RABIES

edited by
Yasuiti Nagano
and
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PREFACE

Today, with the ption exceof Oceania and the Antarctic, the whole world is harassed by the threat of rabies. Although the exact number is not known, several thousand people die of rabies each year. The number of persons receiving prophylactic vaccine, that is, the number of persons in danger of rabies infection, is over one million a year. The number of domestic dogs, cats and other pets and wild animals, such as foxes, found to be rabid has been increasing yearly.

Rabies thus poses a major threat to mankind, and its total eradication greatly desired. Yet, although the disease has been known to mankind since ancient times, there are still many aspects of rabies which are not understood.

For example, we do not know how rabies epizootics occur among wild animals nor do we know a sure way to eradicate such epizootics. Only recently did we learn of the airborne transmission of rabies from bats to humans.

In postwar Japan, a major rabies outbreak lasted until 1956, however, for the past 15 years there have been no outbreaks among humans or animals. Since there is no wild life reservoir of rabies in Japan, our only concern is the control of rabies in the dog population. The vaccination of dogs has been vigorously enforced and in 1956, the last year of the outbreak, more than half of the 1,600,000 registered dogs in Japan were vaccinated. However, the major source of infection was unregistered dogs, estimated to number between 1 and 1.5 million at the time. It is hard to believe that the vaccination of a little over half the registered dogs checked the spread of rabies in the total dog population, but there is no other credible explanation.

The advisability of injecting immune serum together with postbite vaccine inoculation is still a source of controversy.

To prevent rabies infection, the replication of the virus in the central nervous system must be stopped. The best method would be to prevent the virus from ever reaching the central nervous system. However, we do not know whether the rabies virus is transmitted to the central nervous system through the peripheral nerves or through the blood circulation.

There are numerous other matters which need to be investigated and clarified before rabies can be eradicated. The Japan-U.S. Co-

operative Medical Science Program, Panel on Viral Diseases held a working conference in Tokyo on October 12, 13 and 14, 1970, to promote research on rabies. This volume comprises the proceedings of that conference.

I would like to express my gratitude to Prof. M. Matumoto of the University of Tokyo, Dr. K. O. Phifer of the National Institutes of Health, U.S.A. and Miss H. Komatsu of The Kitasato Institute for their editorial assistance.

October, 1971 Yasuiti NAGANO

CONTENTS

RABIES

Historical Review of Rabies in Asia

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Perhaps the earliest reference to rabies in Asia is one that occurs in the pre-Mosaic Eshnunna Code which predates the better known code of Hammurabi of ancient Babylon in the twenty-third century B.C. In this code the following excerpt is found: "If a dog is mad the authorities have brought the fact to the knowledge of its owner; if he does not keep it in, it bites a man and causes his death, then the owner shall pay two-thirds of a mina (40 shekels) of silver. If it bites a slave and causes his death he shall pay 15 shekels of silver."

Activity in the study of rabies in Asia began in the post-Pasteurian period about the turn of this century. Institutes were established in a number of Asian countries, the most notable of which were in India (Kasauli, Coonoor), Indochina (Saigon, Hanoi), Iran (Teheran), and Java (Bandung). Most of these served as centers for the production of rabies vaccine and also for administration of the vaccine to exposed people. As methods for the preservation and distribution of rabies vaccine improved over the years, many of the Asian countries began to decentralize rabies treatment centers making it no longer necessary for exposed persons to undertake long voyages for anti-rabies vaccination regimens.

At least two notable original contributions to the prevention and control of rabies have emanated out of this historical backdrop of rabies research in Asian institutes. The first was from India in 1919 when David Semple, at Kasauli, introduced the first vaccine produced from fixed rabies virus inactivated by treatment of heat and phenol. The Semple vaccine eventually became the biologic of choice in many countries of both the eastern and western hemispheres. The other contribution was the development and utilization of the first practical vaccine for dogs in 1921 by the Japanese workers, S. Umeno and Y. Doi. The success of this canine vaccine, a phenolized rabbit brain product, stimulated interest in trials of dog vaccination in the United States which led ultimately to the eminently effective use of single-dose canine vaccination for the control of dog rabies.

Definitive information on the status of rabies in Asian countries was first made possible by the annual World Rabies Survey begun in 1959 by the Veterinary Public Health Unit of the World Health Organization. The data collected in these annual surveys are based upon replies to a questionnaire (Annex) sent to each member country. The questionnaire requests data relating to the incidence of rabies in animals and man, the incriminating animal vector species, the number of human post-exposure immunizations administered (with and without serum), the number and types of reactions to biological prophylaxis, rabies mortality in treated and untreated individuals and the types and quantity of rabies vaccine produced for use in man and animals.

It is interesting to note that in the decade covered by annual WHO surveys (1958 through 1968), the same five areas continued to report that they were free of rabies. These are Taiwan, Hong Kong, Japan, Malaysia, and Singapore. Taiwan reported that the last case in man was identified on 28 December 1958 and the last case in a dog on 8 March 1959. The last case reported in Hong Kong was in a dog in November 1955; in Malaysia, in January 1958; in Singapore, in a dog in 1953; and in Japan the last human case was diagnosed 16 April 1954 and the last canine case, August 26, 1956. Malaysia has continued to be reported as a rabies-free area, but has reported occasional animal cases and human exposures in its northernmost province.

Included in the responses to the annual questionnaires are comments from the rabies endemic countries which point out that the morbidity and mortality statistics indicated in their reports by no means reflect the actual experience in rabies in their countries. The meager data available to the respondants for the most part cover only those cases in man and animals which occur in areas near institutes engaged in rabies work.

Of those countries in Asia where rabies has continued to be a major communicable disease problem, the two which stand out are India and the Philippines, especially in terms of human mortality. Other countries recognizing it as a sizable problem are Thailand, Burma, Pakistan, Ceylon, Indonesia, and Vietnam. The eighth WHO report (1966) points out the variance in Thailand between the nineteen officially reported human cases and the unofficial observation of several hundred during the year. This discrepancy between official and unofficial data is common in most countries and

is, of course, a reflection of the poorly developed surveillance network in communicable diseases. Burma declared, at the WHO regional seminar on zoonoses in Southeast Asia last year, that the SEARO of WHO should review its communicable disease activities, citing that rabies control programs should be given higher priority in the assignment of projects. Sporadic outbreaks and incidents have been reported in Laos, Cambodia, and Korea.

The following highlights have been recorded regarding the spread of rabies in each of the reporting countries: Cambodia feels that the disease is endemic throughout the country even though most cases have been diagnosed in and around Phnom Penh because of the availability of nearby diagnostic services. In India the disease has been distributed rather ubiquitously throughout the country and indeed seems to be on the increase in some areas. The Philippines reports that the disease is endemic and that cases occur in all provinces. Korea reports moderate incidence throughout the country. In Laos the disease has been identified in the urban regions of Vientiane and Luang Prabang. Mongolia reports an increase of the spread of rabies in the Central Region, particularly in wildlife. In Pakistan the disease has been occurring endemically in both eastern and western wings of the country with no special trend of its spread. Ceylon reports highest incidence of rabies in the Western Province, with the city of Colombo and the Central Province next in incidence rank. Vietnam has reported that the rabies problem has grown in the urban centers of the country.

In all of the Asian countries, dogs have been identified as the principal vector animal in transmission to man and other animals. Among the wild fauna most often implicated as both vectors and natural reservoirs are wolves in Iran; wolves and jackals in Afghanistan; jackals in Pakistan and Nepal; jackals and mongooses in India; khorsacs (a small steppe fox) in Mongolia.

The great majority of Asian countries reported Semple vaccine as the type of vaccine produced for use in post-exposure immunization of man, with little or no change in the ten year period from 1958 to 1968. The areas listing production of Semple vaccine in the first report (1958) were Burma, Cambodia, Taiwan, Hong Kong, India, Indonesia, Iran, Malaya, Philippines and Thailand. Japan reported producing ultraviolet irradiated as well as Semple type vaccine. In the tenth report (1968), the survey revealed that Fermi type vaccine was produced in East Pakistan, Japan, and presumably

in Afghanistan, whereas Semple vaccine was produced in West Pakistan. Taiwan and Japan reported producing U-V vaccine. Sheep and goats have served as the animal of choice for the production of these brain tissue vaccines in all of the Asian countries except Indonesia which has used monkeys as the source of vaccine production. In Japan, Thailand, and Taiwan rabbit brain is also used for human rabies vaccine. The production of anti-rabies serum for passive immunization in severe exposures seems to have been limited over the ten year period to Taiwan, Japan, India, Indonesia, Iran, and Thailand. All of these centers produced equine hyperimmune antiserum.

With the exception of Japan, Taiwan, and to some extent, Korea, Ceylon and Thailand, most of the vaccine produced for animal use in the Asian countries had been for post-exposure immunization of exposed animals. Single dose pre-exposure prophylaxis of dogs has played a minor role in the rabies control activities of a majority of the Asian countries. Successful demonstrations of mass canine vaccination programs have been made by countries including Japan, Malayasia, Taiwan, and the eastern province of the island of Negros in the Philippines, and to varying degrees, cities like Bangkok and Colombo. A variety of types of animal vaccines have been produced in Asia. Like the human product, most of it has been the Semple vaccine produced in sheep and goat brains. Besides the latter, Japan, for instance, has produced goat brain vaccine inactivated by ultraviolet irradiation and by thimerosal for use in animals. Afghanistan has made Fermi type sheep brain vaccine for animals. Burma, India (Coonoor), Korea and West Pakistan have produced varying quantities of LEP Flury vaccine for use in dogs.

In 1958 a preponderence of areas in Asia reported using the Sellers stain and tissue-impression technique, along with animal innoculation, usually the mouse, as the standard techniques for laboratory diagnosis of rabies. In the early 60s a few institutes experimented with complement fixation and gel-diffusion techniques. Some began to add the serum-virus neutralization test for ultimate confirmatory diagnosis. By the time the tenth report was made available, a good many of the major institutes and laboratories in Asian countries had begun to use the fluorescent antibody test for identification of the rabies virus in tissue specimens submitted for diagnosis.

It seems appropriate to note in closing that one of the greatest contributing factors of the past in the standardization and adoption of effective techniques of diagnosis, vaccine production, immuniza-

tion practices and control methods was the highly successful WHO working conference on rabies for countries of Asia held at Coonoor, India, in July 1952.

RABIES QUESTIONNAIRE NO. 11

(covering the year 1969)

Last date for completion and return (one copy only) to the following address, 31 October: 1970:

Chief, Veterinary Public Health
World Health Organization
Avenue Appia
1211 Geneva 27
Switzerland

1. Name and address of laboratory, institute, medical or veterinary service:

2. (a) Is rabies now present in your country? . . . . . .
   (b) If present, does this represent an introduction during 1969? If so, how was it introduced? . . . . . .
   . . . . . .
   . . . . . .

3. If rabies is present in your country
   (a) Which animal species have been found rabid in 1969? Please indicate the number of reported cases in each species, if known.

Name of animal	No.	Name of animal	No.
. . . . .	. . .	. . . . .	. . .
. . . . .	. . .	. . . . .	. . .
. . . . .	. . .	. . . . .	. . .

   (b) Which animals were the most important sources of bite wounds for man that required rabies prophylactic treatment?

Name of animal	No. of humans who received rabies treatment	Name of animal	No. of humans who received rabies treatment
. . . . .		. . . . .	
. . . . .		. . . . .	
. . . . .		. . . . .	
. . . . .		. . . . .	
. . . . .		. . . . .	

4. What has been the trend in the spread of rabies in your country? (Please add recent maps indicating the prevalence of the disease, with reference to dogs, cats and wildlife vectors if you have not submitted these within the last five years.)

5. Human exposures:

(a) Number of human beings who received the following specific antirabies treatment:

Vaccine alone . . . . . .
Vaccine and serum . . . . . .
Serum alone . . . . . .

(b) Number of serious systemic reactions to biological prophylaxis:

Paralytic accidents (vaccine) . . . . . .
Serum sickness . . . . . .

(c) Total number of human deaths from rabies . . . . . .
(specify animal giving fatal bite, if known)

	Incubation period		
	0–30 days	31–90 days	Over 91 days
(i) Number of deaths in untreated individuals (no vaccine or serum)			
(ii) Number of deaths in individuals receiving:			
vaccine alone			
vaccine and serum			
serum alone			

(For treatment failures, we would welcome any further information such as interval of delay in beginning treatment, number of vaccine doses received, etc., on separate sheets.)

6. Type(s) and amount of vaccine for animals and/or man produced in your laboratory (e.g. Fermi Sheep brain, etc.); specify as requested below. State also for each type of vaccine produced which potency test, if any, is used:

Animal vaccine

Type	Quantity produced in doses	Tissue concentration	Potency test
. . . . .	. . . . .	. . . . .	. . . . .
. . . . .	. . . . .	. . . . .	. . . . .
. . . . .	. . . . .	. . . . .	. . . . .

Human vaccine

Type	Quantity produced in doses	Tissue concentration	Potency test
. . . . .	. . . . .	. . . . .	. . . . .
. . . . .	. . . . .	. . . . .	. . . . .
. . . . .	. . . . .	. . . . .	. . . . .

7. Species of animal in which antirabies serum or gamma-globulin for specific treatment is produced in your laboratory; specifythe amount in millilitres.

Species of animal	Amount in ml	Number of international units per ml
. . . . .	. . . . .	. . . . .
. . . . .	. . . . .	. . . . .
. . . . .	. . . . .	. . . . .