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Anti rabies treatment versus neuroparalytic accidents

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ANTI RABIES TREATMENT VERSUS
NEUROPARALYTIC ACCIDENTS

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INTRODUCTION

On two occasions during the Junior year in Medical School hypothetical cases of rabies were presented and students were asked if they would advise anti rabies treatment. Various answers were obtained. It was pointed out, at this time, by the faculty members that the Pasteur treatment was of questionable value, and that neuro-paralytic accidents due to rabies treatment killed more patients than rabies. It was also brought out that anti serum was being used and showed promise. Not being aware of the many problems concerning rabies, I decided to write my Senior Thesis on this subject with regard to the above problems and present to the Senior Class the evidence as to what to do and what they can expect if they treat a person for rabies.

HISTORICAL REVIEW

The following are references as collected by Kock and Babes taken from Webster's book, "Rabies" (1). A review of the ancient period is of interest chiefly for its evidence that rabies was known from earliest times. Aristotle, for example, recognized rabies in dogs and stated that other dogs bitten by rabid dogs likewise became mad. Democritus, Asclepiades, Vergil, Ovid, Plutarch, and others refer to rabies as a well known sickness. Later, Galen recommended excising a wound caused by the bite of a mad dog to prevent development of the disease.

During the pre-Pasteur period, from 1800-1880, the contagiousness of rabies was proved experimentally; and appropriate public health measures were taken for its control. Zinke proved that saliva from

a rabid dog spread on an open wound of a normal dog would incite the disease; Galtier transmitted the disease to rabbits in series; Raymond transmitted human rabies to rabbits. Krugelstein argued that the causative agent must reside chiefly in the central nervous system. Meanwhile, health and police authorities in France, Prussia, Switzerland, elsewhere on the continent, and in England convinced that rabies were transmitted chiefly by the bite of dogs, established quarantines during times of epizootics and required that owned dogs be licensed and taxed, that stray dogs be collected and destroyed, that all animals bitten by a rabid dog be destroyed, and that the rabid animal and its contacts be disposed of by a qualified person. Thus, 100 years ago appropriate machinery was set up for the control of rabies.

Pasteur (2) showed that the causative agent of rabies was present in relatively pure state in the central nervous system alone and that the disease could be transmitted by means of a fragment of nervous tissue from a rabid animal. He likewise, showed that continued passage of the agent from rabbit to rabbit altered the agent, that drying weakened it and finally that this weakened agent could be used as a vaccine to protect animals against subsequent exposure to rabies.

It seems that to determine the value of the Pasteur treatment much could be gained from a close study of the original case. This is a report as quoted by Suzor (3) from the communications of Pasteur.

"Theodore Vone, a grocer from Meissengott, near Schelstadt, bitten on the arm on July 4 by his own dog, which had become mad.

Joseph Meister, nine years old, bitten also on July 4 at eight

o'clock in the evening, twelve hours only after the accident.

The dog had been killed by his own master, and on opening his stomach it had been found stuffed with hay, straw, and chips of wood. The animal was certainly mad. Joseph Meister had been rescued from him all covered with saliva and blood. Mr. Vone had been severely contused on the arms, but he assured me that his shirt had not been traversed by the fangs of the dog. I told him there was nothing to fear, and that he could go home that same day, which he did. But I kept with me little Meister and his mother.

The weekly meeting of the Academie des Sciences was held on that same day, July 6th. I saw there our colleague Dr. Vulpian, to whom I related what had occurred. Dr. Vulpian, joined by Dr. Grancher, professor at the School of Medicine, kindly consented to come at once and see the state and the number of the wounds of little Joseph Meister. He had been bitten in fourteen different places.

The advice of our learned colleague and of Dr. Grancher was, that owing to the depth and number of his wounds, Joseph Meister was exposed to almost certain death from hydrophobia. I then communicated to Drs. Vulpian and Grancher the new results I had obtained in my studies of rabies since the time of my lecture in Copenhagen a year before.

The child, being apparently doomed to inevitable death, I resolved, not without feelings of utmost anxiety, as may well be imagined, to apply to him the method of prophylaxis which had never failed me in dogs.

My set of fifty dogs, indeed, had not been bitten before they

were made refractory to rabies; but that objection had no share in my pre-occupations, for I had already, in the course of other experiments, rendered a large number of dogs refractory after they had been bitten.

On July 6th, then at eight o'clock in the evening, 60 hours after the bites of the 4th, and in the presence of Drs. Vulpian and Grancher, we inoculated into the right hypochondrium of little Meister, under a fold made in his skin, the half of a Pravaz hypodermic syringe containing the marrow of a rabbit which had died rabid on June 21 previous. Since that date the marrow had been kept in dry air, suspended in a bottle -- fifteen days altogether.

On the following days the inoculations were renewed, always in the hypochondria. The treatment lasted ten days, and the total number of inoculations was thirteen. Two fresh live rabbits were also inoculated on the brain with everyone of the marrows used, in order to follow their degrees of virulence.

The observation of these rabbits brought out the following points: the marrows of July 6, 7, 8, 9, 10, were not virulent, for the rabbits inoculated with them did not become mad. The marrows of July 11, 12, 13, 14, 15, 16, were all virulent, in descending progression. The rabbits inoculated from the marrows of July 15 and 16 took rabies after seven days incubation; those inoculated from the marrows of the 12th and 14th after eight days; those from July 11 after 15 days.

I had therefore, in the last days of the treatment, inoculated Joseph Meister with the most powerful rabies virus namely, the virus

of ordinary mad dog, strengthened by a large number of passages through rabbits, a virus giving rabies to rabbits after seven days incubation, to dogs after eight days incubation. My action was justified by what I had observed in fifty dogs of which I have spoken before.

Joseph Meister has, therefore, escaped from the hydrophobia which he might have developed in consequence of the bites he had received and also of the hydrophobia, more powerful than the one resulting from ordinary canine madness, which I inoculated into him to test the immunity imparted by the treatment. As early as the middle of the month of August, I looked forward with confidence to the future health of Joseph Meister. Today, three months and three weeks after the accident, his health is still perfect."

If the above account is correct as quoted by Suzor, it seems almost certain that Joseph Meister was saved from rabies by the treatment given him by Pasteur. One cannot help but think that in this case the Pasteur treatment was helpful.

During the past 67 years that rabies treatment has been given it has been noticed that some patients develop neuroparalytic accidents as a result of the Pasteur treatment and some people have challenged the value of this treatment. In order to determine the value of the Pasteur treatment or its modified forms, it is necessary to compare the mortalities of treated persons with the mortalities of people who are bitten by a rabid animal and are not treated.

It is impossible to determine accurately the number of people

who are bitten by a rabid animal and then go on to develop rabies. The reasons are: 1. It cannot always be established that the animal was rabid. 2. If the animal is definitely proven rabid it cannot always be determined if the person was exposed or had only a very mild exposure and would not have developed the disease regardless of treatment or no treatment.

The following are figures from the pre-Pasteur and Pasteur area, which if taken in their entirety will give an idea of the possibility of acquiring rabies if bitten by a rabid animal and not treated. This will be followed by figures which show the number of patients who die from rabies after the Pasteur treatment has been administered.

Pasteur (4) gives the following figures as based on reports of the commissaries of police and on information supplied by Veterinary surgeons managing hospitals for dogs. It covers a space of six years and shows that for the Department of the Seine there were:

Year	Persons bitten	Death by Rabies
1887	103	24
1879	76	12
1880	68	5
1881	156	23
1882	67	11
1883	45	6

Pasteur's own analysis shows on an average one death by rabies for six persons bitten if not treated.

Banley (5) collected statistics of 14,959 persons bitten by rabid or suspected animals and untreated, and found that the mortality varied greatly in different countries but averages 8.9 per cent. We should expect Banley's figures to be lower since the character of the injury

and the proof of rabies in the biting animal were not considered as they are in other series of cases.

Marx (6) thinks that the older figures were, as a rule, too high and that a mortality of 6 to 10 per cent of untreated persons would approximate the correct figures.

Statistics from Prussia collected by Doeber (7) based on official records, shows a mortality of 14.8 per cent in 122 untreated persons who were significantly bitten by rabid animals within the period of 1902 to 1907. Cases of insignificant bruises and of bites by animals not proven to have been rabid were excluded in the computing of these statistics. He quotes the estimates of other observers as follows: "Horsley 16 per cent, Reifer 15 per cent, Dujordin-Beaumety 14 per cent, Hogyes 15-16 per cent."

For wolf bites, Renault (8) finds that out of 254 individuals bitten, 164 died of hydrophobia, that is about two thirds. Dumesnil (8) quoted by Renault having collected accounts of over 800 cases of bites by mad wolves found a death rate from rabies of 65 per cent.

For bites from dogs Renault gives the percentage of deaths as being one third of the total number bitten. Statistics based on 383 cases collected by Banley (5) between 1862 and 1868 and by the committee d'hygiene from that date up to 1872 gives a death rate of 47 per cent.

Farber (9) in the kingdom of Wurtemberg, finds only 28 deaths out of 125 people bitten; 20 per cent. Some Viennese statistics give a death rate of 11 per cent; Another counts 25 deaths for

125 cases. In Austria, in 1860, out of 115 persons bitten, 25 took hydrophobia; 22 per cent. Farber (9) notes only five deaths out of 36 cases where the biting dogs had been diagnosed rabid at the Alfort Veterinary School; 15 per cent.

The committee d'hygiene in France (2) gave the following figures for the years 1862 to 1872:

	No.	Deaths	Percentage
Bites on face	50	44	88
hands	113	76	67.25
trunk	22	7	31.81
arms	40	12	30.00
legs	33	7	21.21
Multiple (legs, hands, face)	8	6	75.00
Total	<u>266</u>	<u>152</u>	

In the United States there are no available statistics of a general scope upon which a mortality estimate of untreated persons can be based. Among the isolated attempts to form such an estimate is that of Mohler (10) who followed in the news papers such cases of bites and deaths as were reported to have occurred within the Southern states. Of 80 persons untreated except by the "Madstone", there were 16 deaths reported, equal to 20 per cent.

From the above it will be noted that the chances of developing rabies varies from 6 to 88 per cent. As one reviews these figures he wonders why so much difference. The only conclusion that seems logical is the difference in the exposure of the individuals. If a person is severly bitten by a definitely rabid animal his chances are probably well over 50 per cent of developing rabies. If the exposure is mild and on the extremities, the chances of developing rabies de-

creases accordingly, so the discrepancy in the above figures may be that in one series the animal was very vicious and all people attacked by this animal were well exposed, whereas, in other series of cases the animal may not have been so vicious and the exposure not as severe. As nearly as can be determined from the time before rabies treatment was given, the chances of acquiring rabies if exposed and treated is about 15 to 20 per cent. This is a low and very conservative estimate.

Since the Pasteur treatment there are no figures available to give information as to the number of people who would develop rabies if exposed and not treated. The obvious reason is that if a person is exposed the treatment is administered, hence, one cannot decide if the treatment stops the development of rabies or if the patients resistance would have overcome the disease without the treatment. The following are figures which give some evidence as to the value of the Pasteur treatment and the chance of developing neuroparalytic accidents.

McKendrick (11) finds that of 192,682 Europeans given the vaccine treatment following bites by a dog proved or certified rabid, only one out of 510 succumbed to rabies and of 267,815 Europeans similarly treated following bites by a dog unsuspected of being rabid, only one out of 676 succumbed to rabies. This is a most fortunately low figure and signifies an outstanding therapeutic result, provided the low mortality was due definitely and solely to the vaccine. This cannot be definitely proven but it is good evidence of the value of

the treatment because the mortality of rabies is less after treatment than it was in the pre-Pasteur area when no treatment was given. (In the pre-Pasteur area mortality from rabies was 15 to 20 per cent.)

The incidence of paralytic accidents has been tabulated by McKendrick (11) and shows that 152,899 persons treated with cord vaccines, one in 3,398 developed paralysis, of 75,141 treated with diluted virulent vaccines one in 3,194, whereas, 411,795 treated with phenol killed vaccine, only one in 8,887 suffered paralysis. It was also shown by McKendrick that when the bite by a rabid dog is located on the head and is deep the chances of death from rabies is one in 77 and probably greater; when the bite is on the leg or trunk and superficial, the chances of death from rabies following treatment are as low as one in 2,100 to 4,500.

McKendrick has analyzed figures from Pasteur institutes all over the world and no where in the literature has it been possible to find larger series than his. He gives these significant figures, the incidence of neuroparalytic at 1:5,814 in a series of 1,290,758 patients with a mortality of 25 per cent among the accidents occurring. The possibility of developing rabies if exposed and treated is about one in 500 depending upon the location of the bite.

Of 1000 cases treated at the Baltimore Pasteur Institute, Keirle (12) found a mortality rate of .153 per cent. Of this group, 632 cases were bitten by animals absolutely proven rabid. Keirle further analyzed figures from the Pasteur institute taking into consideration

all cases from 1886 to 1908 inclusive, he found of a total of 31,280 cases there were after treatment 188 deaths. This is good evidence in favor of the treatment. It can be seen that the mortality is less than 1 per cent as compared to the estimated 15 to 20 per cent if not treated.

In the city and country area of Los Angeles, some 10,000 animal bites per year are reported, these are almost all by dogs (13). Approximately 70 persons per year are bitten by known rabid animals; thus one bite in 140 is by a rabid animal. On the basis of 10 to 15 per cent human fatality rate following the bite of a rabid animal (14) the chances of getting rabies from known animal bites in the city of Los Angeles is 1:1,400 to 1:2,100. If treatment is given it becomes less than 1 in 10,000 to 15,000.

During the period from 1940 to 1946, nine cases of severe post-vaccinal reactions (13) including one death, occurred among 5,500 persons receiving vaccine in the city and county, an incidence of 1:600.

The North Carolina State Board of Health has distributed approximately 24,000 courses of anti-rabic treatment and has endeavored to record all severe accidents attributable to the treatment. At the present time twenty such cases have been reported (15), the incidence of accidents with treatment has been one per 1,200 (0.083%). The mortality rate of those suffering untoward reactions has been, in North Carolina, approximately 10 per cent.

W. Rubin and N. Bowman of New Jersey (16) find that a mortality rate of only .23 per cent occurs in those bitten by rabid dogs and

vaccinated as compared with the expected rate of 16 per cent if they were unvaccinated.

In Michigan (17) approximately 6,000 patients received 84,122 doses of rabies vaccine from July 1, 1945 through March 31, 1949. During this period, twelve cases of reactions of all types to rabies vaccine occurred, including four cases of neuroparalytic accidents with one death, were reported to the Michigan Department of Health . This represents one case of post-vaccinal involvement of the nervous system for 1,500 patients treated. (0.016%)

Denison and Dowling (18) of Alabama made this observation. During a period of seventeen years, 42,947 persons received anti rabies vaccine in Alabama with a mortality from rabies of only 0.06 per cent. This low rate, according to the usual interpretation of treatment statistics constitutes a very favorable showing for effective treatment.

Denison and Dowling reported four known paralytic accidents in Alabama with administration of 33,147 treatments, an incidence of one in 8,287. (Period of time 1922-1939)

Moss and Palik (19) gave the following figures which covers a period of time from 1934 to 1943 inclusive. They report as follows; 79 per cent (total treated 4,146) of all cases treated were exposed through bites or lacerations. Of these 1,580 were injured by a proved rabid animal and among these patients were five deaths, a mortality of 0.11 per cent. Only 873 or 21 per cent, were exposed to a proved rabid animal and 180 were exposed to a stray an-

imal. There were no fatalities among these patients. A total of seven deaths from rabies, a mortality of 0.16 per cent, occurred in 4,146 cases receiving anti rabies treatment.

The above figures show that the death rate from rabies is much reduced after treatment. They also show that the death rate from rabies is much greater than the death rate from neuromyolytic accidents.

The principal animal experiments in the laboratory from 1884 to 1938 have been assembled and critically reviewed by Webster (20). For this work the reader is referred to the following article; The Immunizing Potency of Anti rabies Vaccine. A critical review, American Journal, Hyg. 130; Sec. B., 113-134 Webster L-T.

A review of all these laboratory experiments shows that critical experimental evidence of the efficacy of vaccine treatment is lacking. There is no definite evidence that vaccine treatment, following exposure to rabies confers any striking protection against the disease. Pasteur's test on dogs have not definitely been confirmed. We must bare in mind that the real test is the value of the treatment in human beings exposed to the disease.

SUMMARY

Rabies develops in 15 to 20 per cent of patients injured by a rabid animal and not given the Pasteur treatment.

Patients who are bitten by a rabid animal and treated by the Pasteur treatment or its modified forms have less than 1 per cent of a chance to develop rabies, probably less than .5 per cent. It

is difficult to establish this figure because it is not known if the treatment protected the patient, possibly if untreated the patient may not have developed the disease.

Neuroparalytic accidents are relatively rare, the largest series in the United States gives an incidence of .06, .083, .016 per cent. World wide statistics reported, place the incidence of these accidents at 1:5418 in a series of 1,290,758 patients with a mortality of 25 per cent among the neuroparalytic accidents occurring. This means that on a world wide basis the mortality rate from rabies treatment is .0045 per cent. The figures show that the mortality rate of rabies is markedly reduced after anti rabies treatment has been given.

Experiments in animals are not convincing that the Pasteur treatment is of definite value in animals. The clinical evidence favoring anti rabies treatment has been far more convincing than the laboratory evidence. Those who are bitten by a rabid animal and treated have less than 1 per cent of a chance of developing rabies, whereas of unvaccinated groups of persons exposed to rabid animals approximately 15 per cent develop rabies.

CLASSIFICATION OF NEUROPARALYTIC ACCIDENTS

These accidents have been classified by Sellars (21) of Georgia, as follows:

1. Peripheral Neuritis. This is a rare type of accident and more apt to occur during the latter part of the treatment. There may be a rise in temperature. The symptoms are referable to the fac-

ial nerve. Further treatment should be discontinued at once regardless of the severity of exposure. All of these patients recover.

2. Dorso-Lumbar Myelitis. This is characterized by fever, gradually increasing weakness, numbness and tingling of the extremities, sphincter disturbances, and within two or four days, more or less, complete paralysis of the extremities, especially the lower. This syndrome usually begins after the tenth to twelfth day and unless death intervenes due to cardio-respiratory complications, may last for several weeks. Complete recovery is the rule. At the very first sign of this type of reaction treatment should be stopped at once. Mortality in this group has been reported as 6 per cent (22).

3. Paralysis of Landry Type.. This is similar to dorso-lumbar myelitis, but more severe and acute at onset. It is ushered in by nausea, vomiting, girdle pains, headache, fever, retention or incontinence of urine, and an ascending paralysis of the extremities. The paralysis may ascend to involve the bulbar nuclei and death from cardio-respiratory failure may occur. The mortality rate is as high as 30 to 50 per cent. (11) Some recover completely while others are left with varying degrees of paralysis.

ETIOLOGY

In a review of the literature dealing with anti rabies treatment paralysis one encounters many conflicting opinions as to the etiology of this complication. At first it was assumed that the reaction represented actual rabies, the clinical course of which was modified by

the vaccine. However, in 1898, Tonin recorded a case of paralysis occurring in an individual bitten by a dog which was later proven to be free of rabies. This observation by Tonin (23), coupled with subsequent findings that a similar reaction can be produced by repeated injections of normal brain tissue (24) proved that post-vaccinal paralysis is entirely independent of the rabies virus. We may mention in passing some other theories offered as an explanation of the treatment paralysis. One of the theories hypothecates that the reactions are due to the fixed virus present in the vaccine, another that the symptoms are produced by an obscure neurotropic virus present in the rabbit's spinal cord, and still another proposes that the post-vaccinal paralysis is a manifestation of anaphylactic reaction due to the vaccine. Many others believe that the reaction is due to the foreign protein introduced during the process of immunization (24). This last idea is supported by the clinical observation that practically every biological product, serum or vaccine, has at one time or another been responsible for the production of a clinical picture closely resembling treatment paralysis. Grinker (25), finding a remarkable similarity in the pathological and clinical manifestation of encephalomyelitis secondary to the anti small pox and anti rabies vaccination, suggested that the "post-vaccinal encephalitis may be due to some unknown, latent virus harbored in the body of the vaccinated person and stimulated to activity by the vaccination."

It is true that all the above theories and many others have their

supporters, but the prevailing opinion of the workers interested in this problem is that the clinical and pathological alterations are due to an allergic reaction to the rabbit brain tissue. This theory is further supported by the studies of Rivers and Schwentker (24), who showed that the brain of a rabbit may function as an antigen which is organ-specific rather than species-specific, and that the clinical and pathological picture seen in the post vaccinal paralysis can be reproduced in animals by repeated injections of normal brain tissue from the same or a different species of animal. Kabat (26) and his co-workers have gone a step further and produced acute disseminated encephalomyelitis in monkeys by injection of their own brain, removed surgically and incorporated with adjuvants.

It was believed by Horack (15), that allergy was important as a factor in neuroparalytic accidents. The following is a survey of his work. It seems significant because the physician who gives treatment could easily obtain a history and if a patient has allergic manifestations the treatment should be very short or not given.

A survey was made of 16 persons known to have had severe accidents as a result of treatment (15). Each individual was interviewed personally and questioned with regard to the following points: (a) the presence of an individual or family history of allergic disease; (b) the type of local reaction and its relation to the beginning of the treatment; (c) the type of accident, its symptomatology and relation to the beginning of treatment; (d) the total number of injections given; and (e) the degree of recovery following the accident. In

addition, such factors as age, race, occupation, site of exposure, type of local treatment, and the presence of the so-called "pre-disposing factors", such as physical or mental strain, nervous or mental disease, living conditions, use of alcohol or drugs, and a history of syphillis were considered.

As a result of this survey it was found that 80 per cent of these patients gave a personal history of asthma, hay fever, urticaria, or marked food idiosyncrasies; that there was a positive family history of allergic disease in 50 per cent of the cases; and that there was either an individual history, family history, or both in 87.5 per cent of the patients interviewed. The local reactions began in the majority of the cases about the third or fourth day after treatment had begun, became progressively more severe, and persisted throughout the time that the vaccine was administered. Evidence of neuro-dysfunction began on an average of 15 days after treatment was started. Recovery had occurred, or was occurring, in all but one case. Of those from whom no allergic history was obtained, one drank alcohol excessively throughout the course of treatment, and the other was a child of unknown paternity and consequently no reliable family history could be obtained.

Following the same procedure as was used in taking histories from those who suffered treatment accidents, a control series of 45 persons who had taken the Pasteur treatment without complications were interviewed. The cases were not selected. From this study there developed 4 interesting facts; (1) a positive individual allergic history was

obtained in 30 per cent; (2) there was a positive family allergic history in 20 per cent; (3) there was either an individual history, family history, or both in 33 per cent of those interviewed; and (4) there was a rather marked correlation between the severity of the local reactions and the presence of a positive history of allergic diseases.

In comparing these percentages of both groups, it will be seen that in those suffering unfavorable reactions to treatment a history of allergic disease, either personal or familial, or both, was obtained in 87.5 per cent of the cases. In the control series, a similar history was obtained in only 33.3 per cent of those questioned. From this it would appear that the much higher incidence of allergic disease in the group suffering treatment accidents, in contrast to the group taking the treatment without the development of accidents, was more than a matter of chance, and that allergy played a role in the development of treatment accidents.

At present it appears that the allergic theory of treatment paralysis associated with anti rabies vaccination is based on rather sound experimental and clinical observation.

ANTI SERUM

Since there is some doubt as to the value of the Pasteur treatment, and neuroparalytic accidents definitely do occur, some workers have used anti rabies serum. Babes and Lepp were among the first to attempt this. Other early workers were Fermi in Italy, Shortt, who worked in India and Proca who employed anti serum in Rumania (27).

A. M. Stimson (1910) observed that the most striking property not possessed by normal serum is that of being able to destroy the activity of rabies virus in vitro by contact with it. The blood serum of a person or animal subjected to a course of Pasteur treatment, when mixed in certain proportions with an emulsion of fixed or street virus, will cause the virus to become inert when injected subdurally into a test animal (27). This property he reports is not possessed by the serum of animals suffering from rabies. Some time is necessary for the development of this property. The duration of this property is believed to be of considerable length. In some patients serum it was found present up to 85 days. Patients examined at the Pasteur Institute after two years were found to have very little anti rabic activity. Stimson found that animals injected with virus serum mixtures and exposed to rabies, died of rabies but there was a relative retardation of the time of onset and death corresponding to the amount of serum used.

According to Marie (as quoted by Harris) the action of the serum upon the virus appears to be of fixation of some component upon some specific body of the virus (28). Serum "saturated" with a portion of virus is deprived of the property of destroying the virulence of another portion after its recovery from the mixture by centrifugation. Normal nerve tissue does not remove the anti rabic property. Marie further states that the union between the hypothetical antibodies and antigen is unstable since the virus so neutralized may regain its virulence after washing with salt solution.

To the time of about 1910, the serum of normal mammals was found inactive against rabies virus by nearly all observers, but the serum of treated mammals was found to have some anti rabies properties in vitro. The action of anti rabies serum in the human body at this time was considered to be of very little therapeutic value. These early investigators believed that the immunity conferred with the use of anti rabies serum is like all passive immunity, transient in character. The organism might be temporarily held in check by an injection of serum; but after the disappearance of the immune properties of the serum the rabies virus would again proliferate and produce the disease.

In 1936, Hoyt (29) and Habel (30) published studies in the use of passive immunization of mice against rabies. They feel that use of rabies anti serum is of definite value. Korprowski proved to his own satisfaction that rabies anti serum was of definite value. He found that anti serum given to hamsters within 72 hours after inoculation with street virus will protect the majority of exposed animals. In contrast Korprowski was unable in any experiments to save the life of a single animal exposed to street virus and then treated only with serial injections of phenolized vaccine. The results of the above experiment seems to warrant extensive clinical trial in man, but it certainly is not conclusive evidence that rabies anti serum has definite value even in animals.

Hoyt and Habel in 1936, proved to their own satisfaction that anti rabies serum has definite protective power in the treatment of

laboratory animals exposed to rabies.

Korproski (31) has performed laboratory experiments with hyper immune anti rabic serum concentrates prepared in rabbits and sheep. He came to these conclusions; one injection of antiserum exerted a definite protective effect in hamsters and in guinea pigs which had been infected twenty four hours previously with street virus. In contrast, a course of fourteen injections of phenolized rabies vaccine instituted twenty four hours after exposure, failed in all instances to protect the exposed animals from rabies.

A combined anti serum plus vaccine treatment of exposed hamsters seemed neither to enhance nor to decrease the protective power of anti serum administered alone. However, it is not possible to duplicate in hamsters the sequence of events occurring in humans, (incubation period in hamsters twenty one days, in humans thirty days, hamsters more susceptible to rabies than humans), so great caution should be exercised by a physician before condemning the Pasteur treatment and using hyper immune anti rabies serum alone.

In this country concentrates of anti rabies serum prepared either in rabbits or in sheep were made available for clinical trials in 1948 (32). Each vial of anti serum was accompanied by a questionnaire and the physician responsible for the case was asked to fill it out and return it to Korproski's Laboratory. Approximately 75 per cent of the distributed questionnaires have now been returned.

A total of 48 cases received anti serum, 11 were exposed to bites of non rabid animals, and this group was not considered. Eight per-

sons were bitten by animals not captured; four were bitten on the head or neck, three on the arms, and one on the leg. The severity of bite was judged by the attending physician and in four cases was considered to be mild or moderate, but severe in four other cases.

The largest group in the series is comprised of twenty nine persons who were treated with anti serum, after having been bitten by animals which were shown to be rabid either by the presence of Negri bodies in the brain tissue or by virus isolation in mice. Of these twenty nine cases, eight were bitten on the head or neck, nineteen on the arms or hands, and two on the legs or feet. Nine were classified as severe exposures, twelve as moderate, and eight as mild.

In most but not all cases, administration of serum was followed by phenolized vaccine treatment of varying duration and intensity. Not a single fatality was observed in this series, but it cannot be stated that this fact indicated significant efficacy of the anti serum, because the presence of Negri bodies and demonstrable virus in the central nervous system is not always correlated with the presence of virus in the saliva.

One of the cases may be worth mentioning as a probable exception. This was an animal attendant who, while cleaning a cage housing guinea pigs inoculated with street viurs, was bitten by an animal inflicted a deep penetrating wound on the wrist. The animal was sacrificed immediately, its salivary glands removed, made into a suspension, and titrated in mice. The LD titer was ten and his case can thus be considered, with only slight reservation, as one of definite exposure.

The principal difficulty, therefore, in statistical evaluation of the effect of anti serum lies in the impossibility of defining an actual exposure. Yet this fact alone should not discourage the use of anti serum. Experimental evidence suggest it has some value. Also we should consider the fact that no one has been killed by the use of rabies anti serum.

It seems that the Pasteur treatment has definite clinical value and that anti serum shows some promise, therefore, it may be advisable that anti serum treatment for the time being, at least, be employed in conjunction with vaccine in all types of rabies exposure. This may possibly shorten the length of the Pasteur treatment and thereby reduce the possibility of neuroparalytic accidents since these accidents usually occur after the tenth day. It would seem advisable that all cases with severe exposure to the head, neck, and upper fore-arms should be given the anti serum and the Pasteur treatment. In these cases anti serum should be used even if of questionable value because the chances of the Pasteur treatment protecting the patient are very small.

SUMMARY

The problem of evaluation of anti serum lies in the fact that it is impossible to define an actual exposure.

Before about 1935, the experimental tools and techniques employed in the evaluation of anti serum were crude and not too reliable. From 1936 to 1948 very little work was done on the use

of anti serum. Since 1948, Korprowski has been finding evidence in animals and some evidence in humans that anti serum is of value, but the amount of experimental and clinical evidence up to the present time is too small to come to a definite conclusion.

INDICATIONS AND CONTRA-INDICATIONS FOR TREATMENT

It is impossible to compose a guide for rabies prophylaxis because inevitably the result will not be universally accepted and can not be accepted because a clinical case may not fit the guide which is purposed. It is up to the physician to use his judgment and to individualize each case, study the patients carefully and observe the animal and then proceed accordingly. The following outline is purposed only as a guide and should by no means be adhered too rigidly. This outline is a composite of the, "Who Expert Committee on Rabies" an outline prepared by Sellers (21) of Georgia, and by Denison and Dowling (18) of Alabama.

A concerted effort is made to limit the administration of vaccine to those most probably infected by direct exposure. (42 per cent had no open wounds reported from Alabama).

Disposition of the Animal -- whether the animal appears normal or sick, it should be quarantined for a period of from ten to fourteen days. If typical symptoms of rabies develop, the treatment need not be further delayed. Confirmation of diagnosis, however, should be made at autopsy. If death occurs within the period of observation, early microscopic examination of the brain is made. If positive, treatment is begun. If negative, the clinical symptoms of the an-

imal must be taken into consideration in an effort to arrive at a diagnosis. The importance of clinical observation is apparent when the limitations of direct microscopic examination for Negri bodies is appreciated. Leach (34) has determined the presence of rabies virus in brain material by both mouse inoculation and direct microscopic examination. He reports positive mouse test for 12 per cent of brains on which Negri bodies were not found by direct microscopic examination, and negative mouse tests among 0.9 per cent of brains on which Negri bodies were reported as found by experienced technicians.

In endemic areas every dog that bites should be considered rabid until known to be otherwise. When the condition of the animal is unknown because it cannot be located or cannot be positively identified or the laboratory examination is unsatisfactory, it is advisable to administer treatment to those bitten.

Actual bites or scratches—for actual bites or scratches made by the teeth or claws, treatment is always advisable. In the case of bites above the shoulders or multiple severe lacerations of the body or extremities, treatment should be started immediately but may be discontinued later if the animal proves not to be rabid. In some instances it is probably safe to wait for twenty-four hours if the history of the dog is known and if it can be observed by an experienced veterinarian; but unless the animal remains perfectly normal, treatment should not be further delayed. For other bites it is safe and usually desirable to delay treatment until a definite diagnosis can

be made either clinically or by laboratory procedures.

Other Exposures Requiring Treatment—The point to emphasize is that treatment is usually advisable only following an actual bite or scratch made by the suspected animal. Other extenuating circumstances, of no great importance sometimes warrant treatment, as, for example, the known contamination of fresh open wounds with saliva. Such an exposure assumes the importance of a bite only if there is some abrading force to carry the saliva into the wound. The wound itself is of importance only if it was of sufficient size to have been easily noticed, and provided it had been made on the day of the exposure to the animal. It is not felt that the mere handling of rabid animals with fresh open cuts on exposed parts is important unless there is direct contamination with saliva and unless such contact is known to have occurred, treatment is not advised.

When infants and young children have had intimate contact with rabid animals for extended periods of time, treatment may be advisable, especially if the parents are unobservant or ignorant of what may have transpired. Fifty per cent of deaths from rabies in Alabama occur in children under 13 years of age.

Treatment has occasionally be advised for highly nervous women, not for prevention of rabies but to avoid nervous collapse or hysteria. It seems that anti rabies serum would be of value in such cases.

When treatment is not advised—Treatment is not advised in the following: 1. contamination of old cuts sores, abrasions, scratches,

or hangnails with saliva of known rabid animals; 2. "pinches" in which the skin is definitely broken but the clothing neither torn nor penetrating; 3. handling, eating after sleeping with, kissing or other intimate exposure to rabid animals; 4. drinking milk of rabid cows, eating meat of rabid animals; 5. bites of any animal living fourteen days from the time of biting; 6. bites from fleas from rabid animals; 7. any exposure to a case of human rabies other than an actual bite, or direct contamination of fresh open wounds; 8. any exposure of a nonrabid animal just bitten by a rabid animal except when infected saliva is directly transmitted to a fresh open wound.

FINAL SUMMARY

In the pre-Pasteur area, the chances of acquiring rabies if exposed and not treated was 15 to 20 per cent.

Patients who are bitten by a rabid animal and treated by the Pasteur treatment or its modified forms have less than 1 per cent of a chance of developing rabies and probably less than .5 per cent.

Neuroparalytic accidents are rare, largest series in the United States gives an incidence of .06, .083, 0.016 per cent. World wide statistics reported place the incidence of the accidents at 1:5418 in a series of 1,290,758 patients with a mortality of .25 per cent among neuroparalytic accidents occurring.

Mortality rate of rabies is markedly reduced after anti rabies treatment has been administered.

Experiments in animals is not convincing that the Pasteur treatment is of value.

A classification and possible etiology of neuroparalytic accidents has been presented.

There is some evidence that rabies anti serum is of some value. The evidence is not conclusive. Patients with severe exposure of the head should have the Pasteur treatment as well as anti serum.

The outline for treatment, which has been presented should be used only as a guide. It should not be adhered to rigidly. Each individual case should be carefully studied to determine if the patient has been exposed and then treat accordingly.

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