ent in peritoneal cell suspensions and can be removed in part by albumin.

The mode of action of phosphatidylserine in enhancing the response of mast cell to dextran and protein antigens is not clear at present. A simple detergent effect is not likely, since other phosphatides with good detergent properties, such as phosphatidylcholine, do not enhance histamine release. In searching for other biologic effects of phosphatidylserine which conceivably could have some relationship to its action on mast cells, it is of interest that this phosphatide has a role in activating Na^+, K^+-adenosine triphosphatase activity in preparations obtained from the kidney and brain (*6*).

It may seem surprising that phosphatidylserine enhances the antigen- and dextran-induced release of histamine, but not that caused by compound 48/80, which in the rat supposedly is very similar. It should be pointed out, however, that there are several other important differences between the two types of histamine release. While the anaphylactic effect is highly dependent on the calcium concentration of the medium, release induced by compound 48/80 is much less sensitive to the influence of this ion (*7*). Also, anaphylactic histamine release can be inhibited by 2-deoxyglucose, while the action of compound 48/80 cannot be prevented by this metabolic inhibitor (*8*). The present findings represent one more example of a basic difference between anaphylactic histamine release and histamine release induced by compound 48/80.

The present findings may explain some puzzling observations on the inhibitory effect of washing mast cells with, or without, albumin on subsequent histamine release by dextran or ovomucoid (*3*, *9*) and the enhancing action of a factor present in brain acetone powder (*1*). This work also focuses attention on the possible modulating role of phospholipids in histamine release from rat mast cells, caused by polymeric compounds and antigen-antibody reactions.

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Mineral Element Correlation with Adenohypophyseal-Adrenal Cortex Function and Stress

Abstract. *A statistical correlation was made between adrenocorticotropin (ACTH) and four elements in rats under control, stress, and stress-recovery conditions. Blood serum zinc showed a strong positive correlation with the rise in ACTH during stress and its decline in stress recovery. Serum calcium, copper, and magnesium demonstrated little correlation with ACTH changes. The strong ACTH-zinc correlation points to an as yet undefined interaction between ACTH and zinc.*

The involvement of trace metals in enzyme and hormone function suggests a relationship between stress and elemental metabolism. The pituitary-adrenal axis is one of the major systems of the body that deals with stress, yet few data have been presented to establish a correlation between adrenocorticotropin (ACTH), adrenal steroid hormones, and mineral elements. Sandstead *et al.* (*1*) inferred such a relationship when they reported that, in zinc-deficient Egyptian dwarfs, exogenous doses of ACTH elicited little adrenal response. Also, the mepyrapone test showed that the pituitary corticotropin reserve was low. Zinc supplementation in these dwarfs seemed to improve their

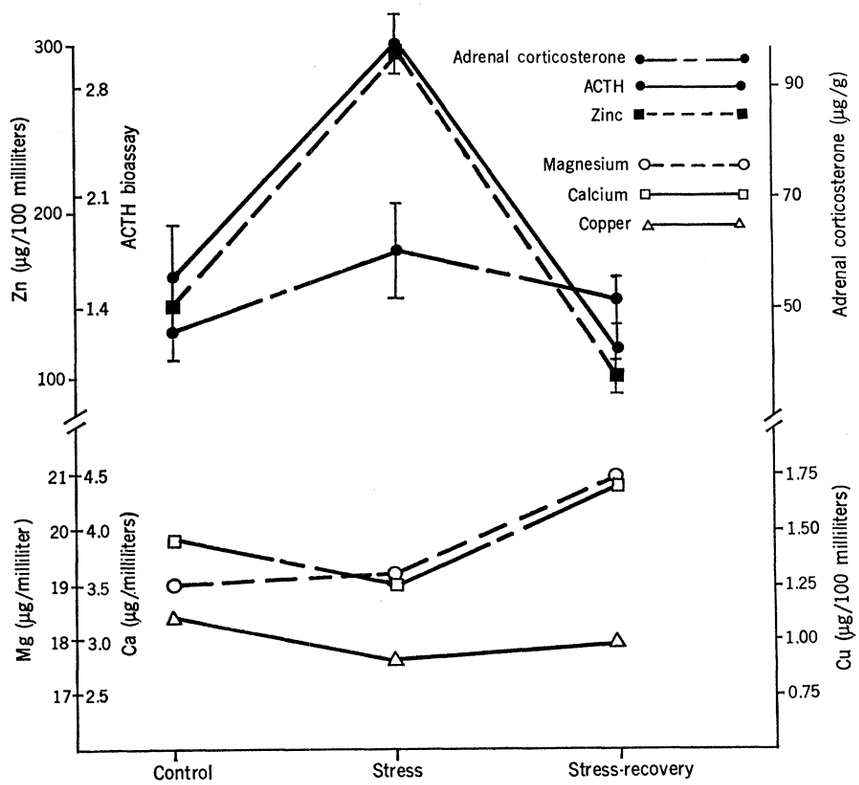

Fig. 1. Comparison of ACTH and adrenal corticosterone with four elements—calcium, copper, magnesium, and zinc—under control, stress, and stress-recovery conditions.

adrenal response to ACTH and suggested that zinc was required for pituitary-adrenal function.

We tested the relationship of stress, ACTH, corticosterone, and four elements in 18 adult, male Sprague-Dawley rats (300 to 425 g), divided into control, stress, and stress-recovery groups of six each. By a corticosterone-based bioassay in 18 additional rats (*2*), ACTH was determined in the pituitaries of the test animals; corticosterone was measured fluorometrically in the rat adrenals (*3*); and four elements (calcium, copper, magnesium, and zinc) in serum were measured by atomic absorption spectroscopy. All animals were anesthetized with pentobarbital sodium (3 mg/kg), and a catheter was inserted into the right carotid artery for withdrawal of blood. Oligemic hypotension, a maintained mean arterial pressure of 50 mm-Hg for 1 hour, was used as stress; the 2 hours after reinfusion was stress recovery. The rats were then decapitated, the pituitary and both adrenals were removed, and homogenates were prepared.

The severity of the oligemic stress episode was reflected in the elevated ACTH levels of approximately twice the control values, which quickly responded during the stress recovery by dropping to levels below control values. The activity of these changing ACTH concentrations was monitored by adrenal corticosterone changes. The ACTH activity was evident in the rise and fall of corticosterone levels during stress and stress recovery (see Fig. 1).

Blood serum zinc was the only one of the mineral elements determined that responded with a significant increase during stress. The zinc levels increased sharply during the oligemic stress episode, whereas control levels of calcium, copper, and magnesium either remained the same or decreased during stress. Figure 1 illustrates the changes in ACTH and elemental levels during stress and stress recovery. Unlike calcium, copper, and magnesium, which varied little during stress recovery, zinc again followed the pattern of ACTH and decreased during recovery.

A Pearson r correlation was computed on the basis of 18 levels for each of the four elements, each level being correlated with the corresponding rat ACTH. The correlations were made to determine if a relationship existed between one or more of the elements commonly associated with stressful states. Zinc had the greatest correlation of the four elements ($r = 0.85$), whereas calcium ($r = -0.22$), copper ($r = 0.14$), and magnesium ($r = 0.16$) correlated with ACTH to a far lesser extent.

The action of ACTH on the adrenal cortex during a traumatic experience has long been established, but little has been said about the involvement of calcium, copper, magnesium, and zinc in stress. The delicate balance of ACTH release is well demonstrated by the relationship of corticosterone levels to ACTH activity. During the stress-recovery period, the corticosterone levels remained elevated over control values, which suppressed the mechanism for ACTH production. The relationship of zinc to ACTH as illustrated in Fig. 1 strongly suggests some type of physiological or coupling action on the part of zinc during stress. The control values for zinc of 150 μg/100 ml were within the normal range for rat serum, as given by Luecke *et al.*, of approximately 147 μg/100 ml (*4*). The remaining three trace elements, calcium, copper, and magnesium, showed little relationship to ACTH responses in stress.

The discussion by Sandstead *et al.* of the Egyptian dwarfs did not clearly define any role for zinc in ACTH (*1*). Zinc, as $Zn_3(PO_4)_2$ or $Zn(OH)_2$, has been found, however, to increase and prolong the physiological action of ACTH (*5*). In the Trace Element Center, a relatively high zinc level was found in two commercial ACTH preparations (*6*). Whether the role is functional or passive, zinc does appear to be linked with the rise of ACTH, which strongly correlates with a stress situation. None of the other three elements determined (calcium, copper, or magnesium) related to the changes in the adenohypophyseal-adrenal cortex function and stress. Further studies are needed to unravel this correlation and zinc's association with ACTH.

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6. Commercial ACTH preparations tested for zinc levels: (i) corticotropin (Nutritional Biochemicals; injectable; bovine; 40 unit/ml; zinc, 396 parts per million); (ii) Acthar [40 units (lyophilized); mixed 40 unit/ml in double-distilled, deionized H_2O; zinc, 112 parts per million].
7. Work supported in part by a grant from the Cleveland Foundation.

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Gonadotropin-Releasing Hormone: One Polypeptide Regulates Secretion of Luteinizing and Follicle-Stimulating Hormones

Abstract. *A polypeptide isolated from porcine hypothalami stimulates the release of both luteinizing hormone and follicle-stimulating hormone from the pituitaries of several species. This polypeptide has been structurally identified as (pyro)Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 and synthesized. The natural and synthetic materials share biological properties. It appears that this peptide represents the hypothalamic hormone regulating the secretion of both luteinizing hormone and follicle-stimulating hormone.*

The hypothalamus controls the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (*1*). The work of various investigators clearly demonstrated that there are, in hypothalamic extracts of animals, including man, substances, or one substance, capable of stimulating release of LH and FSH from the pituitary (*1, 2*). Much evidence also exists that sex steroids are involved in this regulation. Initially, it was thought that two different substances designated luteinizing hormone-releasing hormone (LH-RH) and follicle-stimulating hormone-releasing hormone (FSH-RH) were responsible for stimulating release of LH and FSH, respectively (*1*). However, it became necessary to question this belief when porcine LH-RH, obtained in a