. Anti-bodies raised by lysosomes can also stabilise the lysosomal membrane directly since immunoglobulins in anti-sera produced in the rabbit against rat peritoneal leucocyte granules have been reported to stabilise rat liver lysosomes *in vitro* [31].

Although proteins stabilising lysosomal membrane have properties that suggest that they may be anti-inflammatory, there is no direct evidence that they have an anti-inflammatory action against the usual animal models. Further investigations of the biochemical properties of these proteins would appear to be justified since they could gain access to lysosomes *in vivo* by pinocytosis or alternatively these proteins may be synthesised within cells containing lysosomes (e.g. stimulated lymphocytes) and attached to lysosomes *in situ*.

Anti-proteases

The central role of intra- and extra-lysosomal proteases in the biochemical pathology of inflammatory disease, together with the wide incidence of protease inhibitors throughout the plant and animal world has stimulated investigations into the possible role of both exogenous and endogenous inhibitors in controlling inflammatory disease. The distribution and the clinical use of protease inhibitors has been extensively reviewed [32–34]. A survey of naturally occurring protein inhibitors shows that in the main they are polypeptide in character and that they can be broadly divided into a group of relatively small molecules (6000–12,000 daltons) stable to acids and to heat and a group of larger, more labile, polypeptides (20,000–60,000 daltons). There are some notable inhibitors outside this range such as the important plasma anti-proteases α_1-macroglobulin and α_2-macroglobulin (about 800,000 daltons). There is no common spectrum of action for these inhibitors since some inhibit only one enzyme whilst others are polyvalent against a variety of proteases. It is this latter type of protease inhibitor that is of interest in the study of inflammatory disease.

Direct anti-inflammatory activity has been associated with protease inhibitors. The inflammatory symptoms of kaolin arthritis in the rat are strongly suppressed by the soybean inhibitor (i.p.) [35] and the potato inhibitor (i.v.) [36]. The bovine inhibitor aprotinin (Trasylol) has been used experimentally in the treatment of rheumatoid arthritis where its anti-rheumatic action was found to approach that of the corticosteroids [37]. Trasylol is also anti-inflammatory in the various oedema rat models [38], in the adjuvant arthritis rat model and [39] in the dextran rat model [40] where it was reported to reduce the acid and neutral protease activity in serum. A similar result was obtained with sodium urate induced inflammation in the skin and joints of rabbits [41] where Trasylol was found to reduce the proteolytic activity of polymorphonuclear lysates at both acid and neutral pH. A preparation of rat plasma protein that was anti-inflammatory against the carrageenin and adjuvant arthritic rat models also inhibited trypsin and it was found that 20 mg of the preparation contained the same activity as 5 ml of rat blood [13]. Endogenous protease inhibitors have been found in a variety of mammalian tissues and fluids. The best known are the plasma anti-proteases and since these are polyvalant in their action much interest has been aroused in the possible role of these substances in inflammatory disease. Plasma anti-proteases may have defensive roles in a number of diseases [42, 43]. The possible role of the anti-proteases in rheumatoid disease is part of this commentary.

α_1-Antitrypsin [44]. This anti-protease is the most abundant anti-protease in blood (2 g/l) and is responsible for about 90 per cent of the trypsin inhibiting capacity of blood. It is also present in other tissues, in mast cells [45] and macrophages [46]. The protein is α-glycoprotein with mol wt reported over the range 47,500–55,000 daltons and it migrates on electrophoresis with the α-globulins. Its half-life in plasma is 2–4 days. It is polyvalent in its anti-proteolytic actions and it binds proteases such as kallikrein [47] the granulocytal enzymes elastase and collagenase [48] and skin and synovial collagenases [49, 50] all enzymes associated with inflammation, in a 1:1 molar ratio [48]. However not all collagenases are bound by α_1-antitrypsin. A neutral collagenase isolated from human gastric mucosa is not inhibited by α-antitrypsin [51] and neither are the acid proteases [52]. The main anti-collagenlytic activity of plasma is usually attributed to α_2-macroglobulin rather than α_1-antitrypsin [53]. α_1-Antitrypsin has two overlapping active sites, one contains an arginyl residue and reacts with residues that split peptides at arginyl residues and the second contains an aromatic amino acid or leucyl residue and splits peptides at this type of residue. There is also an inhibitor site that inactivates serine proteases [54].

There is an association between α_1-antitrypsin and rheumatoid arthritis [55]. Heterozygotes for the deficiency gene for α_1-antitrypsin have been found to have a risk factor between three to four times the average for adult classical, or definite, rheumatoid arthritis. The risk is of practical significance, for the average incidence of rheumatoid arthritis in adults aged over 45 yr in the U.S.A. has been reported to be 1.3 per cent of the population. The risk amongst homozygotes for the deficiency gene is probably much higher but there is little data connecting this type of deficiency with adult rheumatoid arthritis. This is not surprising since these individuals usually fail to survive early life due to pulmonary disease. In rheumatoid disease the blood and synovial fluid levels rise over normal values [56]. Its level also rises in serum in acute inflammatory conditions where it behaves as an acute phase protein [57]. The levels of α_1-antitrypsin in rheumatoid synovial fluid appear to be influenced by the protease levels in the fluid since it was found that the amount of active α_1-antitrypsin

present varied inversely with the neutral protease activity of the fluid against hide powder Azure [39]. A similar relationship between protease activity and α_1-antitrypsin levels has been found in the sera and plasma of rats with adjuvant induced arthritis [58]. The levels of α_1-antitrypsin fell as the arthritis developed. At the same time the proteolytic activity of the blood increased, presumably due to the leakage of proteases from the inflamed sites into the circulation. It is of interest that the administration of cortisol to both adjuvant arthritic and normal rats elevates α_1-antitrypsin levels above normal values [58] suggesting the possibility that cortisol may exert at least part of its anti-inflammatory activity by elevating α_1-antitrypsin levels in the circulation. Plasma α_1-antitrypsin levels also rise in pregnancy to double the normal values [59] and in hepatitis [60] and it is known that remission of rheumatoid disease can occur in both conditions. In this laboratory (unpublished) we have repeated the work on the anti-inflammatory action induced by the liver toxin dimethylnitrosamine on adjuvant induced arthritis in the rat [15]. In addition to confirming the anti-inflammatory action induced by the toxin we have found that the toxin elevates plasma α_1-antitrypsin levels and that this anti-protease is also present in significant amounts in the dialysed saline extracts prepared from the livers of rats that had been treated three days previously with the toxin.

Protease-α_1-antitrypsin complexes have only a slightly larger Stoke's radius than the free antiprotease. However, the penetration of the free antiprotease into cartilage may be slow since although the degradation of cartilage proteoglycans by human leucocyte elastase and 'chymotrypsin like' enzyme can be inhibited by preincubation of the enzymes with α_1-antitrypsin, when α_1-antitrypsin was added to the incubation medium it failed to penetrate cartilage slices and thereby prevent its degradation [61]. Both α_1-antitrypsin and α_2-macroglobulin-protease complexes are cleared from the circulation. Experiments in the dog with radio-iodinated trypsin suggest a mechanism for this clearance since α_1-antitrypsin-trypsin complexes were dissociated by α_2-macroglobulin which firmly bound the trypsin. The new complexes were rapidly eliminated from the circulation by the recticuloendothelial cells [62]. The rapid uptake of protease-macroglobulin complexes by rabbit alveolar macrophages has been described [63] but protease-α_1-antitrypsin complexes were not taken up by these cells [63].

Serum β_1-protein inhibitor. This inhibitor has recently been discovered in human plasma [64]. It was separated from α_1-antitrypsin and α_2-macroglobulin by gel filtration on Sephadex G200 and Sephadex G100 superfine with an intermediate ion exchange chromatography step on DEAE-Sephadex. When examined by agarose electrophoresis it migrated as a single band in the β-globulin region. Its mol. wt is about 40,000 daltons. It has inhibitor properties that suggest that it may have a function in rheumatoid disease since it was found to be an effective inhibitor against neutral collagenases present in gastric mucosa, rheumatoid synovium, skin and granulocytes. In view of its smaller molecular size it is likely to be more diffusable than α_2-macroglobulin in tissues and therefore more likely to reach focal points of inflammation. Its activity, as known at present, is directed towards the metal dependent collagenases and the name 'β_1-anticollagenase' is proposed for this inhibitor [65].

α_2-Macroglobulin [44]. The macroglobulin antiproteases are important plasma inhibitors and the plasma levels vary from about 4.5 g/l. at 1 3 yr to level out at about 2 g/l. at 25 yr. The plasma levels in women are about 20 per cent higher than in men [66]. Its mol. wt is in the range 725,000–820,000 daltons but there is no clear picture of its quaternary structure. Electron microscope studies have presented an image similar to two beans facing each other [67]. Several degradation studies suggest an eight chain subunit structure with dimers of these chains forming stable quarter molecular intermediates with a mol wt of 196,000 daltons [68]. α_2-Macroglobulin has a broader spectrum of activity than α_1-antitrypsin. It can bind irreversibly with most of the proteases associated with inflammation [69] such as the serine proteases including kallikrein, the granulocytic enzymes including elastase and collagenases, the thiol proteases including cathepsin B_1, the carboxyl proteases including cathepsin D and the metal proteases with collagenolytic activities. The inhibition of these enzymes is important since neutral collagenases and cathepsin B_1 are capable of attacking the triple helix region of collagen [70] and both cathepsin D and B_1 degrade proteoglycans [71]. Lysosomal enzymes including the cathepsins are elevated in rheumatoid synovial fluid [72] so the presence of α_2-macroglobulin and its concentration may be important in inhibiting degradation of cartilage.

Opinions vary on whether α_2-macroglobulin is monovalent or bivalent in its interaction with proteases [69, 73]. Its broad specificity towards proteases is explained by a theory that the approaching protease induces conformational changes in α_2-macroglobulin which result in the protease being irreversibly bound in a complex with the antiprotease [69].

α_2-Macroglobulin levels are elevated in the plasma during pregnancy [74]. In one survey of patients with rheumatoid disease [75] α_2-macroglobulin was detected in synovial fluid, but, in about 25 per cent of the patients, the inhibitor was present in an inactive form. It was, however, active in the sera from these patients. In patients with osteoarthrosis about 60 per cent lacked the active antiprotease in their synovial fluids. The absence of active antiprotease in some fluids suggests that the supply was exhausted owing to excessive proteolytic activity. Since the molecule has a large Stoke's radius it is probable that replenishment from the plasma is slow. In the rat, α_2-macroglobulin only appears in response to inflammation and is therefore an acute phase protein in that species. In plasma of normal rat and of other species, α_1-macroglobulin has similar inhibitory properties to α_2-macroglobulin. During adjuvant induced arthritis in the rat the trypsin protein esterase activity in plasma due to the two macroglobulin (α_1 and α_2) antiproteases rises in response to inflammation [76]. The administration of cortisol lowers these levels of activity towards normal values, but this is probably due to the anti-inflammatory activity of the steroid since cortisol has no effect on α_1-macroglobulin plasma levels in the normal rat [76]. In a recent paper a suggestion was made for another role for α_1-antitrypsin and α_2-macroglobulin, it was found

that the pretreatment of washed human neutrophil polymorphonuclear leucocytes with the antiproteases increased the transient random migration of the cells but inhibited their chemotactic responsiveness to C_{5A} (a fragment of the fifth component of complement) [77]. It is possible that the interaction of the antiproteases with surface receptors influenced their responsiveness to chemotactic factors.

Other human antiproteases [44]. These are the minor antiproteases and although there is no evidence at present to connect them with anti-inflammatory action they may merit further study. Inter-α-trypsin inhibitor is responsible for about 3 per cent of the trypsin inhibiting capacity of plasma and its concentration in plasma is 0.2–0.7 g/l. Its biological function and variations in disease is largely unknown but it is present in high concentrations in rheumatoid synovial fluid [78]. It may be identical to the inhibitors of secretion in the mucosal membranes of the upper respiratory tract which protect the epithelium from granulocytic proteases [79]. Antichymotrypsin (an α_1-glycoprotein) binds chymotrypsin but not trypsin *in vitro*. Its plasma concentration is about 0.5 g/l. and it behaves as an acute phase protein after surgical trauma, myocardial infarction and acute bacterial infections [80]. Its concentration in bronchial secretions is higher than that of other plasma proteins apart from IgA and this may reflect a defence function for this antiprotease [81].

Other endogenous protease inhibitors. Our knowledge of these is somewhat scanty. However, the wide distribution of these in tissues is established and in some places (e.g. lung) [82] they appear to be identical to the smaller plasma antiproteases. The intracellular distribution of antiproteases may be particularly important in lysosome enriched cells such as macrophages. In the rabbit polymorphonuclear leucocyte a neutral histonase (neutral protease) was located within the azurophil granules but it was inhibited almost completely by an inhibitor in the supernatant obtained by the subcellular fractionation procedure [83]. This inhibitor may have been located in the cytoplasm or in secondary lysosomes that lysed during the separation procedure. Since the plasma is a potent inhibitor of neutral proteases the inhibitor may have been taken into the cells by pinocytosis. This possibility is of interest because it is well known that endocytosis and macrophage activity at inflammatory sites and the uptake of plasma inhibitors by endocytosis from plasma and the consequential intracellular merger with primary lysosomes might inactivate lysosomal proteases *in situ*. This possibility would appear to warrant further investigation. Protease inhibitors of unknown identity have also been reported in rat liver microsomes and cytoplasm [84].

Conclusions

The evidence accumulating for the existence of anti-inflammatory proteins would suggest a real role for their proteins rather than their dismissal as artifacts. Although suggestions as to their mode of action are speculative at this stage, the evidence is consistent with both lysosomal membrane stabilising proteins and plasma antiproteases acting as anti-inflammatory proteins. The disadvantage of the membrane stabilising proteins appears to be their low resistance to proteolytic degradation and the disadvantage of the plasma antiproteases appears to be their relatively slow rate of penetration into connective tissue leading to the possibility of upsetting the protease-antiprotease balance at focal sites of inflammation. The liver would seem to have a central role in the production of anti-inflammatory proteins but its synthetic response to inflammatory stimuli is relatively slow and consequently this response is probably more important in the later stages of inflammation. The early defensive response in acute inflammation may well involve lower mol. wt substances, produced locally and acting against inflammatory mediators.

The endogenous anti-inflammatory proteins offer a possible therapeutic advantage in that they are unlikely to have the side effects associated with conventional anti-inflammatory drugs. Their most promising mode of use would appear to be a lysosomotropic agents [85] entering the cell by endocytosis. Proteins have been encapsulated in liposomes [86] and a target oriented carrier of this type would appear to be a possibility. Another approach to a new therapy would be to search for substances that stimulate the synthesis of anti-inflammatory proteins by the liver, or to increase our knowledge of the amino acid sequences in the active sites of the smaller plasma antiproteases which might lead to the synthesis of low molecular weight peptide inhibitors with low antigenic activity.

Undoubtedly, the best way of treating the rheumatic diseases is to treat the primary source of the inflammagenic stimulus. Failing this a drug that breaks or slows the cycle of self perpetuating stimuli that is the characteristic feature of the auto-immuno diseases would be a useful advance. Since a synthetic drug with this property has yet to be discovered the continued search for an endogenous factor would appear to be justified for it appears to offer a more systematic approach than present methods to the treatment of rheumatic disease.

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