in the poorer parts. In every district a dépôt should be established by the local authority from which the general practitioner could obtain a sterile outfit free of cost.

4. The present statistics are an urgent indication that better organization is required. In various centres, especially in industrial districts, large maternity and gynaecological clinics should be instituted. When possible they should be attached to the teaching schools. These clinics should form base hospitals for wide areas, in the outlying parts of which a few beds should be set aside in existing cottage hospitals, or, failing these, small field hospitals should be established for the reception of maternity cases. In these field hospitals general practitioners would have an opportunity of working under the best conditions when interference was necessary. In cases of special difficulty skilled assistance could be summoned from the base hospital, if the patient were too ill to be moved. Whenever difficulty was anticipated the patient could be sent before the commencement of labour to the base hospital for delivery.

Remarks

ON

THE USE OF PEPTONE IN ASTHMA AND ITS CONGENERS.

BY

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THESE remarks have been largely prompted by the numerous inquiries and requests for further information received since my last paper.¹ Any new treatment necessitates a long period of probation; it must be tested and retested in a large number of cases, and the results scrutinized in the light of any criticisms which legitimately may be raised. It is satisfactory, meanwhile, to be able to state that the reports from many sources, both home and foreign, are such as to justify the general conclusions previously recorded. The treatment has been applied not only to asthma, but also to such of its congeners as hay fever, associated skin affections, angio-neurotic oedema, cyclic vomiting, periodic diarrhoea, and the migraine-epilepsy syndrome; in short, to such conditions as exhibit an anaphylactic character or sensitization.

The Scientific Basis.

The discussion in my previous papers as to the scientific grounds of the treatment had, as its pivot, the identical characters of anaphylaxis and peptone poisoning or shock. But, notwithstanding the arguments employed and the clinical results, it was difficult for many, and especially for those practically acquainted with experimental anaphylaxis, to believe that a substance (peptone) which had lost its specificity, and could functionate no longer as an antigen in the strict sense, was nevertheless capable in small doses of counteracting the effects of a specific antigen. I took the view that the immunizing action of the peptone was directed, not against the antigen itself, but against the antigen-antibody product. This product, by its interaction with the cell-protoplasm, is the cause of the anaphylactic shock, which is identical with the shock produced by the interaction of peptone and the cell-protoplasm. It is usually believed that a substance of great potency, such as histamine, results from this reaction. That there is also a violent dislocation of the colloidal equilibrium of the blood and cells by a coalescence or aggregation of particles is likely, and is even regarded by some as a sufficient explanation of the phenomena. As bearing on this, mention may be made of some clinical experiments (not yet completed) which I made with lecithin. In the course of these I observed that a bile salt solution of the purest lecithin obtainable,* intravenously administered, seemed to exert a more or less inhibitory effect on the anaphylactic reaction. As both bile salt and lecithin reduce the surface tension, their action would be directed against the coalescence of colloidal particles by stabilizing the electric double layer. Possibly it is in this direction that the inhibiting action of narcotics is to be sought.

* Most commercial lecithins are grossly contaminated, and give rise to toxic symptoms.

It appeared to me that the case for the clinical use of peptone might be well served by animal experiments, so some little time ago I put the matter before Dr. H. H. Dale, and urged him to carry out some experiments with small doses of peptone in relation to anaphylactic shock in sensitized animals. This he kindly agreed to do, and lately I received from him a preliminary report in which he says, "The results are definite enough. A dose of peptone not itself large enough to produce any pronounced reaction, will weaken the response of a sensitized guinea-pig to the sensitizing antigen, so that after such a dose it is possible to desensitize without at any time producing any pronounced reaction. This I think ought to be valuable." . . . "The specific desensitization would appear, in part at least, to be due to the detachment of antibody from the cells."

As Dr. Dale intends to have the matter more fully investigated, it is sufficient to remark that as it has now been proved experimentally that peptone in small doses can inhibit the anaphylactic shock, its clinical use in conditions of sensitization has been placed on a solid foundation. Previous experiments with peptone in this connexion were made with massive doses and the results were conflicting. But one usually finds in experimental work that the effects of small doses are not sufficiently studied.

Now this active immunity or desensitization produced by peptone is a totally different process from immunization as ordinarily understood and practised. The immunity produced by a bacterial vaccine or a native protein is associated with the production of antibodies which are stereochemically fitted to the particular antigen and to no other, although there is a certain amount of overlapping in nearly related antigens. These antibodies when circulating in the blood dispose of the antigen, but if they are attached to the tissue cells and the antigen gains access to them, shock results. Peptone forms no such antibodies. When the protein molecule is reduced to proteoses and peptones, its specific architecture is practically obliterated, so that the immunizing action of peptone is independent of the nature or configuration of the antigen. It is a desensitizer in the general sense, though possibly more effective against some antigens than others. Dale, as is seen, thinks that this action on the part of peptone is, partly at least, such as to lead to detachment of antibodies from the cells. They would thus become free in the blood, and destroy or render innocuous the antigen.

Nature and Effects of Sensitization.

It was recognized by our forefathers that heredity and a family relationship were frequently encountered in those disorders which we may now reasonably regard as expressions of sensitization. Recent observations (R. H. Cooke and Van der Veer,² Freeman,³ Buchanan,⁴ etc.) have more fully set out these relationships, in which some have found strong evidence of the operation of the Mendelian law. If sensitization, potentially considered, implies the segregation of determinants in the germ plasma and is transmitted as a dominant factor, much that was obscure becomes luminous. The transmission may not be the particular sensitization but an abnormal susceptibility to form antibodies to foreign proteins, a "vice of nutrition." As regards the nervous system, Buchanan's studies lead him to conclude that the migraine factor is the transmitter, as 75 per cent. of essential epileptics have a migrainous strain. Possibly the rare disease "family periodic paralysis" is also an example of sensitization in which the antigen attacks the mechanism of inhibition.

The earlier the symptoms appear the stronger as a rule the inheritance, which may be double. On the other hand, failure to elicit a positive history is by no means conclusive, as no adequate study of the heterozygotes may have been made in relation to recessive unit characters. The clinical symptoms depend on the locality of the sensitized cells, and it is also likely that the offending protein has a predilection for certain parts or cells. Very often the whole body seems to take a sympathetic part in relation to the sensitization of a particular structure, while in other cases the sensitization seems practically confined to a limited area. In this relationship, cutaneous tests, though in some cases definite enough, play tricks with us, and their full significance is very far from being understood. This is forcibly brought out in the writings of Schloss, Smith, Longcope, Highman, Wells, and others. In some cases

the reactions disappear for a time, to reappear sooner or later; in others they exhibit constancy, as in hay fever. Another pitfall is encountered in the circumstance that after the disorder has subsided, either spontaneously or as a result of treatment, the dermal reaction often persists. This is notoriously the case in hay fever, so that the local reaction is not a guide to treatment. Again, dermal reactions are given to non-protein substances, such as amino-acids and the normal urine of animals, and even to inorganic substances. In the latter case, however, the agent may interact in such a manner with the protein molecule as to change it to what is practically a foreign protein. In regard to the proteins used as foods curious anomalies occur. These reactions are mostly found in children, and may be associated with others to animal emanations, etc. (multisensitization). According to the authorities quoted above, cases occur "in which it is impossible to prove that the substances to which the patient reacted were responsible for the symptoms." Rackemann⁵ in 127 tested cases obtained positive reactions (one or more) in 74, but only in 40 of these were the tests compatible with the patients' history. It has also been shown by Longcope and others that a fair number of individuals who have never had any clinical manifestation of sensitization, will give positive reactions to foods, the limit apparently having been reached when an orthodox Jew was positive to pork, oysters and sturgeon,⁶ so that "cutaneous allergy and systemic anaphylaxis do not necessarily predicate each other," as "the contradictions are such as to defy positive conclusions." It is just possible, therefore, that the skin may be the only sensitive organ in some cases. One may say that the cutaneous reaction has a very real value, but its limitations and vagaries must be recognized.

The conception of the inherent susceptibility or molecular disposition on the part of certain cells to sensitization as a form of potential energy which is easily made kinetic by influences or agents otherwise harmless or almost so, has a clarifying effect on the mutual relationships of sensitization and the offending protein; while it also rescues from the region of mystery the association of asthma with such factors as locality, barometric pressure, nerve shocks, etc., as all these have a disturbing effect on the protein metabolism. As regards the first of these considerations, take for instance the case of eczema. This is often regarded as an anaphylactic condition and dermal reactions sought for. If such be found, it merely proves that the skin is sensitive to certain substances, as the irritant which gives rise to the eczema may be one which is incapable of producing a positive dermal reaction. An experiment by Auer⁷ is apropos. He painted the ears of sensitized and of non-sensitized rabbits with xylol. The ears of the latter exhibited an inflammatory oedema which passed off in forty-eight hours. The ears of the sensitized animals showed in one or two days small haemorrhages, blisters, and subsequent crusts. Here the effect of sensitization was greatly to intensify the symptoms, so that a sensitized structure apparently reacted vigorously to a substance—xylol—which is not itself capable of sensitizing. The explanation is to be found in the inflammatory stasis, producing a local concentration of circulating antigen and its attachment to the tissue antibody. In like manner as regards asthma, the underlying predisposition or sensitive potential of the bronchial muscle may be activated by agents, chemical or bacterial, operating either locally or at a distance, which cause the entry into the circulation, and subsequent local accumulation of substances which are antigenic in relation to the bronchi. Possibly also it is by a similar formation or mobilization of antigen that attacks may sometimes be produced by the inhalation of cleavage products of protein (peptone) and by metallic fumes. It is therefore the more evident that the sensitized or potentially sensitized structure can never be wholly protected from attack, and the only possibility of relief or cure consists in a desensitization which must be more or less lasting.

Clinical Examination.

The investigation of the family and personal history will furnish data which materially assist the prognosis and also the treatment. The main considerations are the degree of inheritance, the age of the patient, the age at onset, the frequency and severity of the attacks, and the associated

diseases or defects. In asthma more or less resistance to treatment is associated with a practically continuous dyspnoea, emphysema, bronchitis, cyanosis, or anoxaemia from whatever cause, anaemia and various toxaeemias. The respiratory excursion should not be under one and a half inches. The pulmonary bases may be congested. Cyanosis or anoxaemia usually arise from obstructive conditions, pulmonary or circulatory. It is interesting to note in regard to these that Wooldridge found a reversed action of peptone on the coagulation of blood through which carbon dioxide had been passed. Also Loevenhart⁸ and his associates record some curious results with sodium iodobenzoate, a substance which induces powerful physiological oxidations. They affirm that its use intravenously will diminish or nearly abolish the cutaneous reaction in serum-sensitized rabbits. This suggests that the more oxygenated the blood the easier the desensitization. Toxic substances in circulation also appropriate a quantity of oxygen and otherwise dislocate the protein metabolism, so that blood and urine examinations for nitrogen estimations may be necessary. The stomach may be dilated; digestive disturbances are frequent and cases occur which seem undoubtedly sensitizations of the gastric and intestinal mucosae. The liver may be enlarged or tender, or the spleen may be enlarged. In women some connexion of the attacks with menstruation or its irregularities may be found. The various mucous passages or the teeth may harbour foci of infection requiring eradication. A careful survey should be made bearing on endocrine function, and small daily doses of thyroid or pituitary prescribed as indicated. In a few unsuspected cases I have found hypothyroidism the chief accessory factor.

The patient should be interrogated regarding the possible association of the symptoms with any particular substance, animal or vegetable, or other influence. Skin tests may be made to pollen, horse dandruff, or any suspected animal's epidermal structures. Reactions to killed bacteria are admittedly valueless. In children positive reactions are sometimes obtained to foods, usually vegetable, but rarely in adults, or at least those over 35. Egg, wheat (or oats), potato, and certain green vegetables are the chief offenders, but even these are found in only a very small percentage of the cases. So far as the peptone treatment is concerned, the performance of the numerous American tests is practically an academic function.⁹ Ordinarily it is sufficient to rub the food in its natural state into a bloodless scratch or puncture. Solid substances may be crushed and rubbed in with a little decinormal sodium hydroxide, which facilitates both solution and absorption. Similarly with horse combings or feathers. A control with the soda solution is made, and in each case a wheal results in a few minutes. A reaction cannot be regarded as definitely positive unless the wheal is half as large again as the control, and over 0.5 cm. in diameter. The dermal response to the peptone (used after the same manner) should also be made. A marked reaction is the signal for smaller doses in treatment.

Treatment.

The patient should be placed in the most favourable conditions, even as regards locality, if practicable. The better the patient's health and the greater the freedom from asthma during the immunization, the better the ultimate result and the capacity of withstanding prejudicial surroundings. Unless there be a well-marked intolerance or idiosyncrasy to any particular food, it is unnecessary to cut out of the patient's dietary articles which give moderate or slight skin reactions, as the peptone rapidly alleviates the symptoms. Indeed, it is much more difficult to desensitize to the east wind than to foods. If a definite infection exists which produces (directly or indirectly) protein products exciting the attacks, it may be capable of removal by a suitable vaccine. Even then a general desensitization of the bronchi is not effected, as the vaccine desensitizes to the related bacteria only. The general desensitization produced by peptone, on the other hand, may be so effective that in cases where the asthma was invariably excited by catarrh the bronchi no longer give the least response to the infection. The same result may be obtained in relation to infections in remote situations contributing to the production of the attacks.

* A warning against fetishism in relation to this has just been given by the *Journal of the American Medical Association* (April 9th).

The groups into which the cases of asthma fall and the corresponding results of treatment were indicated in my last paper. The formula published in the *BRITISH MEDICAL JOURNAL* (July 20th, 1918) has stood the test of time, and by means of it the asthma types in Group I, and many cases of migraine and epilepsy, have yielded, sometimes very quickly. In asthma the relief may last for years, especially in children, and possibly for a lifetime. The formula has also been successfully applied in cases of hay fever, in skin affections associated with asthma, and cyclic gastro-intestinal attacks. In the latter disorder, peptone taken by mouth may give relief, possibly in virtue of a direct action on the sensitized cells. The peptones recommended were Armour's No. 2 (5 per cent.), and Witte's (2 per cent.). The Witte peptone, however, contains too much primary proteose in relation to secondary (according to Dr. R. H. Plimmer, roughly as 1 to 2). The proportion in the Armour peptone is (same authority) as 1 to 7. Therefore, either a 5 per cent. solution of the No. 2 may be used, or else a 5 per cent. solution of a mixture which contains 3 parts of Witte's peptone and 5 parts of a peptone practically devoid of primary proteose, as may be physiologically suitable. The No. 2 peptone has been found very satisfactory for ordinary use, and can be used intramuscularly without causing irritation, but it varies in acidity and solubility. "Peptone siccum" (Armour) is a finer product, but requires the addition of some primary proteose (3 parts to 1 Witte's). When freshly prepared, the solutions are rather more active. To prepare the solution proceed as follows:

Dissolve the peptone or the mixed peptones as far as possible by agitation in hot (56° C.) normal saline. Take the reaction to litmus (usually acid), and add *very carefully* normal or semi-normal sodium hydrate or carbonate, until the solution is faintly yet distinctly alkaline to litmus. The peptone will now be dissolved, except for some insoluble residue. Make up to volume with normal saline, and place in a water bath at 56° C. for half an hour. Filter while hot through ordinary filter paper, and add to the filtrate 0.5 per cent. phenol. If bottled, sealed rubber caps or well-fitting glass stoppers or rubber stoppers should be used. Wait for three days and then smear a loopful of the fluid over an agar slant and incubate for sixteen hours at 37° C. If the result is negative the peptone may be passed for use.

The solution, as above prepared, may be used in a 5 per cent. strength intravenously (or in a 7.5 per cent. strength intramuscularly) in the following dosage: The initial dose is 0.3 c.cm. (5m), and is increased every third or fourth day (twice weekly) by 0.2 c.cm. until 1.3 c.cm. (20m) is reached at the sixth injection. Continue at this dosage for six more injections. Give intravenously as a rule in adults, very slowly delivered.

Now this formula was adjusted to the average case. It is impossible to tell what modifications may be required until the case is under treatment and the history and symptoms are before one. But in any event there are some guiding principles common to all. The aim is to avoid reaction at first while getting close to the reaction point or threshold. The best and most enduring results are obtained in cases which get well from non-reactive doses. The rule, therefore, should be observed of recording the temperature 5 to 6 hours after each injection. Should there be a rise of over 1° F., the subsequent dose is not to be increased. On the other hand, the dosage may be too small, and if after eight injections no satisfactory improvement is made, and if there has been no rise of temperature, a test dose should be given—that is, one which we know will give a mild or moderate reaction (100° to 101° F.). This mild reaction does no harm at this stage, and in some cases, especially if tedious, gentle reactions are beneficial towards the end of the treatment. A reliable indication of the correct dosage is frequently an improvement in the general health and in a sense of well-being. The adjustment of the dose to the particular case is very essential, and in view of the variable character of some kinds of peptone on the market I always have them physiologically tested before use.

Reference now may briefly be made to the resistant cases. They are sometimes very puzzling, as they may present no obvious differences to some of those which yield, but there is usually a stronger inheritance. Then there are the cases which are handicapped by deterrent or incurable accompaniments. Unless the asthma is practically continuous or there is much bronchitis and emphysema, or some permanent constitutional breakdown from infection or senility, much can be accomplished by various

modifications in the treatment, including the peptone itself, the dosage, the reaction, and the duration. Each case is largely a law unto itself, and though it is impossible to particularize, a few leading indications may be set out. As regards the peptone itself, that in use has been made exclusively from meat or blood fibrin. Lately I have been using, in addition, proteose-peptones* made from phospho-proteins, albumins, and certain vegetable seeds. In all of them the amino-acids possessing the benzene nucleus were well represented. As our food is largely vegetable, and as sensitization is more in evidence in this relation, it seemed feasible that vegetable peptone might find some new point of attack or open valence. For, although there is no *essential* difference between animal and vegetable proteins, yet they differ widely in structure and in their reactions to heat and reagents, and no doubt the earlier products of their hydrolysis also present well-marked differences. This peptone I have employed either alone or in combination with one of the animal kinds—compound peptone. These new peptones give promise of most valuable assistance.

In regard to the dosage, in some cases the sensitiveness to peptone is such that even small doses seem to augment the symptoms. The addition of a few drops of Lugol's iodine will obviate this, as the iodine enters into chemical union with a certain fraction of the peptone molecule, without otherwise affecting its value. It may be omitted as toleration becomes established. When, on the other hand, the peptone is well borne, it may be pushed, and though attacks occur for a time, the ultimate result may be quite satisfactory. It may be necessary to continue treatment for nearly three months, and during the latter period the peptone may be given at rather longer intervals and so as to produce some reaction, which, however, should always be mild. A strong reaction upsets the immunization by rendering subsequent smaller doses ineffective, at least for a considerable time. These are a few amongst other considerations which have to be borne in mind.

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THE DIAGNOSIS AND TREATMENT OF GASTROPTOSIS.

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DURING the last few years I have had ample opportunity of studying dropped and dilated stomachs; my experience has convinced me that the existence of gastroptosis is far more common than is usually supposed, and that it is frequently overlooked.

Until the introduction of the x-ray method of examination the condition could not be diagnosed with certainty by any method then at our command.

In the ordinary abdominal examination, which is usually made with the patient lying down, the condition might not be diagnosed, although present. Even with x-ray examination, unless the patient be standing during the examination it might easily be overlooked, for the stomach not infrequently drops to a remarkably low level when the patient assumes the upright position. As a matter of fact, it is only since the introduction of the opaque meal that we have been in a position to describe the true shape of the organ or the position which it normally occupies in the abdomen.

There can be little doubt that in the majority of cases of pure gastroptosis (that is to say of cases in which there is no radioscopic or clinical evidence of stenosis at the pylorus or in the duodenum) the condition starts at or

FIG. 1.—Rest for raising foot of bed. It can be adjusted to heights varying from 8 to 11 inches.

* For certain of these I am much indebted to Messrs. Allen and Hanburys.