ON THE NATURE OF RABIES AND ANTIRABIC TREATMENT.

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X. ANTIRABIC TREATMENT.

PERSONS bitten by rabid animals should apply for treatment as soon as possible; not a day, not even one hour, should be unnecessarily wasted. This applies more especially to cases in which the bites (or other methods of infection) are situated on the head, face, or neck, and to severe bites on the wrists or hands, or on the exposed skin where nerves are plentiful.

The object aimed at is to immunize the patient against rabies before the virus implanted in the wound by the animal which inflicted the bite reaches the nerve centres. Should the virus succeed in reaching the nerve centres before immunity has been conferred, no treatment yet devised will save the patient. These few remarks, taken in conjunction with the explanations in Section IV as to how infection takes place, are the reasons why early treatment is advocated.

Antirabic Vaccines.

The material used for antirabic treatment is prepared either from the spinal cords, or from the brain, medulla, and spinal cords of rabbits which have died from rabies after inoculation with "fixed" rabies virus.

The virus, being of a fixed virulence, may be termed a "vaccine" when prepared for use; but the method of preparation varies in different Pasteur Institutes.

Dried Cord Method.

Pasteur's original system was to dry the spinal cords hung in glass jars over caustic potash or caustic soda, under fixed conditions as to time, temperature, humidity of the atmosphere and the exclusion of light, and for varying periods up to fourteen days from the time the fresh cords were removed from the rabbits. When a cord was treated under these conditions for fourteen days he found that it had lost all its virulence, but when dried for three days the virulence was practically the same as a fresh cord. Attenuation of the virus in the cords commences after the third day of drying, and is completed from the twelfth to the fourteenth day, but is, practically speaking, a weak or attenuated virus after the eighth or ninth day.

From cords treated in this manner a series of vaccines of different degrees of strength can be prepared. Pasteur commenced treatment by injecting vaccines prepared from cords which had been dried for fourteen days, and then from cords which had been dried for thirteen, twelve, eleven, ten days, and so on down the scale to cords which had been dried for three days only. By this means he was able to commence the immunization of his patients with vaccines which were perfectly safe, but established a degree of immunity sufficient to render the subsequent injection of living and virulent virus also quite safe.

The dose for an adult consists of 1 cm. of cord finely ground down in 3 c.cm. of a sterile fluid such as normal saline solution, and injected into the subcutaneous tissue on the side of the abdomen; it corresponds to about a 5 per cent. cord emulsion. This method modified in various directions is what is known as the "dried cord method" of treatment. It has undergone many modifications since Pasteur's time, but the system is essentially that of Pasteur. A modification which is sometimes used, especially when the vaccine is sent to a distance, is to dry the cords from two to six days and preserve them in glycerin in a cool chamber.

Dilution Method.

Some time after Pasteur inaugurated his system of treatment Högyes of Buda-Pesth introduced a method of anti-

rabie treatment by injecting high dilutions of living and virulent virus to begin with, and gradually going on to lower dilutions. In this method, which is known as the "dilution method" of treatment, it is convenient to begin by making a 1 per cent. dilution of virus from the fresh cord or medulla, and from this to prepare any dilutions required. The treatment is commenced by the injection of a highly diluted virus, such as 1 in 10,000, or 1 in 6,000 in some institutes, and 1 in 4,000, or even 1 in 2,000 in others, and gradually going on from day to day to a less diluted virus, such as 1 in 500, 1 in 200, or even a 1 per cent. dilution.

This method has been adopted by several antirabic institutes. It has the merit of being easier to carry out and less expensive than the method advocated by Pasteur and his followers; but whether it is the safest and best method which science can devise in the absence of exact knowledge about the causal micro-organism of rabies is a disputed point.

Antirabic Serum.

In some institutes the use of an antirabic serum prepared by immunizing sheep or horses has been had recourse to either as a preliminary to the usual antirabic treatment being carried out or to sensitize the living vaccine. In 1902, when Director of the Pasteur Institute of India, Kasauli, I immunized two horses to a very high degree with rabies virus; they produced a serum which was highly rabicidal when mixed with living rabies virus. In a mixture of 1 part serum to 3 parts of a strong virus emulsion the virus was destroyed in a few minutes at room temperature; normal horse serum is devoid of this property. I used the serum hypodermically as a preliminary to the ordinary treatment in badly bitten and late cases, my object being to confer a passive immunity pending the acquirement of an active and more lasting immunity as the result of treatment. Preliminary treatment with antirabic serum was administered to 202 cases; but owing to the fact that the serum treatment was followed by ordinary treatment, it is difficult to say whether any real benefit was derived from the serum. In a number of the more severely bitten of these cases, most of them bitten by jackals, the serum was also injected into and around the wounds, with the object of utilizing its rabicidal effects on the virus locally; none of these cases developed hydrophobia; but here again the treatment which followed the serum may have been all that was required to save them. The subject is one which requires further investigation.

It will be noted that in the methods of treatment I have described a living virus is used. In the "dried cord" method a living virus is not used until after the commencement of treatment by a dead or attenuated virus; but in the "dilution" method, and in the method of drying the cords for a short time and preserving them in glycerin, a living virus is used from the outset.

It may be asked why, since in the use of any vaccine safety and efficiency are the objects kept in view, and when these objects can be attained by a dead vaccine, a living one should be employed.

We know that dead bacterial vaccines are safe and efficient in producing immunity in man and animals. No one would feel justified in using living streptococcus, staphylococcus, or plague vaccine on a human subject when dead vaccine would answer the same purpose. On the other hand, we know that a living typhoid or a living cholera vaccine could be used without any risk of conveying the disease to the person inoculated; yet for obvious reasons it would be very inconvenient, and possibly risky, to use these vaccines outside the laboratory where they had been prepared, and not at all convenient and practical in the laboratory, so it is now the custom to use them only after they have been killed and standardized.

Several workers have obtained evidence of the immunizing properties of dead rabies virus. Poor,* recording his own experiments with rabies virus killed by heating, mentions that Fermi, as the result of his experiments, recommended the use of dead virus only, his plan being to kill the virus with carbolic acid, and store the emulsions for future use. He also mentions that Heller, in his work on protective inoculation against rabies (Jena, 1906), gave the experience of others in the use of virus killed in various ways—for example, heat and by glycerin, and his own experiments in the use of virus killed by grinding according to the methods of McFadyen.

Dead Rabies Vaccine.

Early in 1910, when Director of the Central Research Institute of India, I took up the question of the preparation of a safe and efficient antirabic vaccine. A full and detailed account of my experiments on the effects of heat and carbolic acid on various dilutions of rabies virus, the preparation of a dead antirabic vaccine by killing the virus with carbolic acid, and the animal experiments upon which the claims for safety and efficiency are based, will be found in *Scientific Memoir No. 44*.⁶

Method of Preparation.

The vaccine is prepared from the fresh brain, medulla, and spinal cords of rabbits which have died from rabies after inoculation with "fixed" rabies virus. The material is finely ground down in 8 per cent. dilutions in sterile normal saline solution to which has been added 1 per cent. carbolic acid; it is then filtered into a sterile glass receptacle through fine muslin to remove any particles of fibrous tissue which may be present, and kept at a temperature of 37° C. for twenty-four hours. At the end of this period the virus is dead; it is now diluted with an equal volume of sterile normal saline solution, filled into suitable bottles (20 c.cm. bottles), capped with rubber caps and sealed with melted paraffin wax. Aseptic technique is observed throughout. On the preparation of a "brew" two tests are carried out—one for sterility and the other by inoculating a rabbit subcutaneously to prove that the virus is dead.

It will be noted that this method of preparation gives a 4 per cent. dilution of dead virus in 0.5 per cent. carbolic acid normal saline solution—a dilution suitable for treatment purposes, or which could be still further diluted if considered necessary.

This vaccine retains its immunizing properties unimpaired for months, three months at least, and probably for a much longer period, when kept in a moderately cool place and not exposed to the light.

In the preparation of a dead antirabic vaccine it is necessary to choose between two practical methods of killing the virus—namely, by heat or by carbolic acid or preparations of a somewhat similar nature. Carbolic acid is the method which produces least change in the vaccine material and interferes least with its keeping properties.⁷ The time required for weak solutions of carbolic acid to kill rabies virus depends on the dilution of the virus material and the temperature at which the mixtures (virus and carbolic acid) are kept.

One per cent. dilutions of rabies virus in a half per cent. carbolic acid normal saline solution remain alive and virulent for twenty days at room temperature, and are not killed in twenty-four hours at 37° C.

One per cent. dilutions of rabies virus in a one per cent. carbolic acid normal saline solution remain alive and virulent at room temperature for four days, but not for six days; whereas eight per cent. dilutions of the virus in a one per cent. carbolic normal saline solution are killed in twenty-four hours at 37° C.

The vaccine can be prepared in any well equipped bacteriological laboratory, and by any bacteriologist skilled in the technique of the preparation of bacterial vaccines. From such a laboratory it could be sent to various centres for treatment without running any risks of interfering with its efficiency, and where any medical man with a knowledge of the administration of bacterial vaccines could carry out the treatment of patients bitten by rabid animals.

In a country where rabies is prevalent the advantages of such a system in providing a safe and efficient vaccine are enormous. The expenses connected with the preparation of the vaccine and the provision of a few centres are small; long and costly journeys are avoided; and, most important of all, patients come under early treatment, and a treatment which is efficient and free from risks. Knowing that it is a dead vaccine we can dismiss any doubts as to the possibility of its producing the disease which it is intended to prevent. The proof of its efficiency has been established in India, where it has been in use since 1912.⁸

At the Pasteur Institute of India, Kasauli, between the years 1912 and 1916, a total of 22,519 persons were treated by carbolicized vaccine, with 0.68 per cent. of failures. Of the 22,519 persons treated, 2,009 were Europeans, and these gave 0.19 per cent. of failures. These results must be looked upon as extremely good; they compare most favourably with the results obtained by any other method of antirabic treatment.

For a comparison of the results obtained by carbolicized antirabic vaccine in India with the results obtained in

European countries by other methods of treatment the statistics of Europeans in India should be taken, and for the following reasons:

1. Native patients, owing to their thin and scanty clothing, are generally more severely bitten than Europeans, and much more liable to be bitten through the bare skin.

2. Jackal bites are more common in Indians than Europeans.

3. Many of the Indian patients waste valuable time before coming for treatment, whereas Europeans come early as a rule.

4. In only a few cases is cauterization attempted when an Indian is bitten, and, when it is, hardly ever is it early and efficiently carried out.

5. Many Indian patients arrive with neglected and suppurating wounds; in Europeans this is quite the exception. In the treatment of Europeans in India as compared with Indians the factors noted are a minor drawback, and the circumstances in which they are bitten and treated are fairly comparable to what takes place in a civilized European country.

(a) At the Pasteur Institute, Paris, between the years 1886 and 1918 a total of 39,721 persons received antirabic treatment (dried cord system), with 0.39 per cent. failures.⁹ In 1886 the failures were 0.94 per cent.; in 1887, 0.79 per cent.; in 1888, 0.55 per cent., and in 1894, 0.5 per cent. In three of the years, namely, 1908, 1912, and 1913, there were no failures, and in all the other years they were under 0.5 per cent., and in four instances under 0.2 per cent.

(b) At the Pasteur Institute of India, Kasauli, between the years 1912 and 1916, a total of 2,009 Europeans received antirabic treatment with carbolicized antirabic vaccine, with 0.19 per cent. failures.¹⁰

Of these 2,009 patients, 400 were treated in 1912, with no failures; 448 in 1913, with 1 failure=0.24 per cent.; 461 in 1914, with 1 failure=0.21 per cent.; 322 in 1915, with no failures; and 378 in 1916, with 2 failures=0.52 per cent. I have not seen the Kasauli figures for 1917 and 1918, nor have I been able to procure the statistics from the Pasteur Institutes in Southern India and Burma, where carbolicized vaccine is also in use, but the comparison I have drawn between the Paris and Kasauli results is quite sufficient to establish the efficiency of carbolicized antirabic vaccine.

In the statistical figures of the Pasteur Institute, Paris, and of all other antirabic institutes, those who contract hydrophobia during treatment, or within a period of fifteen days of the last inoculation, are not reckoned as failures of treatment, owing to the fact that their nerve centres became invaded by the virus of the biting animal before treatment was completed and immunity established. This is the explanation given by Pasteur, and on it is based the necessity for early and efficient treatment (see Section IV).

Persons receiving antirabic treatment are inoculated daily, and for a period of from fifteen to eighteen or twenty-one days, according as to whether light, medium, or intensive treatment is considered necessary. Each case should be dealt with on its own merits. The points taken into consideration in determining a line of treatment for any given patient are: number of bites, depth and severity of bites; position of the bites—such as whether on the head, face, or neck, or through the exposed skin on any other part of the body; whether through the clothing; whether the wound was treated early and efficiently; the evidence to hand as to whether the animal which inflicted the bites was rabid; and, most important of all, the time which elapsed before the patient came for treatment.

It will be noted that a study of these points means an attempt to arrive at a conclusion as to the amount of virus implanted in the wound, the risks of infection, and the line of treatment indicated.

Antirabic treatment is now being carried out in England with carbolicized antirabic vaccine prepared at the laboratories of the Ministry of Health and sent out to centres where treatment is given. Instructions accompany the vaccine giving all necessary details connected with its administration, and examples of light, medium, and intensive treatment.

XI. THE PREVENTION OF RABIES IN DOGS.

As this is a veterinary subject in the hands of competent veterinary authorities of the Ministry of Agriculture and Fisheries, who may be trusted to deal with it efficiently,

I need only mention that the outstanding points connected with prevention in a country like England are:

1. Application of the muzzling order for a sufficiently long period.
2. Restriction on the movement of dogs into or from scheduled areas when muzzling is applied locally; in the event of universal muzzling being applied it would still be necessary to restrict the movement of dogs.
3. A strict quarantine for a fixed period on the importation of all dogs from abroad.

On the continent of Europe the question is more difficult on account of neighbouring countries, but in the British Isles this difficulty does not arise.

REFERENCES.

⁴ See Third and Fourth Reports of Pasteur Institute of India, Kasauli. ⁵ The Immunizing Properties of Killed Rabies Virus; *Collected Studies from the Research Department of the City of New York*, vol. iv, September, 1910. ⁶ Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India, No. 44: *On the Preparation of a Safe and Efficient Antirabic Vaccine*, by Sir David Semple, Director, Central Research Institute of India, 1911 (obtainable from agents in England for the sale of books published by the Government of India). ⁷ Semple and Matson: *On the Preparation and Keeping Properties of Antityphoid Vaccines*, *Lancet*, August 14th, 1909. ⁸ Sixteenth Annual Report of the Pasteur Institute of India, being the Report for 1916. ⁹ *Annales de l'Institut Pasteur*, Juillet, 1919. ¹⁰ Sixteenth Annual Report of the Pasteur Institute of India, Kasauli, being the Report for 1916.

ACUTE DIFFUSE PERITONITIS:

A SERIES OF TWENTY-ONE CONSECUTIVE CASES.

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THE peritoneal cavity is one large complex bursal sac containing, in addition to several diverticula, the hollow and solid abdominal viscera. The viscera, which are retroperitoneal, possess a liberal blood supply, particularly the intestine. The main diverticula or pouches are the recto-vesical, the kidney pouches, the retro-caecal, the retro-sigmoid, the hepatico-renal, and the pouches about the termination of the duodenum.

It would naturally be surmised that in infection these pouches would form suitable places for the development of sepsis, and eventually localized abscesses, but in reality they do not. The peritoneum, however, offers a large area for the absorption of toxins, and the rate of absorption is remarkably rapid, being greater in the upper half than in the lower. The lymphatics are very numerous, and eventually form the truncus lymphaticus intestinalis, which opens directly into the receptaculum chyli.

Peritonitis is initiated by access of virulent infection into the peritoneal cavity, the organisms being usually intestinal in origin. Peritonitis may be caused either by trauma or disease.

The war has provided abundant material for the study of this grave condition, and different observations and disappointments have suggested a method of treatment which has given most encouraging results in twenty-one consecutive cases.

When infection has gained access to the peritoneal cavity the first change is one of hyperaemia of and exudation into the subperitoneal tissue of the part around the infected focus. This is followed by the exudation of a fluid, which rapidly becomes turbid, into the peritoneal cavity in the neighbourhood of the infected focus. If the fluid be examined microscopically, it will be seen to contain large healthy staining endothelial cells, a few polymorphonuclear leucocytes, also staining well, but no bacteria. This can always be demonstrated in fluid present in a case of acutely inflamed appendix which has not perforated, and for which an early operation has been performed. Further, if the fluid be allowed to stand or be centrifuged, the cellular element will sink and leave a clear supernatant straw-coloured fluid. Cultures have in some instances shown the presence of staphylococci, but it is doubtful if these organisms did not come from the skin. The fluid, differing in no way from that secreted into a large joint after penetration by a septic foreign body, is highly protective in character, and at first possesses first-rate bactericidal powers. While this fluid is being secreted Nature is making a further effort to localize the diseased focus by the formation of adhesions.

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When the gut is damaged, as in a gunshot wound, there is abundant proof that peristalsis is immediately arrested, and remains in abeyance so long as it is not further stimulated. In other words, extravasation of intestinal contents will be small in extent, especially if the patient be given morphine and kept quiet. Transport over rough ground or by motor is sufficient to start peristalsis anew and so increase extravasation, whereby a larger stream of infection gains access to the peritoneal cavity. It is, then, possible, though there is no direct proof, that in acute abdominal conditions other than gunshot wounds peristalsis is arrested or modified.

Should Nature fail in her attempt to localize the inflammatory focus, and should such failure be intensified by treatment—for example, the administration of an aperient for a pain in the stomach—then infection will certainly be disseminated, either slowly or rapidly, throughout the peritoneal cavity, and no factor is more potent in bringing this about than an active peristalsis. The whole surface, especially that clothing the intestine, becomes actively hyperaemic and swollen, it loses its lustre, protective fluid is poured out, lymph of a plastic nature is deposited on the gut binding together coils of small intestine, the flanks and pelvis contain turbid fluid, and the intestine rapidly becomes distended.

The next stage is an impairment of the vitality of the fluid poured out into the peritoneal cavity. The fluid is slowly converted into pus, and this is enhanced by the increasing intra-abdominal tension brought about by an ever-distending gut, which exerts a serious brake upon the circulation in the vessels of the mesentery. The rate of destruction of the vitality of the protective fluid depends upon the degree of intra-abdominal tension, the virulence of the infection, and the patient's general resistance.

Though the fluid at this stage may often be referred to as pus, it is only partially pus; it is a question of degree, and degree in this respect is a highly important question. It is possible to gauge this degree clinically to some extent by the severity of the symptoms of toxæmia.

It seems that the presence of many plastic adhesions binding together coils of small intestine is of good omen and indicative of a high degree of resistance. At this particular stage complete resolution may take place with treatment. On the other hand, if the protective fluid dies it forms pabulum for the bacteria present, and it eventually becomes pus. Septic absorption under these conditions becomes extreme, and finally death follows from toxæmia.

There seems to be little doubt that "peristalsis plays a large part in the dissemination of septic material from any one focus throughout the peritoneal cavity."

Symptoms.

Early symptoms are due to Nature's method of coping with the disease. As soon as infection has reached the peritoneal cavity, a splint is applied in the form of a rigid abdominal muscle. There is pain and tenderness coinciding with the hyperaemic condition of the part of the peritoneum affected, and later there is a definite mass to be felt which is formed by adhesions, adherent omentum, and the diseased part of the gut. As the condition progresses the tenderness becomes more general, the whole abdominal wall is now rigid, distension sets in, and vomiting commences. Constipation is absolute, there is no passage of flatus, the urine is diminished in amount and often passed with difficulty. Vomiting increases in frequency, the patient rapidly becomes dehydrated, there is hiccough and a typical abdominal facies, the tongue is dry and coated, sordes appear on the lips and teeth, vomiting later becomes coffee-ground, the pulse steadily becomes more rapid and thready, and finally the patient dies of toxæmia.

Vomiting which increases in frequency has in the case of gunshot wounds proved to be due to an ever-increasing extravasation of intestinal contents into the peritoneal cavity. Vomiting which continues after forty-eight hours and which is biliary in character is toxic, and is Nature's attempt at excretion. Vomiting of the coffee-ground variety denotes a very grave degree of toxæmia and is of very serious import.

Nature in her attempt to make good is bound to fail unless helped artificially, as she can make no provision for the fluid lost by vomiting.