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REACTIONS TO STRESS

When an animal is injured, develops an infection, is exposed to *x* rays or to cold, or is subjected to almost any circumstances not ordinarily encountered in its day-to-day existence, a series of bodily reactions take place which allow the animal to withstand and adapt itself to the insult. Professor Hans Selye, in Montreal, has carried out extensive and ingenious investigations in an attempt to elucidate the mechanisms by which this adaptation is achieved.[1 2] Out of this work have grown his conception of the general adaptation syndrome and his belief that certain pathological conditions in man and animals—the so-called diseases of adaptation—are caused by some abnormality in this process of adaptation. Some of Selye's ideas are hard to accept, and his terminology does not make the understanding of them easier. Other investigators[3] have not always been able to reproduce his experimental findings, and the interpretation and significance of the results, particularly when applied to man, are not clear.

When an animal is exposed for a long time to a particular noxious stimulus it adapts itself, and a series of bodily changes may occur, such as a fall in body temperature and blood pressure, involution of lymphatic tissue, lymphopenia, a polymorphonuclear leucocytosis, adrenal hyperplasia, and diminished resistance to other non-specific stimuli. The sum of these non-specific bodily reactions constitutes the general adaptation syndrome, and Selye believes that the adrenal cortex plays an essential part in causing the anatomical and biochemical changes found in the syndrome. Certainly adrenalectomized animals and patients with untreated Addison's disease are unable to survive minor traumata which would not cause any apparent disturbance in a normal subject. Other investigators[4 5] have contended that the adrenals play only a permissive role, that the presence of adrenocortical steroids is required for the changes found in the adaptation syndrome to take place but that they are not themselves the cause of the changes.

Selye observed that rats, when exposed to cold, forced exercise, or formalin, developed hypertension, transient arthritis and pathological lesions akin to nephrosclerosis, periarteritis nodosa, and Aschoff bodies, particularly if the animals were previously conditioned by unilateral nephrectomy and a high-salt diet. He postulated that, because these pathological lesions developed during the process of adaptation to a variety of different stimuli, they might be causally related to overactivity or abnormal activity of the adrenal glands. Support for this hypothesis was obtained by observing that the lesions could be potentiated with deoxycortone (D.O.C.) and prevented or attenuated with corticotrophin or cortisone. Selye suggested that for unknown reasons adrenal secretory activity sometimes becomes abnormal during adaptation to prolonged stress, that the balance is disturbed between the amounts secreted of mineralocorticoid inflammation-stimulating hormones (such as D.O.C.) and of glucocorticoid anti-inflammatory hormones (such as cortisone and cortisol), and that in consequence the diseases of adaptation develop.

These hypotheses have been criticized on many grounds.[3 6] There is no satisfactory evidence that non-specific stressors will cause adaptation diseases in laboratory animals under naturally occurring conditions. It is doubtful whether the experimentally induced pathological lesions in rats, previously conditioned by removal of one kidney and fed on a high-salt diet, are the same as those occurring in the human connective-tissue diseases. While certain forms of stress, such as surgical trauma, undoubtedly cause increased adrenal activity, it has not been proved that all types of stress cause such a response.[7 8] Until recently there was little evidence that a specific mineralocorticoid, especially potent in controlling electrolyte metabolism, was elaborated in man, but this objection must be overruled since the isolation of aldosterone (11,21-dihydroxy-3,20-diketo-4-pregnene-18-al), formerly called electrocortin.[9 10] Preliminary reports[11 12] on this substance suggest that it has glycogen-depositing and eosinopenic, in addition to sodium-retaining, properties, but it remains to be seen what are its physiological effects and whether there is any disturbance in the relationship between the amounts of this compound and of cortisol secreted before or after the onset of the so-called diseases of adaptation. There is little evidence to support the suggestion that non-specific therapy is beneficial in

[1] Selye, H., *J. clin. Endocr.*, 1946, **6**, 117.
[2] —— *The Story of the Adaptation Syndrome*, 1952, Acta, Inc., Montreal.
[3] Ingle, D. J., and Baker, B. L., *Progress in Hormone Research*, 1953, **8**, 143.
[4] —— *Ann. intern. Med.*, 1951, **35**, 653.
[5] Engel, F. L., *Progress in Hormone Research*, 1951, **6**, 277.
[6] Bauer, W., and Clark, W. S., ibid., 1953, **8**, 217.
[7] Cope, C. L., and Hurlock, B., *Clin. Sci.*, 1954, **13**, 69.
[8] Thorn, G. W., *et al.*, *Progress in Hormone Research*, 1953, **8**, 171.
[9] Simpson, S. A., *et al.*, *Lancet*, 1952, **2**, 226.
[10] —— —— *Experientia*, 1954, **10**, 132.
[11] Mach, R. S., *et al.*, *Schweiz. med. Wschr.*, 1954, **84**, 407.
[12] Gaunt, R., Ciba Foundation Colloquium on Endocrinology, to be published.
[13] Bayliss, R. I. S., and Steinbeck, A. W., *Lancet*, 1954, **1**, 1010.
[14] *British Medical Journal*, 1951, **2**, 1189.
[15] *Progress in Hormone Research*, 1953, **8**, 128.
[16] Perera, G. A., and Ragan, C., *Proc. Soc. exp. Biol. (N.Y.)*, 1950, **75**, 99.
[17] Bauer, W., *et al.*, *Practitioner*, 1951, **166**, 5.
[18] Thorn, G. W., *et al.*, *Ann. rheum. Dis.*, 1949, **8**, 307.
[19] Goulding, R., Communication to the Society for Endocrinology, 1954.

rheumatoid arthritis, for example, by increasing the secretion of glucocorticoids.[13] Although in a carefully conducted study Caughey and McCoy[14] have reported that D.O.C. aggravated the arthralgia in a patient with pre-existing rheumatoid arthritis who subsequently developed Addison's disease (they did not, to quote Selye,[15] "produce arthritis with D.O.C. at will"), Perera and Ragan[16] failed in a similar case to aggravate the arthritis with D.O.C., and other workers[17–19] have not found that D.O.C. exacerbates the symptoms of rheumatoid arthritis or counteracts the beneficial effects of cortisone.

The communication from Selye published in our opening pages this week is related to the observation that the inflammatory response to a locally applied irritant is much reduced when the experimental animal is exposed to stress. It has been previously supposed, but not proved, that the reduction in the inflammatory response is related to increased circulation of adrenocortical hormones, since it is well known that cortisone and cortisol diminish the intensity of an inflammatory reaction. In the present experiments croton oil was used as a local irritant to produce an inflammatory reaction, and starvation and forced immobilization to produce the general stress. The effects of the presence or absence of the adrenal glands and of the administration of glucocorticoids or D.O.C. were observed. Under the conditions of the experiment a general stress decreased the local inflammation. This decrease was greatest in animals with intact adrenal glands but occurred to a less extent in adrenalectomized animals maintained on small doses of cortisone or cortisol and not in animals maintained on D.O.C. Thus Selye postulates that the anti-inflammatory effect of general stress is mediated by two factors—an increased discharge of endogenous glucocorticoids and a peripheral synergism between the corticoids so liberated and some other effect not mediated through the adrenal glands. He also found that further application of the local irritant caused a greater degree of necrosis in those animals that were subjected to stress and previously had shown the least inflammatory reaction. Selye uses this as evidence that local tissue reactions can be modified by stress applied several days earlier.

What deductions about human reactions may be drawn from these experiments is uncertain. It remains to be shown how much starvation or forced immobilization activates the pituitary–adrenal system, and what is the nature of the non-adrenal factor which reduces the inflammatory reaction and increases the tendency to necrosis. Critics may question whether the condition of an immobilized rat "is not unlike that occasioned by physical and mental fatigue in man." When all has been said, Selye's technical brilliance as an animal experimenter, and his imaginative boldness in theory, continue to act as a provocative stimulus to other workers.

OCCUPATIONAL MORTALITY

The late Professor M. Greenwood[1] described the Registrar-General's decennial studies of occupational mortality in England and Wales as "the most valuable single instrument of socio-medical research our national armoury contains," and many will wish to study the latest contribution in this series, a preliminary analysis of deaths in 1950 related to the 1951 Census 1% sample tables. This publication[2] is the more welcome in that it is twenty years since the previous occupational mortality analysis was undertaken, when deaths in 1930–2 were related to the 1931 Census, and many changes have taken place since then in our national life and in medical science and practice, changes that could have the effect of rendering some of these earlier findings out of date. In due course this report will be followed by a much more detailed one covering the five years 1949–53.

Since 1851 the Registrar-General has taken the deaths registered in or about each census year and has related them to the numbers of people enumerated in various occupations at the census; and since 1911 the occupations have been grouped into a number of so-called social classes. Eight classes were distinguished in 1911, but since 1921 there have been five—I (professional occupations), II (intermediate), III (skilled), IV (partly skilled), and V (unskilled occupations). This social classification is purely an occupational one, and takes no regard of personal circumstances, income, education, and so on except in so far as these are reflected by the individual's occupation. As only one year's deaths have been tabulated for this latest report and as the population estimates are based only on a 1% preliminary sample, most of the mortality rates that are given are for the social classes; little attempt has been made to calculate rates for individual occupations, though a few are shown for one or two large groups such as miners, transport workers, and clerical workers. Mortality indices for various diseases are given separately for men aged 15–64 and aged 65 and over, and for married women classified by their husbands' occupations.[3]

Though it will probably be advisable to await the detailed five-year tables before drawing too many conclusions from this interim report, comparison of

[1] *Some British Pioneers of Social Medicine*, 1948, London.
[2] *Registrar-General's Decennial Supplement: England and Wales*, 1951. *Occupational Mortality, Part I*, H.M.S.O., London, 7s. 6d.
[3] See *British Medical Journal*, May 15, p. 1162.