TABLE II.—Results of Treatment

Age in Years	Cured		Improved		No Difference	
	Female	Male	Female	Male	Female	Male
0-14	2	—	—	1	—	—
15-29	4	—	1	—	—	—
30-44	6	2	3	—	1	—
45-59	—	1	—	2	—	—
60-75	—	—	4	—	—	—
Total	12	3	8	3	1	—

abolished, but they were not counted as cures unless there was no evidence of chilblains on examination. Observations were made on results only during the severe weather.

Every patient was asked if this was the best treatment so far tried, and 26 responded in the affirmative; this gives a failure rate of only 3.7%. The one failure was a female telephonist aged 30, who suffered from very severe chilblains of the hands and feet. Her work may have militated against a cure. She was given only 150 mg. of nicotinic acid daily, and in the light of further experience it was felt that the dose should have been increased.

Four patients blamed a change in the weather, such as a thaw, for the onset of their chilblains; one blamed sitting still for a long time; two blamed sitting in front of a fire; sixteen blamed cold weather and frost; four blamed cold weather and damp. All but two said sitting in front of a fire made the chilblains worse. Fifteen were chronic sufferers and got chilblains practically every year; of these eight were cured and seven improved. Nine were sufferers for the first time: of these six were cured and three improved. The others were only occasional sufferers.

Two patients complained of occasional cracks at the corners of the mouth and one of a sore tongue, but it was difficult to relate these symptoms to a systemic deficiency of the vitamin B complex. Two patients noticed improvement after taking only 50 mg. of nicotinic acid; five noticed improvement after treatment for three days, ten after four days, six after seven days, and three were indefinite.

It is interesting to record that two patients found that they could tolerate the cold with much greater comfort during treatment; this may have been due to a "stoking up" of skin-cell metabolism resulting from the vasodilatation of the subcutaneous arteries.

Untoward effects noticed during treatment were of little significance and were only transitory: constipation was recorded in three cases, sleepiness in two, slight headache in two, and transient flushing and mild irritation of the skin in twelve.

Conclusions Regarding Treatment

On the basis of the action of nicotinic acid—namely, vasodilatation—it stands to reason that this treatment cannot be expected to benefit to any great extent chilblain sufferers who have pronounced arteriosclerosis or other condition of the peripheral circulation which interferes with the vasodilatation of the skin vessels. Nevertheless it is felt that nicotinic acid has a specific action on chilblains, and that the very vast majority of chilblain sufferers will benefit from this treatment.

Treatment should start as soon as the first sign of a chilblain makes its appearance and should be continued, possibly in reduced dosage, until the chilblain season has passed.

Summary

The problem of chilblains is discussed as regards their aetiology and pathogenesis. It is claimed that nicotinic acid, given orally, has a specific effect on chilblains. Twenty-seven cases are quoted to prove this, and it is suggested as the treatment of choice in general practice owing to its ease of administration and its freedom from serious untoward effects.

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HYPOTHALAMUS AND PITUITARY GLAND

WITH SPECIAL REFERENCE TO THE POSTERIOR PITUITARY AND LABOUR

BY

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Marañón (1947) reported the case of a woman who had diabetes insipidus with an associated uterine atony, and discussed the light that this and similar cases throw on the mechanism of labour. Two important facts emerge from a study of such cases: (1) that lesions of the hypothalamus or neurohypophysis which produce diabetes insipidus may also interfere with the mechanism of parturition, and (2) that similar lesions which produce interference with the secretion of the posterior lobe of the pituitary gland (as evidenced by the diabetes insipidus) do not necessarily interfere with the activity of the anterior lobe of the pituitary (as shown by normal menstrual cycles and pregnancy). It is felt that a summary of recent work dealing with these points may be of interest in view of Marañón's paper.

Anatomy of the Hypothalamo-hypophyseal System

The Neurohypophysis (Posterior Pituitary Gland).—It is now generally recognized that the secretory tissue of the posterior pituitary exists in the median eminence of the tuber cinereum, in the infundibular stem, and in the infundibular process, all these parts being included by the term neurohypophysis (Fig. 1). The main anatomical connexion between the hypothalamus and neurohypophysis is a rich nervous pathway, of which the most important element is the supraoptico-hypophyseal tract. There are also good grounds for belief in the existence of a tract from the paraventricular nucleus to the neurohypophysis. The origin and destination of the fibres in the tubero-hypophyseal tract, situated in the posterior wall of the neural stalk, are unknown.

The Adenohypophysis (Anterior Pituitary Gland).—The adenohypophysis consists of the pars tuberalis, pars intermedia, and pars distalis (Fig. 1). These three structures

FIG. 1.—Diagram of a sagittal section through the pituitary and hypothalamus to illustrate the hypothalamic innervation of the pituitary gland. The neurohypophysis—which includes the median eminence (M.E.); infundibular stem (I.S.); and infundibular process (I.P.)—receives a rich innervation from the supraoptic nuclei (S.O.) and a supply from the paraventricular nuclei (P.V.). The tubero-hypophyseal tract (T.H.) enters the dorsal or caudal wall of the tuber cinereum and infundibular stem. The three parts of the adenohypophysis are termed the pars distalis (P.D.), pars intermedia (P.I.), and pars tuberalis (P.T.). A few nerve fibres cross from the neurohypophysis to the adenohypophysis. O.C.=optic chiasma; M.B.=mammillary body.

receive only a meagre innervation, and there is no sound evidence that the few nerve fibres found in them are other than vasomotor to the hypophyseal vessels.

Both the posterior and the anterior lobes of the pituitary possess a systemic blood supply from the internal carotid artery, the venous drainage being in both cases to the adjacent venous sinuses. The vascular fields of the infundibular process and the pars distalis are largely independent, the pars intermedia being relatively avascular. The pars distalis, however, has a rich vascular connexion with the median eminence in the form of a portal system of blood vessels (Fig. 2). These latter vessels were first described by Popa and Fielding (1930, 1933), and later by Wislocki and King (1936), and Green and Harris (1947). Small arterial twigs from the internal carotid arteries supply a rich vascular plexus between the pars tuberalis and median eminence. From this plexus "vascular tufts" or "sinusoidal loops" penetrate the median eminence over an area co-extensive with the pars tuberalis. These loops unite to form the wide trunks of the portal vessels which descend to the pars distalis and so drain into the typical sinusoids of this part of the gland. This vascular system has been found to exist in the rat, guinea-pig, rabbit, cat, dog, monkey, and man. Also, the porpoise, in which the infundibular process is separated from the pars distalis by a thick

dural septum, possesses a typical hypophyseal portal system (Harris, 1947b). Green (1947), in a careful study of the amphibian hypophysis, confirms the presence of hypophyseal portal vessels in the frog and analogous vessels in

FIG. 2.—Diagram of a sagittal section through the pituitary and hypothalamus to illustrate the systemic arterial supply of the pituitary gland, and the hypophyseal portal system. A.H. and P.H., the anterior and posterior hypophyseal arteries; I.C., branches from the internal carotid arteries, supplying the pars distalis and infundibular process, respectively. Small twigs from the internal carotid arteries run to the pars tuberalis (P.T.) and supply a vascular plexus situated between this structure and the median eminence. From this plexus capillary sinusoids arise and penetrate the median eminence in the form of loops or tufts (L). These capillaries unite into the large portal trunks (H.P.V.) and pass down into the pars distalis.

urodeles. Thus it may be said that these vessels are widely distributed amongst the vertebrates. All the evidence points to the direction of blood flow in these vessels being from the median eminence to the pars distalis. Since the pars tuberalis has no proved endocrine function, and since it bears a constant relationship to the upper set of capillaries of the portal vessels, it is suggested that the significance of this structure lies in the fact that it forms a bed for the vascular pathway from the median eminence to the pars distalis (Harris, 1947c).

Influence of the Nervous System over the Hypophysis

The hypothalamus undoubtedly influences the secretion of the posterior pituitary by means of the supraoptico-hypophyseal tract, as first clearly shown by Fisher, Ingram, and Ranson (1938).

There is much evidence that nervous stimuli affect the activity of the anterior pituitary gland, and so indirectly, through the eutrophic hormones, other endocrine glands such as the gonads, thyroid, and adrenal cortex. In the experimental field Marshall (1942, 1947) has collected and summarized the evidence that external influences (exteroceptive factors) affect the reproductive rhythm of many birds and mammals by an action through the hypothalamus and anterior pituitary. Selye and McKeown (1934) uphold the view that suckling stimulates the anterior pituitary through reflex nervous pathways and so maintains milk secretion. Electrical stimulation of the hypothalamus has been shown to excite the anterior pituitary, as evidenced by the occurrence of ovulation in rabbits (Harris, 1937; Markee, Sawyer, and Hollinshead, 1946).

Clinically there are many observations that can be explained only by an action of the nervous system modifying anterior pituitary activity. Hypogonadism may be due to hypothalamic lesions. Hypertrophied genitalia (pubertas praecox) are also found associated with hypothalamic lesions, especially those situated caudal to the tuber cinereum. Weinberger and Grant (1941) suggest that this precocity is due to destruction of a posterior hypothalamic mechanism with release of an anterior hypothalamic innervation of the anterior pituitary. The effect of worry in causing menstrual irregularities, or diminution of milk flow in nursing women, is probably mediated by a nervous

influence over the anterior pituitary. The occurrence of psychic trauma in the history of patients showing endocrine disturbances is well known (Lichtwitz, 1942), and in this respect it is perhaps significant that hypothalamic lesions have been found in cases of thyroid dysfunction (Möschl, 1938) and diabetes mellitus (Vonderahe, 1937).

Since there is no sound evidence that secretomotor nerves to the testis, ovary, thyroid, adrenal cortex, or anterior pituitary gland exist, the most likely explanation of the above and other examples of neural influences over the endocrine glands is that the hypothalamus regulates the activity of the adenohypophysis by vascular transmission of stimuli through the hypophyseal portal vessels, as suggested by Harris (1944) and by Green and Harris (1947). The activity of the other glands of internal secretion would then be brought indirectly under neural control through the intermediation of the pituitary. The upper set of capillaries of the portal vessels are situated deeply in the median eminence, some penetrating to the ependymal lining of the third ventricle. In this region the capillary sinusoids are intimately related to a multitude of nerve fibres from the hypothalamus, and the possibility certainly exists that the hypothalamus could excite or inhibit the activity of the anterior pituitary by liberating some chemotransmitter into the portal vessels and so into the sinusoids of the anterior pituitary. At the present time the evidence regarding this hypothesis is indirect but substantial. Further information with respect to the state of the hypophyseal portal vessels in cases of pituitary dysfunction in man would be of much value. It may be mentioned that these vessels are particularly obvious in human material.

The Posterior Pituitary and Labour

Many workers have found that simple hypophysectomy (leaving the upper end of the neural stalk and median eminence *in situ*) does not necessarily lead to dystocia, and for this reason it was believed that the oxytocic extract obtainable from the posterior pituitary gland was of pharmacological interest only. Fisher, Magoun, and Ranson (1938) and Dey, Fisher, and Ranson (1941) found, however, that a large proportion of cats and guinea-pigs suffering from experimental diabetes insipidus had a prolonged labour or delivered their young dead. Similar results have been found by Smith (1946), working on monkeys. Previous work was criticized by Fisher, Magoun, and Ranson (1938) on the grounds that most workers had failed (a) to control the complete removal of the neurohypophysis, including the median eminence, (b) to control the presence of some normally secreting anterior-lobe tissue, and (c) to record the details of labour such as the type and duration of the different stages. Several cases are on record of prolonged labour in women suffering from diabetes insipidus (see Marañón, 1947). However, the evidence is not entirely clear-cut, for both in animals (Dey, Fisher, and Ranson, 1941) and in man (Dandy, 1940) normal labour has been reported in spite of a concurrent state of diabetes.

Haterius and Ferguson (1938) and Ferguson (1941) have shown that stimulation of the pituitary stalk in anaesthetized post-partum rabbits and cats produced an increase in uterine activity even though all the structures in the neck except the internal carotid arteries, jugular veins, and a flap of skin had been crushed. Ferguson (1941) also described a reflex secretion of oxytocic substance from the infundibular process following distension of various parts of the reproductive canal in rabbits, and suggested that such reflexes play a part in the normal labour. Harris (1944, 1947a) has shown that stimulation of the supraoptico-hypophyseal tract in unanaesthetized rabbits produces a marked increase in uterine activity. Stimulation was performed by inducing the stimuli through the intact

skin into a previously implanted coil, an insulated lead being taken from the coil to the site stimulated. The spread of stimulus was not more than 0.5 mm. The uterine reactions were recorded from a chronic vaginal fistula, and in many cases the sensitivity of the uterus was standardized by ovariectomy and the implantation of a tablet of stilboestrol di-*n*-butyrate. In these experiments the response of the oestrous, or oestrogenized, uterus could be graded at will by varying the intensity of the stimulus, though the response to similar stimuli applied to the oestrogenized rabbits was found to be very constant from day to day. The oxytocic reaction to stimulation could be closely duplicated by intravenous administration of 200-500 mU. of posterior-lobe extracts, especially extracts relatively low in pressor activity. Stimulation or injection of extracts had little effect on the activity of the anoestrous or pseudo-pregnant uterus, or on the organ under the influence of progesterone. From experiments using this (remote control) method of stimulation has accumulated much evidence that the substance secreted from the rabbit's pituitary is richer in oxytocic, relative to pressor, activity than various standard whole posterior pituitary extracts. For example, the uterine response to the injection of whole pituitary extract consists of a stage of increased activity followed by a variable stage of inhibition. This latter effect is probably the result of the pressor fraction causing constriction of the uterine blood vessels and ischaemia of the uterine musculature. The inhibitory pause in the uterine response to stimulation of the supraoptico-hypophyseal tract is short-lived, and is lacking in the response to injection of the purified oxytocic fraction. Thus it would seem the secretion elicited by stimulation of the neurohypophysis possesses (relative to oxytocic content) less pressor activity than whole extracts and more than purified oxytocic extracts.

It may be concluded, then, that evidence is accumulating for the physiological role of the posterior pituitary in labour. It might be suggested, from the results of animal experimentation, that in replacement therapy during labour the purified oxytocic fraction be used instead of whole posterior-lobe extracts. However, more direct evidence on the reactions of the human uterus *in situ* to such extracts is desirable.

It is of interest that stimulation of the neural stalk in rabbits also produces inhibition of a water diuresis, increase in urinary chloride, and an increase in intestinal peristalsis, though no change is obtained in the level of the blood sugar and only slight rises in blood pressure (Harris, 1947a, 1947d).

Conclusions and Summary

The relationship between the hypothalamus and the pituitary gland is reviewed.

There is much evidence that the hypothalamus controls the secretion of both the anterior and the posterior lobes of the pituitary gland. The mechanism whereby control of the anterior lobe is exerted is probably by means of a humoral relay through the hypophyseal portal vessels. Nervous regulation of the anterior pituitary brings the testis, ovary, thyroid, and adrenal cortex indirectly under nervous control via the mediation of the pituitary eutrophic hormones. This offers an explanation of various endocrine disturbances (pubertas praecox and others) associated with psychic trauma or lesions at the base of the brain. The activity of the posterior pituitary is regulated largely by the supraoptico-hypophyseal tract. Evidence is accumulating that this mechanism plays a physiological part in labour, and attention is drawn to the reflexes described by Ferguson. Results obtained by stimulating the pituitary stalk in animals suggests that the secretion of the posterior lobe contains less pressor activity than whole posterior pituitary extracts. It is suggested that replacement therapy for cases

of uterine atony associated with diabetes insipidus can best be performed by use of the purified oxytocic fraction.

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DISORDERS OF THE NERVOUS SYSTEM DUE TO MALNUTRITION*

BY

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Considerable and new interest has been aroused in nutritional disorders of the nervous system as a result of their high incidence among prisoners of war in the Near and Far East. These disorders have of course been recognized for a long time by those familiar with deficiency diseases occurring among more primitive peoples. My own observations began nearly forty years ago.

Three Important Points

If series of these cases showing symptoms of nervous disorder be observed, it becomes apparent that there may be a disturbance in each and every sensory function of the body without the motor system being involved. This is the first point of importance. Thus it is possible to distinguish syndromes correlated with the functions of vision, hearing, taste, and smell, with joint, muscle, positional, and vibration sense, with temperature sense, and with tactile sensibility. This group of syndromes, like all symptom-complexes, may be more or less complete or incomplete in any individual. The factors which determine their several incidences are not known; it is not known why some individuals develop symptoms and others under the same conditions manifest none.

The second point of importance is the fact that if the symptoms, more especially the early symptoms, in each syndrome be studied they will be found to be of the same order; they are homologous, though naturally they differ according to the sensory function under consideration. These symptoms consist of disorders of perception, with what might be called distortion. Though they may be of short duration pointing to a lesion which is reversible, there is a tendency towards complete failure of function.

In each syndrome—whether the disturbance be of the visual, auditory, or tactile function, for example—there may be noted considerable variations in rate of onset and rate of progress, in intensity, in intermission and remission, and in the final stage reached.

The patient who later develops amblyopia with a persisting central scotoma may complain of loss of vision for short periods lasting from a few minutes to half an hour; objects may come into focus and then disappear again; some part of an object may seem to be missing; print appears blurred as if seen through a curtain; there is difficulty in recognizing persons and objects; complaint is made of shimmering and spots before the eyes, of flickering of images, and of rings and haloes about lights, reminiscent of migraine.

The otoneurological manifestations are of similar character though often dismissed by observers with a reference to loss of acuity of hearing. There may, however, be loss of tonal differentiation: the patient can no longer understand wireless music; he may fail to understand the human voice against a background of other sounds.

Tinnitus and vertigo are common; dizziness may come on in attacks lasting a few minutes to several days and may or may not be accompanied by nausea, vomiting, tinnitus, and headache. Vestibular hyperexcitability may be demonstrated in a large proportion of cases, as noted by De Raadt, the only observer to investigate the otoneurological syndrome fully. He points out that, though this and other symptoms may be of peripheral origin in initial stages, they are essentially central symptoms.

Thirdly, consider the disturbances of tactile and pain sensibility: the patient may complain of all manner of paraesthesiae or dysaesthesiae—pins-and-needles, tingling, pricking, formication, aching, burning or shooting pains, a sensation of wetness—there may be hyperaesthesia to touch and pin-prick, followed by numbness, hypoaesthesia, or anaesthesia, characteristically patchy in distribution, incomplete, and changeable. This intermittency and variability is equally characteristic of the ataxia, hypotonia, incoordination, and Rombergism at the onset, though of course there are no accompanying subjective symptoms. To this group of syndromes must also be added mental apathy, mild depression, loss of memory, loss of emotional control, and mental deterioration.

The character of the symptoms in this group of syndromes seems to suggest a widespread disturbance of function in the cortex, both cerebral and cerebellar, and probably in subcortical nuclei. The disturbance at the onset is variable and intermittent, therefore the cause must be reversible, a fact which, it is again suggested, could be explained only by some disorder of metabolism, a disorder of the vascular system, or both.

Dietary Deficiency

That this group of syndromes is associated with malnutrition there can be no doubt. So-called toxic agents can be ruled out, though the possible action of an antivitamin must not be lost sight of. Epidemiological studies show that the prevailing dietary deficiency in all cases is one of protein and the B group vitamins, with a relative excess of carbohydrate.

Without going into details it is possible to exclude vitamins A and C as the factors in causation. Similarly thiamin and nicotinic acid may be disregarded, for though these syndromes may be present in the subjects of beriberi and pellagra they are not due to deficiency of either of these vitamins. There remain the other members of the vitamin B₂ complex to be considered. The association of these syndromes with signs of riboflavin deficiency is very

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