Practical Problems in Rabies Control

At the annual meeting of the American Public Health Association in Buffalo, October 11, 1954, the Conference of Public Health Veterinarians held a panel discussion on recent advances in rabies control. Current methods and problems in rabies control were touched on through a simple and effective device which gave the discussion unity—the story of the prevention of an imaginary rabies outbreak in an imaginary country. The essentials of the discussion follow.

KOPROWSKI: The events forming the basis for discussion during the present session occurred in June 1954 in the State of Simona of the Republic of Neutralia. I may add that Neutralia (with thanks to Evelyn Waugh) is imaginary and composite and represents no existing nation.

Two large dogs attacked a group of 13 children returning from school. Although all the children came into contact with the animals, some suffered only minor wounds or scratches, while severe wounds of the head and neck were inflicted by the biting animals on other children. Passersby and school teachers, alarmed by this savage and unprovoked attack, called police. Several policemen appeared on the scene immediately, and, as Neutralia permits the carrying of firearms, one of the men shot one of the biting dogs through the head because the animal could not be subdued. The other dog was taken into custody.

Before we start our discussion of these events, I would like to acquaint you briefly with the State of Simona. It comprises an area of 45,000 square miles of land and about 1,500 square miles of inland water.

Farm acreage accounts for about 65 percent of the land area, and many farm and domestic animals are kept, including large stocks of dairy cows. In the 25 percent of the country covered by dense forest, there is an abundance of wildlife—foxes, coyotes, beavers, wolves, deer, and so forth. Bats are also quite prevalent in this woodland as well as in the inhabited parts of the state.

Simona has a democratic, progressive government and a well-organized department of health and animal husbandry in the capital. The population of 12 million inhabitants is known for its fondness for domestic pets, particularly dogs, and there is, therefore, a large dog population.

Simona was supposed to be free from rabies during the period 1946–54. However, in all adjoining territories, and particularly in the neighboring State of Granchester, the disease had always existed in enzootic form so that the danger of infection being introduced was constantly present.

Now, after giving you this incomplete and sketchy information concerning the State of Simona, I would like to return to the accident which befell the children and ask the members of the panel some questions.

Did the policeman who shot the dog through the head act wisely? What should have been done with the living dog? Dr. Tierkel?

On Clinical Evidence

TIERKEL: It's too bad the policeman shot the dog through the head. He should have shot him through the heart since shooting through the head damages the brain and makes it less useful for diagnosis. The dead dog's head should be sent to the laboratory for examination for Negri bodies.

If it is possible to capture the biting animal, the apprehended dog should be watched for 7 to 10 days by a qualified observer to see if the animal shows clinical signs of rabies.

Most important, the captured dog should be allowed to die a natural death from the disease if he has it in order to increase the chances that his brain, on examination, will disclose fully developed Negri bodies.

The head should be removed, packed with ice in a watertight double container and sent to the public health laboratory by the fastest means of transportation. It should not be frozen because freezing often distorts and tears the structure of the tissues, making the examinations difficult.

Panel Members

Moderator of the panel discussion on rabies control was Dr. Hilary Koprowski. He is assistant director of viral and rickettsial research for the research division, American Cyanamid Company, Pearl River, N. Y.

The panel members were: Dr. Donald J. Dean, veterinary consultant, New York State Department of Health; Dr. Leland E. Starr, public health veterinarian, Georgia State Department of Public Health; and Dr. Ernest S. Tierkel, director, Rabies Control Activities, Communicable Disease Center, Public Health Service, Atlanta.

Also participating, toward the close of the discussion, were Dr. John P. Fox, professor of epidemiology, department of tropical medicine and public health, Tulane University of Louisiana School of Medicine; and Dr. T. F. Sellers, director, Georgia State Department of Public Health.

Of course, absence of Negri bodies in the brain does not conclusively prove that the dog is free from rabies. If there are no Negri bodies, one grinds up samples from various parts of the brain in a 10 percent suspension and injects this into the brains of mice to see if these test animals will become infected.

In practice, 10 to 15 percent of routine Negri-negative canine brains turn out to be positive on the mouse tests. It's a good idea to do a general autopsy of the dog but not if it delays shipment of the head to the public health laboratory.

Another point—the submaxillary salivary glands should be dissected from the head and shipped to the laboratory so that a test can be made for the presence of rabies virus in the saliva. Again, that is done by inoculation of a 10-percent suspension of the salivary glands into mouse brain. To preclude other encephalitides, a serum neutralization test is made with the virus isolated in mice. This procedure definitely establishes whether rabies is present.

DEAN: Fifteen to twenty-five percent of the dog heads examined annually in upstate New York prove rabid. Diagnosis is made in 95 to 98 percent of the rabies cases through finding typical Negri bodies in impression smears or sections of the dog's brain. The remainder are established as rabid by mouse inoculation tests. All street virus strains isolated in New York State to date have been negrigentic. Fixed rabies strains, on the other hand, early lose the ability to produce Negri bodies.

KOPROWSKI: Some African strains of rabies virus do not elicit formation of Negri bodies.

DEAN: Another problem in diagnosis is the presence of inclusions similar to Negri bodies when rabies doesn't exist—false positives. These structures are artifacts or inclusions associated with other viral diseases. They are particularly common in cats and raccoons. This is important since with hyperimmune antirabies serum decisions on human treatment have to be made earlier.

KOPROWSKI: The necessary steps, then, in determining whether rabies is present in a biting animal may be briefly outlined:

First, a period of observation by a qualified observer.

Second, general autopsy when the animal dies or is killed following clinical signs of rabies, with the use of good pathological procedures.

Third, shipment of the head, packed in ice but not frozen, to a suitable laboratory; or shipment of brain tissue and salivary glands, in glycerol-saline solution.

Fourth, laboratory diagnosis with (*a*) proper staining to reveal the pathognomic Negri bodies, which are sometimes hard to differentiate from nonrabies inclusions; (*b*) the inoculation of mice with brain suspensions which have been treated with penicillin or streptomycin, the observation of mice for sickness or death, and the examination of mouse tissues for Negri bodies; and (*c*) accurately performed serum neutralization tests.

Following these procedures, one of the biting dogs in Simona was diagnosed as suffering from rabies, and in all probability his saliva at the time of the attack upon the children was infectious. We shall return later to the outline of treatment of the children.

Meanwhile, we have to report regretfully that within 2 weeks several more confirmed cases of rabies in dogs were reported from other areas of Simona. After that the spread was rapid, and the disease was not confined to dogs. By the end of September the following cases of rabies had been recorded: 79 dogs, 14 cattle, 8 cats, 2 horses, 3 sheep, 7 foxes, and 1 deer. Almost all counties of the state were affected. What control methods were to be adopted by the State of Simona Public Health Department?

On Dog Vaccination

DEAN: There are two problems: canine rabies, to be solved by vaccination and dog control, and the more complex problem involving rabies in wildlife and farm and domestic animals other than the dog.

Dog control should obviously be tightened although this is difficult to achieve in rural areas. One should next vaccinate as many dogs as possible so as to impose a barrier of immune dogs between infected wildlife and man. Experience has shown that if 70 percent of the dog population is vaccinated, rabies can be controlled.

Two effective vaccines are available. One contains killed virus produced in mammalian brain tissue; it will afford protection for 1 year.

The other, the Flury strain of modified live virus rabies vaccine, produced in embryonated hen's eggs, protects for 4 years, and possibly for life. We have had extensive field experience since 1946 with both types of vaccine.

In upper New York State, where wildlife rabies is endemic in approximately one-third of the area, and where 314 to 1,175 laboratory confirmed cases have been reported annually since 1944, canine rabies has been dramatically controlled since the dog program was initiated early in 1946. We had 233 rabid dogs in 1944, 503 in 1945, and 377 in 1946, the year our control program started. Since then we have had only 16 to 48 annually despite the widespread and continuing wildlife infection.

From 1946 through 1949, brain tissue vaccine was the only product available for rabies prophylaxis. Its use declined during 1950 and 1951. In this period the attack rate for nonvaccinated dogs was 3 to 11 times as great as that for dogs vaccinated with killed virus rabies vaccine.

The modified live virus vaccine was first used in two of our counties in 1950. Its use grew steadily. It has been the only vaccine used in all county vaccination programs since 1952.

The greatest advantage of the modified live virus vaccine is that it confers more profound and more enduring immunity than the killed virus product. We have had fewer vaccination failures.

Of the rabid dogs reported in upstate New York since the rabies control program started in 1946, 82, or 13 percent, of the dogs were previously immunized with brain tissue vaccine. Of these animals, 52 died of rabies more than 1 month but less than 3 years after vaccination. In contrast there have been only 2 vaccination failures and 1 vaccine death among the 200,000 dogs that have been given the chick embryo product.

It is more effective and cheaper to vaccinate individual dogs every 4 years. Successful annual vaccination is difficult to achieve, particularly in areas where rabies does not exist or where infection is minimal.

Another advantage of modified live virus vaccine is that it appears to be safer for injected dogs. Most of us have witnessed untoward neurological side reactions in occasional animals given the killed virus vaccine. In the absence of controlled studies the exact incidence is unknown, but it is probably in the order of 1 to 3,000 or 1 to 5,000 animals injected.

It should be said, however, that many practicing veterinarians have vaccinated thousands of dogs with brain tissue vaccine without observing serious untoward effects. In our experience, neurological side reactions attributed to modified live virus vaccine have been limited to the death of 1 young puppy and 1 cat.

TIERKEL: Puppies should be vaccinated as early as 2 months of age, and they should be revaccinated at 1 year of age.

Two other countries besides the United States have done mass vaccinating with chick embryo vaccine, Israel and Malaya.

In Israel the jackal was the wild animal vector. Israel, like Simona, is surrounded by rabies-infected countries.

Israel got rid of rabies when it vaccinated all dogs and reduced jackal populations by poisoning campaigns.

Malaya was not able to get rid of rabies over years of trying phenolized, killed vaccine in local areas. But now that the country has carried out a well-organized national campaign with chick embryo vaccine, rabies has been wiped out.

On Registration and Licensing

KOPROWSKI: Now that we have discussed vaccination, we should take up the problem of registration and licensing of dogs as one of the methods of control.

TIERKEL: Registration and licensing of dogs is not the most important rabies control measure. It is basically a method for financially supporting rabies control work. It identifies the animals in the community and gives owners a sense of responsibility for their live property. Many areas make vaccination a prerequisite for a license. Still others combine vaccination and licensing in a single operation. The latter is ideal because it entails only one trip for the dog owner, one clerical operation all around.

DEAN: We favor permissive county legislation making vaccination a prerequisite for licensing in rabies-infected areas or in areas adjacent thereto. We agree, however, that effective rabies control can be achieved without linking vaccination to licensing.

STARR: In Georgia we have no State licensing of dogs, but Atlanta has had dog licensing as a city. In Atlanta dogs are vaccinated when they are licensed. However, the number of dogs licensed has been too small to reduce materially the incidence of rabies.

In 1952, vaccination clinics were set up by the city health department at a cost of $1 a dog, but the response was disappointing. Then in 1953, in desperation, the county paid the whole cost and made dog vaccination free. We put on a big ballyhoo—radio, television, loudspeakers on trucks. The veterinarians vaccinated their usual number, but the dogs came in. There are some things I don't like about free vaccination, but it got the dogs in.

On Roundup of Strays

KOPROWSKI: What should be done about stray dogs?

STARR: Rounding up stray dogs requires shelters, rolling equipment, staff. It is a public health problem.

TIERKEL: The roundup of dogs is a public health problem; it should be carried out by dog control men in uniform who are regarded as members of public health teams, not by dogcatchers who are regarded as looking for fees. The dog control men might also be invited to talk to school children on the diseases of dogs, proper care of pets, and importance of rabies control.

STARR: There is a big stray dog problem in Georgia. People have

lots of dogs, but they won't take responsibility for them. It's their dog until they have to vaccinate it.

In Atlanta about 12,000 dogs are always inoculated by private veterinarians. These are well-kept dogs which probably don't have rabies anyway. When dogs are rounded up for vaccination, the irresponsible owners hide their dogs when the truck comes along. They will, however, bring their dogs for vaccination if it's free. When dogs were finally vaccinated free in Atlanta in 1954, there were all kinds of dogs, ill-nourished, diseased, mangy dogs, dogs which should have been destroyed, but what can we do?

There is also a wild dog problem in Georgia—packs of wild dogs running around. The solution to the wild dog problem is to get people interested in getting rid of them.

KOPROWSKI: We want to talk later about wildlife rabies. Before that, I would like to ask whether the panel thinks leashing laws are effective? Dr. Dean?

DEAN: Leashing laws are needed in heavily populated areas to protect the public against dog nuisances. Leashing laws are important whether rabies exists in the area or not. The restraint of dogs, however, is not the most important aspect of rabies control. For example, only 10 percent of the rabid dogs in upstate New York are strays.

KOPROWSKI: Two other points should be mentioned in connection with rabies control in dogs. They are: first, the compulsory reporting of suspicious symptoms and deaths of animals, and, second, the building up of a good diagnostic service.

I think that all members of the panel agree that these are important parts of the framework of a rabies control program. But there is another very important part—the reduction of rabies in wildlife.

On Wildlife Control

DEAN: Wildlife control is the third and most difficult leg of a rabies control program. (First is dog vaccination, second is dog control.) Our knowledge of rabies in wildlife is scanty. Reporting in wild animals is improving but is obviously sketchier than reporting in dogs and cattle. In New York State we have had rabies in dogs since the early colonial era, but only recently have we recognized the disease in wildlife. We do not think that the upsurge in wildlife rabies is just a matter of better reporting. We think there has been an actual increase. Just why is the $64 question.

Wildlife rabies has a bizarre epidemiological and geographic pattern. For instance, skunk rabies is endemic in Iowa but appears to be spreading to other areas, such as the Dakotas. In the northeastern States, the fox is the principal vector of rabies.

In New York we know that wildlife rabies not only rises and falls with fox populations but also that foxes can be thinned out by trapping, bounty payments, and poisoning. Experience suggests that reductions of the fox population to one fox a square mile will reduce vulpine rabies. Present techniques for controlling wildlife, principally trapping and den gasing, are too expensive for widespread economical use.

Poisoning offers hope for the future, but there is the problem of species selectivity. After all, one does not want to poison dogs and domestic animals indiscriminately and to expose children to unnecessary hazards. Our conservationists are actively exploring the use of species selective baits. We confidently believe that our canine rabies problem will disappear once wildlife rabies has been eradicated.

STARR: Trapping certainly works, especially if you have dog vaccination too. But you must have community support. In one Georgia county we poisoned. Cattlemen put out eggs, hamburger, and wieners with strychnine. The bait disappeared, but we didn't find any dead foxes.

Pennsylvania spent $116,000 poisoning in 16 counties. The incidence of rabies fell, but we don't know whether the poisoning did it or not.

KOPROWSKI: There is something important to rabies control, both in wildlife and in domestic animals, which we haven't touched upon, and that is publicity. The public must be kept informed of its responsibility.

The rabies control measures which have been described may be summarized briefly as follows:

First, the vaccination of at least 70 percent of the dog population, compulsory if necessary, since other control measures without vaccination have proved unsatisfactory.

Second, elimination of strays through registration, licensing, and restraint of dogs.

Third, reporting of suspicious symptoms and deaths and the building up of adequate diagnostic services.

Fourth, the reduction of wildlife species by poisoning, trapping, shooting, and so forth.

Fifth, a publicity campaign designed to make the public aware of the importance of the above measures.

On Vaccination of Animals

KOPROWSKI: Now, I would like to have the members of the panel discuss briefly the vaccination of animals other than dogs, chiefly cats and cattle, since they, too, were involved in the epidemic in Simona.

TIERKEL: We didn't include cats in our mass vaccination programs. Private owners can vaccinate cats. We find that rabies in cats disappears when dog rabies is under control.

DEAN: This is undoubtedly true where only canine rabies exists. Our experience indicates that cat rabies is associated with the disease in foxes.

KOPROWSKI: What about the vaccination of cattle?

STARR: Loss of cattle as a result of rabies was so heavy in Georgia that the State legislature considered free vaccination of cattle.

We tried chick embryo vaccine on test herds. On the last round, we inoculated 19 herds in a rabies endemic area, leaving 25 percent unvaccinated for controls (1,107 animals inoculated in all), but since none of the animals were attacked

by rabies, the experiment was inconclusive except to show that on this round the avianized rabies vaccine did not harm the animals.

We then purchased cattle, inoculated them, and challenged with rabies. Five of the 16 vaccinated cows died, but 12 of the 16 unvaccinated cows died of rabies.

It should be noted that the 5 deaths occurred in animals which had been vaccinated as calves. All animals vaccinated as adults survived challenge. This indicates that the immunity induced is not as solid in young adults and that young animals should be revaccinated.

KOPROWSKI: While all these control measures were being discussed in Simona, rabies spread through wildlife species to an alarming degree. In two places bats were reported to have attacked children. However, before we go over to the bat problem, it is perhaps advisable to discuss a comprehensive program of ecologic studies aimed at elucidating the following points:

How many species are involved?

Is there a possibility of silent carriers?

Do all animals infected with street virus die?

TIERKEL: As Dr. Dean has mentioned, one of the first problems we must attempt to solve is a quantitative relationship between population density of wild animal vectors, such as foxes, and prevalence of the disease in those populations. We must find the population density threshold which will no longer support a rabies epizootic.

The bizarre geographic and cyclic pattern of sylvatic rabies outbreaks has suggested to some the possibility of a symptomless carrier state in foxes and skunks. Along this line, information must be obtained on whether there is natural immunity and recovery in these animals.

Still others feel that there may be unknown reservoirs of rabies in the wild, such as in various species of small mammals which may have been overlooked. This also suggests a possibility that there may be other routes of transmission in wild animals.

Other problems which should be studied are velocity of the geographic movement of infection and the relationship of bat rabies to the disease in terrestrial animals.

On Bat Rabies

KOPROWSKI: What about bat rabies?

The two bats which were caught in Simona after attacking children were forwarded to the nearest public health laboratory and subjected to diagnostic studies. Mice inoculated with their brain or salivary gland tissue developed rabies.

TIERKEL: Many bat species are turning up rabid. It started in 1953 when a Florida yellow bat attacked a child. Then in Pennsylvania a woman was attacked by a different species of bat. These episodes aroused the interest of public health workers in many areas and prompted surveys throughout the country.

Thus far, rabid bats have been found in Florida, Pennsylvania, Texas, California, and Montana. Over 40 isolations have been made from 6 different species of insectivorous bats of free-living and colonial or cave-dwelling varieties.

In Texas, Lt. Col. Kenneth F. Burns reports that 65 percent of 207 pooled bat serums showed rabies antibodies by serum neutralization test. There is much research work that needs to be done to determine the epidemiological significance of these findings.

KOPROWSKI: It's hard to recognize rabid bats since we don't know what to expect in the behavior of a normal bat. According to Colonel Burns, it's hard to distinguish the way bats act when rabid from the effect of DDT, which also affects the nervous system.

Are insectivorous bats as great a menace to the animal population as the hematophagous species?

Is there evidence for symptomatic carriage in bats?

TIERKEL: We do not have enough clinical experience with bats so we must rely on laboratory findings. It has been observed that when vampire bats in Latin America are rabid they often fly in the daytime instead of at night. On the other hand, vampires are capable of transmitting rabies to people and animals without showing visible signs of illness. We have yet to discover whether this is true of the rabid insectivorous bats found in the United States.

DEAN: Anything we say about the bat problem is premature. We first thought that only free-living bats were infected but then found rabies in colonial bats as well.

There are two schools of thought. One group thinks that bat rabies in this country represents an extension of the disease from Mexico, Trinidad, or South America, the invasion of a new disease among bats in the United States. Rabies among vampire bats south of the border is an old problem. In this connection migratory bats have been tagged traveling as far as 800 miles. There is a banding program under way to check this. Another group feels that rabies in bats has existed in this country for many years. Knowledge concerning bats and bat rabies is grossly inadequate.

We note that there is an unusually long incubation period in bat rabies with the Florida experience indicating that clinical illness lasts longer before death than in other species. We don't know how bats get the disease except from other bats, but we do know that they pass it on to other species. Unprovoked attacks by rabid bats suggest that they have undergone mental changes.

SELLERS: The finding of infected bats in so many widely separated areas of this country seems to me to strongly indicate that rabies has been in our bats for a long time.

KOPROWSKI: To summarize our knowledge of bat rabies, then:

All bats are suspect, insectivorous as well as hematophagous.

Brain and salivary gland tissue of any bat which attacks a human being should be studied in a laboratory for the presence of rabies virus.

Colonel Burns' finding of rabies antibodies in blood pools of asymptomatic bats caught in enzootic areas, a finding which should be confirmed by other workers, suggests that bats may be a reservoir of the disease.

On Human Prophylaxis

KOPROWSKI: Now we have to return to the treatment of the children who were bitten in Simona. What should be done?

Since time is getting short, I would like to limit our remarks on human treatment to two items: first, the use of antiserum, and, second, preliminary results with chick embryo vaccine.

SELLERS: Georgia has been using rabies antiserum since 1948. We've given it to 60 or 70 individuals, limiting its use to those with severe bites on the face, neck, or hands, and to cases where the exposures were not more than 48 hours old. In all instances the antiserum was followed by appropriate courses of antirabies vaccine, and during this time there were no deaths among those receiving vaccine alone. We therefore have no convincing field evidence of the part played by antiserum in protection. The laboratory protocols, however, are very convincing, and I definitely endorse the use of antiserum in principle.

DEAN: Hyperimmune serum promises to be of value. Since the serum is of equine origin, however, it possesses the hazards inherent in products of this nature. We have observed two serious cases of serum sickness among 35 treated individuals.

FOX: At Tulane University, we have been trying the live Flury virus vaccine in prisoner volunteers to see if it can be used to replace current forms of the Pasteur treatment. The volunteers cooperating are inmates of the Mississippi and Louisiana State prisons. All of our work has been with high-passage virus, about 180th passage level, although 3 or 4 years previously Dr. Koprowski used the low-passage virus, now used for dogs, in about 30 persons. In all, we have given one or more inoculations of this virus to about 170 or 180 persons, and one important fact is that we have observed no adverse effects.

The more important point, however, is that, although we know the Flury virus vaccine works well in dogs, we are still trying to find out if it does in man. A single injection of two dog doses does not induce development of detectable neutralizing antibody. However, it apparently has some effect because a second booster injection of equivalent size usually does produce antibody. Increasing the amount of virus inoculated by giving multiple doses often, and in proportions increasing with the amount, gives rise to antibody. Because of this we feel that the Flury virus probably does not multiply in man, at least when placed extraneurally.

The question arises at this point as to whether demonstrable antibody is essential to the protection of man. Without challenge experiments this cannot be answered. Our feeling is that appearance of antibody is our only possible index of success and that, before we can recommend Flury virus vaccine in place of currently accepted vaccines, we must find a way of using it that will result in as uniform an appearance of antibody as that following current forms of Pasteur treatment. Our goal, of course, is an effective vaccine free from the risk of neuroparalytic accidents.

Currently, we are working with small intramuscular or intradermal inocula. Fairly good results have followed a schedule of 4 doses, 5 days apart. We are now trying more doses with a shorter interval. Because in giving the Pasteur treatment one is working against time, we have set 15 days as the maximum length of a practical dose schedule, even though we have evidence that good results follow as few as 2 inoculums spaced 30 days or more apart. Also, since vaccine may have to be given together with hyperimmune serum, we are trying to determine whether the active response to vaccine is altered by the presence of passively acquired antibody.

DEAN: The use of the Flury strain in man is still in the experimental phase. It is important also that we emphasize presently approved methods of treatment. Thorough local treatment of wounds with 1 percent aqueous zephiran or 20-percent soap solution remains of paramount importance. Local treatment should be followed by a series of injections of brain tissue vaccine containing killed virus with or without the use of hyperimmune serum.

KOPROWSKI: I would like to tell you about the results of the use of antiserum in Iran last summer. In August, a rabid wolf (the virus was isolated from the animal's brain after its death) bit 27 people, of whom 17 received severe head and neck bites. Of the 5 persons who received Semple type vaccine alone, 3 died, while of the 12 persons receiving serum and vaccine, only 1 died. One child, who had a penetrating wound of the head and direct exposure of the brain to the saliva of the biting animal, survived—he was given 6 injections of serum at 2-day intervals, followed by vaccine.

Thus, we are leaving Simona and Neutralia and hope that when we return next year rabies will be eradicated. I should remind you, however, about the epigram of Jerrold concerning hope. "In all the wedding cake, hope is the sweetest of the plums."