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INTERACTIONS BETWEEN SYSTEMIC AND LOCAL STRESS*

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It has long been known that topical inflammatory responses to locally applied non-specific irritants tend to be suppressed during the condition which we now call "systemic stress." Clinical experience had shown, for instance, that in severely malnourished patients—as in individuals damaged by haemorrhage, jaundice, trauma, or systemic intoxications of various kinds—the tissues do not react normally to local mechanical or chemical injuries. Mild insults elicit virtually no visible response, while severe local irritation tends to cause degeneration and necrosis, with little or no exudation and granuloma formation.

A systematic experimental analysis of these empirical observations disclosed a number of facts which began to reveal the underlying mechanism. First it was noted that the antiphlogistic effect is truly non-specific, since it could be elicited by various agents and in various sites. Thus systemic stress induced by several procedures, if it elicited an intense general adaptation syndrome, invariably suppressed the so-called histamine appendicitis (Selye, 1936, 1937a), different varieties of acute inflammatory lung oedema (Selye, 1938a, 1938b), and the anaphylactoid inflammation caused by egg-white in the rat (Selye, 1937b; Léger, 1948). Then it became evident that systemic stress can also facilitate the production of inflammatory lesions—for example, nephritis and myocarditis after exposure to cold—at least under certain "conditioning" circumstances. The adrenals are believed to play an important part in both these types of responses, since adrenalectomy prevents the inhibition as well as the stimulation of inflammation by systemic stress (Selye, 1946).

Later, when pure corticoids became available, it was noted that some, the so-called mineralo-corticoids—for example, desoxycorticosterone—stimulate, while others, the so-called glucocorticoids—for example, cortisone or cortisol†—inhibit inflammation (Selye, 1949; Selye and Pentz, 1943).

These observations gradually led to the concept according to which a major factor in the pathogenesis of many diseases is an inappropriate adaptive response to pathogens, a "derailment of the general adaptation syndrome." Stress undoubtedly plays some part in the pathogenesis of most maladies. However, those

with predominantly inflammatory manifestations—for example, rheumatoid arthritis—are especially clear-cut examples of "diseases of adaptation," because their course is very readily influenced by stress itself and by those hormones—for example, A.C.T.H., cortisol—which are produced in excess during the general adaptation syndrome.

The extensive literature which deals with this stress-concept has been surveyed at length elsewhere (Selye, 1950, 1952), and is currently reviewed in the *Annual Reports on Stress* (Selye, 1951; Selye and Horava, 1952, 1953). Suffice it here to mention two recent experimental studies, which are particularly relevant to the topic of this communication because they demonstrate that even the suppression of inflammatory changes—by systemic stress or by cortisol—is not always advantageous. When the local irritant is highly damaging to tissues the very absence of inflammation facilitates the production of a much more serious type of topical damage—namely, necrosis (Selye, 1953a, 1954).

While the aforementioned observations received ample confirmation in recent years, certain serious objections have been raised against the basic concept of the diseases of adaptation. Perhaps the most important among these are the following :

(1) Although treatment with corticoids undoubtedly combats certain disease manifestations, it has not yet been definitely proved that the therapeutic effect of stress itself—for example, non-specific therapy—depends upon endogenous adrenal hormones (Ingle and Baker, 1953; Bauer and Clark, 1953).

(2) Some authors feel that, even if artificial overdosage with corticoids can cause disease, it still remains to be shown whether endogenous adrenal hormones, secreted during stress, could ever become pathogenic at the dose level and in the circumstances under which they are produced (Ingle and Baker, 1953; Bauer and Clark, 1953).

(3) The assumption that systemic stress—for example, shock—acts upon the manifestations of topical stress—for example, inflammation, necrosis—predominantly through an increased secretion of A.C.T.H. and glucocorticoids, is difficult to reconcile with certain facts. In particular, it has been noted that the antiphlogistic effect of systemic stress is greater than that of a corresponding degree of hypercorticism induced by hormonal therapy (Selye, 1953b). For example, the antirheumatic efficacy of starvation, of jaundice, and of various non-specific therapeutic agents is more pronounced than that of raising the blood and urinary corticoids to the same level by actually giving cortisone or A.C.T.H.

(4) Transient overdose with a mineralo-corticoid (desoxycorticosterone) can cause delayed so-called "metacortical" lesions—for example, nephrosclerosis, hypertension—in ex-

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†In agreement with the suggestion made by Shoppee (1953), the term "cortisol" is used here in preference to "hydrocortisone," since it eliminates confusion with 4,5-dihydrocortisone and obviates the possible implication that hydrocortisone is to be regarded primarily as a mere derivative of cortisone.

perimental animals. This implies that, even if diseases are caused by an excess of such hormones, the corticoid concentration in the blood and urine may have returned to normal by the time the patient consults a physician (Green, 1953). It remains to be demonstrated, however, that natural adrenal hormones, secreted during stress, could also exert such delayed pathogenic actions.

(5) Some investigators consider it paradoxical to assume that the same factor, stress, can both inhibit and produce disease manifestations (Rosenberg, Woodbury, and Sayers, 1952).

We have now devised an experimental model on which these points can be tested by quantitatively measurable objective indicators. To permit generalizations a simple pathogen was used which produces such fundamental disease manifestations as inflammation and necrosis—that is, lesions commonly encountered in clinical medicine. As outlined below, the basic elements of this model are: the “pathogen” or topical stressor (the principal immediate cause of disease), the direct effect of the topical stressor (the local disease manifestations, such as inflammation and necrosis), the systemic stressor (which influences the local disease manifestations), and the adrenals (upon which the actions of the systemic stressor could depend) (Selye, 1954).

The purpose of this communication is to report upon three series of animal experiments, performed with a technique of this type.

Materials and Techniques

Experimental Animals and Their Maintenance

In all these investigations we used female Sprague-Dawley rats, weighing 120–150 g. at the beginning of the experiment. They were fed on “Purina Fox Chow,” and, since some of them were adrenalectomized, for uniformity's sake all received 1% NaCl as drinking fluid.

Topical Stress

The “granuloma-pouch” technique, which has been described in detail elsewhere (Selye, 1953a, 1953b), was used to produce and assess topical stress. In essence, the test is performed by injecting 25 ml. of air under the shaved dorsal skin of the rat, this being immediately followed by the injection of some irritant, the “local pathogen,” into the regularly shaped, ellipsoid connective-tissue chamber thus formed. In the present experimental series various dilutions of croton oil (in corn oil) have been used as examples of mild and severe local stressors, respectively.

The resulting amount of a haemorrhagic inflammatory exudate can be assessed approximately, day by day, by transillumination of the pouch with an electric flashlight; it can subsequently be measured accurately by withdrawing the fluid into a graduated syringe. This serves as an indicator of inflammation.

If the granuloma is weak, and the croton-oil solution comparatively strong, then the skin which covers the granuloma pouch undergoes manifest discoloration and necrosis. This serves as an indicator of local tissue death. As will be seen below, usually there is an inverse relationship between the intensity of inflammation and of necrosis.

Systemic Stress

In the first experiment, systemic stress was produced by fasting on the third, fourth, sixth, and seventh days after the granuloma pouches were prepared. However, the animals were allowed drinking fluid *ad libitum* at all times.

In the second and third experiments, forced restraint of the animals' free movements was used as a systemic stressor. The advantage of this procedure is that it does not necessitate the introduction into the body of any foreign materials or the infliction of traumatic tissue injuries. In principle, this technique (also described in more detail elsewhere—Selye, 1954) consists in temporarily restraining free loco-

motion by fastening the animal to a wooden board with adhesive tape. Since the procedure is irritating and provokes a certain amount of struggling, the condition of the rat is not unlike that occasioned by physical and mental fatigue in man.

Earlier experiments had shown that inflammation in the granuloma-pouch can most readily be inhibited by corticoids or systemic stress during a “critical period,” at about the third and fourth days in the development of a granuloma pouch (Selye, 1953c, 1954). Hence we applied the stress of forced restraint between the 72nd and the 96th hour of the experiment, both in the second and in the third experimental series. It should be added that, although during immobilization the animals received no food, many earlier control experiments had shown that a single day of fasting has no measurable effect upon the development of the granuloma pouch.

Assessment of the Adrenal Factor

All adrenalectomies were performed through the lumbar approach—in the first experiment 24 hours before, in the second and third experiments on, the day the granuloma pouch was prepared.

Some form of corticoid therapy was given in all three experimental series. In the first experiment, in which all animals were adrenalectomized, the rats of Groups I and II received cortisone acetate, those of Groups III and IV desoxycorticosterone acetate (D.C.A.), in the form of aqueous microcrystal suspensions, as distributed by Merck and Co., Inc. Both steroids were administered subcutaneously, twice a day, at the dose of 500 gamma in 0.2 ml. of suspending agent, between the 48th and the 168th hour of the experiment—that is, during the “critical period.”

In the second and third experiments, only some of the rats (Groups III and IV) were adrenalectomized, and hence in need of corticoid substitution therapy. Yet for uniformity's sake all animals were given 1 mg. of cortisol acetate microcrystals subcutaneously in 0.2 ml. of suspending agent twice daily. Unlike in the first experiment, this slowly absorbable cortisol ester was given throughout the period of observation (instead of the rapidly absorbed cortisone acetate during the “critical period”), to ensure a more constant blood-corticoid level. Numerous preliminary tests had shown that at this threshold level both corticoids increase the systemic resistance of adrenalectomized rats sufficiently to permit survival under considerable stress, and yet in themselves they do not greatly alter such reactions to local stress as exudation or tissue necrosis in the granuloma-pouch test.

Experimental Observations

First Experiment: The Effect of Fasting Upon the Topical Actions of Croton Oil in Adrenalectomized Rats Maintained with Cortisone or D.C.A.

This experiment was performed in order to establish whether the well-known anti-inflammatory effect of starvation is due exclusively to a stimulation of antiphlogistic corticoid (A–C) production by the adrenals, or whether it can also manifest itself in adrenalectomized animals if they receive maintenance therapy with such a corticoid.

Four groups, each consisting of ten adrenalectomized rats, were treated as outlined in Table I. The amount of exudate was measured, after aspiration into a graduated syringe, on the tenth day following the preparation of the granuloma pouch. In the table the mean volume of exudate is given with the standard error.

TABLE I.—Effect of Fasting Upon Exudation Due to Croton Oil in Adrenalectomized Rats (Maintained with Cortisone and D.C.A. Respectively)

Group	Treatment	Exudate (ml.)
I	Cortisone	5.5±0.5
II	Cortisone and fasting	0.5±0.16
III	D.C.A.	7.7±0.36
IV	D.C.A. and fasting	5.5±0.34

It will be noted that, in itself, the small dose of cortisone given to these animals failed to suppress exudation (Group I). Yet it caused almost complete inhibition of inflammatory fluid formation in the fasted animals (Group II). On the other hand, the rats maintained with D.C.A. developed considerable amounts of exudate, whether they were otherwise untreated (Group III) or exposed to starvation (Group IV).

It may be concluded that, although fasting has little or no effect upon exudation in adrenalectomized animals maintained with D.C.A., it considerably augments the antiphlogistic effect of cortisone. This augmentation is manifest in the absence of adrenal tissue—that is, under conditions when the stress of starvation could not act by stimulating the production of endogenous corticoids.

Second Experiment: The Effect of Restraint (Neuromuscular Stress) Upon the Topical Actions of Croton Oil in Intact and in Adrenalectomized Rats

The second experiment was performed on two groups of ten intact and two groups of ten adrenalectomized rats. Their treatment is summarized in Table II. A compar-

TABLE II.—Effect of Systemic Stress (Immobilization), in Intact and in Adrenalectomized Rats, Upon Topical Actions of Croton Oil

Day	Group I	Group II	Group III	Group IV
1	0.5% Croton oil	0.5% Croton oil	Adrenalectomy 0.5% Croton oil	Adrenalectomy 0.5% Croton oil
4	—	Stressed	—	Stressed
15	Exudate: 9.2 ml.	Exudate: 0	Exudate: 10.5 ml.	Exudate: 5.2 ml.

tively dilute croton-oil solution was introduced into the cavity of each granuloma pouch at the beginning of the experiment. On the fourth day one of the intact and one of the adrenalectomized groups were exposed to the neuromuscular stress, occasioned by forced immobilization (as outlined in the introductory section of this paper). On the 15th day the exudate content of the pouches was measured after aspiration into a graduated syringe, and the mean value so obtained is shown in the Table.

Perusal of Table II indicates that a large amount of exudate was formed in the non-stressed intact (Group I) and adrenalectomized (Group III) rats, while no trace of exudate could be demonstrated in the intact stressed animals (Group II). In the adrenalectomized stressed rats (Group IV), exudation was reduced by about 50% as compared with the adrenalectomized non-stressed controls.

Evidently, under these circumstances, stress proved to be a very effective antiphlogistic factor in intact animals. In the adrenalectomized rats the inhibitory effect of stress was still very obvious, but not as marked as in intact rats. This was so despite the fact that threshold amounts of cortisol were administered to all groups. Previous experiments had shown that, in adrenalectomized rats maintained with D.C.A. (which has no antiphlogistic properties), systemic stress of this kind causes virtually no inhibition of inflammation (Selye, 1954); hence it was postulated that two factors may be involved in this effect: (1) an increased discharge of endogenous antiphlogistic corticoids (which can occur only in the intact stressed rats); and (2) a peripheral synergism between the corticoids so liberated and some non-adrenal-mediated effect of stress.

It was then decided to perform a third experiment, with a still more dilute croton-oil solution, to see whether its exudate-forming action could be completely inhibited by systemic stress even in adrenalectomized rats if they are maintained on threshold doses of cortisol. At the same time, in this last experiment we wanted to test the resistance of the granuloma-pouch wall to the necrotizing action of more concentrated croton oil, given at a time when the non-stressed rats had already developed a strong granulomatous barrier. Such an experimental arrangement would permit the assessment of the functional value of

granuloma tissue as a barrier against the production of necrosis in adjacent tissues (in this case the skin).

Third Experiment: The Effect of Restraint (Neuromuscular Stress), in Intact and in Adrenalectomized Rats, Upon the Topical Actions of Weak and Strong Croton-oil Solutions Respectively

In this experiment we used two groups of ten intact and two groups of 20 adrenalectomized rats. They were treated as outlined in Table III. A weak croton-oil solution was introduced into the cavity of each granuloma pouch on the first day of the experiment. Then one of the intact and one of the adrenalectomized groups was exposed to the stress of immobilization during the "critical period." The degree of inflammation was first estimated on the seventh day by transillumination of the pouches. Subsequently, on the eighth day, a strong (normally necrotizing) croton-oil solution was injected into the pouch cavity, and the incidence of skin necrosis was noted on the 15th day.

TABLE III.—Effect of Systemic Stress (Immobilization), in Intact and in Adrenalectomized Rats, Upon Topical Actions of Weak and Strong Croton-oil Solutions Respectively

Day	Group I	Group II	Group III	Group IV
1	0.25% croton oil	0.25% croton oil	Adrenalectomy 0.25% croton oil	Adrenalectomy 0.25% croton oil
4	—	Stressed	—	Stressed
7	Exudate: + + +	Exudate: 0	Exudate: + + +	Exudate: 0 to +
8	50% croton oil	50% croton oil	50% croton oil	50% croton oil
15	Necrosis: 10%	Necrosis: 100%	Necrosis: 10%	Necrosis: 90%

It will be noted that, under these conditions, stress prevented inflammatory exudate formation not only in intact rats (Group II), but also in those adrenalectomized and maintained with comparatively small doses of cortisol (Groups II and IV). On the other hand, large amounts of exudate had formed both in the intact (Group I) and in the adrenalectomized (Group III) non-stressed rats, although they received the same amount of cortisol as the others. Thus the findings on the seventh day confirmed the observations of the first and second experimental series, under slightly modified circumstances.

Interestingly, the subsequent injection of strong croton oil caused necrosis of the skin in all the intact stressed (Group II) and in 90% of the adrenalectomized stressed (Group IV) rats, while all but 10% of the intact (Group I) and of the adrenalectomized (Group III) non-stressed rats resisted this necrotizing action of the strong topical irritant.

It may be concluded that, here, the same stressor, which protected against the local disease-manifestations (exudation) usually produced by a weak topical irritant, actually sensitized the tissues to the more severe damage (necrosis) normally elicited by higher concentrations of the same local pathogen. It is also evident that a transitory exposure to systemic stress on the fourth day considerably altered tissue-reactivity to local irritants introduced into the pouch, either before or after this time.

Discussion

Let us now consider the information which these experiments have furnished concerning the much-debated points enumerated in the introduction.

The first experiment gives objective evidence in support of what I have called the "antiphlogistic-corticoid-conditioning effect: (A-CC)" (Selye, 1953b; Selye and Horava, 1953). Adrenalectomized rats maintained with small doses of cortisone are still capable of responding to topical injury by intense inflammatory exudation. If these animals are exposed to the stress of fasting they lose this ability. Here starvation obviously could not have acted by increasing endogenous corticoid secretion, since the rats had no adrenals, yet the animals, by the withdrawal of food, were conditioned for the antiphlogistic effect of exogenous antiphlogistic corticoids.

On the other hand, under similar circumstances, adrenalectomized animals maintained with D.C.A. (a steroid

devoid of antiphlogistic properties) retained their ability to produce inflammatory exudate even during prolonged starvation. Hence the inhibition of inflammation by food withdrawal cannot be the unconditional direct effect of inanition as such.

The adrenalectomized rats of the second and third experimental series showed that this antiphlogistic conditioning potency is not a specific characteristic of starvation, because it can be duplicated by an entirely different kind of stressor—namely, the neuromuscular exhaustion resulting from forced immobilization. These same animals also demonstrate that cortisone is not the only antiphlogistic hormone whose activity can thus be augmented by stress, since they were maintained on cortisol.*

The probable mechanism of these responses to systemic and topical stress is illustrated by the accompanying schematic drawing.

Another point illustrated by the second and third experiments is that tissue reactivity to topical damage can be altered not only during, but even several days after, exposure to a transitory period of systemic stress. The delayed susceptibility (predisposition for necrosis) or refractoriness (resistance to inflammation) to disease, which is thus produced by stress, depends upon endogenous corticoids, since it is not seen in the absence of the adrenals unless suitable substitution therapy is given.

Finally, the third experiment demonstrates that the same factor, stress, can both inhibit and facilitate the production of local disease manifestations, since it inhibits the phenomena of inflammation and aggravates those of necrosis.

These observations also help to understand the mechanism through which the biological reactions of systemic and local stress are integrated. The so-called “local adaptation syndrome” (L.A.S.), the characteristic triphasic adaptive response to topical injury, comprises both necrosis and

*It should be mentioned in this connexion that, in additional unpublished experiments, adrenalectomized rats were maintained on threshold doses of cortisone and injected with lyophilized thymic, lymphatic, and splenic tissue, or subjected to complete ligation of their main bile duct. These animals likewise showed complete inhibition of exudate formation in the granuloma-pouch test. Here, again, the inhibition could not have been due to the direct unconditional effect of the extracts or of biliary retention, since it was not manifest in adrenalectomized rats maintained with threshold doses of D.C.A. A variety of purified A.C.T.H. preparations (including “corticotropin-B,” kindly furnished by Merck and Co., Inc.) also proved highly effective in augmenting the antiphlogistic effect of cortisone in adrenalectomized animals. The question arises whether the various “A-CC agents” act through different mechanisms or through the intermediary of their ability to stimulate the A.C.T.H.-production of the animals’ pituitary. This point is now under investigation.

inflammation. It has been demonstrated and discussed at some length by several participants of the International Symposium on the Mechanism of Inflammation (Jasmin and Robert, 1953). The experiments reported in this paper furnish additional evidence in support of the view expressed at that Convention, that a close relationship exists between the general adaptation syndrome, as a systemic manifestation of stress, and the local adaptation syndrome, as its topical counterpart. In particular, local stress can cause systemic stress, and the latter can, in turn, greatly modify the course of the former. Indeed, various combinations of these two responses represent integral parts of many among the common maladies of man.

Our experimental model is directly concerned only with the role of the adrenals in determining the production of inflammation and tissue necrosis by a topical irritant, during systemic stress. However, inflammation, necrosis, topical irritants, and systemic stress are fundamental elements of most, if not all, maladies. Actually, there is no evidence to prove that any tissue damage (no matter where and no matter by what agent it be produced) would fail to be similarly regulated through the adrenals during the systemic stress of disease.

Summary

Using the granuloma-pouch technique, it was shown that, depending upon circumstances, systemic stress can either inhibit or aggravate the topical damage caused by exposure of a limited tissue area to a pathogen—for example, a chemical irritant, such as croton oil.

The antiphlogistic effect of stress is not merely due to increased secretion of cortisol-like hormones, since it is also observed in adrenalectomized animals maintained on (in themselves inactive) threshold doses of injected cortisol.

The aggravation of topical tissue injury by systemic stress also depends only in part upon endogenously produced adrenal hormones; it is abolished by complete adrenalectomy, but not if suitable substitution therapy with antiphlogistic corticoids (cortisone, cortisol) is given.

Both these effects of systemic stress upon topical tissue reactions can be delayed, becoming manifest only after the systemic stressor has ceased to act.

The interrelation between systemic and local manifestations of disease in general are discussed in the light of these findings.

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