typically in the legs and distal portions of the arms, and the peripheral blood vessels, which rupture easily and account for the bruises, ecchymoses, and "petechial haemorrhages." The third group consists of substances identified in the urine as the neutral 17-ketosteroids, which include all the adrenal androgens. According to Albright these are the substances responsible for nitrogen retention, and he refers to the group as the N-hormone ("nitrogen" hormone). S-hormone and N-hormone are mutually antagonistic, in so far as the latter is protein-anabolic and the former "anti-anabolic." Thus the effects of excessive S-hormone production, which depletes protein storage and leads to muscle wasting and weakness (as seen typically in Cushing's syndrome in the atrophy of the muscles of the buttocks and thighs), are similar to those due to deficiency of N-hormone, as indicated by lowered 17-ketosteroid excretion. The conditions associated with lowered or absent 17-ketosteroid excretion are pan-hypopituitarism (true pituitary infantilism and Simmonds's disease), eunuchoidism, Addison's disease—especially in women, though in men testicular androgens account for some degree of 17-ketosteroid excretion—and myxoedema. In all these disorders therapeutic administration of androgens leads to beneficial effects, though to a varying degree. Perhaps the most remarkable changes are seen in Simmonds's disease, in either sex, where an implantation of four to six 100-mg. pellets of testosterone overcomes the characteristic muscular weakness and is followed by an appreciable gain in weight, with increased muscular development and a positive nitrogen balance. In eunuchoidism there is also an increase in weight and muscular strength. In Cushing's syndrome the administration of androgens has been reported to have cured the osteoporosis. The therapeutic applications of this concept of the protein-anabolic action of androgens are still largely in the experimental stage, but it seems to be true in a general way that where the 17-ketosteroid excretion is low there is a tendency to muscular atrophy and weakness, and where it is high there is nitrogen retention and increased muscular strength. For instance, the "infant Hercules" with a prepubertal adrenal cortical tumour is not only bulging with muscle but is also abnormally strong.

Conclusion

The object of this paper has been to provide a brief account of the modern trends in sex-hormone therapy, with an attempt to rationalize the principles involved. It has not been possible to do more than wipe the dust off the cover of this rapidly expanding loose-leaf volume in the encyclopaedia of modern therapeutics. No references to original work have been cited, for such writings have not been consciously referred to. In holding myself responsible, therefore, for the views herein expressed I must run the risk of perpetrating such errors, both of omission and commission, as commonly accompany the necessarily dogmatic oversimplification to which a postgraduate lecture lends itself.

The West of England Child Health Group was formed in March, 1948, to foster co-operation between doctors and others who are concerned in the various aspects of child health. At the first meeting Professor A. V. Neale and Professor R. H. Parry opened a discussion on "The Integration of the Preventive and Curative Aspects of Child Health." At subsequent meetings, which are held at monthly intervals, discussions have taken place on a wide range of subjects, including gastro-enteritis, thoracic surgery, and upper respiratory disease. During the present session, 1948-9, the group has held a discussion on orthodontics and a clinico-pathological conference on mongolism. Dr. William Hobson (professor-elect of social and industrial medicine, University of Sheffield) gave an address on "Social Medicine."

ALTERNATING ORTHOSTATIC HYPOTENSION AND HYPERTHYROIDISM OF PROBABLE HYPOPHYSIAL- HYPOTHALAMIC ORIGIN

BY

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No final conclusions can be drawn from the following report, since considerations based on a single case lack sufficient foundation and must always be hypothetical.

Case Report

The patient, a married woman aged 24, was sent for examination of her circulatory system. Her father died at the age of 57 from a liver disease, her mother is alive and well, aged 57, and three brothers are also alive and well. One brother died at the age of 9 months, from an unknown cause.

Personal History.—Birth and early development were normal. She had measles and whooping-cough in early childhood, without complications, and very frequent attacks of sore throat, and has always suffered from constipation, anorexia, and asthenia. Menarche was normal, at the age of 14, with a normal menstrual cycle. From the age of puberty onwards, and for several years, she has suffered from dizziness. Perspiration has always been scanty. Immediately after menarche she found that on getting up after lying down for some time she always had a sensation of mistiness and progressive loss of vision, and a feeling that she was going to faint; she had to take hold of something quickly and sit or lie down again. These phenomena sometimes progressed to actual fainting, and appeared at odd times totally unconnected with the taking of meals or fasting.

These symptoms persisted until soon after her marriage at 22 and improved immediately afterwards, though at this time she was very nervous, suffered from palpitations, became thinner, and developed a slight swelling in the neck. She became pregnant six months after marriage. At that time the dizziness had disappeared; but, simultaneously with pregnancy and when the attacks of dizziness were becoming less frequent, there appeared other phenomena of endocrine origin: loss of weight—progressive though not excessive and less marked than before—trembling, and bad temper (she always had a certain tendency to depressive neurosis). The slight goitre persisted, and there was some fever, with attacks of palpitation and paroxysmal tachycardia. Her usual pulse rate was 90-100, and she sweated at night.

This syndrome was considered to be due to focal sepsis in the tonsils, and in the third month of pregnancy they were removed. In spite of this the neurosis persisted and the paroxysms of tachycardia continued. At this time the slight thyroid enlargement was noted and the basal metabolism was found to be +28, and a month later +37.

A corrected diagnosis of gestation hyperthyroidism was made, and treatment with methyl thiouracil was prescribed, but the patient did not notably improve, the B.M.R. remaining unaltered. She then had a normal confinement but did not nurse her baby. The slight hyperthyroidism continued. Treatment with methyl thiouracil, alternating with Lugol's solution, was now instituted and the signs and symptoms of hyperthyroidism disappeared. She put on weight, though not enough to compensate for the previous loss; the thyroid became normal in size and the attacks of tachycardia gradually disappeared. Surprisingly enough, however, just as she was recovering from the hyperthyroidism and was getting well again, she noticed a return of the postural dizziness—i.e., the orthostatic hypotension syndrome reappeared after having been latent, or having disappeared, during the phase of hyperthyroidism.

Clinical Examination.—The patient was of asthenic constitution, with dry skin, waxen pallor, and prominent superficial veins. The mouth was healthy, without dental sepsis. The lungs were normal. The heart was normal on palpation and percussion. Cardiac sounds were lively but normal, and the pulse

was soft, compressible, and of normal frequency and rhythm. Arterial pressure in the right arm, in sitting posture, was 90/50, pulse rate 80. Without being able to make her rest beforehand, we took her arterial pressure in a vertical posture, when the figures dropped slightly to 80/40, with pulse rate 84.

On finding such low pressures and confirming our clinical impression that her dizziness was due to postural hypotension we proceeded to examine her orthostatic reactions on a tilt-table. After ten minutes' rest in the horizontal position the B.P. was 90/50. On changing rapidly to the vertical the successive pressures were: immediately after the change, 95/60; and 30 seconds later 60/40. 60 seconds later still the pressure dropped to about 40, and auscultation revealed sounds only in the region of 45 and 35 without our being able to determine accurately the systolic and diastolic pressures—i.e., without pulse pressure. The patient now had a sudden sensation of weakness and dizziness and became very pale, but without any sweating and without any noticeable change in the pulse rate on auscultation. The phenomena became more pronounced until, a little before two minutes had passed, the patient fainted, and only some very soft sounds were audible around 30 mm.; but, in view of the alarming circumstances of the moment, we could not study the pulsation index on the oscillogram, which had previously dropped from 20 to 10 mm. The patient was placed supine slightly tilted in the Trendelenburg position, and was given rapid passive movements of the limbs with centripetal massage. She quickly recovered, her blood pressure rising progressively to 60/40, 80/40, 90/45, and 108/60—i.e., to a figure slightly above the initial one. Sinocarotid sensitiveness and eye-compression tests were made, and proved negative, there being not even a fall in pressure or bradycardia, or syncopal or presyncopal phenomena of a cerebral type.

Pre-carotid pressure (according to Engel's technique), applied to ascertain whether the case was one of elective derangement of the cerebral circulation, gave completely normal results. An atropine test (2 mg. given intravenously) did not prevent a certain amount of postural reaction; neither did it produce a sufficiently high tachycardia; but we must point out that the slight atropine tachycardia was enough to substitute a simple dizziness for the postural fainting, although the arterial pressures had dropped in the same way as happened without atropine: a compensating effect through increase in the minute-volume. Valsalva's and Flack's tests produced syncope even at 45 degrees on the tilt-table.

Investigation revealed:—Abdomen: flaccid, no tender points; neurological examination quite normal; special senses, normal. The arm-to-tongue circulation time was 17 seconds (decho-line) and the arm-lung time 8 seconds (ether). X-ray examination of the chest revealed a normal vertical heart, with normal outlines in all positions.

In the electrocardiogram the complexes were normal in all the leads and of the vertical heart type. Other curves in the vertical posture showed rather the phenomenon of a "hanging heart" and, furthermore, noteworthy alterations of the S-T intervals; in the first curve in the vertical position S-T 2 was depressed, but there was still a positive T wave and the T 3 wave became more negative. In the second curve, taken after 90 seconds, the T 2 wave became negative and was preceded by a somewhat curved previous interval. Among the other data we also observed a shortening of the electrical systole and high and ample P 2 waves that were not seen in the horizontal posture.

The blood picture was almost normal; there was slight macrocytic anaemia (average cell diameter 8.10 μ), with normal leucocyte count and distribution. Total plasma proteins, 6.9%, with an albumin-globulin ratio of 1.03. Cholesterol, 120 mg. per 100 ml.

Test meal, normal. By duodenal drainage, bile was extracted in which a *Proteus* organism was cultivated; in the faeces, Type I *Bact. coli* was cultivated as well as the *Proteus*. Ophthalmic examination showed only a slight vascular invasion of the limbus (Dr. C. Costi). X-ray examination of the digestive system (Dr. E. Castillo) revealed an enteropathy of the small intestine with marked colonic atony; cholecystography revealed the gall-bladder, but it showed no emptying. Finally, the basal metabolic rate was normal: +6%.

Discussion

This syndrome corresponds exactly to that of orthostatic hypotension syncope. The differential diagnosis would have to exclude the other syncope that are more or less related to the vertical position, and especially the so-called vasodepressor syncope. The direct and invariable relation to the vertical position and the abrupt fall of blood pressure are sufficient for exact diagnosis. The absence of sweating and the fact that the orthostatic hypotension syncope have never been produced by other stimuli (emotion, trauma, etc.) differentiate them from neurogenic or psychogenic vasodepressor syncope; it is evident, therefore, that the present case is not the kind of vasodepressor syncope observed in the processes of infectious diseases, heart-shock, etc.

The negative result of pressure on the carotid sinuses (examined successively and conjointly) and on the eyeballs rules out the reflex and vagus factor. Atropine, though it slightly raised the heart rate (from 80 to 90) and prevented total orthostatic syncope, could not prevent a feeling of dizziness and loss of vision, which the patient remedied by moving her limbs as she was ordered—a manoeuvre that was less quickly effective in total syncope. This proves that the syncope was not of the orthostatic vasodepressor type of sinocarotid origin and that the vagus factor was secondary. Neither is it a case of reflex or arrhythmic cardiogenic syncope, since there are no electrocardiographic data of alterations of the intracardiac conduction of the electric stimulus, nor any extrasystoles or other signs leading one to suspect a cardio-irritative syncope (of paroxysmal tachycardia type). The electrocardiographic anomalies observed in this patient are very typical of orthostatic hypotension; they have been related to postural coronary insufficiency (Akesson, 1936; Meesen, 1937) and to a heightening of the sympathetic tone (Nordenfelt, 1941, 1942), but they are not so marked that the attacks of dizziness affecting the patient can be ascribed to them, nor can they be related to "coronary shock" (Bezold type).

The history and the neurological examination exclude all possibilities of a neurological lesion being responsible for the orthostatic hypotension (tabes, syringomyelia, etc.). Other processes that generally give rise to orthostatic hypotension (pituitary insufficiency, adrenal insufficiency, etc.) were not found here either. Therefore there can be no question of a secondary orthostatic hypotension.

By exclusion, a diagnosis of syncopal disease due to *chronic essential orthostatic hypotension* (Pont, 1945) was made.

We may observe that during adolescence and puberty the patient developed a syndrome of postural hypotension, very rare at this age, since practically all the cases of orthostatic hypotension syndrome recorded were in persons over 50 years of age, and this is not the classical "orthostatic vasoneurosis of second childhood" described by Seckel.

When the patient was married, and particularly in the nuptial phase, her postural troubles disappeared at the same time as a slight hyperthyroidism syndrome set in. It is therefore evident that her hyperthyroidism, which is not of Basedow type, caused circulatory changes sufficient to lessen or even suppress the postural syndrome and to cause the subjective symptom of postural dizziness to disappear in spite of the persistence of hypotension from which the patient says she suffered throughout pregnancy.

It is evident, as Marañon (1947) and others have recently insisted, that the genetic basis of these types of hyperthyroidism must be sought probably in an organic or humoral disturbance of the kind now called hypophysohypothalamic block. The nuptial-phase hyperthyroidism,

owing to the emotional characteristics attributed to it, enters into this syndromic group for two reasons: its discrete character with mild hypermetabolism, the emotionalism, fever, slight resistance to medical treatment, the increase in weight during treatment without entirely regaining the weight previously lost, and the absence of adenomatous goitre all characterize it as hypophysio-hypothalamic, according to Marañón's latest revision.

On the other hand, it is well known—and I have dealt with this elsewhere—that the mechanism underlying the orthostatic hypotension syndrome may also be based on hypothalamic physiopathological factors. From time to time investigators have described successive hyperpressor and hypopressor centres of the hypothalamic region, culminating in the recent work of Hess (1946) with a relatively accurate location of such centres in experimental animals.

Essential orthostatic hypotension in Pont's sense—i.e., excluding orthostatic hypotension secondary to other processes (endocrine, Addison's disease, Simmonds's disease) or diseases of the central nervous system (tabes dorsalis, etc.)—is the result of an associated series of factors causing a sudden reduction of the heart minute-volume on assuming a vertical posture.

In hyperthyroidism the peripheral vasomotor tone is really increased whether or not there is any degree of capillary dilatation (in this case, indicated by the fever and sweating); the regional pooling of blood is difficult owing to the increase in quantity and speed of the blood circulating through the tissues. Although pregnancy did not improve the digestive atony in this patient, the mesenteric accumulation (also accentuated by colitis) may have been reduced during the phase of hyperthyroidism. The hypotonia of the skeletal muscles may also have been counterbalanced by the increase of muscular activity caused by the hyperthyroidism which is observable in the muscular tremor of cases of hyperthyroidism. Finally, the faulty regulation of the cardiac output in orthostatic hypotension—i.e., the lack of cardiac adaptation to inflow reduction, lack of compensating tachycardia—is here overcome by the real increase of the minute-volume characteristic of hyperthyroidism, which in this case was further conditioned by the permanent tachycardia. We may consider that the hypothalamic disturbance which produces the hyperthyroidism is directly related to the hypothalamic disturbance which conditions the orthostatic hypotension and the digestive atony, and even that the tachycardia and the attacks of paroxysmal tachycardia were not of direct endocrine origin but were due to an irritating affection—possibly hormonal—of the sympathetic nuclei of the hypothalamus.

Summary

A clinical case is described in which a juvenile orthostatic hypotension syndrome with orthostatic syncope was followed by a slight nuptial hyperthyroidism accentuated during pregnancy, at which time the orthostatic hypotension disappeared only to reappear when the former was cured by antithyroid medication.

A hypothalamic origin is ascribed to both syndromes, and the hyperthyroidism and the attacks of paroxysmal tachycardia are explained as a teleological mechanism of defence in the gestation period.

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ORAL REACTIONS TO PENICILLIN

BY

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In the second half of 1946 several cases of reaction to penicillin used locally in the mouth had been reported, and these, together with the occasionally unsuccessful results of penicillin therapy in oral infections, led to the investigations which gave rise to this paper, and which were carried out in the Dental Department, Guy's Hospital, in 1947, as the subject of the Ernest Hart Memorial Scholarship of the British Medical Association.

A review of the literature up to the end of 1947, when the investigations were concluded, reveals a limited number of cases of reaction to penicillin. Bedford (1946) describes two cases of black tongue occurring in patients treated with pastilles and lozenges for three days on the one hand and pastilles and spray on the other. The discoloration appeared on the fifth and fourth days and cleared in 13 and 12 days respectively. Thompson (1946) describes glossitis arising from penicillin lozenge therapy in three patients suffering respectively from tonsillitis, pharyngitis, and aphthous ulceration. Different batches were used in all three cases.

Cameron (1946) reports two cases of stomatitis occurring after four to five days' treatment with 50 lozenges. Murphy (1946) describes a case of stomatitis occurring after two days' treatment. Bradley (1946) inhaled penicillin spray—total dosage 800,000 units in first 10 days, then 1,000,000 units during the next five days. He developed soreness and dryness of lips and nostrils and a sore tender tongue.

Ellinger and Shattock (1946) report the case of a woman subject to attacks of nicotinamide deficiency in whom 15 penicillin lozenges, together with drops of a solution containing 500 units of penicillin per ml. pipetted on to the tongue for five days, brought about a slaty colour. They consider that the discoloration was due to pigmentation of the filiform papillae, and suggest that the penicillin thus taken is swallowed and passes through the stomach in sufficient quantity to inhibit the growth of intestinal organisms responsible for the synthesis of nicotinamide, and that the oral reaction was largely one of nicotinamide deficiency. In this connexion a number of patients treated by me were given lozenges containing 500 units of penicillin and 2 or 6 mg. of nicotinamide, taken in the usual way, and about 20% of these patients developed a discoloured tongue.

Goldman (1946) describes a case of vesicular cheilitis in a patient treated thrice daily with a mouth-wash containing 500 units of sodium penicillin per ml. of saline. A patch test was positive for sodium penicillin and negative for calcium penicillin.

Wright and Rule (1946) report 19 reactions among 189 patients treated with penicillin lozenges. Of these six occurred among 38 patients on calcium penicillin lozenges and 13 among 151 patients on sodium penicillin lozenges. They consider the sodium salt to be less toxic.

Blyth (1947) describes a case of glossitis following the use of penicillin lozenges for four days that recovered in three days. Ackers (1947) reported reactions in 49 patients treated: four had discoloured tongues, which took three weeks to resolve, one had glossitis, and one was able to taste penicillin four days later.