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HORMONES, BRAIN FUNCTION, AND

HORMONES, BRAIN FUNCTION, AND BEHAVIOR

Proceedings of a Conference on Neuroendocrinology Held at Arden House, Harriman, New York, 1956

Edited by

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Foreword

This book constitutes the report of a conference on neuroendocrinology held in May, 1956, at Columbia University's Arden House on the Hudson. Twelve papers were presented on aspects of neuroendocrinology during the two-day meetings. Each paper was followed by informal discussion.

Recent years have shown a renaissance of interest in neuropharmacology resulting in large measure from the discovery of new drugs, especially lysergic acid diethylamide, that produce experimental psychotic episodes in man. The discovery of the value of tranquilizing drugs in relation to mental disorders has also added impetus to studies of biochemical determinants of conduct. The hormones are endogenously produced drugs regulating the internal environment of the cells and modifying many aspects of behavior.

Communication between cells and between organs may be classified roughly into two major categories: (1) communication by nerve impulses which are efficient discrete messages in the form of waves of electrochemical change coursing over specific fibers from sensory receptors to cells of the central nervous system, from cell to cell within this integrating system, and thence out to effector organs; (2) intercellular and interorgan communication either by short-distance diffusion of metabolites from cell to cell or by transportation by the blood stream to remote organs of metabolites such as CO_2 as well as the special metabolites of endocrine glands.

Such metabolic messengers which include the hormones have been referred to by Norbert Wiener as "to whom it may concern" messages. Formed in glands of internal secretion and released into the blood stream, the hormones may be carried to all the tissues of the body before becoming inactive metabolites. Relatively few of the molecules so broadcast reach target organs where they react with appropriate chemical receptors and so act as regulating messengers affecting tissue and organ function. The papers and discussions of this symposium are aimed at elucidating selected aspects of hormone actions in relation to brain function and behavior.

The symposium was made possible by generous aid from the G. D. Searle Company of Chicago. We are especially indebted to Dr. I. C.

Winter, Director of Clinical Research of the Searle Company, and his staff for assistance in organizing the conference.

As chairman of the conference, I wish to express my sincere appreciation not only to the contributors of the papers but also to those participants whose lively and spontaneous discussion did so much to make the meetings profitable to all who attended.

HUDSON HOAGLAND

Shrewsbury, Massachusetts
November 1956

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EFFECTS OF STEROID HORMONES ON THE NERVOUS SYSTEM

Steroid Hormones in Relation to Neuropsychiatric Disorders

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I. INTRODUCTION

The more one pries into the bewildering complex of interactions between mind and bodily functions the less one feels able to name precise mechanisms responsible for any one disturbance. This has been said in many ways, many times, but perhaps not more aptly than in the perplexed words of Dr. William Buchan of Edinburgh in his treatise on disease, in 1779 (12). In this he says, "The passions have great influence both in the cause and cure of diseases. How mind acts upon matter will, in all probability, ever remain a secret. It is sufficient for us to know that there is established a reciprocal influence betwixt the mental and corporeal parts, and that whatever disorders the one, likewise affects the other."

The history of man is, however, illuminated with repeated examples of refusal to accept obscurity as the answer to his endeavors to fathom and control his environment and himself. So we see the gradual accretion of knowledge bringing more and more of the universe within his ken. The development of endocrinology, which arrived rather late on the biological scene, is now contributing to an understanding of man himself (18). As it develops, it is becoming increasingly apparent that the endocrines are almost inextricably associated in function with that other major homeostatic regulator, the autonomic nervous system, in both central and peripheral activities (19). But as Mirsky (61) has said, "The paucity of information that is available concerning the specific role of humoral agents in the regulation of behaviour is due, primarily, to the fact that it is impossible to distinguish where one regulatory mechanism stops and another starts." Consequently, in this paper attention will be given to certain neurogenic functions which might, at first sight, be considered irrelevant to steroids and mental disorder. Old, as well as newer, data will also be reviewed, in the hope that they may suggest fresh points of departure for investigation in this field which promises so much but presently seems to yield so little of a definitive nature.

II. NATURAL ALTERATIONS IN CEREBRAL FUNCTION ELICITED BY STEROIDS

Estrogens contribute to certain regulatory functions of the hypothalamus (20). For example, the release of lutinizing hormone (LH) by the adenohypophysis can be advanced 24 hours in the 5-day cyclic rat by giving progesterone on the third day of diestrus, this being signified by ovulation. In the pregnant rat, precocious ovulation, which reflects LH release, can be precipitated by estrogen given on the fourth day of pregnancy, ovulation occurring 36 hours later. These experiments of Markee *et al.* (60) show that these steroids facilitate LH release by lowering the threshold of a sex center which appears to lead to the liberation of an adrenergic neurohumor which suitable blocking agents inhibit.

The above experiments represent steroid influence on discrete hypothalamic mechanisms. Relatively precise information also exists in support of the view that steroid hormones influence the participation of the hypothalamus in the control of more complex acts associated with mating. For example, progesterone, in a dose well below the subcutaneously effective level, if placed in the lateral ventricle leads to estrous behavior in a castrate hamster (55). Further, it has been shown that lesions in the posterior hypothalamus of the guinea pig preclude mating responses elicited by estrogens, presumably because the integrating area for estral behavior has been disturbed (28).

Androgens have not been so definitively studied, but in the young dog the micturition pattern has been observed in relationship to sex and testicular function. Berg (7) observed that the adult male act of leg elevation while urinating did not appear till 19 weeks, but could be prevented by castration or advanced to 8 weeks by androgen injections. This is an instance of activation of an innate pattern.

Courtship and mating in mammals has associated much complex integrated behavior that has been described often, but in particular connection with hormones in the monograph by Beach (5). In these acts, steroids play an essential role in developing the pattern which, once established, can be very resistant to extinction in certain species, and especially in the male, despite gonadectomy. In man, the strength of the sexual drive of the adult is reinforced by gonadal influences, but the direction is not. It is not possible to correct homosexual behavior by hormones, for instance. The detailed morphologic and psychoanalytic studies of Benedek and Rubinstein (6) have demonstrated the delicate dependence of sex drives and attitudes, at conscious and unconscious

levels, on ovarian secretion and their inter-dependence on psychological factors. In the human, hormones definitely play a less defined role in sexuality. Castration in adults does not always lead to a loss of interest in sex (87), though it leads to an altered endopsychic concept of the self (88). Psychotherapy alone may enhance sexual expression in castrates (27), though this does not deny the validity of a similar result achieved by testosterone.

Aggression is of no less importance in man and animals than sexuality as a major drive, but, if anything, it is less well understood. Without exploring the well-documented interrelationships between the two, attention will now be paid to some observations which bear more particularly on generalized aggression, which has been reviewed in some detail by Beach (5). One experiment which seems most pertinent for mention here is that conducted by Clark and Birch (16) on dominance in adult male chimpanzees. Using a food-reward situation, it was found that methyl testosterone increased dominance in the eunuchoid male, while estrogen led to a subordinate status.

Estrogens have been used in humans for the suppression of assaultiveness associated with heterosexual offenses or bothersome homosexual trends, stilbestrol being used as a rule. It is apparently capable of controlling the aggression and, unlike castration, appears to abolish libido during the period of administration (30, 82, 83, 86). While testosterone may increase aggression in castrates, it has not been extensively exploited for this purpose in intact males. In the last few years, several reports have appeared indicating the usefulness of epi-dehydro-isoandrosterone (diandrone), an adrenal cortical steroid. This substance allegedly comprises 8–15% of the 17-ketosteroids. Studies in schizophrenic patients by Reiss *et al.* (73), led to its use. Trials of diandrone on a few adult schizophrenics and schizoid psychopaths showing a low beta excretion, by Strauss (86), gave a few favorable responses. More decisive results were obtained by others (83, 96) in immature adolescents. Sands (82) gives as indications the presence of timidity, lack of confidence, apathy, in young, inadequate psychopathic types. Aggression is promoted, but sex effects are not apparent. More definitive studies will have to be made in order to establish the validity of these claims, which have both theoretical and practical importance. The substance would seem to supplement a lack which has wide psychological repercussions.

Genetic factors would seem to be operative in the control of what may liberally be termed aggressive behavior, in lower forms at least. For example, the behavior of the laboratory Norway rat is one of compliance,

within reason, but in the short space of a hundred years since it was first utilized for experimental purposes, it has changed mightily. Its wild cousin, as collected in Baltimore and studied by Richter (76), is a different animal. Untamable, vicious, and suspicious, it would appear to bear these characteristics in its germ plasm, for the young, foster-mothered by tame laboratory types, grow up true to their wild forebears. Endocrinological characteristics of the wild strain include small pituitaries and enormous adrenals. While not endeavoring to suggest that the glandular morphology affects the behavior, the association is worth noting. The genetics has been neglected, and only now receives revived attention. It is of current interest that a recent paper provides evidence that the adrenogenital syndrome represents an inborn error of metabolism (15). In extension of this theme, it should be noted that it is tacitly assumed in endocrine studies that, despite a certain deviation consistent with biological results, a unit of hormone produces the same unit of response. This is apparently not so, for careful experiments by Young and his associates with different strains of guinea pigs show very considerable quantitative differences in the response to injected testosterone (77, 90). This result, too, should cause us to be less rigid in making distinctions between certain differences in hormone levels.

III. ALTERED STEROID SECRETION IN ENDOCRINOPATHIES WITH MENTAL DISORDERS

The first association of endocrine dysfunction with mental disorder was probably Plattner's recognition of mental deficiency in cretins in 1600. The adult form was not identified for another 270 years, and the high incidence of psychoses clearly indicated in 1888 by the Committee of the Clinical Society of London (18). This association, neglected for many years, has been reemphasized by Asher (4) and well defined by Lidz (58). While the thyroid secretions are not of a steroid nature, being derived in part at least from tyrosine, thyroid deficiency is associated with a marked decrease in the excretion of 17-ketosteroids (1). It is not implied that this is the cause of the mental aberrations, but it indicates an association between thyroid function and steroid metabolism that has not been fully explored.

The decreased steroid output in Addison's disease is clearly a direct consequence of the deficient adrenal cortex. Electroencephalographic records show brain function is altered in that abnormally slow EEG waves occur (33, 34, 54, 89). A similar slowing of the EEG pattern has been found in adrenalectomized rats (8). Cortisone restores the

slow activity to normal (54, 89). In rats there can also be demonstrated a decrease in the electric shock seizure threshold following injections of cortisone, and an increase after deoxycorticosterone (48, 95). Clinically, there are frequent alterations in the personality (19, 33, 34, 85). Apathy and negativism are prominent in three-quarters of the cases, seclusiveness, depression, and irritability in about one-half, while paranoid states are seen in 5 to 10%. Without going into great detail, further salient points can be made. The incidence of psychopathy shifts from a premorbid rate of 25 to 60% after the development of the disease (85); the mental aberrations may occur independently of any significantly identifiable electrolyte disturbance; cortisone, in small amounts, may not only lead to correction of the personality disturbance, but also to temporary exacerbation of the mental defect of psychotic proportions (24). Persistence of treatment fortunately leads to cure of the psychosis. An exception has been reported by Cumming and Kort (26). They found a psychotic Addisonian refractory to electroconvulsive therapy (E.C.T.) and to cortisone, but who recovered with E.C.T. after the cortisone. Whether or how the steroid facilitated a favorable response to E.C.T. cannot be decided, but such unique instances sometimes provide unexpected clues. It supports an opinion of Cohn *et al.* (25) who, in 1951, alleged that cortisone enhanced the effects of E.C.T.

The increased steroid secretion occurring in Cushing's syndrome carries with it a high incidence of psychiatric symptoms of great diversity (19). Depression with retardation, agitation, anxiety, paranoid ideation, and hallucinations are all seen. Organic mental changes, such as memory defect, distortion, and confusion occur in half the severe cases. Since the psychological changes may precede the physical, there is good evidence that it is not just a reactive phenomenon (19).

It is asserted by Bleuler (9) and Reiss (71), that there is no characteristic difference in the psychopathologic changes seen in Addison's or Cushing's syndrome. The writer believes that there are similarities, but that the application of projective techniques to significant groups of such cases would reveal objective differences, which he thinks he has detected by clinical appraisal. Be that as it may, another point remains to be made, and that is, as Reiss remarks, that many such endocrinological disturbances do not show psychopathologic symptoms, and that therefore one must postulate a constitutional or personality predilection for those who do.