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HORMONAL PRODUCTION OF ARTHRITIS

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MONTREAL

Administration of desoxycorticosterone acetate in comparatively high doses causes nephrosclerosis with increased blood pressure and disturbances in electrolyte metabolism, a fact which has been demonstrated in the chick, dog, cat, rat and monkey. Unilateral nephrectomy and a high intake of sodium chloride facilitate the production of these toxic actions of desoxycorticosterone acetate.¹ In addition to the nephrosclerosis, the most striking features of this overdosage are the formation of "Aschoff bodies" in the heart and the presence of periarteritis nodosa,² a condition occasionally seen in man following an attack of rheumatic fever. Since in addition choreiform twitches and a few rare cases of arthritis were also encountered in desoxycorticosterone acetate treated animals, it may be said that all the elements of the complex rheumatic syndrome were reproduced in the experimental animal. However, the great frequency of joint manifestations in the spontaneous disease of man and its comparative rarity in the experimentally elicited syndrome remained inexplicable. The main object of this communication is to show that changes in the internal medium of the body may determine the localization of the noxious effects of desoxycorticosterone acetate in the joints. This view is supported by observations showing that the arthritic lesions, which are rarely seen in the intact desoxycorticosterone acetate treated rat, develop with great frequency in similarly treated thyroidectomized or adrenalectomized animals especially if these are kept in cold surroundings. Indeed, under such conditions the joint changes

may be evident at a time when none of the other morphologic manifestations of desoxycorticosterone acetate overdosage have as yet become conspicuous.

EXPERIMENTAL

Since our previous experiments revealed that unilateral nephrectomy and sodium chloride treatment increase the sensitivity of rats to many overdosage effects of desoxycorticosterone acetate, all animals of the first experimental series were sensitized by ablation of the left kidney five days before injections were started. Instead of ordinary drinking water, all animals were given a 1 per cent aqueous sodium chloride solution beginning on the day of operation. Twenty-eight female albino rats, weighing 40-60 Gm., were used for this experiment. Ten of these were bilaterally adrenalectomized and 10 were thyroidectomized simultaneously with the ablation of one kidney, while the remaining 8 served as controls having intact adrenals and thyroids. All three groups received 2 mg. of finely ground desoxycorticosterone acetate crystals subcutaneously twice daily in an aqueous suspension containing 20 mg. per cubic centimeter. Their food consisted of "purina fox chow," which was complemented in the case of the thyroidectomized animals by the administration of calcium lactate powder ad libitum in order to compensate for possible parathyroid deficiency due to ablation of the internal parathyroids.

Signs of arthritis (figs. 1-3) were first noted on the fourteenth day of desoxycorticosterone acetate treatment, at which time 6 animals in the adrenalectomized group and 2 in the thyroidectomized group exhibited hyperemia and swelling in the tarsal joint region of one or both hind feet. Only occasionally did we note any macroscopically prominent swelling in other joints. The swollen regions were tender to touch. Subsequently the swelling tended to disappear and reappear somewhat irregularly, but with definite predilection for the joints of the hind feet. It should be noted that on the fourteenth day of treatment, when these joint lesions were first observed, 2 animals of the adrenalectomized group and 7 of the thyroidectomized group had succumbed from pneumonia or thyroparathyroid deficiency. In the desoxycorticosterone acetate treated control group of this series only 1 rat showed signs of mild arthritis on the fourteenth day and, while this animal recovered during the subsequent course of the experiment, another showed moderate arthritic manifestations on the twentieth day of treatment. On this day all surviving animals were killed. At autopsy macroscopic signs of nephrosclerosis, periarteritis nodosa or rheumatic nodules in the heart were observable in almost every animal of all three groups, there being no clearcut correlation between the arthritic manifestations and the severity

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2. Selye, Hans, and Penty, E. I.: Pathogenetic Correlations Between Periarteritis Nodosa, Renal Hypertension and Rheumatic Lesions, Canad. M. A. J. **49**: 264, 1943.

of the lesions in the internal organs. The knee joint and one entire hind foot from each animal were taken for section. The histologic changes in these tissues will be discussed simultaneously with the corresponding material of our second experiment, which appeared to be essentially the same.

For this series 34 female albino rats, weighing 30-50 Gm., were used. All were sensitized by ablation of the left kidney and were given 1 per cent aqueous sodium chloride solution to drink on the day injections were started. We subdivided them into four experimental groups, one consisting of 10 bilaterally adrenalectomized and the second 10 thyroidectomized animals, with two control groups of 8 desoxycorticosterone acetate treated and 6 nontreated rats. The first mentioned three groups received two daily subcutaneous injections of 3 mg. of finely ground desoxycorticosterone acetate crystals in an aqueous suspension containing 30 mg. per cubic centimeter, while the fourth group received no treatment. Their diet was the same as that of the first experimental series.

The swelling was most evident in the tarsal or ankle joint region and was usually accompanied by hyperemia. Although the total number showing arthritis during the experiment was 4 in group 1, 4 in group 2 and 3 in group 3, it should be emphasized that the severity and duration of the articular lesions was much greater in groups 1 and 2 than in group 3. None of the animals of the nontreated control group ever showed any arthritis. Most deaths during the experiment were due to pneumonia. All surviving animals were killed on the twenty-sixth day. At autopsy macroscopic signs of nephrosclerosis, periarteritis nodosa or rheumatic nodules in the heart were, generally speaking, more pronounced in the adrenalectomized and thyroidectomized than in the intact desoxycorticosterone acetate treated rats and were absent in all noninjected, partially nephrectomized controls.

In view of the fact that both adrenalectomy and thyroidectomy seriously disturb thermoregulation, a group of 6 adult rats treated essentially as those of

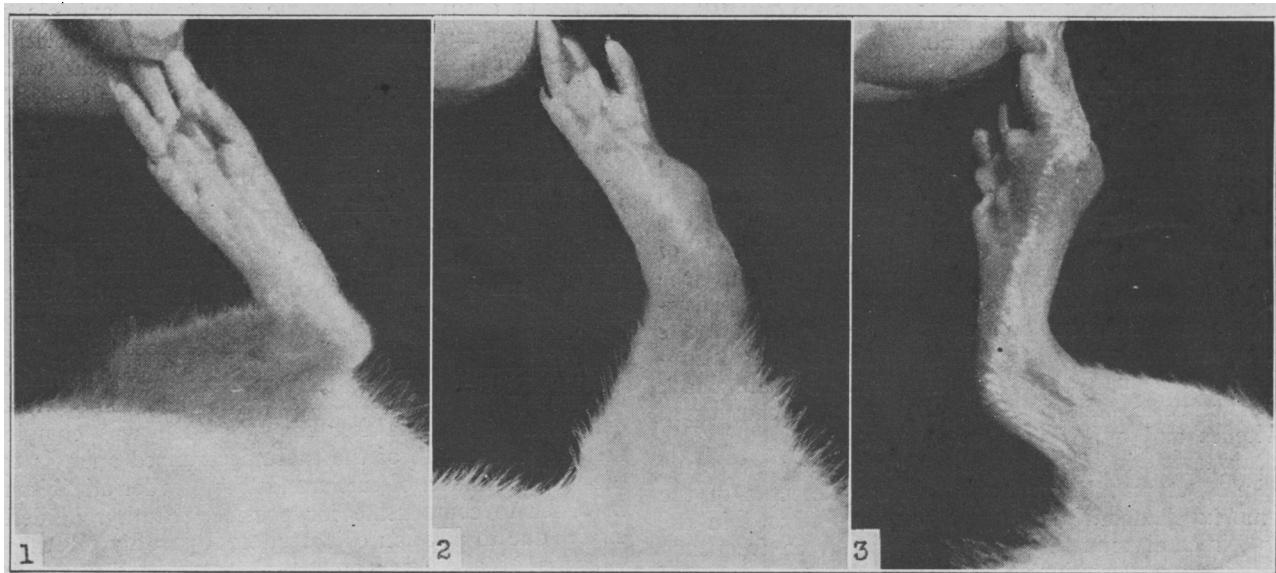


Fig. 1.—Hind foot of a normal control rat.

Fig. 2.—Acute stage of metatarsal arthritis in an adrenalectomized, desoxycorticosterone acetate treated rat of the first experimental series. Note the swelling of the metatarsal and ankle joint regions.

Fig. 3.—Chronic arthritis localized in the distal metatarsal joints in an adrenalectomized, desoxycorticosterone acetate treated rat, in which the hormone was administered for six weeks. (This animal is taken from an earlier experimental series, which is not described in detail in this communication.)

The first signs of arthritis were noted on the tenth day of treatment, after which daily records of the joint condition were made, some of which are given in

Appearance of Arthritis in Adrenalectomized, Thyroidectomized and Desoxycorticosterone Acetate Treated Rats

| Day of Treatment | Group 1 | | Group 2 | | Group 3 | |
|------------------|----------------------------|------------------|----------------------------|------------------|--|------------------|
| | Number of Adrenalectomized | Having Arthritis | Number of Thyroidectomized | Having Arthritis | Number of Desoxycorticosterone Acetate Treated | Having Arthritis |
| 10th | 2 slight | 8 | 2 slight | 7 | 0 | 8 |
| 18th | 2 pronounced | 8 | 3 pronounced | 4 | 0 | 8 |
| 20th | 3 pronounced | 7 | 2 pronounced | 2 | 2 pronounced | 6 |
| 26th | 1 moderate | 5 | 1 moderate | 1 | 1 moderate | 5 |

the accompanying table. The arthritic manifestations subsided and recurred in the same joint or subsided in one joint only to reappear in another articulation of the same animal.

group 1 of the preceding experiment for fourteen days, but showing no signs of arthritis, was placed outdoors for twenty-four hours on a cool, windy November day. At the end of this period 3 animals had succumbed and 1 of these, as well as all survivors, had enormous tarsal swellings of the type described.

These observations, as well as the fact that in the two preceding experimental series arthritic changes occurred suddenly in a large number of animals on days when the temperature in the animal room happened to fall below the usual, leads us to assume that temperature changes play an important role in the pathogenesis of the arthritis.

A histologic analysis of the joint lesions—which were essentially identical in all groups—revealed them to be surprisingly similar to those seen in acute cases of rheumatic polyarthritis in man. Comparatively few such cases come to autopsy, but an excellent description of their pathology will be found in a pertinent com-

munication by Fahr.³ In our experimental material the acute cases show pronounced edema of the periarticular connective tissue and synovial villosities, generally accompanied by hydrarthrosis (figs. 4 and 5). In a somewhat more advanced stage the mesothelial lining of the synovial membranes disintegrates and the underlying tissue undergoes a process of hyalinization

develops which may become very cellular in some cases (fig. 7). It consists of immature large fibroblast-like, slightly basophilic cells containing voluminous vesicular nuclei. The outlines of these cells are irregular and ragged, and most of them contain only one nucleus, although some are polynuclear and resemble "Aschoff cells." While all these changes are very similar to

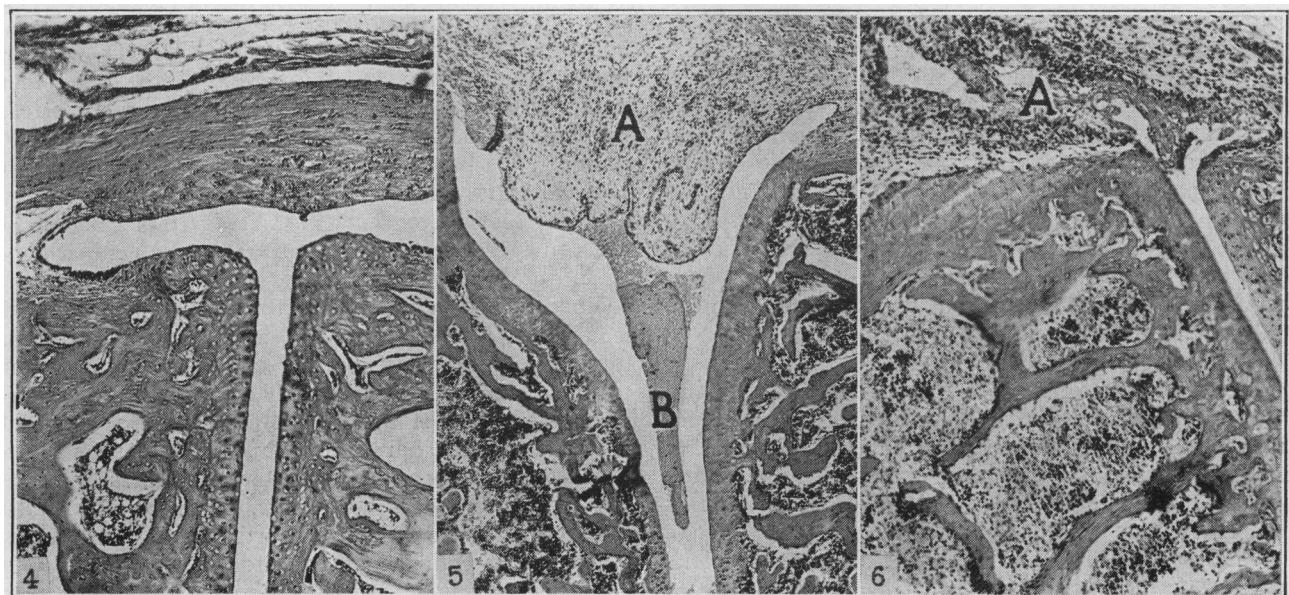


Fig. 4.—This and all subsequent photomicrographs represent sections of the metatarsal region in adrenalectomized desoxycorticosterone acetate treated rats of the first experimental series, described in the present communication. The section shows the appearance of a normal joint which shows no pathologic change in spite of treatment. Note the thin synovial membrane and the regular appearance of the underlying connective tissue. The joint cavity contains no pathologic constituents.

Fig. 5.—Acute edematous stage of arthritis. Note the swollen edematous synovial villosities (A) and the fibrinoid transudate in the joint cavity (B).

Fig. 6.—Severe arthritis with hyaline necrosis of the synovial membrane and cellular infiltration of the surrounding connective tissue (A).

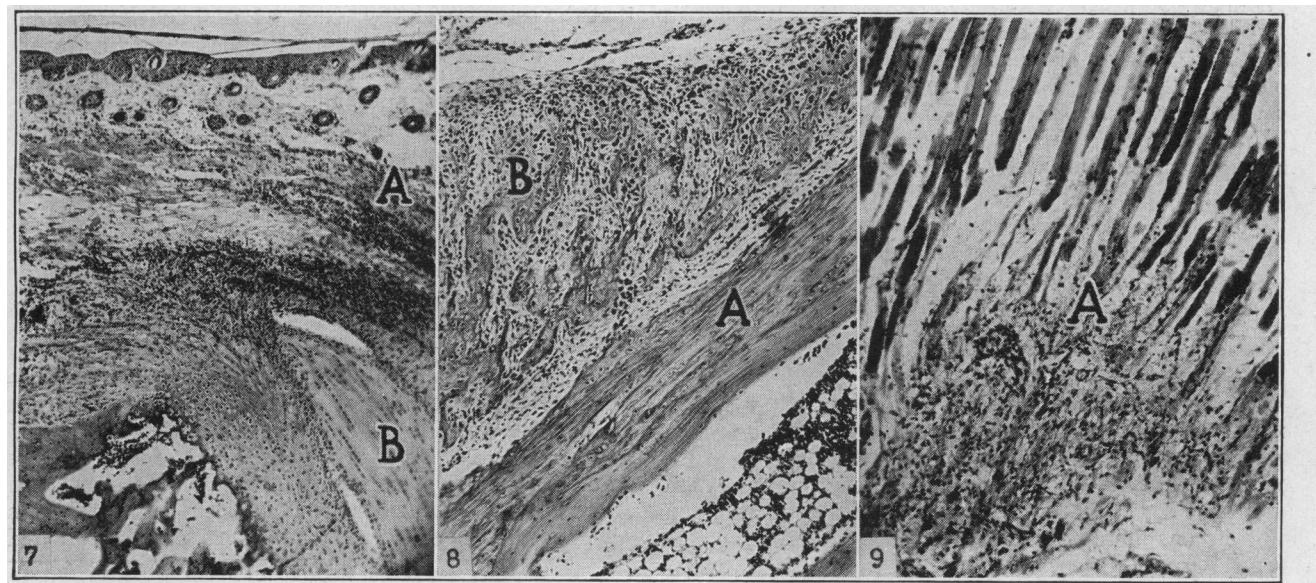


Fig. 7.—Fibrinoid necrosis and cellular granuloma in the derma underneath the epidermis (A) in the vicinity of a tendon (B).

Fig. 8.—Normal compact metatarsal bone (A) and newly formed periosteal bone (B) in a comparatively chronic case of arthritis.

Fig. 9.—Normal striated muscle fibers (top) and granulomatous nodule (bottom) from a muscle in the metatarsal region. The muscle fibers at the border of the nodule have undergone degeneration (A).

and necrosis (fig. 6). At the same time fibrinoid necrosis is also seen in the tendon sheaths and the subcutaneous tissue of the periarticular regions. Around these hyaline fibrinoid deposits a granulation tissue

those seen in rheumatic fever, we should also like to record the frequent occurrence of large round eosinophilic cells with a small dense nucleus within the granulomatous area. The exact nature of these cells is still under investigation, but they do not appear to have been seen in man.

³ Fahr, T.: Beiträge zur Frage der Herz- und Gelenkveränderungen bei Gelenkrheumatismus und Schärlach, *Virchows Arch. f. path. Anat.* **232**: 134, 1922.

In still more advanced cases the edema subsides almost completely and the granulomatous tissue becomes increasingly dense. Infiltrations are also noted in the sheaths of the nerves in the affected regions. This may perhaps partly explain the painfulness of the lesions. Where hyalinization and granuloma formation occur in the immediate vicinity of the periosteum, new bone formation is stimulated. In such regions it appears that the eosinophilic fibrinoid deposits are gradually transformed into osteoid tissue, while the surrounding immature fibroblasts change into osteoblasts. As a result of this process, rather irregular callus-like bone proliferations arise in the periarticular regions. These changes are strikingly similar to those of the chronic hypertrophic arthritides (fig. 8). The striated muscles between the tarsal bones are frequently infiltrated by nodules of granuloma tissue similar to that seen in the synovial villi and the surrounding connective tissue. In the vicinity of such nodules the muscle fibers undergo degeneration (fig. 9).

Subcutaneous nodules, which are so characteristic of rheumatic joint diseases in man, are not very typical in our experimental animals, mainly because the subcutaneous foci tend to coalesce, thus forming rather diffuse infiltrations which may extend into the derma proper. In some instances these are reminiscent of the proliferative stage of scleroderma.

Although the knee joints did not show any obvious swelling or other macroscopically detectable change in the animals of these groups, microscopic examination revealed massive infiltration of the panniculus adiposus by a granuloma tissue similar to that seen in the vicinity of the arthritic joints of the foot. Other joints have not been examined microscopically but, judged by the lesions in the knee, it is quite possible that several articulations which showed no macroscopic change were similarly affected and sensitized by the treatment in such a manner that additional local damage (draft, cold and the like) might have provoked acute phenomena in their infiltrated tissues.

In conclusion it should be mentioned that the joint cartilages themselves were not visibly affected in any of our animals. This may explain the fact that the arthritis often regresses without leaving any permanent disability. It will be noted that in this as in most other respects the experimental joint lesions elicited by desoxycorticosterone acetate are strikingly similar to those observed in spontaneous rheumatic fever.

COMMENT

Among the various factors which were combined to produce arthritis in these experiments, the causative agent appears to be the corticoid hormone desoxycorticosterone acetate. Exposure to cold, thyroidectomy or adrenalectomy greatly facilitated the production of joint lesions but were effective only as predisposing agents. Indeed, even at room temperature desoxycorticosterone acetate had produced arthritis in a few of the animals that were neither thyroidectomized nor adrenalectomized. Furthermore, the characteristic morphologic lesion of rheumatic fever, the Aschoff nodule, was found in the heart and elsewhere after very long desoxycorticosterone acetate treatment even in the absence of organ extirpation or salt administration.⁴

The clinical and histologic similarity of the arthritis observed in our animals with that seen in the acute

rheumatic fever of man suggests that the human disease may be a clinical manifestation of adrenal cortex hyperactivity. It has often been emphasized that rheumatic fever, as well as nephrosclerosis and hypertension, tend to develop following exposure to a variety of rather nonspecific damaging agents such as exposure to cold, emotional shock and infectious diseases. On the other hand, these same agents are known to cause adrenal enlargement with histologic signs of increased cortical hormone production, a phenomenon characteristic of the "alarm reaction."⁵ It has even been found that immediately after exposure to various types of stress the corticoid hormone content of the urine rises above normal.⁶ It has also been demonstrated in rats that concomitantly with the adrenal cortex hypertrophy similar exposure to damaging agents (especially cold) causes nephrosclerosis with hypertension and that here again unilateral nephrectomy and treatment with sodium chloride exert a sensitizing effect.⁷ Although it is too early as yet to give a definite interpretation to these observations, it may be said that they are compatible with the assumption that exposure to various damaging agents stimulates the production of corticoid hormones by the adrenal cortex. This is probably a defense mechanism, since these compounds increase resistance in general. However, under certain conditions this defense reaction may defeat its purpose, as the resulting endogenous overproduction of corticoids may elicit changes similar to those produced by the exogenous administration of desoxycorticosterone acetate. Evidently this endogenous corticoid overdosage would be most detrimental to patients who are sensitized to the toxic actions of cortical hormones by renal disease or a habitually high intake of sodium chloride.

In the light of this preliminary discussion, it appears that the role of cold, thyroid or adrenal deficiency would be to favor a localization of the desoxycorticosterone acetate action in and around joints. It is not clear as yet why the joints and the periarticular tissues should become more readily affected by desoxycorticosterone acetate in the absence of either the adrenals or the thyroid, but the detrimental effect of these gland deficiencies on thermoregulation may be involved. At any rate, the present observations show that complex interrelations exist between the endocrine glands and the joints and that the adrenal and thyroid exert a demonstrable effect on the articulations.

In view of the great frequency and social significance of arthritic lesions in man,⁸ it appears desirable to correlate our experimental findings with those recorded in clinical papers. The most striking fact which emerged from a perusal of the voluminous literature on arthritis was that, in spite of the countless recorded observations of joint lesions in patients suffering from various endocrine diseases, no investigator presented

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8. The Magnitude of the Chronic Disease Problem in the United States, National Health Survey No. 6, Washington, D. C., Government Printing Office, 1935. Bigelow, G. H., and Lombard, H. L.: *Cancer and Other Chronic Diseases in Massachusetts*, Boston, Houghton, Mifflin Company, 1932.

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a unified concept of their pathogenesis. In the absence of any systematic review of the relevant literature, we should like to summarize the data on "endocrine arthritis" in order to expedite further clinical investigations in this field. The rheumatic and rheumatoid joint lesions will be considered together, and we shall not try to differentiate sharply between the various types of chronic arthritis (hypertrophic, atrophic, and so on). As suggested by some of our results (compare figures 2 and 3), it appears quite possible that, depending on the acuteness or chronicity of the condition or other incidental factors, the same etiologic agent may manifest itself in different ways and give rise to different types of arthritis. However, the purulent arthritides with demonstrable microbial contamination of the joint cavities will not be considered here, as they are obviously not of endocrine origin.

For the evaluation of our experimental results, special interest is attached to those clinical observations which tend to correlate arthritis with thyroid or adrenal deficiency. Hypothyroidism appears to influence the joints in a rather specific manner. Since Kocher⁹ developed his concept of "rheumatismus thyreoprivus chronicus," the frequency of rheumatic and especially rheumatoid conditions in frank myxedema and latent hypothyroid conditions has been established by numerous observations.¹⁰ In those cases in which arthritis appears in combination with signs of thyroid deficiency and a decreased basal metabolic rate, thyroid medication often proved of great value.¹¹

Although clinical observations also reveal the possibility of producing arthritis with thyroid hormone¹² we have been unable to do so in animal experiments up to the present. However, it is perhaps pertinent to mention that thyroxin overdosage is effective in causing nephrosclerosis and hypertension especially in the unilaterally nephrectomized sodium chloride treated rats and in this respect resembles desoxycorticosterone acetate overdosage.¹³

A deficiency of the adrenal gland has not been seriously considered by clinicians as playing a role in the production of arthritis, although in Addison's disease¹⁴ and in status thymicolumphaticus¹⁵ arthritis has been recorded.

Surprisingly, joint lesions have also frequently been reported in cases of either thyroid or adrenal hyperactivity. Thus frank toxic diffuse goiter is often accompanied by acute or chronic arthritis and in such cases thyroidectomy or x-ray treatment of the thyroid region

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proved beneficial.¹⁶ Similarly chronic arthritides are frequent complications of Cushing's disease in which the adrenal cortex is usually hyperplastic or adenomatous.¹⁷ In conclusion, the most prominent fact about the clinical syndrome of endocrine arthritis is that both hyperfunction and hypofunction of several endocrine glands may elicit joint manifestations.

Among the joint lesions which do not appear to be directly related to the thyroid or adrenals, the chronic arthritides, periarthritides and arthralgias of the menopause received particular attention because of their great frequency and practical importance.¹⁸ According to Charcot¹⁹ 8 to 10 per cent of women between 40 and 60 years of age suffer from arthritis as against 1 to 2 per cent of old men. Among 1,000 menopausal women investigated by the Council of the Medical Women's Federation²⁰ 23.7 per cent exhibited evidence of "arthritis and fibrosis." The British Ministry of Health points out that between the ages of 37 and 54

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years five times as many women as men suffer from arthritis. Thus—although the figures given by the different observers vary—the prevalence of arthritis among women of menopausal age is definitely established. Joint lesions may also appear during the artificial menopause elicited by x-ray castration and—perhaps somewhat less frequently—following ovarectomy.²¹ An arthritis presumably due to eunuchoidism in women has been reported by Liesched and Sellheim²² and by Muñoz Areños.²³ An intermittent type of hydrarthrosis, "hydrops articulorum intermittens," has been described by Schlesinger;²⁴ in many of these cases the fluid accumulation in the joint cavity coincides with the menstrual bleeding.²⁵ Other types of joint swellings may also be related to the sexual cycle.²⁶ In all these cases of "menstrual arthritis" it is stated that the joint manifestations disappear during pregnancy and are not seen before puberty. In fact Hench²⁷ states that even ordinary rheumatoid arthritis is favorably influenced by gestation. The beneficial effect of various natural and artificial folliculoid preparations is particularly obvious in cases of menopausal arthritides and arthralgias.²⁸ Folliculoids have likewise been shown to be of use in Schlesinger's "hydrops articulorum intermittens,"²⁹ in chronic rheumatoid arthritis³⁰ and in other less well defined types of chronic arthritides.³¹ In relation to the present work the most interesting feature of "menopausal rheumatism" is that according to some clinicians it develops most readily in

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hypothyroid women³² and that it is often beneficially influenced by thyroid hormone therapy.³³

The hypophysis, which regulates the function of the thyroid and adrenals, is probably also involved in the pathogenesis of endocrine arthritis, although it is difficult as yet to formulate its etiologic role. The hypertrophic osteoarthritis of acromegaly, which usually has a predilection for joints of the spinal column, is so well known as hardly to need much comment.³⁴ Hypopituitary dwarfism has also been claimed to act as a predisposing factor for the development of arthritis.³⁵ Malfunctions of the posterior lobe of the pituitary, such as are found in diabetes insipidus³⁶ or adiposogenital dystrophy,³⁷ facilitate the production of joint lesions.

There are also a number of reports on rather complex and vague relations of rheumatism to endocrine glands; thus several investigators considered the possibility of an "endocrine arthritis" mainly on the basis of the frequent coincidence of chronic joint lesions with various, often ill defined, endocrinopathies.³⁸ Others envisaged the possibility of an "endocrine rheumatism," including in that term different manifestations of acute rheumatic fever and rheumatoid arthritis which may have been elicited by hormonal imbalance.³⁹

Finally, we should like to mention in connection with the arthritis eliciting effect of cold in our experiments

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that Lauber and Ramm⁴⁰ claimed arthritides are especially common in women who do cleaning work which makes it necessary to spend a good deal of time with their hands in cold water. Additional reports of this type are commonly found in the literature.

This brief survey of the clinical literature reveals manifold correlations between endocrine malfunctions and joint lesions and makes it obvious that in human pathologic conditions, as in our animal experiments, hormonal factors can act either as causative or as predisposing agents in the production of joint lesions.

SUMMARY

Experiments in the rat indicate that under certain experimental conditions overdosage with desoxycorticosterone acetate elicits a polyarthritis which histologically resembles that seen in acute rheumatic fever. These joint lesions are frequently accompanied by the appearance of Aschoff bodies in the heart and sometimes also by periarthritis nodosa.

Joint lesions are more readily produced by desoxycorticosterone acetate in adrenalectomized or thyroidectomized than in intact rats, especially if they are exposed to cold.

The great similarity between the experimental lesions elicited by desoxycorticosterone acetate and the manifestations of rheumatic fever are interpreted as indicating that the adrenal cortex may play an important role in the pathogenesis of rheumatic and rheumatoid conditions in man.

ORAL SODIUM LACTATE IN THE TREATMENT OF BURN SHOCK

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The shock syndrome which follows severe burns is accompanied by hemoconcentration and diminished plasma volume.¹ Early efforts to combat the shock symptoms by intravenous administration of electrolyte solution or dextrose or both were disappointing. Therapeutic emphasis then shifted to the use of serum or plasma because it was expected that these protein containing fluids would remain longer in circulation and thus would have more time to reduce the hemoconcentration and to restore the diminished plasma volume. Concentrated human albumin² has also been used to accomplish these objectives by the additional mechanism of drawing fluid into the circulation.

40. Lauber, H. J., and Ramm, C.: Prognose und Therapie der Arthropathia ovaripriva, *Münch. med. Wochenschr.* **77**: 89, 1930.

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Owing to lack of space, tables 2 and 3 are omitted from the *JOURNAL* and table 1 has been abbreviated. The complete article appears in the author's reprints.

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2. Heyl, J. T., and Janeway, C. A.: Use of Human Albumin in Military Medicine, U. S. Nav. M. Bull. **40**: 785 (Oct.) 1942.

Actually, however, the problem is far more complicated. Recent accounts of two catastrophes involving many burn cases, the Japanese attack at Pearl Harbor³ and the Cocoanut Grove fire in Boston,⁴ have indicated the relatively high mortality from severe burns even when large amounts of plasma are used. The English experience with serum or plasma also revealed a high mortality from burn shock.⁵

The recent experimental work of Elman⁶ suggests that intravenous administration of plasma does not invariably correct the hemoconcentration following severe burns. The careful studies of Scudder and Elliott⁷ in 1 case showed that, "in spite of 2,000 cc. of serum, 500 units of adrenal cortical extract, and 2,500 cc. of normal salt solution with 50 grams of

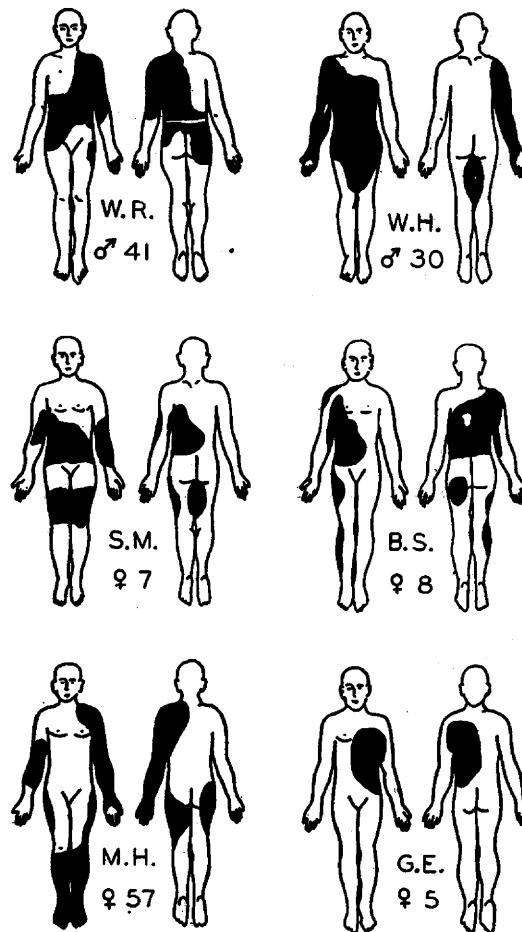


Fig. 1.—Extensive full thickness burns treated with oral sodium lactate. The blackened areas represent the actual areas of full thickness third degree burns that were skin grafted. The initials refer to the cases in table 1. The less extensive cases are not included in this illustration.

glucose . . . the hematocrit instead of decreasing, increased to 73 per cent." Rhoads, Wolff and Lee⁸ also found that, "when large plasma transfusions were administered soon after the receipt of the burn, there was not as great a rise in the plasma volume as had been

3. Hayden, Reynolds: Activities of the Naval Hospital at Pearl Harbor Following the Japanese Air Raid of December 7, 1941: Comments on the Care of Battle Casualties, *Am. J. Surg.* **60**: 161 (May) 1943.

4. Symposium on Management of the Cocoanut Grove Burns at the Massachusetts General Hospital, *Ann. Surg.* **117**: 801 (June) 1943.

5. Symposium on Treatment of Burns, *Lancet* **2**: 621 (Nov. 16) 1940.

6. Elman, Robert, and Brown, F. L.: Experimental Burns: I. Methods, Mortality and Hemoconcentration Curves, *War Med.* **3**: 477 (May) 1943.

7. Scudder, J., and Elliott, R. H. E.: Controlled Fluid Therapy in Burns, *South. Med. & Surg.* **104**: 651 (Dec.) 1942.

8. Rhoads, J. E.; Wolff, W. A., and Lee, W. E.: The Use of Adrenal Cortical Extract in the Treatment of Traumatic Shock of Burns, *Ann. Surg.* **113**: 955 (June) 1941.