

## PREVENTION OF HUMAN RABIES

### Treatment of Persons Bitten by Rabid Wolves in Iran \*

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#### SYNOPSIS

Treatment by the classic methods of persons bitten by rabid wolves gives results, but these results are unsatisfactory: the case-fatality-rate is decreased, but only to an inadequate extent. New and more effective methods are indisputably required.

In the course of 13 years, 325 persons bitten by wolves have been treated at the Antirabies Service of the Institut Pasteur, Iran; almost all, namely 307, had bites of exceptional severity, only 18 having superficial wounds. In 186 cases the bites were on the face, skull, or neck, in 74 cases on the upper limbs, in 5 cases only on the lower limbs, and in 60 on the trunk.

From 1936 to 1946 the vaccine used for treatment was one of the Pereira de Silva type (phenolized rabbit-brain); after 1946 a vaccine of the Semple type (sheep-brain) was employed. Tests were also made using Ferran's hyperintensive method; other trials were carried out with respect to the increase, repetition, and prolongation of the doses.

The results of the treatment must be considered as disastrous. Out of the 325 persons treated, 60 died of rabies, i.e., 18.5%, within periods of time indicating failure of the method. In point of fact, 127 persons who had been bitten arrived at the Institut Pasteur from one to seven days after the bite: 35 of them, i.e., 28%, died. Out of 186 persons bitten on the head, 53, i.e., 28%, developed rabies.

Several viruses were isolated, either from the wolf brain, or from the brains of persons dying in the course of treatment. None of these viruses differed appreciably from the street virus isolated from dogs in Iran or in other countries; none of them showed any special virulence or aggressive potency. Consequently the failures observed must be attributed to the

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severity of the bites and above all to their site, since the case-fatality-rate among the 74 persons bitten on the arms was only 9% and fell to zero for the 65 persons bitten on the trunk or legs. In the case of certain grave bites, exceptionally short incubation periods were observed : in two cases rabies developed 11 days after the bite, in one case less than 9 days after a grave bite on the head. The most frequent incubation period is 19-25 days, more rarely it is 26-40 days and only exceptionally 41-45 days.

Experimental treatment with hyperimmune serum, carried out at the request of the WHO Expert Committee on Rabies over the course of the past two years, has not given evaluable results because the conditions imposed for the test with respect to the period elapsing since the bite were too exacting.

We should like to make the following comments on the above facts and figures :

(1) Since, because of the very conditions existing in regions still infested by wolves, the presence of rabies can be proved in the wolf causing the bite only in exceptional cases, all persons attending our antirabies service after having been bitten by wolves have been systematically treated. However, many of the wolves causing bites are not rabid, and we may quote as an example a small town, Zendjan, in the mountains, near which in 1951 there was a pack of about 50 wolves, led by a particularly audacious old male. Although this town is very busy and populous (50,000 inhabitants) and traversed by a main road over which numerous lorries pass by day and night, the wolves on several occasions came down and attacked the town during the night or the early hours of the morning, making off with several young children even from the courtyards of the houses, and wounding more than 40 people during veritable pitched battles between them and the inhabitants, until an extensive " battue " freed the region from their depredations. There was not a single case of rabies among the people bitten.

The inhabitants of these regions are perfectly familiar with rabies and readily recognize its symptoms in the wolf. They do not confuse an attack by a pack of this nature, or the defence of a female surprised in her lair, or the cautious incursions of hungry wolves in winter, with the sudden attack of a mad, foaming, and enraged animal, which almost always takes place in daytime in the middle of the village and ends, after a frightful struggle, with the death of the wolf under the sticks and pick-axes of the peasants.

As these cases almost invariably occur in remote mountain villages, those bitten must generally themselves reach a decision whether or not to come to Tehran for treatment, and usually, when they consider it certain that the wolf or wolves causing the bites were not rabid, they remain in the village and the story becomes known only much later. However, if there is an official authority in the village or a representative of the central government, even if simply a policeman, those bitten are sent, despite their

resistance, to the Institut Pasteur. Clearly a certain number of the "series" figuring in our statistics<sup>1</sup> are of this nature and as a matter of fact, in all cases in these series where the persons concerned stated that the animal causing the bite was not rabid, no death occurred.

The average death-rate of 18.5%, which we indicate in accordance with the usual statistical practice, consequently does not precisely correspond to the actual state of affairs. On eliminating the series (and these series only) where the biting wolf was very probably not rabid and where no death resulted, we arrive at a case-fatality-rate of about 22%.

(2) If we consider only those series where the presence of rabies in the biting animal has been proved by the death of one or more of those bitten, eliminating on this occasion all series where no death has occurred, we arrive at a case-fatality-rate of about 25%. Among those bitten on the head the figure becomes 42%.

(3) Considering only cases treated without marked delay we reach a still higher total, namely 28%.

### Discussion

What is to be made of these figures? It is such statistics which, submitted to hypercritical examination, have been used by the opponents of antirabies treatment to disparage its value, certain of them going so far as to affirm that without treatment the case-fatality-rate would probably be no higher.

Nicolic<sup>2</sup> has recently reviewed anew historical and current data on the results of treatment of persons bitten by rabid wolves. His paper, based on documentation from several countries (including Iran) and retaining only thoroughly sound results—i.e., series of cases of bites where there was proof of rabies—is an absolutely rigorous analysis, displaying the most strictly critical attitude towards the treatment. On the basis of scientifically reliable documents published before the discovery of antirabies treatment, Nicolic arrives at a case-fatality-rate of 61%, i.e., 103 deaths out of 169 persons bitten. In comparison with this figure, and using, as already mentioned, only documents of indisputable reliability, the author cites 256 cases of bites treated by various methods with only 69 deaths, i.e., 27%, which figure is almost identical with the one we have given above for our observations extending over 13 years in Iran, after revising the statistics concerned.

It would seem, therefore, that, even when the most critical attitude possible is adopted, the figures speak definitely in favour of treatment whatever the method employed, since the case-fatality-rate is reduced by more than half.

<sup>1</sup> Ghodssi, M. (1947) *Ann. Inst. Pasteur*, 73, 900

<sup>2</sup> Nicolic, M. (1952) *Z. Tropenmed. Parasit.* 3, 283

The only figure which might be open to question is the death-rate among those not treated, for which Nicolic has adopted the figure of 61% in accordance with old documents.

However, in this connexion mention may be made of a tragic occurrence which recently took place in Iran, and was reported by Gremliza,<sup>3</sup> a German physician in charge of a clinic in the south of the country. A group of 32 persons bitten by the same rabid wolf remained without treatment, for reasons which Gremliza summarizes as follows :

“ According to the Health Ministry regulations, bitten persons who are rabies suspects should here, too, be sent as rapidly as possible to the Institut Pasteur at Tehran for antirabies treatment. However, the implementation of this regulation is impeded by trivial technical difficulties and the pronounced touchiness of the Arab population. Consequently, of the 32 cases described here only 6 could be sent to Tehran for treatment, using force, and with considerable delay ”.<sup>4</sup>

Of these 32 persons, 15 died of rabies; the statistical data derived therefrom by Gremliza are, however, falsified by an error which we have requested him to correct in a coming number of the journal concerned. His group II, i.e., the 6 persons he sent to Tehran 11 days after the date of the bite, actually only arrived there 23 days after that date. In view of this delay, the bitten persons cannot be considered as “ treated ”, and those among them who survived cannot be omitted from the statistics, as Gremliza has done. Furthermore, the author arrived at a diagnosis of rabies on the basis of clinical symptoms in the case of 2 of the 6 bitten persons after 8 and 9 days' incubation, whereas in reality these 2 patients only developed rabies much later, namely after 18 and 30 days respectively. His conclusions are consequently invalidated as concerns both the average incubation figures and the case-fatality figures; the average case-fatality-rate should be 47% instead of 53.6%.

It may be said that, although this figure of 47% is much lower than that accepted by Nicolic (61%), it still remains very different from the most pessimistic one which we have given, namely 27%. The case-fatality-rate among persons bitten on the head reaches 54.5% in the series given by Gremliza, whereas it is 45% in Nicolic's statistics, and 42% in our own rectified statistics.

If this is so, why have we nevertheless used the phrase : “ The results of treatment must be considered as disastrous ” ? It is because, in an institute such as ours, which can show extremely satisfactory figures as regards canine rabies—since in the course of 13 years only 9 persons bitten by rabid dogs have died despite treatment—the arrival of such a group of wolf-bite

<sup>3</sup> Gremliza, L. (1953) *Z. Tropenmed. Parasit.* 4, 382

<sup>4</sup> “ Laut Gesetzen des Gesundheitsministeriums sollen auch hier suspektae Verletzte so rasch wie möglich zur antirabischen Behandlung dem Pasteur-Institut Teheran eingewiesen werden. Indessen vereiteln banale technische Schwierigkeiten und sehr temperamentvolle Ressentiments der arabischen Bevölkerung die Durchführung der Verordnung. So konnten von den hier beschriebenen 32 Fällen nur 6 mit Gewaltanwendung und erheblicher Verspätung zur Behandlung nach Teheran überwiesen werden. ”

cases represents a real disaster. We know that inevitably several of these terribly mutilated people will die of rabies, despite the ritual gesture of treatment.

Consequently it is useless to compare statistics and to congratulate oneself on having reduced deaths among those with head wounds, for example, by 10% or 15%; it cannot be disputed that in Iran the antirabies treatment of persons bitten by rabid wolves is considered a failure by everyone.

### Conclusions

Must it be inferred that the very principle of antirabies treatment is in doubt? In no way: we can only conclude that the treatment in its present state, and whatever the vaccine so far used, is not sufficiently effective.



**FIG. 1. TYPICAL SEVERE WOLF-BITES ON HEAD AND HANDS OF A PATIENT**

Thus, as we have said, it is to the severity of the bites and their site (see fig. 1 and 2) that the failure of treatment in the case of those bitten by rabid wolves must be imputed. These lacerations, where the virus is deposited in depth over an extensive anfractuouse surface, result in massive inoculation at the site of the large cranial nerve trunks. In the case of less severe bites, treatment seems to give much more favourable results, comparable to those obtained with dog bites. Thus, although we have given above a figure of only 9% for the case-fatality-rate among 74 persons bitten on the arms, and although after the strictest rectification this figure cannot be put at more than 13%, in the series observed by Gremliza 3 people out of 10 bitten on the arms, i.e., 30%, contracted rabies.



**FIG. 2. EXTENSIVE MUTILATION OF FACE IN A PATIENT BITTEN BY WOLVES**

It is in an attempt to remedy this inadequacy of the method of treatment that we have undertaken for the past three years, on behalf of WHO, experiments in the treatment with hyperimmune serum of cases of wolf-bites, at first only with persons presenting themselves less than 72 hours after the bite, and then, in recent months, systematically in all cases of bites by wolves. The results of these trials, which are not yet evaluable, will be made known in due course.

However this may be, the position is as follows : antirabies treatment in its present form is perfectly valid in principle but is not sufficiently effective. The problem of this treatment cannot continue indefinitely to be viewed in the rosy light of unduly favourable statistics, particularly those of countries where rabies no longer exists. Future developments should favour research aiming at the production of more-active antigens in small volume, of powerful antibodies, or, better still, of avirulent living viruses which would restore to Pasteur's discovery its original significance.

### RÉSUMÉ

Depuis 13 ans, 325 personnes mordues par des loups — dont 307 présentaient des blessures d'une exceptionnelle gravité — ont été traitées au Service antirabique de l'Institut Pasteur de l'Iran. De 1936 à 1946, on a utilisé un vaccin type Pereira de Silva (cerveau de lapin phéniqué) et après 1946, un vaccin type Semple (cerveau de mouton). Sur ces 325 personnes, 60, soit 18,5 %, sont mortes de la rage. Sur les 186 mordus à la tête, 28 % ont contracté la rage. Les virus isolés ne présentaient pas un pouvoir agressif anormal ni une virulence particulière. C'est à la gravité des morsures et à leur

siège (face, crâne, cou) qu'il faut attribuer les échecs observés. La mortalité, en effet, n'a été que de 9 % chez les mordus aux membres supérieurs; elle a été nulle chez les mordus au tronc ou aux membres inférieurs. L'auteur considère ces résultats comme un échec incontestable.

Après avoir exposé les faits et commenté les chiffres qui les expriment, l'auteur aborde le principe même du traitement antirabique, dont les adversaires nient l'efficacité. Des statistiques établies par Nicolic, à partir de la documentation de plusieurs pays, dont l'Iran, après élimination très sévère des séries et des cas entachés d'erreur, ont montré qu'avant la découverte du traitement antirabique, la mortalité chez les personnes mordues par des loups enragés s'élevait à 61 %. Depuis que le traitement est appliqué, cette proportion a été de 27 %, dans des séries de cas choisies, du point de vue statistique, avec la même rigueur que les précédentes. Les chiffres semblent donc nettement en faveur de l'efficacité du traitement.

De la somme d'expériences accumulées, l'auteur conclut que le traitement n'est pas encore assez efficace. Les échecs doivent être imputés à la gravité des morsures de loups, qui provoquent une inoculation massive de virus, en profondeur, au niveau des gros troncs nerveux crâniens. Dans les cas de morsures moins graves, le traitement paraît donner des résultats plus favorables, comparables à ceux obtenus chez les mordus par chiens.

Des essais sont poursuivis actuellement à l'Institut Pasteur de l'Iran, à la demande de l'OMS, avec du sérum hyperimmun qui, depuis quelques mois, est administré à tous les mordus par loups. Pour assurer, à l'avenir, un traitement plus efficace, les études doivent porter sur la recherche d'antigènes plus actifs sous faible volume, d'anticorps plus puissants ou de virus vivants avirulents.

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