RABIES OR HYDROPHOBIA*

by Jeff Mast M D.¹

I. General

Rabies is a viral disease of animals and man transmitted by infected saliva gaining entry to the body by a bite or by inoculation of an open wound. It was accurately identified as early as 2000 BC and was first recognized by Aristotle. The agent is a neurotropic virus which closely resembles the measles virus. It is readily inactivated by heat, drying and sunlight.

The incubation period of rabies may range from 10 days to 2 years. The average is from 3-7 weeks. According to Buff the incubation period is from 10 days to 1 year; however, symptoms usually appear in less than 25 days.

Although it is generally agreed that rabies virus is transmitted by saliva introduced directly into the subdermal tissues of man; there are cases on record of rabies being transmitted by inhalation of infected saliva droplets suspended in the static air of a cave containing rabid bats. Two persons who entered a cave in Texas known to be infested by rabid rats subsequently developed rabies and died. These two incidents occurred in 1956 and 1958. No history of bite was noted. Subsequent experiments with caged animals kept in the same cave corroborated the hypothesis of an airborne mechanism of transmission.

The virus ascends along peripheral nerves to the brain, multiplying there. The Negri body, indeed has recently been identified with electron microscopy as virus particles associated with cellular constituents surrounded by a cytoplasmic matrix. It was first described by Negri in 1903. Histopathologic lesions in the CNS are modest in comparison to the symptoms. They consist of neuronal degeneration, perivascular infiltration, and focal aggregates of round cells. The hippocampus, gasserian ganglion, and cerebellum show Negri bodies.

The virus then migrates along efferent nerves to the salivary glands. According to an article presented in August 2, 1965 issue of JAMA, experiments in dogs have shown that virus was detected in saliva 3 days before the onset of symptoms. The excretion continued until the dogs died. Their conclusion was where possible, Rx should be administered to a person bitten by an animal which shows signs of rabies up to 10 days later. The virus can be recovered from CNS, salivary glands, mammary glands, pancreas, and lacrimal glands. It is not reported in the reproductive glands.

On day 1 following exposure the virus is found in the inoculation site. On day 2, it is found in the spinal nerves and on day 4, it reaches the CNS.

Evidence for the fact that the virus does ascend the peripheral nerves is :

1. No viremia is noted.
2. The closer the inoculation site to the CNS, the shorter the incubation period.
3. When the virus is injected into the hind limb of experimental animals it is found in the spinal cord before it is found in the brain.
4. The virus has been located in peripheral nerves.

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II. Clinical Findings

In the dog, symptoms are present following a prodroma of 2-4 days. Key points are a sick dog without fever that exhibits change of personality, purposeless movements, snapping and drooling, laryngeal and pharyngeal, spasm and paralysis.

Key in differential diagnosis is dystemper, hepatitis, and stomatitis.

In humans, the disease is often heralded by recurrence of pain in the region of the bite, change in personality—rage with intervals of calm. And laryngeal spasm peculiarly triggered by attempting to take fluids. Treatment at this point is considered palliative.

Later symptoms of muscle spasm, convulsions, and inevitable death occurs as a result of cardiac or respiratory failure or generalized paralysis. Throughout characteristic thick tenacious sputa is discharged from the salivary glands. According to Buff in 1958, the disease is 100% fatal. Dr. J. Kraut in a letter to JAMA, July, 1966 contests this. He reports five references pertaining to individuals who were supposed to have survived documented cases of rabies. Most reports involved the use of high doses of human serum from individuals with high titers against rabies virus from active immunization with rabies vaccines.

However, these five references were neatly queried by H. Weiss in a letter to JAMA, May 27, 1968. Because of lack of documentation of laboratory data, Weiss ascribes the recovery of two of these persons to the proposal that they were suffering from rabies hysteria rather than rabies. The other three cases cited, thru Sherlock Holmes inquiry turn out, in Dr. Weiss's opinion, to be the same case. Weiss contacted this individual and found that he (1) was discharged from the hospital without a diagnosis. (2) a "late blood test" for CF antibodies against rabies virus was negative. Antibody during hospitalization obviously represented passively transferred antibody during treatment with ARS. (3) The patient concluded the original diagnosis remains in question.

Other case of presumed rabies cure also fall to question and the issue remains unresolved. Most experts still feel rabies is 100% fatal.

Rabies, however, poses a unique problem for the attending doctor. In few other diseases does one have the dilemma of observing a basically healthy patient and prescribing a regimen that may on one hand cause morbidity, but on the other hand, represent the only possible way of preventing an inevitable death weeks or months in the future. About the time the patient forgets that he was ever bitten by an animal. The problem is complex in many cases—involves many people and compromising circumstances. In the USA, more people have died from reactions to rabies vaccines than from rabies.

The results of a 1958 WHO questionnaire provided the following data : 865 people died from untreated rabies. Of 500,000 people who were treated, 82 people died of rabies. Of the same 500,000, 47 developed neuromuscular complications.

The doctor in charge must be well aware of the facts so that he may best make the necessary decisions, regarding the regimen for the patient.

In a report of known rabies covering a 10 year period, 521 humans were bitten by rabid animals. Of these, 415 received a full series of vaccine treatment while 106 had no treatment. In the treated group the mortality rate was 8.8%. In the untreated group 48% died of rabies.

III. Therapeutic Tools— New and Old

1. It is not facetious to start with soap and water— as too often the obvious is lost for the esoteric.

In a study reported by Jones with experimental animals, a rabies take was avoided in animals bitten by dogs with proved infected saliva by the liberal use of soap, water, benzalkonium chloride, single or in combination with topical ARS.

In this study, only 10% of the dogs treated in this fashion contracted the disease while 95% of their controls became rabid and died.

Benzalkonium chloride 1-2% or other quaternary ammonium compounds are the agents of choice, and all equal or superior to fuming nitric acid to reduce the take.

Of humans bitten by known rabid animals and given no Rx probably only 50-75% will contract the disease. Buff's figures are in a bit wider range, he states 20-75% will contract the disease after exposure to a known rabid animal.

2. Anti-rabies-Hyperimmune Horse Serum. If the wound is seen by a doctor within 72 hours of it's occurrence ARS should be given. According to Van der Scheer and Black, serum is best given within 24 hours to be effective, and within 72 hours to be partially effective. After 72 hours there is no indication for ARS.

Habel has ascribed the effectiveness of ARS to the prolonged incubation period it forces upon the virus.

Hildreth cites 2 human deaths from rabies which represented failures of combined therapy. On both instances antisera was given on the third day following exposure and vaccine on the fourth day.

ARS being of equine origin may be expected to cause side rxns in 20% of treated patients. The usual rxn is a delayed hypersensitivity reaction of the serum sickness type.

Experiments, however, in Hamsters and Guineas pigs using ARS and vaccine alone or in combination found invariably that vaccine alone failed to protect laboratory animals.

These investigators concluded that ARS has definite value and recommended a single dose of ARS combined with a full course of vaccine following exposure.

ARS produces a greater than the minimal protective titer of 1:50 within 24 hours and with combined vaccine this titer usually be maintained throughout the incubation period.

Does ARS interfere with the antibody response to the vaccines ?

The Expert Committee on Rabies of WHO in their report showed that 1 dose of ARS reduced but did not completely suppress the antibody response to 14 doses of Semple type NTV. Two doses of days 1 and 5 did suppress the antigenicity of this vaccine schedule.

The consensus of opinion favors a dose schedule of 40 IV to 50 IV per kilogram body weight. Part of the total should be injected directly into the bite wounds, the rest should be given by deep intramuscular injection.

The USPHS dose schedule is identical for ARS, they suggest 1000/units/40 lbs.

Before using ARS skin testing or conjunctival testing should be accomplished to exclude immediate type hypersensitivity.

At present, anti rabies immune serum globulin is being tested. The homologous passive

immunity appears to be far superior and causes almost no reactions. According to Sikes, et al, ARS equine protects passively for 12-14 days during which time active immunity from the vaccinations usually becomes measurable.

Sikes reports that 16% of individuals will develop serum sickness reactions when ARS is used. Over the age of 15 years, this % increases to 46%.

The disadvantages of HRISG is its expense. At present, it takes 4 units of blood from individuals with antibody titers against rabies 1:400 to make 5cc. of HRISG. These individuals maintain high titers thru regular vaccinations with DEV.

The HRISG potency is 165 IU/cc., but it is equal in neutralizing effect to comparable amounts of ARS.

The 1/2 life of ARS in the body is 1.5 days. The 1/2 life of HRISG is 7 days.

The disadvantage of HRISG is that it will suppress the DEV response until its titer is below 1:20.

Vaccines

Three types of vaccine are now generally available, of which two are accepted and used. There are two types of rabies virus, street virus and fixed virus. The fixed virus is used to prepare the vaccines. It is obtained from sheet virus that has been passed thru lab animals. It has a short, constant incubation period and is less virulent than sheet virus. It does not produce Negri bodies.

According to Tierkel, JAMA, 201, 1967, DEV produces a significantly higher antibody response than chick preparations. However, according to the Expert Committee of WHO and Jones Experimental studies have shown that the antibody response is more rapid with DEV stimulus than with Semple NTV of rabbit origin, but that higher titers are stimulated by the latter.

Historically the death rates from rabies in individuals treated with the two vaccines compare favorably.

The rabies death rate with NTV is 1:20,800 people treated; while for DEV the rate is 1:28,100 exposed people treated.

Because Neuroparalytic reactions are rare with DEV compared with NTV it is currently the vaccine of choice.

DEV is a fixed virus which has been grown in the duck embryo. The rabies' virus must grow in the neural cell and it is therefore necessary to include some myelin tissue in the vaccine, but it is minimal by comparison to the rabbit brain preparation. The virus is killed. The standard dose of DEV is 1 ml.

Semple NTV is a sterile penetration of killed rabies virus in 0.5% phenolized saline containing a 20% suspension of the brains of rabbits that had died after inoculation with fixed virus. The standard dose is 0.5cc.

Reaction rates differ according to authors especially with NTV. DEV became available in 1957. Local reactions at the injection site are common. Generalized reactions are occasionally observed. Neuroparalytic reactions have been reported in five people, according to Jones' paper in 1968; he, however, reports no deaths. Contrary to Jones, the USPHS Advisory Committee on Rabies Immunization 1969, reports the incidence of neurologic complications with DEV to be

1/23,000 and death to be 1/172,000. Eli Lilly, makers of DEV, claim 11 cases of transient myelitis or encephalitis with no permanent sequelae.

This contrasted to the USPHS' figures for the dangers with Semple as 1/4000 neurologic complications and 1/35,000 death !

The current explanations for the difference in reaction rates centres around the amount of brain tissue present in the vaccine. The older Semple vaccine is known to produce neuromyolytic accidents. In a series reported by Sharp and McDonald in the BMJ the incidence was 5%. Presumably, these rxn's are caused by the production of antibodies against the brain tissue in the vaccines with subsequent autoimmune phenomenon against the recipient's own central nervous system.

The neuromyolytic episodes are of three types— peripheral neuritis, transverse myelitis, or encephalitis. They usually appear on or after the 4th day of treatment. According to Buff, the incidence of the most serious reaction is 1/3000 and consists of an iso-allergic encephalitis of the demyelinating type. Mortality in this group is 10–25%. However, other investigators give incidence of reactions to Semple from 1/20 to 1/8,287 with wide discrepancy.

Reactions to the Semple and DEV seem to increase in both severity and frequency with age.

If one must continue vaccines in an individual who is reacting to it, hospitalization and coverage with ACTH is necessary. ACTH is preferred over cortisol because it has less of a depressive effect on antibody formation.

IV. Rationale of Therapy— Five Points to Consider

1. Species of animal should be considered : In order of risk, wild carnivorous and domestic animals, dogs and cats should cast suspicion. There is an old saying, "Bats are batty, but rodents rarely rabid."

According to an article in NEJM, rabies in rodents is extremely rare, however, there is a documented case of rabies in the Institute of Laboratories of the Mass. Public Health Centre which was discovered in a gray squirrel. In the USA skunks have the highest incidence of rabies according to the USPHS reports in 1969.

2. Circumstances of attack— provoked vs. unprovoked.

3. Extent and location of the wound. Severe risk : deep puncture wounds of head, face, neck, hands and fingers take precedence.

Mild risk : teeth inflicted scratches, lacerations, or single bites on areas other than above.

Rabies can be inflicted by saliva from licks inoculated into fresh open wounds. It can not be inflicted thru intact skin. Theoretically, it can be transmitted thru intact mucous membranes. Drinking the unboiled milk from rabid cows could conceivably produce an exposure.

4. Vaccine status of biting animal. An adult animal with one or more doses of rabies vaccine has only a minimal chance of developing rabies. Vaccines are 60–80% effective in animals.

5. Presence or absence of rabies in the area. Great Britain, Australia, and Hawaii are free of rabies.

Approach to Rx— Three Guidelines :

1. Capture and quarantine a sick animal 10 days. Observe a healthy animal, if it can be identified, 10 days. If dog is lost or unknown must assume it's rabid.

2. Immediate local Rx— Start test for ARS Sensitivity.

- (1) Thorough flushing with soapy solution
- (2) Thorough rinsing to remove soap
- (3) Quaternary ammonium compounds, swab lesion
- (4) ARS in partial total dose into wounds
- (5) Tetanus toxoid
- (6) Bacterial infections anticipated
- (7) Suturing wounds is not advised.

3. Post Exposure

- (1) Remainder of ARS
- (2) Vaccine
 - a. DEV or NTV
 - b. 1st immunization
 - mild : 14 days of double dose or
 - 7 days of single or
 - 21 days of single
 - boost at 10 days and again after 20 days
 - antibody levels, if possible.

Shots may be given subq wherever convenient. They do not have to be given into the abdomen.

V. Pre-exposure DEV : A New Concept in Prophylaxis

DEV 1 cc.—subq.

1 cc.—1 month

1 cc.—6-7 months

*80-90% will have neutralizing after third dose.

In our volunteers, however, we treat all as though they had no vaccine before, if they get bitten. Rationale :

- (1) Good, because we can't get to them instantly
- (2) Amnestic response → 8 days
- (3) Facial bites

NO CASE OF RABIES have been reported in individuals with pre-exposure ARS and post-exposure Rx regimen. There have been deaths with all other combinations. There have been no cases of rabies in the Peace Corps.

For mild exposure in an individual with known antibody against rabies (by pre-exposure vaccines) a single dose of booster is recommended.

For severe exposure in similar individuals, a regimen of five daily doses followed by a booster in 20 days is recommended.

**Latest statistics reveal even a higher take = 99% Study to be submitted from the University of California at Davis.*

New Frontiers

It is held that no one has ever lived once he has suffered the onset of symptoms of rabies. However, with modern intensive care, there is a feeling that rabies may not need to be a terminal event. Recently a patient survived for 52 days in an intensive care room. She was being maintained by a respirator.

Beta phenylserine, a competitive inhibitor of phenylalanine hydroxylase, has proved to be efficacious in decreasing the death rate in animals by 70-80% after they have been exposed to laboratory rabies. No human trials are reported.

There is a new vaccine in Canada according to Wikter and Koprowski, cultured in human diploid cells. This vaccine in tests has been shown to be significantly more antigenic than previous vaccines only 1-3 inoculations being required to produce immunity in experimental animals.

Recently, it has been shown that some persons who have had no contact with rabies virus have been found to have antibody titers against rabies virus. This observation raises the question as to whether the findings are due to sub-clinical rabies or naturally attenuated strains of virus.

Rabies is on the decline in the U. S. In 1938, there were 46 deaths due to rabies. In 1967, there were two deaths due to rabies. In 1968, there was one death due to rabies. Most of this has been due to epidemiologic control of vectors, particularly, dogs and cats. Another full presentation could be devoted to this very important, albeit less dramatic subject.

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