FURTHER REMARKS ON THE TREATMENT OF ASTHMA BY PEPTONE.

BY

A. G. AULD, M.D.,

MEDICAL LECTURER, PRINCE OF WALES HOSPITAL, LONDON, ETC.

OVER a year's further experience has led to a modification of the peptone treatment of asthma described in my note in the *JOURNAL* of May 5th, 1917. The cases best suited for the treatment remain much as indicated therein—those, namely, characterized by favourable intervals, with freedom from bronchitis and much attendant emphysema. The more recent the disease, and the more regularly spaced the intervals, the better the result. Young patients as a rule do well. But old-standing cases respond provided the intervals are of a certain length. Irregular cases also respond if the disease is of comparatively recent origin (under five years). These findings serve to support the view as to the anaphylactic nature of the cases amenable to peptone. It is evident that after each main attack one would look for a certain minimal period of comparative quiescence, due to desensitization. Cases of practically continuous asthma are either non-anaphylactic in nature, or else the anti-anaphylactic mechanism has completely broken down.

If a certain quantity of a suitable peptone, such as Witte's, be introduced into the blood the symptoms of anaphylactic shock quickly supervene; no previous dose is necessary to induce the condition of sensitization. The late R. Weil¹ showed that if a normal liver be perfused with peptone, it quickly presents the same severe congestion and swelling as characterizes the sensitized liver after perfusion with the antigen. Hence the view arose that after the first or sensitizing dose of any antigen the anaphylactic shock due to the second dose was due to the rapid formation of peptone from proteolysis of the antigen by antibodies or enzymes called forth by the first dose, such antibodies being free in the blood and likewise attached to the tissue cells. This view, however, seemed to be no longer tenable after it was found that inert and non-protein or entirely non-nitrogenous substances, such as agar, parafaline (Bordet and Zuntz), silicic acid, were likewise capable of inducing anaphylactic-like shock. The explanation thereupon given was that the peptone was formed from the blood itself. These non-protein antigens were supposed to adsorb the antiferment (lipoidal in character) of the serum, leaving the ferment free to proteolyse the serum—a true autolysis. Jobling and Bronfenbrenner have vigorously supported this idea.² They affirmed that in these cases the blood would be found to contain peptone in excess, but this failed of confirmation by van Slyke's very delicate nitrous acid test for aliphatic amino-nitrogen. Van Slyke and Auer³ also failed to find any difference in the content of protein cleavage products between normal and anaphylactic guinea-pig lungs. Bayliss showed that for such a ferment action several hours were necessary, whereas the anaphylactic reaction is merely a matter of minutes. The most recent explanation is that of Professor Novy,⁴ and is based on the fact that normal serum, just in the pre-clot stage, is toxic, due to a catalyzing agent, and is a parallel phenomenon with fibrin formation. A molecular change is induced in the matrix, resulting in tautomeric modifications. Thus the well-known acceleration of clotting produced by peptone is an expression of this change. When serum is digested with Witte's peptone, agar, or certain bacterial proteins, a similar but more intense toxicity is induced, which Novy believes to be identical with that occurring in the body cells and fluids during anaphylactic shock, as a similar explosive effect follows the injection of such toxified serum. In the body the toxicity, however, is of short duration owing to the mass action of the colloids. Novy holds the antigen to act merely as an inducing agent, of no toxicity in itself, and, at least in the case of agar, to be entirely recoverable from the toxified serum. Specific anaphylactic shock is due to the production of this poison from the blood and tissues by the inducing action of the antigen-antibody product.

If this view be correct (and no doubt there is a good deal to be said for it), there would apparently be no reason to select one substance in preference to another for purposes of desensitization, provided only it were capable of

inducing this toxic effect after injection into the blood. Professor Novy, indeed, goes so far as to affirm that the toxicity of pathogenic bacteria is of the same order as that of agar, the intoxication of the host being invariably caused by the change induced in the plasma, the term "endotoxin" being a misnomer. But this must surely be limited to the production of the anaphylactic attack, without reference to the ulterior and specific effects of the antigens. Novy, indeed, seems to have overlooked certain important facts recorded by himself. He points out that in peptone anaphylaxis there is marked exophthalmos, both in rabbits and guinea-pigs, a symptom not found in anaphylaxis produced by any other agent. This undoubtedly proves a subsidiary specific action on the part of the peptone itself. As the asthmatic attack is usually characterized by a certain degree of exophthalmos, we are on safe ground in preferentially selecting peptone in its treatment, apart from its suitability as a medicinal agent as compared with most other substances.

Another important consideration refers to the range of action of peptone. No matter what the natural antigen responsible for the asthmatic attack, desensitization may be effected by peptone, as it exhausts the anaphylactic mechanism not only towards itself but also towards all other agents, as the experiments of Weil have shown. For instance, if egg-white be the sensitizing agent, a sufficient dose of peptone given during the period of sensitization will render a second dose of egg-white abortive. The desensitization therefore is non-specific in character, and from this it follows that skin tests for allergic reactions in respect of the proteins of various foods are rendered superfluous. Desensitization may therefore be accomplished by injecting a single large dose of peptone, but this is comparatively short-lived; small and increasing doses spaced over a considerable time are much more effective, as they produce a degree of immunization which is the equivalent of a prolonged desensitization. This is the method to be employed in asthma, but it may be mentioned that there are certain exceptional cases which appear to respond best to a preliminary large dose, followed by smaller and decreasing doses. It is a method, however, only to be used by those thoroughly conversant with the effects of the various dosages, and shall not be alluded to further.

The suggestion will naturally be made that the desensitization or immunization effected by peptone in asthma can only be temporary. This is true. The attacks cease for a time, but recur. Cases vary greatly in this respect, but in view of the painless method of treatment about to be described the repetition of the injections becomes a negligible factor so far as the patient is concerned. The peptone stops the attacks over a period roughly proportionate to their former frequency. Thus, if the attacks occurred at about weekly intervals, there should be a minimal remission of from six weeks to two months; if three-weekly, one of three or four months. In one case presenting a very severe attack every three months, there was a remission of nine months. Here one is tempted to put the question, If such cases are not anaphylactic in nature, how is this action of peptone to be explained, seeing the doses employed have no measurable effect on the circulation, etc.? Perhaps certain experiments of Abderhalden may be cited, showing that the proteolytic or peptolytic activity of blood serum is enhanced by the injection of a foreign protein. But here again one has to postulate protein as the causal agent, which always involves the possibility of anaphylaxis.

A consideration of the experimental work led me to try the intravenous injection of the peptone, and this was justified by the results. Not the least advantage of the method is its painless character, whereas subcutaneous injections create in certain subjects a considerable degree of pain and swelling after some hours. Intravenous injections demand great accuracy in respect of dosage, and so it became necessary to note carefully the effects of various preparations of peptone. Wide differences were encountered. As Witte's peptone became available, it was found to be of much greater potency than any other variety tried. The only other which gave satisfactory results was Armour's "ordinary" peptone.^{*} It is unfortunate that at the first time of writing I was not aware that the Armour Company make two varieties of peptone—"ordinary"

* Armour and Co., Kingsway, London.

peptone and peptone "siccum." The latter is of inferior value for the purpose in hand, although it is to be feared that not a few practitioners have been supplied with it. The clinical results indicated that about two and a half parts of Armour's "ordinary" peptone are the equivalent of one part of Witte's peptone. Discussing the matter with Professor Halliburton, he very kindly undertook the examination of several varieties of peptone, and his analysis, weighed to the second place of decimals, is subjoined:—

	No. 1, Witte's Peptone.	No. 2, Armour's "Ordinary" Peptone.	No. 3, Armour's "Siccum" Peptone.	No. 4, Fairchild's Peptone.
Primary proteoses ...	0.92	0.4	0.02	0.07
Secondary proteoses..	1.6	2.2	1.2	1.68
Peptone	0.3	0.2	1.55	0.9
Total	2.82	2.8	2.77	2.65

Professor Halliburton's figures are of great interest, particularly as showing the primary proteoses to constitute the deciding factor. For instance, although there are more secondary or deuto proteoses in peptone No. 2 than in No. 1, the latter contains considerably more than twice the amount of primary proteoses, and this corresponds with the clinical effects. No. 3, on the other hand, contains but a comparatively minute quantity of primary proteose, which explains its inefficiency. The purely peptone ingredient may be discarded, except that note may be made of the fact that it appears to act deleteriously when injected in large amount with the view of making up the deficiency in primary proteose.* That the primary proteoses are the ingredients almost entirely responsible for the specific physiological effects has also been proved experimentally in the careful work of W. H. Thompson.⁶

Technique and Dosage.

A 2 per cent. solution of Witte's (No. 1), or a 5 per cent. of Armour's (No. 2), are convenient for use. Witte's peptone is not entirely soluble, but it is more effective when partly in a fine suspension than it is after filtration. Dissolve the peptone as far as possible in normal saline (made up to three-quarters volume) by slightly agitating and warming at 37° C. Then add 1 mil. of a 2 per cent. solution of sodium carbonate for each gram (5 grains) peptone. This ensures the requisite degree of fineness of the suspended portion. Make up to volume with normal saline, adding 0.25 per cent. phenol as a preservative. Care is to be taken in adding the alkali, as any excess may cause racemization of the peptone, rendering it inactive. Peptone No. 2 is similarly prepared, the alkali being employed in this case to neutralize its acidity.

As regards the dosage, it is only possible to make a general statement, as variations may be necessary. When the main attacks, whether occurring singly or more or less broken up, occur at fairly pronounced intervals, a limited number of measured doses is usually sufficient. Should slight attacks persist, the dose may require to be increased. A feeling of chilliness and discomfort indicates that the limits have been overstepped. On the other hand, the dosage must be reduced when the attacks present great frequency and irregularity. In such the anti-anaphylactic mechanism is weak, or, in other words, the immunity reserve is small and will only tolerate gentle stimulation. Experience alone can enable one to decide the dosage, according to the symptoms and progress of the case; also, patients differ very considerably in their response to peptone. Generally speaking, the initial dose in all cases may be fixed at 5 decimils (5 m). This contains ½ grain of Witte's peptone (No. 1) or ¼ grain of No. 2. Increase by 2 decimils (roughly 5 m) every fifth day, until six injections have been given. Three or four more injections are to be given, employing in each the same dose as that given in the sixth injection. To this rule, however, there are exceptions. No reaction appears if the patient occurs. At any time during the course modifications in the dosage may be called for, as already indicated. In the case of children but a very slight reduction in the dose is necessary. No injection is to be given during attacks, and, when the latter occur at long intervals, begin the treatment about three weeks before one is expected. In all cases the diet should be low, and easily digested.

To administer the injection, cleanse the bend of the elbow with spirit (some hypersensitive patients may require local anaesthesia). Charge the syringe, and place the needle (a small one) apart. With the left hand grasp the patient's upper arm,

the thumb passing across the biceps, and make gentle pressure. Pass the needle into the vein, and as soon as blood issues freely from it, but not before, withdraw the left hand, and maintain the needle immobile by it; affix the syringe, and make the injection slowly. No after-dressing is necessary.

I should like to take this opportunity of thanking those medical men who have sent me their observations. Up to the present, the reports received have been favourable.

REFERENCES.

¹ *Journ. Immunology*, 1917, vol. ii, p. 439. ² *Journ. Exper. Med.*, 1914-15, various papers. ³ *Ibid.*, 1913, xviii, p. 210. ⁴ *Journ. Infec. Diseases*, May and June, 1917. ⁵ *Journ. Physiol.*, July, 1899.

A NOTE ON EPIDEMICS.

BY

JULIUS BURNFORD, M.B., M.R.C.P., D.P.H.,

CAPTAIN R.A.M.C.(T.C.).

EPIDEMICS in war time assume a special significance, for though the symptoms, at least at the outset, may be mild, so that, as far as the individual is concerned, it may have but a brief or transitory effect, in the aggregate the loss of man power, reckoned in days, may be enormous. As all classes are concerned the importance of this is obvious.

Furthermore, judging from the history of epidemics in the distant past, even a type of disease apparently trivial may in time intensify itself with most serious results, and it might well be supposed that in war, with its herding together of armies of men and workers of all kinds, this time element might be considerably shortened and the process of exaltation correspondingly hastened. Consequently, it seems important to visualize with the greatest possible precision any unusual circumstances connected with the health of armies and populations at the present time.

Bearing these points in mind, it seems to me that certain features in the prevailing epidemic are worthy of consideration.

There can be no doubt that it is widespread and advancing. The clinical manifestations are reproduced in each fresh case with the striking regularity which I had already observed at the beginning of an analogous if not the same epidemic overseas earlier in the year. Unfortunately my notes on these are all filed in — General Hospital, and are beyond my reach. There is much doubt, however, as to its real nature. With the limitations of the present nomenclature we are driven to a diagnosis of influenza or pyrexia of unknown origin. The latter term, however, has become so closely associated with trench fever as to be almost synonymous with it, and, indeed, is unsatisfactory in any case; whilst the former is so loosely employed in various indefinite states of disease that it is equally unsatisfactory. And, indeed, there is some doubt as to the present epidemic being due to the influenza bacillus.

It is obvious that we are dealing with a specific infectious disease which, like all the zymotic fevers, has an incubation period, leading up to the onset and followed by stages of fastigium, acme, and defervescence by crisis. But what the specific infective agent is remains to be ascertained. We are faced with the possibility of its being as elusive as that of the other zymotic diseases. That it is infectious under certain conditions is evident, but it is undoubtedly dependent on environmental conditions, such as overcrowding, etc. For though cases have been admitted into general wards only a comparatively few sporadic cases have broken out amongst the patients in these wards. But in camps and billets and various outposts cases have occurred in preponderating numbers. Overseas, where the epidemic first came to my notice in the beginning of April, it was at first confined to one large convalescent camp and apparently to the huts forming one subdivision of this camp. It would appear that no cases occurred at home at the time, but in the beginning of June, whilst stationed at a general hospital, cases presenting identical symptoms were admitted in large numbers, and in a week or two the epidemic had reached large proportions. It was evident there had been no change in the type of the disease.

Briefly the history is as follows: The onset is sudden, often the exact hour is given by the patient—as on parade, at meals, or in bed. There are severe pains in the head,

* As Armour's peptone is not guaranteed of absolute uniformity in composition, it is advisable to use Witte's peptone, if obtainable. A peptone may be roughly tested before use by adding an equal volume of saturated aqueous solution of ammonium sulphate to a 10 per cent. solution of peptone and stirring with a glass rod. In a satisfactory sample a sticky precipitate comes down in considerable abundance, which adheres to the stirring rod.