

## SPECIAL ARTICLE

## SOME BIOCHEMICAL ASPECTS OF FIBROGENESIS AND WOUND HEALING\*

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THIS review is not intended to be exhaustive since it is aimed not at the specialist in this field but rather toward the physicians and surgeons whose work brings them into close contact with the problems of the structure and function of the connective tissues and their maintenance and repair. These tissues are the most ubiquitous of all the animal tissues, and through them must pass the nutritive substances and metabolic products of the cells. This means that any impairment of the integrity of these tissues must inevitably have widespread implications. Their function as structural elements is, of course, also of paramount importance.

This review is mainly concerned with the biochemistry of fibrogenesis, but use is also made of the results of histologic and biophysical studies to supplement the biochemical studies, in order to present a more complete picture. Considerable confusion exists in the literature concerning the nomenclature of the collagenous proteins and the identity of the ground substance, these being the two main extracellular components of most connective tissues, and some space is devoted to an attempt to clarify this situation.

## COMPONENTS OF CONNECTIVE TISSUE

Morphologically, the connective tissues are made up of a number of components present in varying proportions depending on the type of connective tissue. The main division is between cellular and extracellular elements. The latter are also complex and contain the fibrous components collagen, reticulin and elastin, and an amorphous material collectively known as the ground substance.

## Collagen

This fibrous protein was studied mainly as a source of raw material for the leather and gelatin industries until recently, when the increased interest in the so-called collagen diseases led to a considerable amount of work on collagen as a biologic entity. Collagen has a unique amino acid composition with high concentration of proline, hydroxyproline and glycine and low concentrations of aromatic amino acids such as tyrosine.<sup>1-3</sup> From studies of collagen in solution it has

been concluded that the macroscopic fibers are built up from a fundamental collagen particle, which has been named "tropocollagen"<sup>4</sup> and which behaves as an elongated, stiff rod having the dimensions 3000 Å in length and 14 Å in diameter.<sup>5</sup> The underlying molecular structure of the protein as determined by x-ray diffraction studies is one of a three-chain helix whose rigidity comes from intramolecular hydrogen bonds.<sup>6,7</sup> Examined under the electron microscope collagen has a characteristic periodicity of 640 Å, which shows a number of intraperiod bands the significance of which is uncertain.<sup>8</sup> As it occurs in connective tissue, collagen is largely insoluble in aqueous solvents, but it can be taken into solution as gelatin, when its structural integrity is lost. However, in certain circumstances a proportion of connective-tissue collagen is soluble under mild conditions.

Zacharidès<sup>9</sup> first found that a proportion of the collagen of rat-tail tendon could be extracted with dilute acetic acid. Since then a number of collagen fractions have been described and given a variety of names, resulting in considerable confusion of nomenclature. Following Zacharidès, Nageotte<sup>10</sup> showed that addition of salt to, or neutralization of, an acetic acid solution of collagen resulted in the formation of a fibrous precipitate having all the tinctorial properties of native collagen. Since the proportion rendered soluble in acetic acid decreased with age Nageotte believed that the fraction was the soluble precursor of the insoluble fibers and called it "précollagène." Later this fraction was shown to be identical with native collagen in many respects having the same wide-angle diffraction,<sup>11</sup> 640-Å periodicity<sup>12-15</sup> and almost exactly the same amino acid composition.<sup>1,3</sup>

A group of Russian workers,<sup>16,17</sup> studying the change in skin proteins in the area around transplanted tumors, isolated a collagen fraction by extraction with acid citrate buffer and found the fraction in a wide range of connective tissues. This is probably a more clear-cut fraction than that extracted with organic acids, which will dissolve almost all the insoluble collagen with prolonged extraction<sup>18</sup> or after treatment with hyaluronidase,<sup>19</sup> whereas in both instances a definite end point is reached with citrate buffer at the same pH.<sup>20</sup> This fraction was also found to decrease with age; it was identified as the precursor of collagen fibers and named procollagen.<sup>16</sup>

A further collagen fraction was isolated after extraction of tissues such as skin with slightly alkaline

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buffers<sup>21</sup> and named "alkali soluble collagen."<sup>22</sup> Further fractions were isolated by extraction with 0.45-molar sodium chloride (0.45 M NaCl)<sup>23</sup> and by 0.2-molar sodium chloride (0.2 M NaCl).<sup>24</sup> Both these fractions were shown to form gels at 37°C. consisting of a network of very fine fibrils having the typical 640-Å periodicity of native collagen,<sup>23,24</sup> and to have the same amino acid composition as native collagen.<sup>3</sup>

The behavior of collagen in solution has been studied intensively, particularly its reconstitution and precipitation by a variety of different methods as visualized by the electron microscope. These studies have been reviewed extensively by Gross.<sup>25</sup> Briefly, it was found that several different types of precipitate could be formed having different morphologic characteristics and that these different forms are interconvertible.

They have the same chemical composition and once in solution behave in the same way — that is, as elongated, rigid rods. More drastic treatment of the collagen, particularly acid conditions and elevated temperature, results in the formation of gelatin that cannot be reconstituted into fibrous forms having the characteristic properties of collagen. On the basis of these studies a collagen particle was defined as the smallest unit that can be directly incorporated into a characteristic collagen fiber, and named tropocollagen.<sup>4</sup> This was an operational definition, but the presence in solution of such a particle was confirmed in solutions of ichthyocol<sup>5</sup> and citrate extracts of calf skin<sup>26</sup> and found to be approximately 3000 Å long, with a diameter of 14 Å and a molecular weight of 340,000.

Two other types of collagen have been described — namely, "collastromin"<sup>27</sup> and "metacollagen,"<sup>28,29</sup> — but the methods by which they were derived would undoubtedly lead to a considerable alteration in the structural integrity of the collagen and hence must be considered of doubtful biologic significance.

From biologic considerations that are discussed below there are probably four important collagen fractions that can be isolated from developing connective tissue\*:

Neutral-salt-extracted collagen extracted with 0.2 M NaCl.<sup>3,24</sup>

Neutral-salt-extracted collagen extracted with 0.45 M NaCl.<sup>23</sup>

(These fractions may be purified either by repeated precipitation with high concentrations of sodium chloride<sup>3</sup> or by precipitation of noncollagenous protein with trichloroacetic acid followed by precipitation of the collagen with ethanol at low temperatures.<sup>31</sup>)

\*Recent evidence obtained in this laboratory suggests that there are actually no clear-cut fractions, and that neutral-salt-extracted collagen consists of a continuous spectrum of aggregates of collagen molecules of varying size and strength of crosslinking. The collagen extracted with isotonic saline solution appears to be most closely associated with the cells.

Citrate-extracted collagen (0.2 M citrate buffer at pH 3.6).<sup>16</sup>

Insoluble collagen — that is, the collagen remaining after extraction with neutral salts and acid buffer that can be rendered soluble by gelatinization. This fraction is purified after gelatinization by precipitation of noncollagenous protein with trichloroacetic acid to a final concentration of 5 per cent followed by precipitation of the gelatin with acetone or ethanol.<sup>30</sup> Recently, it has been suggested that all gelatins contain a noncollagenous fraction that can be removed by fractionation of the gelatin on an ion-exchange column.<sup>32</sup> Whether this noncollagenous protein is an impurity or is split off from the collagen molecule during gelatinization has not yet been decided.

#### Reticulin

Reticulin consists of very fine fibers, characteristically staining black with silver.<sup>33</sup> It is predominantly seen in relation to the basement membrane in parenchymatous organs, between connective tissue and epithelium and around muscle and nerve fibers. The term has also been used to describe similar fibers present in developing connective tissue.<sup>34</sup> Since Mall claimed that it was distinct from collagen, the nature of reticulin has been the subject of considerable dispute. Recent chemical and biophysical studies have resolved the difficulties to some extent. It is now known that the basement-membrane type of reticulin is composed of collagen fibers<sup>35</sup> in very firm association with a carbohydrate and a lipid component that are released only after hydrolysis.<sup>36,37</sup> It has also been shown<sup>38</sup> that antiglomerulus serum rendered fluorescent by the technic of Coons and Kaplan<sup>39</sup> stained the basement-membrane reticulin but not collagen fibers, indicating that an antigen not present in collagen is a component of reticulin.

Robb-Smith<sup>34</sup> found that extraction of thin slices of human kidney with a variety of solutions, including dilute acetic acid and sodium hydroxide, had no effect on the structure or staining properties of reticulin but had a marked effect on the staining of collagen fibers and also on the reticulin of granulation tissue. Independently of this work it was shown that extraction of the carrageenin granuloma<sup>42</sup> with neutral salts abolished the silver staining of the reticulin in the tissue, and extraction with acid citrate buffer removed the fibers completely.<sup>40</sup> It was concluded that the reticulin of developing connective tissue is in fact citrate-extractable collagen and hence different from the reticulin of the basement membrane of the parenchymatous organs. Thus, at least two distinct types of reticulin should be distinguished. Further biochemical and biophysical studies may also reveal differences between the various types of basement-membrane reticulins.

### Elastin

Elastin is a rather ill defined fibrous protein characterized by its extreme insolubility. Since it is not an important constituent of the final product of wound healing and in view of the limited scope of this review it is not considered further.

### The Ground Substance

This term is a mistranslation of the term used by the early German histologists, who gave the name "Grundsubstanz" (meaning "fundamental substance") to the amorphous interfibrillar material demonstrated by a variety of histologic methods. However, in the minds of many authors this has become associated with the mucopolysaccharides, of which chondroitin sulfate and hyaluronic acid are examples, despite the fact that the ground substance is a complex mixture containing protein, mucoprotein and mucopolysaccharide. It contains at least 4 per cent of the total proteins of skin, consisting of plasma-type proteins,<sup>22</sup> some of which may be synthesized locally.<sup>41</sup> Further confusion has arisen from the use by many authors of hexosamine determinations on unfractionated tissue as a measure of the mucopolysaccharide content. Although it is true that all mucopolysaccharides contain hexosamine by definition<sup>42</sup> there are other components, such as the serum glycoproteins, that contain hexosamine. Boas<sup>43</sup> showed that about 50 per cent of the bound hexosamine of rat connective tissue could be extracted with veronal buffer at pH 8.6, and that this hexosamine was largely associated with the extravascular serum proteins.

A variety of mucopolysaccharides have been isolated from the connective tissues, the most important of which appear to be the chondroitin sulfates A, B and C, hyaluronic acid and keratosulfate, which occur in several combinations in the various connective tissues. The distribution of these substances has been reviewed by Meyer et al.<sup>44</sup>

Thus, the ground substance contains mucopolysaccharides, serum proteins and mucoproteins and neutral-salt-extractable collagen,<sup>31,32</sup> as well as the small-molecular-weight substances such as the electrolytes and probably other components as yet undefined.

### BIOSYNTHESIS OF COLLAGEN

Protein synthesis in its simplest form involves the synthesis of the constituent amino acids followed by the linking up of the amino acids by peptide bond formation. In collagen synthesis these are preliminary phases leading up to the formation of visible collagen fibers. Consideration of collagen synthesis is further complicated by the fact that two of the amino acids, hydroxyproline and hydroxylysine, unique to collagen, cannot apparently be incorporated directly into the protein.

### Incorporation of Hydroxyproline and Hydroxylysine

Stetten and Schoenheimer<sup>45,46</sup> showed that proline is a precursor of hydroxyproline and that exogenous hydroxyproline is not utilized for collagen synthesis. A similar situation was found for hydroxylysine.<sup>47-49</sup> On the basis of these results it was suggested that proline and lysine are hydroxylated after the formation of peptide linkages and that a series of intermediates, ranging from unhydroxylated to fully hydroxylated, could be formed.<sup>49</sup> However, free hydroxyproline is known to exist in growing connective tissue, including skin<sup>50</sup> and the carrageenin granuloma.<sup>51</sup> It has also been reported that the injection of cortisone into chick embryo causes growth to cease and free amino acids, including hydroxyproline, to accumulate.<sup>52</sup> The free hydroxyproline could, of course, arise from the breakdown of collagen. Nevertheless, the evidence does not irresistibly lead to the interpretation given above. Amino acids are probably not incorporated into protein directly from the free state, but must first be activated probably as nucleotide derivatives. It is possible therefore that activated hydroxyproline and hydroxylysine can only arise from the corresponding activated proline and lysine, and cannot be activated directly. This is analogous to the situation that arises in mucopolysaccharide biosynthesis in which it was found that glucosamine could only enter into the mucopolysaccharides via glucose, glucose-1-phosphate being aminated to glucosamine-1-phosphate and free glucosamine itself apparently being incapable of phosphorylation.<sup>53</sup>

### FORMATION OF COLLAGEN FIBERS

It is generally agreed that the fibroblast (and its variants, the osteoblast, chondroblast and so forth) is the cell responsible for the formation of collagen,<sup>54</sup> and there have been many histologic and electron-optical studies of this formation in connective tissues, tissue culture and tissue explants. Only recently have these been supplemented by biochemical studies.

### Histologic and Electron-Optical Studies

Schwann,<sup>55</sup> who first described the connective-tissue cell, believed that the collagen fiber developed directly from the cell, and Virchow<sup>56</sup> suggested that the cell secreted a soluble substance that became fibrillated outside the cell. More recent evidence supports this hypothesis and indicates that collagen fibers are formed largely outside the cell. Stearns,<sup>57</sup> using the transparent-chamber technic in the rabbit ear, described cytoplasmic granules that, she concluded, secreted a soluble precursor that was transformed extracellularly into a fibrous form of collagen. Electron-optical studies have confirmed and extended these findings. Porter and Vanamee,<sup>58,59</sup> studying fibroblast tissue cultures, showed that the earliest fibers are found at the cell surface and appear to develop

extracellularly by the accretion of material from the extracellular, nonfibrillar matrix. These findings have been confirmed and extended by studies of embryonic bone and tendon and of fibroblast tissue culture by Fitton Jackson,<sup>60,61</sup> and of regenerating tendon by Wassermann.<sup>62,63</sup> Filaments 80 Å in diameter, first seen in the eight-day embryo, differentiated into the characteristic collagen fibril by accretion of soluble collagen particles from the extracellular space.<sup>60</sup> The diameter of the fibrils increase with age and are remarkably uniform at any one age, suggesting that fibrils develop simultaneously. The same author<sup>64</sup> has observed cytoplasmic granules that upon isolation and analysis appeared to contain the elements of both collagen and mucopolysaccharide. In these electron-optical studies fibril bundles have been found well inside the fibroblast cytoplasm,<sup>65</sup> but these may well have arisen by invagination by the cell of fibrils originally formed outside the cell.

An important piece of evidence in favor of extracellular fibrillation has been provided by Robbins et al.<sup>66</sup> These authors found that fibrils failed to form in tissue cultures of fibroblasts grown in the presence of an anticollagen serum. Instead, amorphous masses developed extracellularly, having the tinctorial properties of collagen and devoid of a characteristic collagen structure under the electron microscope. These amorphous masses are apparently antigen-antibody complexes formed in the extracellular space before the soluble collagen precursor had had time to aggregate to form the normal collagen fibril.

#### Biochemical Studies

If a soluble form of collagen is the precursor of collagen fibrils, it must be sought among the three soluble collagen fractions so far isolated. These are the two neutral-extracted fractions<sup>25,30</sup> and acid-citrate-extracted collagen.<sup>16</sup> It is likely that all three fractions are extracellular and that a soluble precursor will be found intracellularly.

It was first shown that citrate-extracted collagen incorporated C<sup>14</sup>-labeled glycine at a greater rate than insoluble collagen<sup>16</sup> and that the rate of incorporation was reduced considerably in the skin collagen of scorbutic guinea pigs<sup>17</sup> (it has long been known that ascorbic acid is essential for the formation of collagen<sup>67</sup>). It was concluded that citrate-extracted collagen was the soluble precursor. Subsequently, Harkness et al.<sup>22</sup> found a much higher rate of incorporation of C<sup>14</sup>-labeled glycine into the collagen fraction extracted with alkaline buffer, and these authors concluded that this fraction was the true soluble precursor, citrate-extracted collagen representing fibrillar collagen recently laid down, probably extracted from the surface of large fibers. This last suggestion is supported by the finding that the fibers from skin and tendon appear frayed and disordered after extraction with citrate buffer.<sup>23</sup>

Robertson and Schwartz<sup>67</sup> have shown that carageenin, a sulfated polysaccharide isolated from seaweed, stimulated the production of large amounts of new connective tissue when injected subcutaneously into guinea pigs. This was confirmed,<sup>30</sup> and this source of growing connective tissue used to study collagen formation.<sup>30,68</sup> It was found that the collagen fraction extracted with 0.2 M NaCl was the first fraction to appear, and that it was metabolically very active. C<sup>14</sup>-labeled glycine was incorporated very rapidly into this fraction, maximum specific activity being reached within ten hours, with an equally rapid fall in specific activity within twenty-four hours. The rate of incorporation into citrate-extracted collagen was much slower and comparable to that into insoluble collagen. It was concluded that collagen extracted with 0.2 M NaCl was the soluble precursor of fibrous collagen. This fraction and the alkali-soluble collagen of Harkness et al.<sup>22</sup> are probably identical, so that the two studies are entirely in agreement.

Further evidence in support of this is provided by the studies of Gross<sup>32</sup> on the occurrence of collagen extracted with 0.45 M NaCl in the skins of young guinea pigs under various conditions. These studies have shown that the rate of growth of the guinea pig is correlated only with the amount of collagen extracted in this way, no correlation existing with any of the other parameters measured such as hexosamine and tyrosine.

Starvation of the animal resulted in the almost complete disappearance of this fraction, which was also absent from the skins of scorbutic guinea pigs. It should be pointed out that extraction with 0.45 M NaCl dissolves out a larger proportion of the total collagen than that with 0.2 M NaCl. It is possible that the latter fraction exists in a less aggregated state and is an earlier precursor than that extracted with 0.45 M NaCl. This is also suggested by a study of Gross's data,<sup>32</sup> which indicate that the fraction extracted with 0.14 M NaCl disappears more rapidly from the skins of guinea pigs on a restricted diet.

#### PROCESS OF FIBROGENESIS

From the evidence so far discussed it appears that neutral-salt-soluble collagen is the extracellular precursor of fibrous collagen and is present in the ground substance of developing connective tissues. It is also probable that the citrate-extracted fraction has its morphologic origin in two places. In the early stages of developing tissue the thin argyrophilic fibers, which are a feature of such tissue, are extracted with citrate buffer.<sup>40</sup> Later in this development collagen extracted with citrate probably comes from the outer layer of the mature fibers more recently deposited on fibers. Acetic acid will gradually remove the remainder of the fiber.<sup>22,68</sup> Thus, the origin of all the extracellular collagen fractions can be accounted for.

The process of fiber formation either in vivo or in vitro must involve the aggregation of the collagen molecule through some type of crosslinking. Gustavson<sup>69</sup> has shown that the crosslinking of collagen molecules takes place largely through hydrogen bonding between hydroxyl groups of hydroxyproline and the keto-imide groups of adjacent helices. It is the breaking of these bonds by thermal agitation that leads to the phenomenon of hydrothermal shrinkage,<sup>69</sup> the temperature at which shrinkage takes place being directly related to the strength of the crosslinking. This crosslinking will also be responsible for the resistance of collagen fibers to dissolution — the stronger the bonds, the more drastic the treatment necessary to bring the constituent collagen molecules into solution. Reconstituted collagen fibers have a low shrinkage temperature, and hence a poor degree of crosslinking,<sup>70</sup> and are readily redissolved in dilute acid or acid buffer although not in neutral salt solutions.<sup>22</sup> Gross<sup>71</sup> has also shown that the gel formed from neutral solutions at 37°C. becomes increasingly insoluble in neutral salt at low temperatures as the time it is held at 37°C. is increasing. Solubility in citrate buffer also eventually decreases. I have observed increasing insolubility of precipitated neutral collagen stored in a wet state in the cold. This increasing insolubility probably reflects an increasing degree of crosslinking as the collagen particles move into a more favorable steric apposition under the influence of thermal agitation.

If this process takes place in vivo, the final stages of fiber formation will consist of two processes. The length and diameter of the fibers will increase by deposition of collagen molecules, and the outer layers will be easily extractable with citrate. Simultaneously, the inner layers will become increasingly insoluble owing to the formation of increasing numbers of centers of maximum strength of crosslinking. This process will expand to the outer layers as the fiber ages, leading to the observed decrease in the proportion of extractable collagen. This hypothesis would also account for the findings of Verzar,<sup>72</sup> who reported that the load necessary to inhibit the hydrothermal shrinkage of rat-tail tendon fibers of the same length and diameter increases with age. This cannot be due to an increase in the strength of the crosslinking since this would lead to an increase in the actual temperature at which shrinkage occurred — a fact not observed. However, on the hypothesis presented here, there would be an increasing number of crosslinkages with maximum strength, the breaking of which would contribute to the force acting against the load during shrinkage, which would only act at the normal shrinkage temperature. The outer layer would shrink at lower temperatures because of the weaker crosslinking and would not contribute to the final massive shrinkage of the central core.

It will be noted that the formation of collagen

fibers from neutral salt solution of collagen takes place in vitro in the absence of mucopolysaccharide or mucoprotein.<sup>73,74</sup> The role of these substances in fiber formation is still obscure and is discussed below in the section on wound healing.

#### FIBROGENESIS IN WOUND HEALING

The evidence so far presented can now be gathered together and applied to the problem of wound healing. For the purpose of this discussion it will be assumed that the primary cellular reaction to the initial wound is concerned with preparing the site for fibroblastic proliferation and that fibrogenesis follows this preparative phase.

Fibroblasts appear about the second day and rapidly proliferate. Before any visible fibers can be observed there is an increase in an amorphous material having the staining properties of acid mucopolysaccharide. Toluidine blue metachromasia reaches a peak on the fifth or sixth day and declines rapidly thereafter.<sup>57,74-77</sup> Wolbach<sup>74</sup> believed that at least part of the amorphous matrix had the staining properties of collagen. Hexosamine determination paralleled to some extent the metachromasia,<sup>76</sup> and chondroitin sulfate was isolated from the granulation tissue formed after tendectomy and shown to be the source of bound sodium sulfate that followed administration of sulfur<sup>35</sup>-labeled sodium thio-sulfate ( $\text{Na}_2^{35}\text{SO}_4$ ).<sup>77</sup> These facts and the in vitro precipitation of collagen by chondroitin sulfate<sup>25</sup> have led to the idea that mucopolysaccharides are precipitating agents necessary for the formation of collagen fibrils in vivo.

However, it has been shown that the concentration of bound hexosamine of a wound immediately after it has been made is the same as in plasma and falls exponentially with time.<sup>78</sup> This is paralleled by the tyrosine concentration, suggesting that most of the hexosamine is contained in the serum glycoproteins. Study of the distribution of bound hexosamine in sponge-biopsy tissue<sup>61</sup> indicates that chondroitin sulfate and hyaluronic acid account for only about 5 per cent of the hexosamine, 80 per cent being in the plasma proteins. The hexosamine-nitrogen ratio of the sponge tissue is almost identical with that of serum from the same animal. Thus, there is no strong evidence that the presence of mucopolysaccharide is essential for the formation of collagen fibers in the healing wound.

After the formation of the amorphous matrix collagen fibers appear, first as thin, wavy fibrils staining strongly with silver and then increasing in thickness to form typical mature collagen fibers. The increase in collagen concentration, which occurs very rapidly between the fifth and the fourteenth day, is paralleled by the increase in tensile strength. From the biochemical viewpoint the fibroblast probably begins synthesizing the collagen precursor as early

as the third day.<sup>30</sup> The precursor is secreted into the extracellular space, where it begins to aggregate into a fibrous structure. At this stage no fibers will be visible histologically. As development proceeds two processes will take place. More and more sub-microscopic fibrils will be formed, and the earlier fibrils will accumulate more and more collagen molecules, increasing in length and thickness until they become visible histologically as the thin, wavy argyrophil fibers known as reticulin. As these fibers increase in length and thickness by further accretion of extracellular precursor, closer packing of the constituent molecules will result in increasing intramolecular crosslinking, leading to increasing insolubility and increasing tensile strength and also to a change in staining properties, so that the fibers will appear as typical mature collagen fibers. The process probably goes on long after healing is clinically complete. This is indicated by the slow, continuing increase in tensile strength and by the finding by Banfield<sup>79</sup> that collagen can be extracted from scar tissue by acetic acid several months after healing, when none can be extracted from the surrounding tissue.

A fairly clear picture of the process of fibrogenesis outside the cell is now emerging. But little is known about the intracellular processes that must take place before the extracellular process occurs. Nor is much known about the factors that control the formation and maintenance of collagen. A more detailed biochemical attack on the problem of wound healing seems to be required. This would involve studies of the metabolism of the cells and of each component of the products of wound healing and the effect of various nutritional deficiencies and hormonal influences on the metabolism of each of these components.

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## MEDICAL PROGRESS

### CURRENT STATUS OF STEROID THERAPY IN RHEUMATIC DISORDERS

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CORTISONE, the first of a growing family of corticosteroids, was introduced to the medical profession by Dr. Philip S. Hench nine years ago. All the investigators who were fortunate enough to obtain some of the scarce hormone were immediately impressed by its power to bring about striking, widespread changes in the human physiology. They confirmed its capacity for suppressing the signs and symptoms of rheumatoid arthritis and other rheumatic diseases when it was given in daily amounts greater than those normally produced by the patient's own adrenal glands.

In the past nine years a great deal of basic and clinical research has increased knowledge of the physiology, pharmacology and therapeutic usefulness of cortisone, other chemically analogous steroids and ACTH, the anterior-pituitary hormone that stimulates the patient's own adrenal cortexes to produce the desired steroids. Once their ability to suppress any type

of inflammation, to improve nutrition, to elevate the mood, to raise the hematocrit and to interfere with allergic reactions had been demonstrated, it was inevitable that they should be tried on every disease that remained a problem in treatment.

#### GENERAL THERAPEUTIC PRINCIPLES

Some generalizations about the use of these hormones as therapeutic agents are now possible. When they are used for replacement therapy, as in Addison's disease, they act as a specific remedy. They may be given in other endocrine diseases, such as adrenogenital syndrome, with an equally specific hormonal effect. However, they are also beneficial to patients suffering from a host of diseases that are not hormonal. Here, the physician utilizes the general, non-specific, metabolic effects of the corticosteroids. Since their precise manner of action is not known, Hench<sup>1</sup> suggests that they be classified as anti-inflammatory, antiallergic, antitoxic and regulatory. The first two need no explanation. The antitoxic action may be

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