be when we shall be able to allocate to each gland its responsibility for a particular toxin that time is not yet; so that our only rational course is so to husband the resources of the endocrines by protecting them from unnecessary poisons as to keep them fresh and alert to deal with such as are inevitable in our present artificial communal life. If we fail thus to protect them they become prematurely worn out by the ceaseless conflict with poisons which come from without. That is why a gradual decline in vitality so often begins at about 50 years of age, why cancer comes, and arteriosclerosis and other degenerative conditions. The endocrines thus gradually retreating before the advancing toxins are at last driven to capitulate, and the end comes. Now, looking at the matter from the point of view of comparative biology, there is no reason why man should be senile and effete at 70. If we argue from analogy we must admit that in relation to the time which it takes him to arrive at maturity man ought to live to the age of 100 or 120 years. That he does not do so indicates quite clearly that the kind of life he is now leading is not in accordance with physiological laws; that the poisons which he introduces into his system are either too concentrated or too persistently applied for the endocrines to withstand for more than a relatively short period.

It is an interesting fact that the glands in both sexes which show the first signs of fatigue are those which seem to have the closest connexion with the gonads—namely, the suprarenal in man and the thyroid in woman. In woman the reproductive capacity is definitely brought to a close at the menopause, and it does not surprise us that the necessity for redressing the endocrine balance consequent upon the withdrawal of the ovary from practical politics should give rise to considerable constitutional disturbance. It is nevertheless, to me at any rate, rather surprising to find that the gland to which we appeal most effectually in such cases is the thyroid. And here let me say, with all the emphasis at my command, that the appeal to thyroid extract should always be made cautiously at first—that is, with very small doses, never more than 1 grain per diem. I have been preaching this gospel for many years, and, although I am pleased to say I have made many converts, even now scarcely a week passes without my being profoundly shocked by the seemingly light-hearted manner in which members of the profession throw 5-grain tablets at their patients as though they were dealing with confetti at a carnival. That the combative gland, the suprarenal, shows declining vigour as the years advance is a matter of common observation. Bacon tells us that "men of age object too much, consult too long, adventure too little, repent too soon, and seldom drive business home to the full period, but content themselves with a mediocrity of success," which is only another way of saying that the gland of fright and fight has lost its recoil.

It is often said that a train of phenomena takes place in men between 60 and 70 in many ways comparable with the menopause in women. I have never been able to support this view. It is undoubtedly true that in most men the copulative and reproductive capacity begins in that decade sensibly to decline and ultimately to peter out. But by no means in all men. We could all of us cite outstanding instances of men who have retained a large measure of sexual power well into the following decade, but no one except the biographer of Sarah has ever recorded a case of a woman who has reproduced her kind at such an advanced age. There is obviously no reason why a man should lose his copulative and reproductive power so long as his gonads retain their efficiency, and this efficiency usually becomes impaired about the sixties because of the accumulation of poisons in the system. We have already seen that certain poisons (and I have instanced two only among many) cause an atrophy of the seminal tubules and an hypertrophy of the interstitial glands. Now it is more than likely that the interstitial hypertrophy represents an endeavour on the part of these glands to repel a chronic toxæmia. The hypertrophy succeeds for a time in supplying the extra quantity of necessary antidote, but at last, overwhelmed by the strength of the invader, the gland succumbs. We see this train of events so often in the case of the thyroid—the goitrous cretin, for example—that it seems reasonable to offer the same explanation in the case of the interstitial gland. Then there is the senile hypertrophy of the closely associated prostate to account for. Is it possible to doubt that this too is an anti-toxic gland, or that its gradual enlargement with advancing years is due to the constant endeavour to prevail in the unequal combat against lethal poisons introduced from without? The removal of the gland—which is, after all,

a simple surgical procedure—has been shown to be followed at no very long intervals by symptoms which go far to support this view.

And so we come to the question as to what are these toxins which the endocrine system is at such pains to neutralize and nullify. The answer is altogether outside the terms of my present reference, but to indicate the sanction for the views which I hold very strongly let me remind you that man is the only animal who has lost the instinct of physiologically selecting his food; that man is the only animal who cooks his food; and that the Almighty no more invented the kitchen than He ordained the gin palace or the opium den. Cooking destroys vitamins, and vitamins are to endocrines what endocrines are to the economy. The kindly fruits of the earth to which we do lip service in the Litany are ruthlessly relegated to a back seat in our everyday lives, and until we see reason in this respect while it is yet day we shall continue to poison our endocrines and to pass ignobly into nothingness with our allotted tasks but partially accomplished.

NOTE ON THE PEPTONE TREATMENT.

BY

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IN the use of peptone for certain cases of asthma and other conditions of sensitization we have, as a rule, to rely on commercial products. These differ widely in composition, and consequently in their pharmacological actions. The latter are at present undergoing investigation, and some very divergent preliminary results have been obtained by Professor A. J. Clark with some samples submitted to him. What is really needed are preparations physiologically standardized. The proteoses are by far the most important constituents. A peptone solution fit for clinical use may be roughly tested by adding to a few cubic centimetres in a test tube two or three drops of strong nitric acid. A copious white precipitate is immediately produced, consisting of primary proteoses. On heating, the precipitate entirely dissolves, and reappears on cooling.

In a former paper¹ it was stated that Witte's peptone, even in the small doses of the 2 per cent. solution, may produce an immediate sharp reaction in certain subjects. Flushing, salivation, headache, palpitation, cyanosis, and dyspnoea are the usual symptoms. The dyspnoea is asthmatical in character, and may last a considerable time. Faintness, sickness or vomiting, purgation, and localized oedema or urticaria may supervene in very sensitive subjects. In the mildest cases flushing, alone or with a sense of constriction in the chest, occurs. Any combination, however, may be encountered. There seems to be no doubt that this almost instantaneous and sometimes alarming syndrome is caused by histamine in the peptone. The above symptoms can be faithfully reproduced when histamine is administered intravenously, and are due to a sudden injurious dilatation of the capillaries and venules, peripherally induced, together with stimulation of smooth muscle. Hanke and Koessler,² by an ingenious and exhaustive process, though finding no histamine in blood, fresh tissues, casein, etc., as originally affirmed by Abel and Kubota, nevertheless recovered it from Witte's peptone in the proportion of 0.00335 gram to 100 grams peptone. It might be urged that this represents too small a quantity in the intravenous injections to be effective, and that the symptoms must be referable to the peptone itself. Now these figures give 1/1,500 mg. histamine (the equivalent of 0.3 c.cm. of a 1 in 500,000 aqueous dilution) in about 1 c.cm. of a 2 per cent. solution of Witte's peptone (an average dose). This dilution, I found, gave a positive dermal reaction (0.5 cm. and over) in many subjects, but the intravenous injection of 0.3 c.cm. in the subjects tested was either very slight in effect or negative. However, when this amount was mixed with the usual doses of a histamine-free peptone, the injections, previously negative, gave the histamine effect in numerous instances. Apparently, therefore, the peptone reinforces in some manner the action of the histamine. The intensity of the effect depends on the amount of histamine-peptone present in the blood per unit of time—in other words, on the rapidity of the injection. The reaction to the peptone (protease) itself, should it occur, requires some time and is pyrexial in character.

It is necessary to recognize that histamine is a degradation product (by decarboxylation) of the amino-acid histidine, and acts after the manner of a powerful drug. Its presence in a peptone is a drawback, as it not only may entail a limitation of the dosage, but is itself quite useless in the immunizing process, if not actually harmful. It was found by Hanke and Koessler that peptone which was perfectly histamine-free produced the typical peptone shock. Histamine shock has indeed the more obvious features of peptone shock, but is shorn of certain essential attributes of the latter—namely, extensive katabolism of body tissues and incoagulability of the blood (supposed due to antithrombin formation from the interaction of peptone and hepatic cells).³ Ringer and Underhill⁴ were unable to produce any increase in tissue katabolism by shock doses of histamine enormously greater than those contained in a toxic dose of Witte's peptone. Further, histamine is unable to produce swelling of the liver in dogs, or to produce pyrexia, or to desensitize. Histamine has been occasionally detected in the intestines, but whether it escapes the action of the liver and produces the symptoms of disease is an open question. It certainly can be swallowed in considerable amount, comparatively speaking, without the production of any symptoms. But in the katabolism of tissue associated with anaphylactic or anaphylactoid shock it is quite possible that histamine may be produced where cell-oxidation ceases, just as it is supposed to be formed in the tissue destruction leading to wound shock.

The dermal (scratch) test may give evidence as to the presence of histamine in a peptone (conc. solution), as all individuals give a marked though varied response to extremely dilute solutions of histamine. For testing purposes one of Burroughs, Wellcome and Co.'s ergamine tabloids may be dissolved in water or saline in various dilutions and used as a control. A peptone giving a wheal of 0.4 cm. and upwards in diameter in a series of cases may be suspected, the size of the wheal depending on the sensitiveness of the patient to histamine, though it must be remembered that sensitiveness to the peptone itself may also be present. Of the peptones I have tested in this way, the largest wheal (up to 1 cm.) has been constantly given by Parke, Davis's peptone (which contains no primary proteose). Confirmatory evidence is afforded in the immediate histamine effect produced by the intravenous injection of very small doses of this preparation.

A patient may be hypersensitive to both peptone and histamine, but the same patient may react differently to histamine on separate occasions, owing to unknown causes; also, the dermal and constitutional reactions do not always correspond. Sometimes intradermal tests are made, but they are usually unnecessary and may be dangerous, unless a very dilute (2 per cent.) solution of the peptone or suspected peptone be used, and then only 0.1 c.cm. should be injected. The injection of a strong solution may cause histamine shock. Also, if after a negative intradermal injection the ordinary intravenous injection be soon made, the two may summate and cause shock. According to Dr. Chandler Walker,⁴ intradermal injections are very erratic, far too sensitive, and practically non-specific.

Ordinarily, therefore, and especially for those requiring a higher dose of proteose—sufficient, that is, to produce a slight constitutional reaction—the Armour No. 2 peptone† should be employed, which, in my experience, never gives the histamine effect. It will be found that the maximum dosage will approximate 2 to 2.5 c.cm. of the 5 per cent. solution. Witte's peptone is of particular value in certain cases owing to the nature of its proteoses, but it is best given diluted with a weaker peptone, as recommended in my last paper.⁵ But the Armour peptone (intramuscular or intravenous) gives the best results in the majority of cases, and may be safely administered to the youngest child. Should toxic symptoms unexpectedly supervene, suspect contamination of the solution—a not infrequent occurrence. It may be added that a satisfactory immunizing process is characterized by a slight leucocytosis, particularly as regards the large mononuclears, and by increase in the haemoglobin and red cells.

REFERENCES.

¹ BRITISH MEDICAL JOURNAL, vol. i, 1922, p. 563. ² *Journ. Biol. Chem.*, vol. 43, 1920, p. 567. ³ *Journ. Biol. Chem.*, vol. 48, 1921, p. 510. ⁴ *Journ. Med. Research*, vol. 37, 1917, p. 287. ⁵ BRITISH MEDICAL JOURNAL, vol. i, 1921, p. 698.

* Evidence of a new kind, contrary to this view, has lately been advanced (*Proc. Roy. Soc.*, Series B, vol. 93, p. 367).

† The Armour Company have given an assurance that this peptone will be maintained of a uniform composition.

A CASE OF NON-RHEUMATIC AORTIC STENOSIS
IN A YOUNG SUBJECT.*

BY

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DR. L. GALLIVARDIN has recently described in an interesting paper a group of cases of aortic stenosis in young persons which he believes to be non-rheumatic in origin.¹ The case I bring before you seems to belong to this group.

The special features of the group are:

1. Aortic stenosis with loud murmur and marked thrill in young persons.
2. The stenosis generally "pure"—that is, unaccompanied by regurgitation, or, if aortic regurgitation coexists, its murmur much less marked than the murmur of the stenosis.
3. A long period without symptoms.

The causation Dr. Gallivardin considered doubtful: some cases he thought might be of congenital origin; most, he suggested, might be due to a post-natal valvulitis of unknown nature. Eight male cases were described in his paper, aged respectively 21, 25, 19, 20, 17, 19, 21, and 25. Of these the first only had been also observed at an earlier age—namely, at 7 or 8.

H. C. P., aged 17½, a bricklayer's apprentice, a florid, well-nourished, healthy-looking, intelligent lad, was sent to me by Dr. Waite of Heavitree, complaining of shortness of breath on exertion. This had been noticeable for six months, but only troublesome for three months, during which he had been put on a man's job, carrying hods and working eight hours a day. He had had no pain, faintness, giddiness, cough, or blueness on exertion. At 11 years old a school doctor had forbidden him to play football on account of "incurable" heart trouble, but he had continued to play because he felt no ill effects from doing so. The boy has never had rheumatism, chorea, or scarlet fever. No doctor attended his birth. At nearly a year old he was in this hospital for large glands in his neck which subsided without operation; no mention is made in the surgical notes of any tonsillitis, nor, unfortunately, of the state of the heart. As a child he had whooping-cough and chicken-pox. On leaving school he worked first as a compositor, then as an Army Pay Corps messenger, then for sixteen months as a tailor's porter, with much bicycling and some lifting of heavy weights, finally at his present job, which has proved too much for him. He has never had any serious accident or sudden overstrain; influenza in 1918 was the only illness since childhood in which he needed a doctor.

There is no family history of acute rheumatism or chorea. His father is a strong-looking man of 55 who has had some "rheumatic gout" for ten years, never syphilis. His mother died of phthisis at 46; she was subject to "fainting attacks," but was not said to have heart disease; she had no miscarriages. A brother of the patient in the army died of phthisis at 26. Two sisters and another brother are alive and well; the surviving brother has had his tonsils removed, but is stated never to have had acute tonsillitis.

The circulatory condition is as follows: Pulse regular (84), not "water-hammer," giving the anacrotic, flat-topped tracing of

aortic stenosis. After brisk exercise the rate rises to 108, but drops back to 84 in two and a half minutes. There is visible pulsation above the manubrium and clavicles, but little further up the neck. In the erect position the heart's apex beat is in the fifth space, half an inch inside the left mammary line, and the dullness reaches transversely from that point to three-quarters of

FIG. 1.—a, a, Limit of thrill in upright position. b, b, Ditto in recumbent position. c, c, Limit of systolic murmur, upright position. x, Maximum point of murmur and thrill.

an inch to the right of the mid-sternal line—practically a normal width. Over the upper part of the chest there is a marked systolic thrill and a loud, rasping systolic murmur; both have their maximum close to the right sterno-clavicular joint and just over the manubrium in the neck; the murmur is heard in the carotids up to the ear, and almost all over the chest. Fig. 1 shows the area

* Read at a meeting of the Exeter Division of the British Medical Association, February 17th, 1922.