became apparent. The development of ascites is in itself a problem of considerable interest. Most of the results of biochemical investigation were neither striking nor consistent. There is some evidence that administration of cortisone caused an increase in serum potassium. In four cases the values for uric acid decreased significantly on cortisone treatment, but in the others this change was not observed. The figures for plasma protein were not consistently related to cortisone. Except in three cases in which the initial figure was already low, the values of 17-ketosteroid excretion showed a fall related to cortisone therapy, which may be due to inhibition of the anterior pituitary by the cortisone with consequent reduction of adrenal cortical activity. It would seem from these results that cortisone is not converted to a 17-ketosteroid type of compound, at least in late pregnancy. Eosinophil counts, when raised, generally showed a marked fall on cortisone therapy—a result which has been repeatedly recorded by other workers.

Summary

Eight cases of toxæmia of pregnancy were treated with cortisone by intramuscular injection.

The ages of the patients varied from 22 to 42 years. Five were primigravidae; in one it was her second pregnancy; and in two it was their fourth pregnancies. The period of gestation at the start of cortisone treatment was 37, 40, 28, 31, 36, 37, 34, and 31 weeks, respectively.

All patients, when admitted, were seriously ill, with raised blood pressure and albuminuria. Five had well-marked oedema. One of the cases had had four eclamptic convulsions immediately preceding admission, one had had one convulsion before admission, and one had a convulsion during labour. In all seven cases in which the foetus was viable the indications were for a termination of the pregnancy on, or soon after, the patient's admission. In the eighth case the foetus might have been expected to die.

Cortisone treatment was continued for 27, 5, 14, 8, 14, 7, 17, and 15 days, respectively, before the onset of labour.

In all cases the outstanding feature following treatment was the considerable clinical improvement. The need for sedatives was reduced, headache was relieved, oedema, when present, was reduced, albuminuria was usually diminished, and diuresis seemed to be promoted. Blood pressure was not significantly affected. Ascites developed in five cases.

In three cases labour started spontaneously, and in five it was induced.

Seven of the patients were delivered of live babies. In the remaining case the baby was stillborn, the cause of death being a subtentorial haemorrhage. Two of the babies were premature and died, but in one of these post-mortem examination showed an intracranial haemorrhage.

Five of the patients left hospital apparently normal. One was transferred 34 days after delivery to a general hospital, where she died of congestive heart failure. One developed schizophrenia on the fifth day after cortisone treatment was discontinued. The last case was also transferred to a general hospital for investigation of her cardiovascular and renal systems.

We are grateful to Dr. Maurice Hickey, of the Mater Misericordiae Hospital, Dublin, and to Dr. Frank Geoghegan, of the National Maternity Hospital, Dublin, for having carried out some of the biochemical estimations on samples of blood from these patients, and to Dr. T. E. T. Bradshaw, of the Department of Physiology, Royal College of Surgeons in Ireland, for having carried through all the estimations of 17-ketosteroids in his laboratory at the Rotunda Hospital, Dublin. The charts were drawn by Mr. Ronan Kernan, of the Department of Anatomy, University College, Dublin.

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POST-TRAUMATIC DISTURBANCE OF HYPOTHALAMIC FUNCTION

BY

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The detailed anatomy of the hypothalamic region and its connexions with the cortex of the neopallium have been described by various authors (Rioch, 1931; Le Gros Clark and Boggon, 1933; Walker, 1938; Meyer *et al.*, 1947; Mettler, 1947), while the work of Fulton *et al.* (1940) has enabled us to form a concept of hypothalamic function which, though admittedly incomplete, has added considerably to our knowledge of some of the mechanisms by which this ancient portion of the brain reinforces and co-ordinates certain bodily reactions to physiological and psychological stimuli coming from an ever-changing milieu.

It is known that several well-defined pathological entities (such as diabetes insipidus, obesity, abnormal somnolence, and genital atrophy) may arise after damage either to hypothalamic nuclei or to their connexions with the neurohypophysis, but it is perhaps not so widely recognized that fixed lesions in the central nervous system outside the hypothalamus can give rise to marked disturbance of hypothalamic function, with repeated displays of exaggerated hypothalamic activity (Fulton and Ingraham, 1929; Penfield, 1929; Engel and Aring, 1945).

The hypothalamic syndrome described below is of interest for several reasons. Two of its features are common to the syndrome described by Kleine (1925) and Levin (1936), and are periodic in nature. The

condition is post-traumatic in origin, and its clinical features differ in some respects from those commonly found in post-traumatic lesions.

The number of reported cases of hypothalamic disorders following head injury is not large. This may, however, be due to the fact that in most of the reported cases the diagnoses have been made more simple by the presence of fairly obvious static signs and symptoms indicating lesions in the hypothalamus itself—that is, diabetes insipidus, obesity, and disorders of sleep. The significance of less obvious post-traumatic sequelae such as disturbances of autonomic function may often pass unrecognized, as these disturbances are not discoverable by the usual routine methods of examination of the nervous system. In the undermentioned case, for example, no clinical investigation was carried out until almost four years after the occurrence of the original head injury.

As this case did not come under my care until several years after the initial injury, the description of the onset and the early manifestations of the syndrome is based on the observations of the boy's mother. The latter is a reliable witness and an accurate observer, with the added advantage of a training as a nurse, and from the account given by her there is every reason to believe that the features now present existed from an early stage after the initial injury.

The syndrome is made up of the following abnormalities: thermohyperaesthesia; periodic abnormal hunger; periodic psychomotor restlessness; disturbances of autonomic function and abnormal reactions to certain drugs; occasional bouts of pyrexia associated with intestinal colic, nausea, vomiting, and bladder irritability; and a compulsive habit of chewing and swallowing various articles and substances.

Case History

The patient, a boy aged 11, was a healthy child until the age of 4½, when he sustained the head injury mentioned below. He began to walk and to talk at the average normal age, and did not suffer from fits or convulsions in infancy. There is a clean family history, and the home background is a happy and normal one. He has two older brothers and one younger sister, all of whom are intelligent and likeable children.

On the morning of October 12, 1943, when running to school, he tripped and fell forward, striking the base of his forehead forcibly against the edge of a stone kerb. He was momentarily stunned and a massive haematoma developed over the frontal bone. He was taken to the local hospital and kept there under observation for three weeks. Unfortunately the case notes made at the time are incomplete, and, apart from the fact that there was no bony injury shown on an x-ray film of the skull, little information can be gained from the clinical observations then recorded. He was kept in bed for a further week after returning home and did not go back to school until the beginning of the next term. About six weeks after his discharge from hospital his mother noted the development of changes in behaviour and the onset of the compulsive habit which he now exhibits. During the next few months, and especially during the warm weather in the summer of 1944, other abnormalities were noticed by his parents. These still persist, and are referable to a disturbance of autonomic function.

The first abnormality noticed was the onset of the chewing and biting of his nails and fingers, a habit to which he had not previously been addicted. In the next month or so he had begun to chew and swallow a variety of sub-

stances—namely, his clothes, the edges of his cuffs and pullover, his handkerchiefs, and pieces of the bedclothes. He began to eat portions of thread, string, and plasticine, later vomiting matted masses of these substances. Pieces of chalk and crayons were also eaten, and on occasion he has been found with small metal objects in his mouth. This abnormal behaviour appeared to be intermediate in nature between a reflex and a voluntary action, for it was noted to occur even when his attention was wholly concentrated on some subject of absorbing interest. It did not seem especially to be connected with any situations which, in a child, might give rise to mild anxiety, but appeared at intervals for no apparent reason, and can now be brought on at any time in intensified form by the action of certain drugs.

The second abnormality noted was one affecting appetite. This was also periodic, and when the urge developed his hunger was almost insatiable. Tachyphagia was a prominent feature of a feeding ritual in which he showed a preference for certain foods similar to that described by Arieti (1945) as occurring in certain cases of mental disease. During a recent attack he consumed a 14-oz. (400-g.) loaf before his lunch, at which he proceeded to eat as much as both his brothers. This was followed by a large apple and a glass of milk, and after this he still asked for more.

About this time it was observed that he sweated heavily about the face when eating. This phenomenon was much more marked on the right side of the face, and was accompanied by flushing of the skin. Dilatation of skin vessels was maximal on the ears and along the border of the lower jaw. Sweating was most pronounced in the periorbital region and along the side of the nose and the upper lip. It is occasionally accompanied by lacrimation from the right eye. The sight, smell, and even the thought of certain articles of food will cause sweating on the face, and it can be rapidly elicited by the taste of bitter substances.

During hot weather, on physical exertion, and when emotionally excited, profuse sweating occurs over the whole body. Sweat literally streams from him, and during very hot weather he becomes somewhat pinched and dehydrated in appearance. It is stated that on one occasion, when a particularly profuse bout of sweating occurred, a tingling sensation was felt in the skin of the face and scalp, and the sweat was faintly tinged with blood. Profuse sweating occurs over the face and scalp for an hour or so before he goes to sleep.

Coincident with the periods when the chewing-swallowing habit emerges a marked restlessness occurs, and the autonomic over-reactions become more noticeable. He seems quite unable to keep still or to concentrate on any subject for any length of time, nor will he allow the other members of his family to do so. During these attacks he becomes a trial to his parents and to his older brothers, who are unable to get on with their studies owing to his continual interference with them. This restlessness can be brought on at any time, and in a marked degree, by giving small doses of certain drugs.

The attacks of hyperthermia associated with intestinal colic have occurred both in cold and in hot weather. They are accompanied by nausea and, at times, vomiting. Frequency of micturition and marked general irritability are present during the attacks. The temperature has ranged from 100 to 102.5° F. (37.8 to 39.15° C.), and there is marked flushing and sweating. The duration of attacks in the past has been from 24 to 48 hours. The attack I saw was associated with minor infection (coryza), and it is felt that previous attacks had a similar aetiology.

The only disturbance noted affecting sleep is a delay of an hour or so in the onset of sleep after going to bed. This delay is more prolonged when attacks of restlessness are present, and at these times he showed a resistance to the action of barbiturates, a dose of 2 gr. (0.13 g.) of sodium amylobarbitone or 1½ gr. (0.1 g.) of quinalbarbitone sodium having but little effect.

During the periods of restlessness he is easily roused to anger and becomes aggressive. His aggressiveness is always directed against boys bigger and older than himself. He is kind to smaller children and animals, and there are no traits of a cruel nature. He is an intelligent boy, and is in an advanced class at school. He has the usual hobbies and traits common to boys of his age, is a keen philatelist, is fond of music, plays the piano, and sings in the church choir.

Investigations

Physical examination by ordinary methods revealed nothing abnormal: weight, 69 lb. (31.3 kg.); height, 53½ in. (136 cm.); span, 54 in. (137 cm.). Both testes are in the scrotum. His blood pressure has varied on successive examinations from 114/70 to 130/80.

Special Examinations.—Urine acid: specific gravity 1016; no albumin or sugar; chloride content, 960 mg. per 100 ml. The blood Wassermann reaction was negative. Radiographs of the skull did not reveal any abnormality, the size and shape of the pituitary fossa being within normal limits. An electro-encephalogram showed "some instability, but no more than would be expected in a boy of his age." A fractional test meal showed an acid curve on the lower side of the average normal range. A barium meal showed that the stomach emptied in less than an hour, and that the meal had reached the middle of the transverse colon in six hours.

Investigation of Temperature Regulation

There is a tendency to hypothermia, with an average daily reading of 96.4° F. (35.8° C.) (oral). Thermohyperaesthesia is present, for it has been noted that since shortly after his head injury he has never been able to stand with comfort a bath at a temperature of over 99° F. (37.2° C.).

Reaction to Bath at 103° F. (39.4° C.)

	°F.	°C.
Oral temperature before immersion	96.2	35.7
" " after 5 minutes' immersion	100.2	37.9
" " after 10 minutes' immersion	101.6	38.7

When the oral temperature reached 98.4° F. (36.9° C.) marked flushing of the face occurred, and at 100.2° F. (37.9° C.) marked flushing accompanied by profuse sweating was observed. He was removed from the bath after 10 minutes, and within a further 15 minutes his oral temperature had fallen to 98.2° F. (36.8° C.).

Reaction to Bath at 85° F. (29.4° C.)

	°F.	°C.
Oral temperature before immersion	98.2	36.8
" " after 5 minutes' immersion	96.0	35.6

Shivering and vasoconstriction of skin vessels then occurred, and in the next four minutes his oral temperature had risen to 97.2° F. (36.2° C.). The reactions observed were "full-blown" ones, and can be regarded as exaggerated in view of the fact that neither of the bath temperatures to which the patient was exposed appears to be deserving of the intensity of the response exhibited.

I saw only one attack of hyperthermia—101.5° F. (38.6° C.)—associated with intestinal colic. It occurred at the onset of an attack of coryza, and was accompanied by marked restlessness, flushing, and sweating. Bladder irritability was also present, and the chewing habit was well in evidence, the patient having eaten away a hole in the sheet. The symptoms were easily controlled by tepid sponging, and during one period of severe intestinal colic immersion in a tepid bath quickly relieved this symptom.

The hyperhidrosis affecting the face is readily elicited by the smell or sight of a bitter food (lemon), while application of bitter substances to the tongue produces a similar effect.

Reactions to Drugs

Abnormal hunger is usually associated with gastro-intestinal hypermotility. In an effort to counteract this,

and to prevent the occurrence of attacks of this nature, a dose of 50 mg. of "syntropan" was given by mouth three times a day, and continued over a period of several weeks. During this time he did not develop any attacks of abnormal hunger, though he was still restless on occasion, but his habit of chewing was a little less in evidence. He has since been kept on 5 minims (0.3 ml.) of tincture of belladonna, three times a day, and his appetite has been for the most part normal.

As amphetamine has been observed to counteract the psychomotor restlessness in some cases in which this feature is present, he was given a single initial dose of 2.5 mg. This produced the most marked attack of restlessness he had ever had. His behaviour resembled that of a caged animal; he ate a hole in the sheet and gnawed the embroidered border off his pillow-cases. The restlessness subsided in about six hours. Small doses of ephedrine produce a less marked effect of similar nature.

Diphenhydramine hydrochloride ("benadryl") has been reported to be effective in relieving spasm of smooth muscle (Loew *et al.*, 1946), and it was considered worth while to observe its effect in this case. Accordingly, 100 mg. daily, divided into three doses, was given for five days. Its effect was similar to that of amphetamine: he showed very marked restlessness, began to chew his clothing, bit his nails down to the quick, and chewed the skin from the tips of his fingers.

A course of phenytoin sodium ("epanutin") produced no effect whatever, while phenobarbitone simply blurred the general symptom picture.

A careful inquiry from the child's parents and teachers revealed no evidence of psychological maladjustment. He was a happy and popular boy with a good school record: he had always faced up to all his problems, and had never attempted to make use of his symptoms in an effort to evade unpleasant situations. He admits to the usual mild anticipatory anxiety before school examinations and the like, but the external expressions of this mood appear to be exaggerated out of all proportion to the depth of feeling tone with which they are associated.

Clinical Features

Two of the clinical features of this case merit further comment.

1. *The Similarity of Effects Produced by Diphenhydramine to those Effected by Sympathomimetic Drugs.*—It is not easy to explain why this should be the case. From the chemical constitution of this compound one would not expect it, or its degradation products, to have any direct sympathomimetic effect. Its most common side-effect is the production of drowsiness, and this is no doubt central in origin, but there is no clear evidence of the precise mechanism by which this is brought about. It seems reasonable to surmise that part of the central action of diphenhydramine is concerned with inhibition of the parasympathetic side of the autonomic nervous system, and that a relative preponderance of the sympathetic side is thus effected.

2. *The Abnormal Reactions to Pyrexia Associated with Minor Infection.*—These reactions are modified by the fact that the thermal stimulus is in this instance a sustained one. We seem to be dealing here with a mass reaction affecting the anterior hypothalamus, for, in addition to the normal response to hyperthermia (flushing of the skin and sweating), there is frequent emptying of the urinary bladder, and abdominal colic and vomiting due to gastro-intestinal hypermotility.

The work of Ranson (1940) and Ranson and Magoun (1939) indicates that the centres which prevent overheating are situated in the suprachiasmatic and preoptic areas; but it has also been shown (Kabat, Ranson, and

Magoun, 1934) that in the preoptic area are cell masses concerned with contraction of the urinary bladder, and there is experimental evidence that increased gastrointestinal activity follows stimulation of the anterior hypothalamus (Massermann and Haertig, 1938).

Discussion

In the patient whose case is described above there is exhibited a series of exaggerated somatic and vegetative reactions to physiological and psychological stimuli. Some of the somatic features bear a resemblance to disorders of behaviour, and the emergence of these latter features can be brought about by the administration of sympathomimetic drugs. Their periodic emergence in the past was no doubt due to increased activity of the sympathetic side of the autonomic nervous system. It is evident from the foregoing clinical findings that there has been preserved the functional integrity of the various hypothalamic centres which, by discharging into descending pathways, produce the responses described; and, in the absence of any evidence of infundibulo-tuberal damage—that is, diabetes insipidus or obesity—it can be safely assumed that the hypothalamus itself is intact. Some explanation, however, must be sought for the uninhibited nature of the reactions observed.

Disturbances of hypothalamic function, which may be permanent or transient in nature and mild or profound in degree, are observed to result from lesions in areas outside the hypothalamus. These lesions may be produced by surgical intervention for experimental or therapeutic reasons, or may occur as a result of disease processes. (It is customary to regard as release phenomena the abnormal vegetative and somatic patterns which emerge after damage either to those areas of the cortex in which autonomic functions are represented or to the indirect pathways by which these areas are connected with the hypothalamus. By this it is assumed that the neopallial cortex exercises an inhibitory or controlling effect on the central levels of autonomic function.)

Marked hypothalamic dysfunction has been described (Engel and Aring, 1945) in a case in which an old-standing lesion had affected the dorso-medial nucleus, internal medullary lamina, and the lateral nucleus of the right thalamus. Periodic displays of exaggerated hypothalamic activity occurred mainly in response to situations provoking anxiety, and an interesting feature of the vegetative reactions was the occurrence of hyperhidrosis on the side of face contralateral to the thalamic lesion. That the patient also showed marked psychological maladjustment is not surprising in view of the important part played by the thalamus and its connexions in personality organization.

It has been shown (Messimy, 1939) that in animals marked motor restlessness, abnormal hunger, and exaggerated reactions to sympathomimetic drugs occur after severance (by bilateral excision of the prefrontal regions) of the indirect connexions between the prefrontal cortex and the hypothalamus; and Reitman (1946) has described changes in autonomic balance in man, following prefrontal leucotomy, in which operation connexions between the prefrontal region and the dorso-medial nucleus of the thalamus are severed. In the cases described by Reitman the changes noted were transient ones, while in Messimy's animals the distur-

bances observed "tended to pass off with time," this regeneration of function after damage being in accord with the behaviour of the brain as a whole.

More profound and more slowly subsiding changes in hypothalamic activity are seen in decorticate animals—that is, animals in which all portions of the brain above the hypothalamus have been removed. It has been observed (Bard, 1929) that in decorticate cats violent motor and autonomic reactions accompanied by widespread activity of the sympathetic nervous system occur in response to physiological stimuli. As the motor and autonomic reactions exhibited are similar to those which characterize rage in the intact animal, the phenomenon is known as "sham rage." It has been noted that when left undisturbed these decorticate animals exhibit alternating periods of repose and activity (Hinsey, Ranson, and McNattin, 1930), and the ultimate subsidence of "sham rage" reactions in chronic decorticated animals has been observed by Kennard (1945). As phylogenetic progression has brought about representation of autonomic functions at cortical levels, it is to be expected that after removal of these higher controlling levels uninhibited reactions would occur when the hypothalamus is excited by physiological stimuli. The eventual subsidence of the "sham rage" reaction is regarded by Kennard as a manifestation of homeostasis, which is probably brought about by adjustment of the entire remaining autonomic system.

A more interesting observation, however, is that effects similar to and more prolonged than those brought about by decortication can be produced in intact cats by the placing of bilateral lesions just in front of the optic chiasma (Fulton and Ingraham, 1929), and that in monkeys states akin to "sham rage" can be produced by bilateral lesions placed in the same areas (Fulton, 1947, personal communication). Associated with the "rage" there is evidence of diffuse discharge of the sympathetic nervous system. It is evident that in these areas are situated pathways by means of which an overall control of hypothalamic activity is exerted, and that the release phenomena resulting from lesions affecting these pathways are more prolonged and profound than those which follow section of the indirect cortico-hypothalamic connexions which relay in the dorso-medial nucleus of the thalamus.

In the case described above, signs of exaggerated hypothalamic activity following head injury have persisted for over six years; the syndrome features, both somatic and vegetative components, and the somatic components can be readily elicited by the administration of sympathomimetic drugs. (It appears that a slow subsidence of symptoms is taking place, for some of the features are stated to be now less marked than formerly.)

The nature and persistence of the abnormal reactions described, and their association with increased sympathetic activity, would justify a conclusion that the initial head injury had produced a contusion in the area just anterior to the chiasmal region, that the damage was bilateral in extent and possibly more severe on one side than on the other, and that the sequelae are manifested in the syndrome described.

The factors underlying causation of the chewing-swallowing habit are obscure. As the habit invariably

accompanies the restlessness produced by sympathomimetic drugs, there is reason to regard it as a release phenomenon, and from its unusual and frankly regressive nature one would surmise that it is mediated through some phylogenetically ancient pathways.

The significance of primitive habits of this nature has been discussed by Arieti (1945). He notes that what he terms the "placing into mouth" habit is found in children approximately 1 to 2 years of age, that it is also found in advanced cases of schizophrenia, and that in these latter cases it is often accompanied by bulimia, tachyphagia, and a stereotyped feeding ritual. He considers that the habit represents a primitive response, in the mechanism of which a short-circuiting takes place between the functions of reception and those of reaction, with exclusion of the usual normal paths which involve higher centres, and suggests that instead of the normal path a circuit is used similar to that involved in the relatively primitive physiological complex which Edinger has called the "oral sense." He has also noted the development of this habit in a case following bilateral prefrontal lobectomy. A similar habit has been found in cats after removal of both frontal poles (Langworthy, 1944), while Von Braunmühl and Leonhard (1934) have reported its occurrence in cases of Pick's disease. The habit is often observed in amentia and dementia from various causes.

Though this release phenomenon has been found to emerge after damage or degeneration affecting the prefrontal areas in man, there is evidence that it may represent a primitive archipallial expression. Grünthal (1947) describes the phenomenon (accompanied by a return of the sucking reflex) in a woman, aged 62, in whom the only evidence of cerebral damage found at necropsy was a circumscribed bilateral degeneration of the cornu Ammonis, and it has long been noted that marked perversion of feeding habits occurs in the early stages of rabies in dogs, in which disease the cornu Ammonis is severely affected. It would thus seem that efferent pathways from the hippocampus can exert an inhibitory action on lower centres in the rhinencephalon concerned with simple feeding reflexes, and it is possible that this inhibitory function in human primates is partially vested in the prefrontal areas, presumably in those portions of the orbital area from which the direct pathways to the hypothalamus arise. Exaggerated hypothalamic activity might well be associated with a spill-over of excitation into the primitive pathways described above, and these, by discharging into subthalamic motor centres, would give rise to those movements which form the somatic framework of the "placing into mouth" habit.

Summary and Conclusions

A case is reported in which disturbance of hypothalamic function has persisted for over six years following head injury.

The various components of the syndrome exhibited are described, and an account is given of the patient's reaction to various drugs.

The neuro-physiological mechanisms which govern certain features in the syndrome are discussed.

A possible explanation is advanced in accounting for a primitive habit which forms part of the clinical picture in the case described.

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PREVENTION OF HORMONAL EOSINOPENIA AND LYMPHOPENIA BY INHIBITION OF CLOTTING IN BLOOD

PRELIMINARY REPORT

BY

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It has already been well established that phenomena of eosinopenia and of lymphopenia follow the administration of potent preparations of adrenocortical steroids with C11 oxygenated, or the application of hormones or agents which stimulate their endogenous secretion. The mechanism and the meaning of these phenomena are not clearly understood. Dougherty *et al.* (1944) demonstrated that the amount of gamma-globulins in the blood plasma rose significantly, parallel with the degree of lymphocyte diminution after the administration of A.C.T.H. or of cortisone or cortisone-like steroids. At the same time the titre of the specific antibodies also increased significantly. They concluded from these findings that disintegrating cytoplasm of the lymphocytes is the source of gamma-globulins, which are closely related to the specific antibodies, and that they are discharged from lymphocytes under the activity of the adrenocortical steroids. Those authors' observations, however, were not confirmed by others (De Vries, 1950), since the N-antibodies did not rise in the blood at the time of the lymphopenia after A.C.T.H. injection. The pheno-