and a rapid pulse, and sweat freely. Such cases I have described as the "vascular group," and as a rule they show only a moderate reaction and rapid improvement after operation. The second group I have designated the "nervous type." Here the patient is more commonly between the ages of 40 and 45; the thyroid is smaller and more nodular, the pulse is less rapid, though often more irregular, and the nervous symptoms are much more prominent. These patients show considerably more reaction and make a slow post-operative recovery. Even when these two groups have been recognized and separated, a careful study of the immediate post-operative results will show a very considerable variation in the reaction, and it is to one cause of this variation that I wish to direct attention in this communication.

It has long been realized that the thyroid secretion has a very marked effect on the heat regulation. All cases of myxoedema feel the cold very severely, while those of hyperthyroidism are in a like degree affected by the heat, so that they are much more comfortable during the cold weather. In my own cases the post-operative distress in hot weather has been much accentuated, and special precautions, such as the use of electric fans, of ice, and of cold sponging, have long been used. In spite of all such precautions it has been my steadily increasing opinion that the mortality during the hot periods has been abnormally high. A careful analysis of my cases from this point of view shows very clearly that such is the case. In my own series there have been two deaths, occurring respectively in the months of January and December. Both of these were in patients with advanced degrees of the disease and were dependent upon secondary cardiac changes. All the others occurred during the hot months of June, July, and August, and all were what may be described as unexpected deaths in that they occurred in patients who by no means showed a pre-operative hyperthyroidism in excess of the others and in whom all the usual precautions had been taken. They also all showed extreme post-operative reaction passing on to acute hyperthyroidism and death. In the accompanying chart I have plotted out the percentage mortality among the total cases operated upon in the individual months of the year, and it is seen that whereas in February, March, April, May, September, October, and November there is no mortality, in the three months of June, July, and August it is in the region of 20 per cent. The effect upon the curve in January and December of the two deaths mentioned above is also shown.

Chart showing the percentage mortality among cases of exophthalmic goitre operated upon in the individual months of the year.

These figures have been collected over a period of ten years, and hence are of considerable value, for it is unlikely that any accidental factor should give so marked an alteration in the mortality which occurs for these three months. Moreover, a mortality of 20 per cent. which is present when the cases operated upon in June, July, and August are considered alone, is one that is much too high and must in fact be considered as an unjustifiable risk. These figures have made it manifest to me—and I publish them in the hope that they will warn others—that no operation on a case of exophthalmic goitre should be undertaken in extremely hot weather, for under such conditions the risk in spite of all precautions is too great and can be easily countered by awaiting more suitable conditions. Fortunately from this aspect the English climate is so variable

that seldom would it be necessary to postpone operation for more than two or three weeks.

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INTRAVENOUS INJECTIONS OF PEPTONE AS AN AID TO VACCINE TREATMENT.*

(Abridged.)

BY

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DURING the last eighteen months I have used intravenous injections of peptone in some seventy odd cases of patients who were very sensitive to vaccines, with satisfactory results. Patients to whom one could not give 100,000 streptococci or the same number of *M. deformans* without producing a reaction and general malaise, after peptone treatment were able to tolerate much larger doses.

For a good many years now Dr. Auld has given intravenous injections of peptone in cases of asthma, and claims a fair proportion of successful cases. It is fairly well established that most cases of asthma are due to an extreme sensibility on the part of certain cells of the body to a foreign protein. The slightest trace of this specific protein produces an attack of asthma. The disease, then, depends on a toxic idiopathy, and is strictly comparable with hay fever, urticaria, angioneurotic oedema, and possibly a large variety of other diseases.

Apparently the poison may be air-borne and conveyed directly to the cells, as we suppose it to be in hay fever; or it may be derived from the blood stream, as is the case when food or certain intestinal bacteria excite the attack. There are a great many different proteins which are poisonous in this way. Susceptible individuals may be affected by several of them widely differing in source (Freeman,¹ Chandler Walker²). Dr. Auld³ first brought forward peptone as a general non-specific immunizing substance, but its action in combating the cell sensibility is extremely obscure. There is no doubt that in some cases the effect is dramatic.

In Dr. Auld's present view, peptone acts by immunizing the system against any protein whatever, although itself incapable of acting as an antigen or producing any antibody, as he himself has shown by experiment. I cannot altogether subscribe to this view, because if peptone cannot function as an antigen, it does not seem to me possible that it should act as an immunizing agent.

It seemed a hopeful procedure to try the injection of peptone in other states of sensitiveness as well as in asthma. In my own experience the treatment of conditions like rheumatism, arthritis, and neuritis by streptococcal vaccine and *M. deformans* vaccine has frequently been rendered extremely difficult owing to sensitiveness—that is to say, that however small the dose given the patient gets a reaction and feels ill. Many cases have failed to benefit, or have obtained benefit only after very prolonged treatment with infinite patience and minute doses.

It is difficult to say why this condition of sensitiveness should arise; it may be that my method of giving frequent small doses excites sensitiveness, as some hold occurs in tuberculosis. On the other hand, patients are sometimes sensitive to the first dose. In a recent case half a million

* Read before the Leeds Medico-Chirurgical Society.

stock streptococcus vaccine as an initial dose in a very chronic case of arthritis was followed by an acute flare-up of nearly every joint, lasting a week. In another case a similar initial dose of half a million *M. deformans* was followed by extreme suffering and four days' confinement to bed. Whatever the cause, hypersensitivity to vaccine is an extremely troublesome and annoying complication of vaccine therapeutics. Dr. Pratt Johnson⁵ regards sensitiveness to vaccine as an anaphylactic phenomenon comparable with toxic idiosyncrasy, and treats his cases by repeated small doses until this sensitiveness is overcome. He expects no real improvement until he can give large immunizing doses. I must, however, join issue with him in regard to his conception of a small dose. Ten million streptococci, which Dr. Pratt Johnson suggests as an initial dose, is, in my view, dangerously large.

I have tried many methods of getting over this sensitiveness. The first was combining the vaccine with beta eucaine lactate⁴—a method quite successful in a proportion of cases. Sensitized vaccine I have used, and also detoxicated vaccine, but neither of these have I found satisfactory. Since using intravenous peptone I have had no further difficulty, except when the patient did not tolerate the drug. The following are given as some outstanding examples.

CASE I.

A male, aged 61, had a history of having had osteo-arthritis in the left hip-joint for twelve years, and in the right hip-joint for two years. He had acute pain on walking, but not much in bed. There was a large bony outgrowth over the left hip-joint and very considerable changes in the right hip-joint. Little movement was possible. This patient had very bad teeth and also a heavy infection of streptococci (four different varieties) in the faeces.

On December 27th, 1921, a dose of 500,000 of his dental vaccine was followed by a severe reaction lasting three days. He was extremely stiff, the pain was increased, and the weight dropped 2 lb. On December 30th injection of 500,000 of his faecal streptococci was followed by an attack of lumbago. On January 3rd, 1922, the dose was reduced to a tenth of a million and no reaction followed, but on the 7th of the same month a tenth of a million of his faecal streptococci was followed by a slight reaction.

From January 10th vaccines (dental and faecal streptococci combined with eucaine) were administered by his own doctor. The dose was always one-fifth of a million, and there was a focal reaction every time, lasting four to five days. Doses were given once a week. The general health improved. I then decided to give him a course of peptone. Simultaneously with this peptone a subcutaneous dose of vaccine of 500,000 streptococci was given twice a week. No reaction followed. The dose was then rapidly pushed up to 20 million without any trace of a reaction.

From December 27th, 1921, to March 19th, 1922, no progress was made whatever, and only very small doses could be tolerated. After the course of peptone which began on April 29th and was carried on until May 18th, doses were rapidly increased until the end of August—that is to say, within three months, 20 million could be tolerated.

Summary.

Osteo-arthritis of hip-joints. For three months reactions followed every dose of 200,000 streptococci. After peptone the patient was soon able to take 20 million without reaction.

CASE II.

Male, aged 47; a case of true rheumatoid arthritis involving the right wrist; twelve months' history. X rays showed nothing abnormal beyond some loss of calcium, but there was a very enlarged swollen joint, cyanotic in appearance, extremely painful, with gnawing and aching pains at night. The wrist was very tender and there was practically complete limitation of movement. Teeth had been extracted in the hope that this would cure the condition, but without result.

On January 13th, 1921, 500,000 *M. deformans* was given; this was followed by some pain in the left wrist. On January 21st he received a million *M. deformans*; there was some reaction the same night and the joint was worse for two days. Then an injection of a million *M. deformans* combined with eucaine was given; no reaction followed. On relapse three days later, 2 million combined with eucaine were injected; this was followed by reaction and swelling. The dose was then dropped on January 29th to half a million with eucaine. Again no reaction took place, but from this time onward to July 11th the dose had to be continually reduced owing to constant reactions, until extremely minute doses were given with eucaine. Even 20,000 *M. deformans* were frequently followed by a focal disturbance. On July 11th I decided to try detoxicated vaccine. It was specially prepared for me by the Genatosan Company. Fifty million *M. deformans* and, later, 100 million were not followed by a reaction; 200 million produced a reaction—exactly the same result as with ordinary vaccine, the only difference being in the nominal amount of the dose. Up to this time the urine had been sterile, but on July 15th I found a streptococcus in considerable numbers. A vaccine was made, and until the end of November small doses¹ were continued, the patient being just as sensitive to the streptococcus as he was to *M. deformans*—that is, 20,000 streptococci produced a reaction, but the reaction of the streptococcus took a different form inasmuch as the areas surrounding the knee and hip-joints were affected, whereas when *M. deformans* excited reaction the wrist and feet always suffered.

On December 22nd a course of peptone was started. The vaccine doses when this was completed were very rapidly carried up to 5 million streptococci and 10 million *M. deformans*. It was after the course of peptone that real improvement started, and the patient rapidly progressed to complete cure. In this case occasionally a certain degree of sensitiveness supervened. One or two odd doses of peptone were then administered.

Summary.

A rare case of monarticular rheumatoid arthritis. For nearly twelve months minute doses caused reaction—for example, 20,000 germs. After peptone, doses were rapidly raised to 5 million streptococci and 10 million *M. deformans* without reaction, and the result was most satisfactory.

CASE III.

A female, aged 50, nine years ago had rheumatic pains in the left shoulder which moved about and were improved by massage. There was slight stiffness in the jaw and neck and some creaking. The wrists were swollen and fluid was present. The metatarsophalangeal joints in both feet were greatly enlarged. To my mind the condition was a typical streptococcal arthritis. X rays showed the teeth to be clear of any apical infection. The patient had been an extreme sufferer from hay fever for several years, and was also very sensitive to margarine and vinegar. Marked urticaria would appear after aspirin, presumably excited by the acetic acid radical. The mother, sister, and brother suffered from asthma, and one sister had had rheumatoid arthritis with extreme crippling for many years. This case is a particularly interesting one as demonstrating the frequent association between arthritic conditions and toxic idiosyncrasy—500 units of pollen vaccine on the skin produced a large wheal. In my experience it is the disease known as rheumatoid arthritis which is more frequently associated with conditions of sensitiveness, but in this case there was no symptom of that disease, except the slight creaking of the neck. The faeces were very heavily infected with a good many varieties of streptococci.

Treatment was commenced on April 13th, 1921. Alternating pollen and streptococcus vaccines were given to begin with, and then *M. deformans* vaccine was added in small doses of half a million. This was given on account of the suspicion that rheumatoid arthritis might develop. There was never any reaction, and the condition improved and cleared up apparently completely in the course of about three months. The doses were gradually increased from half a million to 10 million of combined *M. deformans* and streptococci. The pollen units were on an average 250. During the hay fever season itself they were dropped to 100. No hay fever developed.

The following spring the patient had a severe attack of tonsillitis. After that some symptoms of arthritis began to develop again, and she came under my charge once more in April, 1922. I treated her with pollen to prevent hay fever if I could, and found the skin less sensitive than it was before. The neck symptom was now very marked, and there were quite definite signs of commencing rheumatoid arthritis—pain and tenderness in the feet and weakness of the small muscles of the hands. I started to give vaccines of faecal streptococci, both from the old vaccines and from a new specimen, and combined them with *M. deformans*. The result, however, was not satisfactory, and although there were no definite reactions the patient felt ill. The hands grew more painful and weaker, and the feet were also tender. A little massage was given, but that made the condition worse. Under-water massage also had to be omitted for the same reason. I tried all sorts of doses, large and small, but the patient got steadily worse. I then came to the conclusion that possibly there were really reactions all the time, and that it was an atypical form of sensibility with which I had to deal. Consequently peptone was given—on June 1st 0.2 c.cm. of a 2 per cent. solution, on June 3rd 0.4 c.cm., and on June 4th 0.8 c.cm.—together with 1 million streptococci; following this dose there was a very decided reaction and a drop in weight of 2 lb. lasting three days. On June 7th 1.4 c.cm. of a 2 per cent. solution was given with a million *M. deformans*. This was followed by a quite severe reaction lasting three to four days. On June 11th I repeated the dose of peptone with half a million streptococci; there was no reaction. On June 14th 1.4 c.cm. of a 2 per cent. solution and 100,000 *M. deformans* were given; again there was no reaction. On June 18th a million streptococci and half a million *M. deformans* were injected, and no reaction followed.

Now comes the interesting part of the case. The doses were carried on by Dr. Healey of Preston up to approximately two and a half million streptococci and a million and a quarter *M. deformans*. There was no reaction at all, but the patient still was getting no better. This time it was perfectly clear that there was no reaction, and I thought it worth while to push the dose, inasmuch as it seemed that the patient might have been desensitized completely by the peptone. On August 10th 4 million streptococci were given and 2 million *M. deformans*; on August 17th 6 million streptococci and 3 million *M. deformans*; then 15 million streptococci and seven and a half million *M. deformans*. No reaction followed any of these injections. I therefore sent three further doses—20 million and 10 million each. It was at this point that improvement began to set in.

Summary.

A successfully treated patient relapsed after an attack of tonsillitis. Treatment was very difficult owing partly to toxic idiosyncrasy and partly to sensitiveness to vaccine. Peptone injections marked the turning point of the disease.

It is quite clear in this case that the patient was desensitized, and so able to take larger doses, but that there was no improvement until after very considerable doses had been taken. Before the course of peptone it is probable

that the immunity mechanism was in a state of continuous irritability. Perhaps this may be the condition quite frequently when patients do not improve under vaccine treatment, and yet suffer no obvious reaction. So greatly was I impressed with the value of peptone injections, that it seemed possible that here might be a solution of the problem one often has to deal with—namely, that of the patient who can only come for three weeks' or a month's treatment, and then has to return to her own doctor to have her vaccines, and who for financial reasons will certainly not be able to return if the treatment does not succeed. The following case illustrates this. I started straight away with peptone injections, so as to prevent the development of sensitiveness. After returning home the patient's own doctor was able to carry on the treatment without difficulty.

CASE IV.

On June 28th, 1922, I saw in consultation a case of general and severe arthritis, chiefly affecting the knee-joint, in a woman aged 48. She had not been out of bed for four months and was quite unable to walk, but happily there were no contractures. The knee-joints were at the time the worst parts, but practically every joint with the exception of the spine was affected.

Owing to financial and other reasons, it was impossible for the patient to come under my care except for a very short time. However, with only eight days to work upon, I started at once, on July 1st, with 0.1 c.cm. of a 2 per cent. solution of peptone. On July 3rd 0.2 c.cm. was given, on July 4th 0.4 c.cm., on July 5th 0.8 c.cm., on July 6th 1.4 c.cm., and on July 7th 1.4 c.cm., which I combined with half a million *M. deformans*. At the same time I had a bad tooth removed and cultured, and examined the faeces. There were nine varieties of streptococci at the apex of the tooth, and six varieties in the faeces. These were combined in one vaccine, and her doctor carried on with small doses, beginning with half a million combined streptococci and *M. deformans*. On September 29th much stronger doses were required. There have never been any severe reactions and the patient is improving.

Method of Preparing Peptone.

Normal saline prepared from distilled water plus 1 per cent. carbolic acid is autoclaved in a flask at 120° C. for twenty minutes with a funnel fitted with rubber tubing and a clip. Vaccine bottles and caps are also sterilized. Ten per cent. of Armour's peptone is added to the hot carbolized saline and shaken up. The vaccine bottles are filled with the aid of the sterile funnel, capped and wired. After forty-eight hours a sample is removed and tested for sterility. When proved sterile, 1 and 2 per cent. solutions are put up in vaccine bottles already fitted with the requisite amount of 0.5 per cent. carbolized saline.

Method of Dosage.

I have tried a good many different series of peptone doses, and find that for all intents and purposes the following method results in a fairly complete and satisfactory desensitization.

On the first day 0.1 c.cm. of a 1 per cent. dilution of peptone; on the second day 0.2 c.cm. of a 2 per cent. dilution; on the third day 0.4 c.cm. of a 2 per cent. dilution; on the fifth day 0.8 c.cm. of a 2 per cent. dilution; and on the seventh day 1.4 c.cm. of a 2 per cent. dilution; and thereafter, at three- or four-day intervals, 1.8 c.cm. two or three times. Having arrived at 1.4 c.cm., a subcutaneous dose of vaccine can be given at the same time, and this dose may be rather larger than the one the patient was sensitive to before treatment. No reaction will occur.

Indications for Peptone Treatment as an aid to Vaccine Therapy.

From what has gone before, it will be clear that as soon as it is definitely determined that a patient is excessively sensitive to vaccines a course of peptone should be started without waste of further time; and secondly, if the patient is likely to be sensitive (and only experience, of course, can tell us when that will be) and can only give a very short time to special treatment, it is advisable to give a course of peptone before the vaccines are started.

Contraindications.

Provided the proper form of peptone is used (Armour's No. 2 peptone, as recommended by Dr. Auld), there are very few contraindications to the use of the drug intravenously.

A few people seem to be unable to tolerate it, and after as small a dose as 0.4 c.cm. of a 2 per cent. solution complain of nausea and occasionally cardiac distress at night. In cases like this I have not pursued the treatment.

I should not give peptone to cases of grave anaemia or other serious constitutional diseases. The most important contraindication seems to be the presence of albumin in the urine, and especially any history of chronic or acute nephritis. In three cases I have seen recrudescence of nephritis which I think might be ascribed to the injections of peptone. On ceasing treatment, however, the symptoms have disappeared.

Summary.

A good many cases of infections by streptococci and *M. deformans*, particularly in the arthritic group, become so sensitive to vaccines that treatment is very difficult and tedious. It is in these cases that intravenous peptone will do away with the sensitive condition, and enable treatment to be renewed.

Peptone provides the best method of overcoming the difficulty of sensitiveness in vaccine treatment.

In cases where sensitiveness is likely to occur peptone can be given as an initial course before vaccines are started.

The contraindications to the treatment are personal intolerance, grave anaemia, severe illness, and chronic nephritis.

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CARBON TETRACHLORIDE AND OIL OF CHENOPodium IN HELMINTHIASIS.

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AN article appeared in the *BRITISH MEDICAL JOURNAL* of July 1st, 1922, reporting favourably on the use of carbon tetrachloride for hookworm infection. The drug also expelled *Oxyuris vermicularis* in large numbers and some *Trichuris trichiura* and *Ascaris lumbricoides*. The drug acts as a moderate purge and it is not necessary to prepare the patients as for thymol treatment. Oil of chenopodium is soluble in carbon tetrachloride, and a mixture of the two was suggested for ascariis infection. Since then several other articles have appeared on the subject.

Treatment with the drug was commenced in the General Hospital, Kuching, in August, 1922, and the immediate results warranted its continuance. It has been given to 82 patients in the hospital. It has been given also to several school children and to one European; the results from the former have been very good, but they have not yet been tabulated as it is hoped to examine the faeces of all the school children in the near future, and to give treatment to those who require it. The European patient showed no ova in his faeces after one dose of m 60, and during the six weeks following he gained 5 lb. in weight.

The faeces of the majority of patients in the General Hospital, including all those who showed any signs of hookworm infection, have been examined in the pathological department. The films have been made direct from the faeces; three slides have been examined before the specimen has been considered to be free from ova, and, wherever possible, two such examinations have been made before the patient has been pronounced free from worms. Of course it is realized that such methods are not absolute—a fact which in a few cases has been demonstrated by post-mortem examination.

It has been found that carbon tetrachloride alone is a fairly efficient anthelmintic for ascariis, but in combination with oil of chenopodium it has a much higher efficiency and practically never fails. This combination is believed