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FURTHER STUDIES CONCERNING THE PARTICIPATION OF THE ADRENAL CORTEX IN THE PATHOGENESIS OF ARTHRITIS

BY

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A few years ago we noted that rats chronically treated with large doses of desoxycortone acetate (D.C.A.) often develop joint lesions which exhibit the histological characteristics of rheumatic arthritis and periarthritis. Curiously, arthritides occurred only in a certain percentage of our experimental animals, although other "rheumatic" changes (e.g., a "rheumatic type" of arteritis, myocarditis, and encephalitis) were constantly present. Furthermore, even when an arthritis developed during the first weeks of treatment it tended to disappear in spite of continued D.C.A. administration; only rarely did such lesions progress towards what might be called an experimental replica of rheumatoid arthritis (Selye, Sylvester, Hall, and Leblond, 1944). In this respect the joint affliction again differed from the other manifestations of D.C.A. overdosage which tend to progress as long as a hormone excess is given.

During subsequent years we occasionally observed an acute joint swelling in D.C.A.-treated monkeys and dogs. Others pointed out that Addisonian patients may develop "rheumatic-like" joint swellings under the influence of D.C.A. overdosage (Dejean, 1947; Dejean, Mahoudeau, and Bricaire, 1947; Laroche, 1947a, 1947b). All these observations revealed that this corticoid exerts a rather specific effect upon joint structures in various species, but the production of arthritis was not constant enough to serve as the basis for systematic studies concerning its pathogenesis.

In the course of experiments planned to increase the incidence of this lesion we noted that, under the influence of D.C.A. overdosage, adrenalectomized rats developed arthritis more frequently than intact controls (Selye, Sylvester, Hall, and Leblond, 1944). This fact was subsequently confirmed on a very large experimental material by my pupil O. Hall (1946). Some actions of mineralocorticoids (such as D.C.A.) are inhibited by gluco-corticoids (such as "cortisone") (Selye, 1949a). Hence it was reasonable to assume that adrenalectomy sensitizes to the toxic effects of D.C.A. because it removes the source of endogenous gluco-corticoids and thereby predisposes to the development of a particularly unfavourable gluco-corticoid/mineralo-corticoid balance.

Several earlier observations had called our attention to the importance of this balance, inasmuch as a mineralo-corticoid (D.C.A.) exhibited effects which are diametrically opposed to those of gluco-corticoids. Thus, chronic pretreatment with D.C.A. tends to cause thymus hypertrophy (Selye, 1941; Selye and Beland, 1943), while gluco-corticoids exert an opposite effect (Selye, 1946). D.C.A.-pretreated rats respond to various stress-producing agents (cold, formaldehyde injections, atropine injections, surgical trauma, exercise) with hypoglycaemia instead of the usual hyperglycaemia characteristic of the alarm reaction (Selye and Dosne, 1942); conversely, adreno-cortical extracts (rich in gluco-corticoids) increase the hyperglycaemic response to stress even in the adrenalectomized animal (Selye and Dosne, 1941). The development of shock after surgical trauma is aggravated by D.C.A. pretreatment and mitigated by corticosterone (a gluco-corticoid compound) (Selye, Dosne, Bassett, and Whittaker, 1940). It has been noted, furthermore, that the hypertension which can be elicited in sensitive patients by D.C.A. overdosage is abolished by an adrenal extract rich in gluco-corticoids (Perera and Pines, 1949).

On the basis of these and many other observations we came to the conclusion that D.C.A., when it is given in toxic concentrations, may create a "partial hypo-corticoidism"; in other words, it can cause a condition in which manifestations of hypo- (decreased resistance to stress, thymus enlargement, hypoglycaemia) and hyper-corticoidism (sodium retention, hypertensive disease) are simultaneously manifest. It is also noteworthy in this connexion that, although the clinical condition of Addisonian patients is improved by moderate doses of D.C.A., they are hypersensitive to the toxic effects of this steroid—presumably again because these individuals are deprived of the antagonistic gluco-corticoids (Selye, 1949a).

Quite recently Pirozynski and Akert (1949) noted that, even when no macroscopically visible arthritis develops in D.C.A.-treated rats, one consistently finds histological evidence of a "rheumatic-like" joint involvement. These authors confirmed that adrenalectomy sensitizes the rat to the production of joint lesions by D.C.A. They discovered, furthermore, that even the extra-articular manifestations of D.C.A. overdosage (such as cardiovascular and renal lesions) are aggravated by adrenalectomy, probably because the source of the protective gluco-corticoid had been removed.

Subsequently it was found that "rheumatic" changes in the heart and joints, similar to those produced by D.C.A., can also be elicited by a crude lyophilized anterior pituitary (L.A.P.) preparation, but only in the presence of the adrenals. Since adrenalectomy prevented these effects of L.A.P., it was concluded that they are largely, if not entirely, mediated through the adrenal cortex, perhaps owing to the discharge of some D.C.A.-like mineralo-corticoid compounds (Selye, 1946).

In the course of our work on the general-adaptation syndrome, it became obvious that in response to a variety

of stress-producing agents (emotional tension, infections, intoxications, exposure to cold, etc.), the organism responds with an increased corticoid-hormone production. This is a useful adaptive reaction which helps to raise resistance in general (Selye, 1937). However, under abnormal conditions it may derail, perhaps because the production of gluco-corticoids cannot keep pace with the excessive elaboration of mineralo-corticoids. Under these conditions the fundamentally useful general-adaptation syndrome may itself become the principal cause of disease. The "rheumatic" and some hypertensive diseases, the so-called collagen diseases—nephrosclerosis, gout, etc.—were among the derangements interpreted as "diseases of adaptation" (Selye, 1944, 1946, 1949a).

Perhaps the most important weakness of our theory is that an increased formation of D.C.A.-like mineralo-corticoids has not been actually demonstrated (by urine or blood analysis) in patients exposed to stress or those suffering from "diseases of adaptation." There is no doubt that stress causes an increased elimination of gluco-corticoids as judged by urinary bio-assays, but a concomitant increase in the formation of mineralo-corticoids is postulated almost entirely on the basis of indirect evidence, because of the great technical difficulties involved in the determination of these latter compounds. It should be kept in mind, however, that even if the absolute amounts of mineralo-corticoids were not increased their effect could be augmented owing to sensitization (e.g., by sodium retention or renal failure), or the gluco-corticoid/mineralo-corticoid quotient may become unfavourable.

At the time of our first observations the assumption of a pathogenetic relationship between the adrenal cortex and the "rheumatic-rheumatoid type" of arthritis appeared rather far-fetched. However, this view received strong support from recent clinical observations. It was noted that adrenal-cortical extracts (Bassi and Bassi, 1946), which are notoriously rich in gluco-corticoids, and especially cortisone (Hench, Kendall, Slocum, and Polley, 1949), a typical gluco-corticoid compound, produce spectacularly beneficial effects in patients with chronic rheumatoid arthritis. It is of special interest in this connexion that purified adrenocorticotrophic hormone (A.C.T.H.) is also effective in rheumatoid arthritis (Hench, Kendall, Slocum, and Polley, 1949), since normally this compound appears to stimulate particularly the production of gluco-corticoids.

On a purely empirical basis, so-called non-specific therapeutic procedures (e.g., parenteral injection of foreign proteins or colloidal metals, blood-letting) have long been used in the therapy of rheumatoid arthritis. It is presumably due to the same mechanism that this joint lesion can improve under the influence of a variety of other non-specific stress-producing conditions, such as pregnancy, icterus, traumatic injuries, and starvation (Hench, 1949). All these are highly effective "alarming stimuli"—that is, they can produce a condition of systemic stress with the characteristic endogenous discharge of pituitary A.C.T.H. (Selye, 1946, 1949a ; in the press). As we have said elsewhere, probably the most important factor in the therapeutic action of "non-specific therapy," "fever therapy," and "shock therapy" is the fact that such drastic measures stimulate defence by eliciting a general-adaptation syndrome, and, more particularly, an increased production of A.C.T.H. (Selye, 1949b ; in the press). The observation that potent gluco-corticoid and A.C.T.H. preparations are especially effective in combating rheumatoid arthritis agrees with this view.

It remains to be seen why certain impure anterior pituitary preparations (e.g., L.A.P.) often produce arthritis (Selye, 1946), while pure corticotrophin tends to inhibit its development. Perhaps some principle present in the crude extracts so modifies their A.C.T.H. effect that a predominantly mineralo-corticoid discharge results in the adrenal cortex. However, there is no definite evidence to support this hypothesis, and various points of view have been expressed concerning the probable relationship between the experimental production of arthritis with certain corticoids and pituitary extracts on the one hand and its prevention with other corticoids and pure corticotrophin on the other (Pirozynski and Akert, 1949 ; Editorial, 1949a, 1949b).

Until quite recently the progress of our work concerning the role of hypophyseal and adreno-cortical hormones in the pathogenesis of arthritis was seriously handicapped by two technical difficulties : (1) neither D.C.A. nor L.A.P. produces arthritis with sufficient constancy to permit systematic investigations concerning the value of therapeutic measures ; (2) until a few months ago only the arthritogenic preparations (D.C.A. and L.A.P.) were readily available to us at this institute.

Recently we succeeded in developing a simple technique for the consistent production of arthritic and periarthritic changes, and, having now obtained adequate amounts of the anti-arthritic hormone preparations (A.C.T.H. and cortisone), we were able to analyse further the role of the pituitary adreno-cortical system in the production and prevention of arthritis. It is upon this work that we report in the present communication.

Methods

The *experimental animals* used in this study were adult male Wistar albino or piebald rats. The *experimental arthritis* was produced by the injection of dilute formaldehyde solutions of varying concentration (see description of individual experiments) just beneath the plantar aponeurosis of the hind paws. Normally, this strong irritant produces an intense hyperaemia and oedema of the entire paw within a few minutes.

As we shall see below, the action is increased by pretreatment with D.C.A. or L.A.P. and diminished by previous administration of A.C.T.H. or cortisone. We had noted in earlier experiments that the effect of various hormones largely depends upon the sensitization or desensitization of the target organs by peripherally acting "conditioning factors." Thus, the production of nephrosclerosis or arteriosclerosis by D.C.A. depends upon the sodium content of the diet (Selye, 1949a). In the present instance, however, formaldehyde as an irritant is the actual eliciting factor, while the hormone preparations appear to act as "conditioning factors" determining the degree of response.

About 10 days after the first hyperaemic and oedematous response vanishes, a secondary more chronic type of joint reaction becomes manifest. By this time most of the oedema has subsided, but the surrounding skin remains intensely hyperaemic and the periarticular connective tissue begins to proliferate, especially in the ankle-joint region. It is somewhat unexpected that the injection of the irritant at some distance from the ankle-joint should produce a secondary response in this articulation, but numerous observations leave no doubt concerning the selective responsiveness of the ankle-joint region during the chronic indurative stage. Probably the stretching of tissues incident to the great mobility of this joint is responsible for this.

In the course of our preliminary experiments we compared the inflammatory response to a given quantity of formaldehyde in various organs—for instance, the

connective tissue surrounding large joints, the derma, loose subcutaneous connective tissue, liver, spleen, muscle, testis, etc. These experiments revealed that the intensity of the inflammatory response (especially the initial oedema and the secondary induration) differs in various regions of the body. Apparently the connective tissue surrounding the large joints has the greatest "inflammatory potential," that of the derma and the loose connective tissue coming second. Most other tissues respond only with a very slight and transitory oedema followed by actual necrosis of the parenchymatous cells, without any long-lasting secondary proliferative inflammatory response.

The chronic periarthritic indurative changes were most readily obtained in animals which received several formaldehyde injections at a few days' intervals. Although this did not lead to any abscess formation, the resulting arthritis and periarthritis in the ankle-joint became a self-maintaining chronic inflammatory process which showed little or no sign of regression for weeks after the last injection. Indeed, frequently it continued to progress after treatment had been discontinued, so that eventually the joint became enormously enlarged, stiff, and extremely painful to touch. We shall report upon the histogenesis of this lesion elsewhere; suffice it to say here that, microscopically, in the acute oedematous stage it resembled the rheumatic, in the chronic stage the rheumatoid, type of arthritis. For the sake of simplicity we shall merely refer to these changes as the acute and chronic phases of "formalin-arthritis" (see Fig. 1).

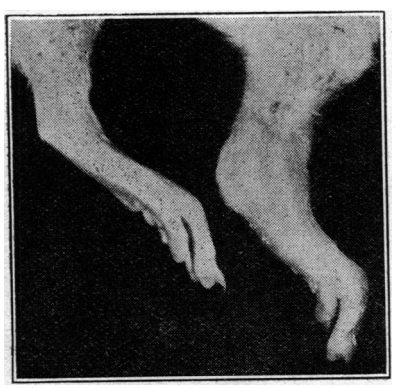

FIG. 1.—On the left, hind paw of a normal rat; on the right, hind paw of a rat which received three injections of a 1% formaldehyde solution under the palmar aponeurosis at two-day intervals one month before this picture was taken. Note the typical appearance of the chronic "formalin arthritis." The lesion is largely limited to the ankle-joint, which became almost immobilized by the hard cartilage-like indurating granulomatous vegetation. The skin covering this region is very hyperaemic and the joint extremely tender to touch.

Corticotrophin (*A.C.T.H.*) was administered subcutaneously in the form of a solution containing 5 mg. per ml. of physiological saline. Two highly purified preparations were supplied by the Armour Company, of Chicago: "lot 60–61," which has a biological potency of 100% Armour Standard La-I-A, contains 0.03 unit of oxytocin and 0.06 unit of vasopressin per mg.; "lot 64–A" has a biological potency of 180% of Armour Standard La-I-A and contains 0.03 unit of oxytocin per mg. Both these preparations are contaminated by only negligible amounts of the remaining known pituitary factors.

Lyophilized anterior pituitary (L.A.P.) was injected subcutaneously in the form of a preparation containing 40 mg. of lyophilized cattle anterior pituitary powder, suspended in a 10% aqueous alcoholic solution.

Cortisone was given subcutaneously as a saline suspension of cortisone acetate microcrystals, each millilitre containing 25 mg. The preparation was that distributed by Merck and Co., Rahway, N.J., in which suspending agents (to keep the microcrystals from settling) and 1.5% benzyl alcohol (as a preservative) are added.

Desoxycortone (D.C.A.) was administered subcutaneously as a microcrystal suspension containing 50 mg. per ml. of corn oil or in the form of pellets weighing 25 mg. each, as furnished by the Schering Corporation, of Bloomfield, N.J.

The techniques used for the production of the alarm reaction are described in the experimental section below.

I. Experiments with Corticoids

Effect of D.C.A. upon the Chronic Stage of "Formalin Arthritis"

In our first experiment we planned to examine the effect of D.C.A. upon the development of the "formalin arthritis." Twelve piebald rats, weighing 110–118 g., were unilaterally nephrectomized and given 1% NaCl instead of tap-water to drink, since previous work has shown that partial nephrectomy and a high sodium intake sensitize to the toxic actions of D.C.A. (Selye, 1946). These rats were then subdivided into two groups of six animals each. Group I acted as untreated controls, group II received 5 mg. of D.C.A. in 0.1 ml. of corn oil subcutaneously twice daily in the form of a microcrystalline suspension. Fourteen days later all animals of both groups were injected with 0.1 ml. of a 4% formaldehyde solution into the right hind paw, as described above. A second similar injection was given into the same paw four days later. Immediately after each injection the initial hyperaemic and oedematous response to the local irritation was approximately the same in both groups. However, a few days after each injection the oedema tended to subside much more in the untreated than in the D.C.A.-injected rats. The experiment was terminated on the 14th day after the first formaldehyde injection, at which time the oedema, induration, and hyperaemia of the paw were significantly more pronounced in the D. C. A. - pretreated than in the control rats (see Fig. 2). It must be emphasized, however, that the high concentration of formaldehyde used in this first experiment caused actual necrosis in the plantar skin, and hence the inflammatory response was quite intense and diffuse (not limited to the ankle region) even in the controls. In spite of this intense local damage, D.C.A. pretreatment aggravated the inflammatory response.

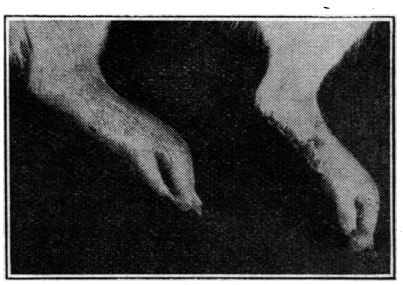

FIG. 2.—Hind paw of a rat pretreated with D.C.A. (left) and a not pretreated rat. Both animals were injected with the same amount of formaldehyde into the joint region, yet the D.C.A.-treated animal developed a much more pronounced inflammatory reaction.

Effect of D.C.A. and Cortisone upon the Subacute and Acute Stage of "Formalin Arthritis"

The second experiment was designed to examine the effect of D.C.A. and cortisone (both in themselves and in combination with each other) on the development of "formalin arthritis." For this purpose we used 40 male piebald rats weighing 120–150 g. All animals were bilaterally adrenalectomized on the first day of the experiment in order to eliminate any complicating endogenous corticoid formation. They were then subdivided into four groups of ten rats each: group I, no hormone treatment; group II, D.C.A.; group III, D.C.A. and cortisone; group IV, cortisone. D.C.A. was administered in the form of two 25-mg. pellets subcutaneously on the day of the

adrenalectomy. Cortisone was given in two 2.5 mg. injections daily subcutaneously. All animals received 1% NaCl as drinking fluid in order to help their survival after adrenalectomy and also because a sodium supplement aggravates D.C.A. intoxication.

An injection of 0.1 ml. of a 1% formaldehyde solution was given in the usual manner into the right hind paw on the second and fourth days after adrenalectomy. On the fifth day the swelling was very mild in the groups receiving cortisone or cortisone and D.C.A., while it was pronounced in the remaining two groups. There was no clear-cut difference between groups I and II (no hormone treatment or D.C.A. alone) nor between those of groups III and IV (cortisone alone or in combination with D.C.A.). At this time another injection of 0.1 ml. of a 2% formaldehyde solution was administered into the left hind paw, with the remarkable result that even three hours after the injection of this rather concentrated solution none of the two cortisone-treated animals (groups III and IV) responded, while the untreated animals, and especially those bearing the D.C.A. pellets, developed a marked hyperaemia and oedema, especially in the ankle region (see Fig. 3).

FIG. 3.—Cortisone-pretreated (left) and D.C.A.-pretreated adrenalectomized rats. Both animals received the same amount of formaldehyde, yet the cortisone-pretreated rat failed to respond, while the animal receiving D.C.A. developed a very pronounced and persistent inflammatory reaction. Adrenalectomized rats of this group receiving both cortisone and D.C.A. also failed to respond, while not pretreated adrenalectomized controls reacted violently, though not quite as much as those receiving D.C.A.

II. Experiments with Hypophyseal Preparations

Effect of A.C.T.H. upon the Acute Stage of "Formalin Arthritis"

Having learned that both in more chronic and in acute experiments cortisone inhibits, while D.C.A. tends to aggravate, "formalin arthritis," it appeared of interest to determine whether A.C.T.H. would act like cortisone, since in so many other respects these two hormones have similar properties. Twelve male Wistar albino rats weighing 120–180 g. were subdivided into two groups of six animals each. Group I received no hormone treatment, while in group II each animal was given 2.5 mg. of A.C.T.H. ("lot 60–61") subcutaneously. Twenty-five minutes later all animals of both groups received 0.1 ml. of a 1% formaldehyde solution into the left hind paw in the usual manner. Again the controls showed an almost immediate hyperaemic and oedematous response at the site of injection, while the A.C.T.H. pretreated animals exhibited only a very slight hyperaemia with almost no oedema. Two hours after the first injection an additional 2 mg. of A.C.T.H. was administered in group II. It was noted that in these animals the local response to the formaldehyde, though detectable, was extremely mild, even several hours after the second A.C.T.H. injection; by this time the paws of the control animals were very hyperaemic and so intensely swollen that the skin covering the plantar surface became shiny from extreme distension (see Fig. 4).

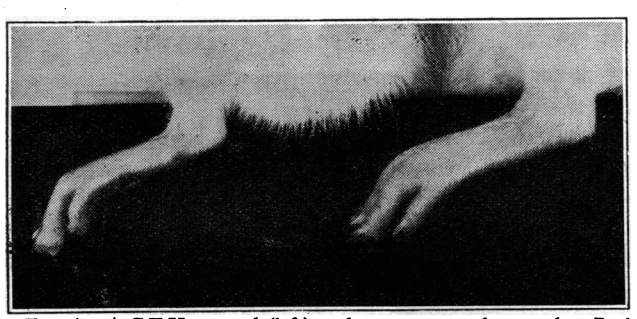

FIG. 4.—A.C.T.H.-treated (left) and not pretreated control. Both animals received the same amount of formaldehyde, yet the A.C.T.H.-treated animal almost completely failed to respond, while the control developed a pronounced oedema of the periarticular tissue and a pronounced hyperaemia of the skin almost immediately after the formaldehyde injection. Unlike the intact control, the A.C.T.H.-pretreated rats of this group gave no particular manifestations of pain when the joint region was touched.

Effect of A.C.T.H. upon the Chronic Stage of "Formalin Arthritis"

Having thus established that the acute local response to formaldehyde is inhibited by an immediately preceding injection of A.C.T.H., we undertook another experiment to examine the influence of prolonged A.C.T.H. treatment upon chronic "formalin-arthritis." Twelve male piebald rats weighing 120–136 g. were subdivided into two groups of six. Group I acted as controls, group II received 5 mg. of A.C.T.H. (lot 64-A) daily subcutaneously, subdivided into five injections of 1 mg. each. After two weeks of this pretreatment the animals of both groups received 0.1 ml. of a 4% formaldehyde solution administered into the right hind paw in the usual manner. With this dosage the immediate oedematous reaction was almost the same in the A.C.T.H.-treated and in the control animals, but in the former the swelling subsided rapidly while in the latter it persisted for several days. Seven and again 12 days later 0.1 ml. of a 1% formaldehyde solution was injected into the same paw in all animals.

After each injection the immediate response was almost as pronounced in the A.C.T.H.-pretreated as in the control animals, but, while in the former only a trace of oedema persisted a few days after each

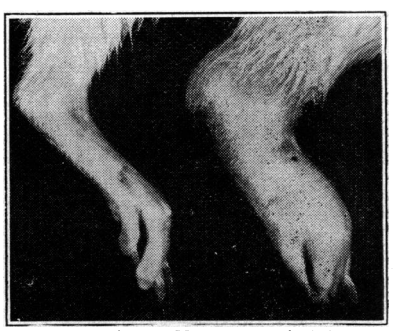

FIG. 5.—A.C.T.H.-pretreated (left) and not pretreated control. After a few A.C.T.H. injections both these animals were given repeated injections of the same amount of formaldehyde into the paw. The controls developed marked indurative chronic arthritic and periarthritic lesions; the A.C.T.H.-pretreated animals showed only a negligible response.

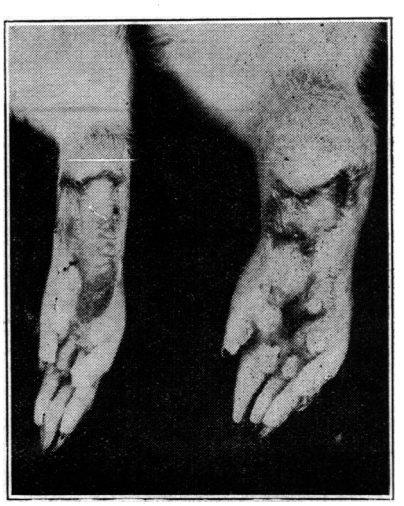

FIG. 6.—Plantar view of the specimens shown in Fig. 4. Note that although the direct necrosis-producing effect of the formaldehyde injection was the same in both cases, the A.C.T.H.-pretreatment (left) almost completely prevented the proliferative inflammatory response to the local tissue injury which is so evident in the control.

injection and no cumulative effect was detectable, in the latter the inflammation became increasingly more pronounced and gradually proceeded towards induration. By the 25th day after the first A.C.T.H. injection all the control animals had developed a pronounced and proliferative indurating inflammatory lesion, especially in the ankle-joint region, but to some extent also around the metatarsal joints. In several of the A.C.T.H.-treated rats there was also a barely detectable oedema of the paw, but without predilection for the ankle-joint region and without induration. In this series, where the first injection consisted of the concentrated (4%) formaldehyde, definite necrotic changes were obvious in the plantar region of all animals in both groups. This necrosis presumably resulted from the protein-precipitating (fixative) action of the formaldehyde, which of course could not be inhibited by the hormone treatment. It is especially instructive to note that in spite of the creation of an equally severe necrotic focus the inflammatory response to the irritation was so effectively suppressed by the hormone treatment (see Figs. 5 and 6).

Comparative Study of the Effect of L.A.P. and A.C.T.H. upon "Formalin Arthritis"

It will be recalled that in our earlier experiments L.A.P. occasionally produced arthritis even without any local trauma to the joints, while in the above-mentioned groups A.C.T.H. inhibited the development of "formalin-arthritis"; hence we wanted to compare the effect of the two hormone preparations under similar experimental conditions. For this purpose 18 male piebald rats weighing 120–150 g. were subdivided into three groups of six animals each. Group I received no hormone preparation; group II were given 40 mg. of L.A.P. daily, divided into five doses; and group III received 10 mg. of A.C.T.H. (lot 60-61) daily, divided into five doses. On the first, second, and third day of the experiment the rats of all groups were given 0.1 ml. of a 1% formaldehyde solution into the right hind paw in the usual manner. Here again the immediate response to the irritant was only slightly less pronounced in the A.C.T.H.-pretreated than in the other two groups. However, about 24 hours after each injection the oedema had subsided most markedly in the A.C.T.H.-treated animals and remained especially pronounced in those receiving L.A.P. This difference became quite obvious two days after the last formaldehyde injection. Thus A.C.T.H. greatly diminished, while L.A.P. slightly increased, the arthritis-producing effect of formaldehyde.

Our earlier observations had revealed that A.C.T.H. (like cortisone) causes rapid involution of the thymus and other lymphatic organs. This response is also manifest during the alarm reaction produced by any agent capable of causing systemic stress effects (e.g., nervous stimuli, infections, intoxications, exposure to cold), while L.A.P. tends to enlarge the thymus and the lymph nodes (Selye, in the press). It had been observed, furthermore, that during the alarm reaction the phagocytic power of the macrophages is considerably augmented, presumably due to increased A.C.T.H. and gluco-corticoid hormone production (Selye and Timiras, in the press). Since phagocytosis plays an important part in inflammatory reactions we added a few drops of commercial indian ink (Higgins's "American India ink") to the formaldehyde used in this experiment for the production of arthritis. This made it possible simultaneously to follow the process of phagocytosis. Upon necropsy of the rats on the second day after the last formaldehyde injection it became immediately obvious that, on the formalin and indian ink injected side, the popliteal and iliac lymph nodes were most markedly stained in the A.C.T.H. group and least markedly in the L.A.P.-treated animals. The size of these lymph nodes, on the other hand, was smallest in the A.C.T.H.-treated and largest in the L.A.P.-treated rats. Thus, apparently, the removal of the indian-ink particles was accelerated by the A.C.T.H. and inhibited by the L.A.P. preparation, while the morphologic

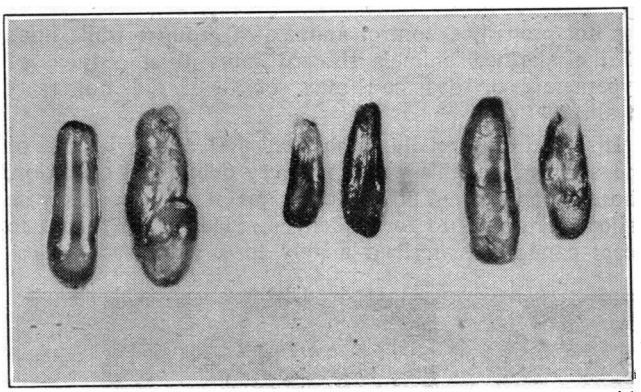

FIG. 7.—Iliac lymph nodes of rats which were injected with formaldehyde and indian ink into the joint region. On the left, not hormone treated control; in the middle, A.C.T.H.; on the right, L.A.P. pretreated animals. Note the A.C.T.H. increases phagocytosis but diminishes the size of the lymph nodes, while L.A.P. exerts contrary effects.

development of the lymph nodes was promoted by L.A.P. and diminished by A.C.T.H. (see Fig. 7). At the same time we confirmed that A.C.T.H. causes pronounced thymus involution while L.A.P. tends to augment the development of the thymus. This latter finding is all the more remarkable since the adrenal cortical enlargement produced by A.C.T.H. and L.A.P. was almost exactly the same at the dose level employed in this experiment. The adrenals of the untreated controls weighed 21±1 mg., those of the A.C.T.H.-treated rats 30±3 mg., and those of the animals receiving L.A.P., 32±2 mg. This would imply that at the dose level used the corticotrophic effect of the two preparations was quite comparable in degree, as judged by the ability of these preparations to cause adreno-cortical hypertrophy, yet the thymolytic and lympholytic effect was manifest only with pure A.C.T.H. Perhaps some contaminating substances present in the L.A.P. but absent in the A.C.T.H. counteract certain manifestations of the pure corticotrophic hormone.

Effect of the Alarm Reaction Upon the Development of Formaldehyde Arthritis

The last experiment of this series was planned to examine the effect of an alarm reaction (produced by various means) upon the response of the joint tissues to local formaldehyde injection.

Fifty male piebald rats weighing 150–200 g. were subdivided into five groups of ten animals each. Group I served as not pretreated controls. In group II an alarm reaction was produced by forced exercise in a drum cage 12 in. (30 cm.) in diameter and revolving at a speed of 12 revolutions per minute. The animals were forced to run three to four hours at a time, the revolving cage being stopped for a few hours whenever one or two animals of the group were too tired to run. Group III were exposed to a temperature of +1 to +3° C. during 24 hours. In group IV stress was produced by transection of the spinal cord at the level of the seventh cervical vertebra. In group V 0.5 ml. of a 10% formaldehyde solution was injected subcutaneously in the region between the shoulder blades four times during 24 hours. Since fasting increases the ability of various damaging agents to cause an alarm

reaction, all animals of groups II to V inclusive were fasted 24 hours before, as well as during the exposure period. Since all stresses were applied during 24 hours, the total period of fasting was 48 hours. At the end of this time 0.1 ml. of a 2% formaldehyde injection was injected in the usual manner into the right hind paw. Fifteen minutes later pronounced hyperaemia and oedema had developed in the not pretreated control animals of group I while none of the alarmed animals showed more than a trace of hyperaemia or oedema; most of them did not react at all.

It should be specially emphasized that, although some of the alarmed animals were in a very debilitated condition, those which showed no obvious signs of weakness likewise failed to respond to formaldehyde. Hence the failure to react cannot be ascribed merely to a decreased vitality.

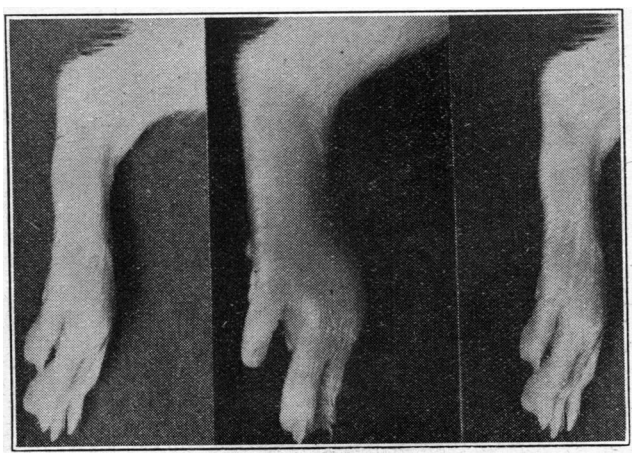

FIG. 8.—On the left, untreated control. Note normal appearance of the hind paw. In the middle, unpretreated control showing pronounced oedema and hyperaemia of the paw after local formaldehyde injection. On the right, paw of an animal in which an alarm reaction was produced by spinal-cord transection. Note almost complete absence of hyperaemia and oedema. The paw is practically indistinguishable from the intact control, although the same amount of formaldehyde was injected into it. A variety of other alarming stimuli (cf. text) exerted the same inhibitory effect.

This view receives further support from our previously mentioned observations on adrenalectomized animals. Many among these were almost moribund at the time of formaldehyde injection and yet responded with pronounced periarticular swelling. We are inclined to assume, therefore, that in this experiment endogenous secretion of A.C.T.H., and consequently of gluco-corticoids, was responsible for the inhibition of the "formalin-arthritis" (see Fig. 8).

Discussion

If we now attempt to evaluate these observations the concept of "non-specific resistance" or "crossed resistance" first comes to mind. We had repeatedly observed that during an alarm reaction, produced by diverse means, both the specific and the non-specific resistance of the organism rise above normal. That is, the exposed individual becomes more resistant not only to the particular damaging agent with which the alarm reaction was elicited but also to entirely unrelated stimuli. Thus an alarm reaction produced by cold, forced muscular exercise, spinal-cord transection, etc., increases resistance against the fatal lung oedema produced by toxic doses of adrenaline, anaphylactic and anaphylactoid reactions, etc. Since such manifestations of crossed resistance were invariably accompanied by histological signs of increased adreno-cortical activity, and since they were never observed in adrenalectomized animals exposed to stress, they had tentatively been ascribed to an increased production of corticoids during the alarm reaction (Selye, 1946; in the press).

We have reported elsewhere upon experiments showing that in the rat anaphylactoid reactions to egg-white can also be effectively inhibited by A.C.T.H. and cortisone (Selye, 1949c).

It is rather probable that in the final analysis the inhibition of "formalin-arthritis" by A.C.T.H., cortisone, and the alarm reaction is due to the effect of cortisone-like gluco-corticoids upon the directly injured tissues. The mechanism of this response is still unknown. It may be related to the anti-hyaluronidase effect of gluco-corticoids (Seifter, Baeder, and Dervinis, in the press), or to their well-known antihistaminic action. It has long been assumed that histamine-like compounds are liberated from tissues at the site of injury, and that these play an important part in inflammation. It is noteworthy, therefore, that the phenomena of "crossed resistance" which can most effectively be compared by the alarm reaction are also markedly inhibited by antihistaminic drugs (e.g., lung oedema, anaphylactic and anaphylactoid reactions). In view of this observation it would be interesting to examine the value of antihistaminics in some of the clinical conditions (e.g., rheumatic fever, rheumatoid arthritis, and lupus erythematosus) which have been effectively combated with cortisone or A.C.T.H.

It is particularly difficult to explain the apparent antagonism between D.C.A. or L.A.P. on the one hand and cortisone or A.C.T.H. on the other. Perhaps D.C.A., being a close chemical relative of cortisone, prevents the latter from reaching its target organs; this might be due to some mechanism of "competition for the substrate," such as has been demonstrated to exist between adrenaline and certain adrenaline derivatives, or vitamins and their corresponding anti-vitamins. However, this possibility is meanwhile purely hypothetical.

It is curious that the impure pituitary preparation L.A.P. acts like D.C.A., while purified A.C.T.H. exerts cortisone-like effects. L.A.P. contains A.C.T.H., and under the conditions of our experiments it produced an equally pronounced adrenal cortical enlargement; hence we must consider the possibility that the pituitary contains additional principles which antagonize the A.C.T.H. effect or so modify it that a D.C.A.-like action results. This may be important in the pathogenesis of the "diseases of adaptation." It will be recalled that under certain conditions chronic exposure to stress (e.g., cold, parenteral protein administration) causes nephrosclerosis, myocarditis, hypertension, and arteriosclerotic changes similar to those produced by D.C.A. or L.A.P. (Selye, 1946; in the press).

Finally, it must be kept in mind that the "anti-arthritic effect" of A.C.T.H. and cortisone is by no means specifically directed against the hypothetical pathogen which causes rheumatoid or rheumatic joint lesions. Clinical observations have shown A.C.T.H. to be highly effective also in gouty arthritis (Thorn, Bayles, Massell, Forsham, Hill, Smith, and Warren, 1949), and our observations reveal that even the arthritis caused by formaldehyde—an obviously entirely non-specific inflammatory reaction—is effectively prevented by A.C.T.H. and cortisone. It should be mentioned that upon discontinuation of A.C.T.H. treatment in patients predisposed to gout an attack of arthritis can be elicited (Hellman, 1949; Thorn, *et al.*, 1949). Correspondingly, in many of our experiments (not reported here) we noted that if a "formalin-arthritis" is inhibited by an

alarming stimulus during a period of one to two days it usually flares up in a particularly severe form upon discontinuation of the stress—e.g., cold, muscular exercise. Indeed, sometimes the arthritis developed after a latency period even if the stress was continued. Such observations raise the question whether it will be possible to combat clinical "diseases of adaptation" indefinitely by continued A.C.T.H. or cortisone therapy.

Summary and Conclusions

A technique has been developed which permits the production of an acute arthritis and periarthritis by the local injection of formaldehyde into the vicinity of joints. If large doses of formaldehyde are administered the acute stage is followed by a very prolonged chronic arthritis and periarthritis, characterized by moderate oedema and very pronounced connective-tissue proliferation, with stiffening of the joint and hyperaemia of the surrounding skin. The resulting chronic granuloma is self-maintaining, as it continues to proliferate for weeks after the administration of the local irritant.

This "formalin-arthritis" is slightly aggravated by pretreatment with desoxycortone or crude anterior-pituitary preparations; on the other hand it can be almost completely inhibited by cortisone or A.C.T.H. Thus there seems to exist an antagonistic relationship between D.C.A. or crude anterior-pituitary preparations on the one hand and cortisone or purified A.C.T.H. on the other.

The possible role of such an antagonism is discussed in connexion with the concept of "crossed resistance" and of the "diseases of adaptation."

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TUBERCULOSIS IN EUROPE DURING AND AFTER THE SECOND WORLD WAR

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THE TUBERCULOSIS SERVICES*

Before describing the reorganization of the tuberculosis services in the different European countries it may be helpful to say something of the conditions Unrra found in some of these countries at the end of the war. A preliminary stage of the Unrra programme was to study these conditions at close quarters, assess the damage, and make proposals for a programme of relief and rehabilitation on the basis of this assessment. Travelling throughout the countries as we did, discussing problems with people of all kinds, we were in a position often to get an exceptional overall view of the situation, and were in fact able to report back to the central authorities much that was unknown to them. It is only by remembering what these conditions were that we can appreciate what has been achieved since then.

It is difficult in this country to realize the extent of the disruption and destruction in some of the countries. Of those we saw, none had suffered more than Poland. The occupation had been brutal against a continuous opposition—the avowed German policy had been one of systematic reduction of the Poles to the status of a slave people, and a part of this policy had been the killing of professional and skilled workers. Some six million people of the total population of 33 millions had been killed in concentration camps, at their work, in their homes, or elsewhere. All higher education was stopped. The city of Warsaw was systematically destroyed till less than 10% of buildings were left standing, and other cities were similarly destroyed. The tragic war years were reflected in all we saw: when we went in we found towns that had throughout their area the look of some patches we know around St. Paul's or in the East End. Vast areas of farmland had been laid waste. People were living in cellars, dug-outs, in shells of buildings—one, two, or three families together in a room. Nearly all had lost relations in concentration camps or had spent years in camps themselves; there were half a million orphans; thousands of people were migrating from one area to another; thousands were returning from other countries. In the midst of all this the Polish people were attempting to rebuild—to provide homes, food, and services.

Dr. Gould, who visited Yugoslavia for Unrra, tells a similar story. In his words: "All the factors which tend to increase the incidence and mortality of tuberculosis became particularly acute during the war years. Entire villages had been burned after being plundered of food, clothing, livestock, and valuables. Men and women had been deported as slave labourers. With the combination of enemy action and civil strife the public health service was completely disorganized. Trained tuberculosis doctors and nurses were dispersed and lost."

Dr. McDougall reported from Greece: "In spring, 1945, when Unrra was invited to make a survey of tuberculosis requirements in Greece, after four years of German, Italian, and Bulgarian occupation and a month or more of civil

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