BULLETIN No. 8
FROM THE
INSTITUTE FOR MEDICAL RESEARCH
FEDERATION OF MALAYA

RABIES IN MALAYA

By
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and

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DEPUTY DIRECTOR OF VETERINARY SERVICES
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RABIES IN MALAYA

INTRODUCTION

This Bulletin is written to provide doctors and veterinary surgeons with a short, readily accessible account of present-day knowledge of rabies. As it is written for the clinician and field worker, the laboratory techniques used will be described briefly in the appendices only. Previous Bulletins of the Institute dealing with rabies were issued in 1924 and 1925: a short account of rabies and Pasteur treatment by Kingsbury (1924), and a joint account of rabies in man and animals together with a description of laboratory techniques, by Kingsbury and Symonds (1925).

Rabies has been known in Malaya since 1884, although numerical records of its incidence are available only from 1924 onwards. Since 95 per cent. of all laboratory-confirmed cases of rabies in animals in Malaya since 1924 have been in dogs, it is evident that the dog is the principal, if not the sole vector of rabies in this country. Prior to 1945 the majority of cases of rabies occurred in the States bordering on Thailand. A few sporadic minor outbreaks were reported in other States but were quickly suppressed. In 1945, possibly due to the arrival of large numbers of Allied troops from India and Burma, many of whom brought their dogs with them, the disease was detected in Province Wellesley and Perak. There was, at that time, no Civil Administration to enforce importation restrictions. Sporadic cases continued to be reported annually from Province Wellesley, but in Perak the disease reached serious proportions and remained at a high level of incidence until 1953. There was no extension southwards, however, until 1952, when a sudden spread to Selangor occurred. The severity of this outbreak prompted the introduction of more energetic and widespread control measures than had previously been in use: the compulsory mass vaccination of dogs in all rabies-infected States was introduced and a vigorous campaign to eliminate ownerless and unvaccinated dogs was initiated. The success of these measures is shown by the following data:

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Selangor</th>
<th>Federation of Malaya</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td>105*</td>
<td>198</td>
</tr>
<tr>
<td>January to June, 1953</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>July, 1953 to December, 1954</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

It is to be emphasised that these figures refer only to cases confirmed as rabies in the laboratory. They do not include clinical cases not submitted for laboratory confirmation.

In April, 1954, it was possible to declare Malaya free from the disease and to permit the uncontrolled movement of dogs about the country.

Malaya is fortunate in having no known wild animal reservoir of rabies; the control of the disease in domestic animals is sufficient to eradicate it.

The chicken embryo vaccine used for immunization of dogs in the 1952-1954 control campaign gave results superior to those obtained with the brain tissue vaccine used previously in Malaya. Chicken embryo vaccine is reported to confer immunity for at least 3 years in adult dogs (Tierkel et al, 1953). If this type of vaccine were used, therefore, it is probable that the following measures would ensure that any future introduction of the disease would be of minor importance, as the outbreak would be self-limiting:

(i) the maintenance of a cordon of immunized dogs to a depth of 30-50 miles, depending on topography, along the Malayan side of the Malaya-Thailand border;

* In Selangor there were no cases before April, 1952.
Erickson et al (1954) described two cases in which the main features were vomiting, polymorphonuclear leucocytosis and focal pneumonia with only slight central nervous system abnormalities. This draws attention to the need to keep rabies in mind when obscure fatal diseases with signs of central nervous system disorder are encountered.

Clinical pathology.—There may be a relative or absolute polymorphonuclear leucocytosis. The cerebrospinal fluid is usually normal: pressure is not raised; the protein may be slightly increased; the cell count rarely exceeds 100 lymphocytes per c.mm. There is usually marked albuminuria and may be glycosuria.

Clinical diagnosis.—The definitive diagnosis of rabies during life depends on isolation of the virus from the patient’s saliva. This is seldom done and a negative result would not exclude the disease. The diagnosis is evident if the following are present:

1. A history of a bite.
2. Sensory symptoms at the site of the bite.
3. Excitement and convulsions.
4. Hydrophobia.

Apart from the isolation of virus from saliva, certain diagnosis can be made only from histological examination or animal inoculation of brain obtained at post mortem. Saugrain (1952) described 4 typical cases in which isolation was attempted from saliva and cerebrospinal fluid. Virus was obtained from saliva in one case and not at all from the cerebrospinal fluid.

In the differential diagnosis the following conditions must be considered:

1. Poliomyelitis may closely resemble the paralytic form of rabies. There is, however, seldom a history of a bite and local sensory symptoms do not occur if there is one.

2. The viral encephalitides must be considered in the same context.

3. Tetanus may follow bites but the incubation period is generally shorter (usually 6-14 days). Tetanus spasms do not completely relax between attacks and are not evoked by water. There is general spasticity as compared with the flaccidity of rabies between spasms. The typical trismus of tetanus is not found in rabies.

4. Hysteria precipitated by the fear of rabies after a bite must be borne in mind—the “incubation period” is short.

5. Neuroparalytic accidents of vaccine treatment may be very difficult and, if fatal, sometimes impossible to differentiate from rabies. They are dealt with in greater detail below. Negri bodies are not found in the brains of people dying of paralytic accident, but, as they are not demonstrable in every case of rabies, failure to find them does not exclude rabies.

Prognosis.—Once the disease is established death is believed to be inevitable—commonly within 5 days. Recovery from rabies has never been proved although in view of the difficulties of ante-mortem diagnosis especially in paralytic cases, it is not impossible that such cases have rarely occurred.

Treatment.—There is no specific treatment. Sedatives will be necessary—probably barbiturates in early stages of anxiety. Later, the strongest narcotics and even anaesthesia (e.g. pentothal) may be necessary to control maniacal attacks. It is desirable to spare the patient hydrophobic spasms by all possible means, remembering that death is inevitable.

Late in the disease there is often difficulty in keeping the mouth and throat clear of ropy tenacious saliva. It is essential that the nursing staff should be warned that the saliva is infective. It may for example get on the patient’s hands and he may scratch someone during a paroxysm.
Rabies in Man

The Clinical Picture

Rabies is an acute infectious virus disease of mammals transmitted by the saliva of a rabid animal. It is characterised by a rather long incubation period, symptoms of encephalomyelitis including acute excitement and paralysis, and death.

Incubation period.—Although it varies from ten days to about seven months it is usually about six weeks. Incubation periods longer than three months are uncommon. Bites with large and deep lacerations, bites in children, and bites of the head, neck and upper limbs, are all associated with a short incubation period. Reasons for more rapid onset in bites of the head and neck are: (1) the head and neck are not usually covered with clothing which, elsewhere in the body, often absorbs much of the saliva which might be left in the wound; (2) bites of the head and neck tend to be severe as they imply a much more determined attack than do, for example, bites of the leg; (3) these areas are very abundantly supplied with sensory nerves and muscle tissue is especially superficial. They are also the areas with the thinnest skin. It is probable that the infection spreads to the central nervous system along peripheral nerves so that the shorter path from the head and neck to the brainstem may also be a factor.

Premonitory stage.—This lasts for from one to four days. There is usually low pyrexia, malaise, anorexia, nausea, and often headache. Respiration is often so shallow that the patient has to stop speaking and take a long sighing breath. Changes in personality and nervousness are common and there may be attacks of acute anxiety. In more than three quarters of cases there is some form of abnormal sensation around the causative wound. It may be itching, aching, stabbing pains, etc., and there may be mild local inflammation due to scratching or the application of counter-irritants. The patient may be hypersensitive to stimuli such as cold, draughts, bright lights, noises. He may complain of pain in the back, epigastrium or elsewhere. Vomiting may occur, often associated with severe headache.

Stage of excitement.—The majority of patients show increasing excitement often continuing until death which usually occurs within one to three days. Aimless wandering about the room is common and speech is often incoherent. Periods of acute mania may alternate with depression and acute morbid anxiety. Convulsions which may be fatal often occur during these maniacal attacks. Pyrexia is usual and may reach 103°F. The classical, although not constant, symptom of hydrophobia is very characteristic: when the patient tries to drink, or even sometimes thinks of drinking, the muscles of the pharynx go into sudden acute spasm so that any fluid taken is violently ejected and the head is thrown back. Cases with typical hydrophobia yet able to swallow solids have been described. The respiratory muscles may be affected causing apnoea followed by cyanosis and severe dyspnoea. In the late stages Cheyne-Stokes breathing is not uncommon. The patient is unable to swallow his saliva and becomes dehydrated due to lack of fluid intake. The saliva, which is infective, becomes very ropy and tenacious. Tremors and weakness especially of the ocular and facial muscles may be observed. The reflexes may be increased in the early stages but later are usually absent. There may be some stiffness of the neck but Kernig's sign cannot be elicited. Babinski's sign may be positive.

Stage of paralysis.—Patients seldom live longer than three days after the onset of acute excitement and may die during this stage. Those who survive the acute excitement usually pass into a stage of increasing apathy and paralysis leading to coma and death, often within a few hours.

Such patients may, however, live in this stage of apathy and paresis for as long as ten days. Consciousness is usually retained until shortly before death. Rare cases are predominantly paralytic from the onset and may present as (1) Landry's ascending paralysis, (2) transverse myelitis, or (3) a paralysis indistinguishable from poliomyelitis, or a neuraparalytic accident of vaccine treatment.
Erickson et al (1954) described two cases in which the main features were vomiting, polymorphonuclear leucocytosis and focal pneumonia with only slight central nervous system abnormalities. This draws attention to the need to keep rabies in mind when obscure fatal diseases with signs of central nervous system disorder are encountered.

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4. *Hysteria* precipitated by the fear of rabies after a bite must be borne in mind—the "incubation period" is short.
5. *Neuroparalytic accidents* of vaccine treatment may be very difficult and, if fatal, sometimes impossible to differentiate from rabies. They are dealt with in greater detail below. Negri bodies are not found in the brains of people dying of paralytic accident, but, as they are not demonstrable in every case of rabies, failure to find them does not exclude rabies.

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Late in the disease there is often difficulty in keeping the mouth and throat clear of ropy tenacious saliva. It is essential that the nursing staff should be warned that the saliva is infective. It may for example get on the patient's hands and he may scratch someone during a paroxysm.
AETIOLOGY

The causative organism of rabies is one of the larger viruses (100-150 μ in diameter). It is most easily isolated from the brain or salivary glands of infected persons or animals. The virus can be isolated from nearly all animals dying of rabies. Transmission depends on the ability of the virus to reach the salivary glands and multiply there, and different strains of virus vary in their ability to do this. Probably only about 75 per cent. of rabid dogs have infective saliva. Diffusion of the virus into the tissues from a bite is ensured by the hyaluronidase in dog saliva—the absence of hyaluronidase from human saliva probably explains why it is less constantly infective (Lépine, 1954). The parotid gland is less often infected than the submaxillary. Other glands such as the lachrymal, adrenal, and the pancreas have been found to contain virus.

Infected tissues stored in neutral glycerol retain infectivity for several weeks at room temperature and for months in the refrigerator (about 4°C). The virus is destroyed by heating for 15 minutes at 50°C, for 5 minutes at 60°C, or for 2 minutes at 100°C (Lépine, 1954).

The virus which causes the natural disease is known as “street virus”. When such a virus is passed in series by injection into the brain through about fifty of the same species of animal the incubation period in the animal shortens progressively. In the rabbit, for example, it shortens from about 21 days in early passages to 6 or 7 days after which the incubation period remains constant—the virus is then said to be a “fixed virus”. Fixed virus is unable to pass from the central nervous system to the salivary glands; it does not normally produce Negri bodies; and it will not ordinarily infect the animal except by injection into the brain. Fixed virus killed with phenol is used in Semple-type vaccines for the prophylactic treatment of persons bitten by rabid dogs. The rabies virus can also be grown in the chick embryo and one strain (Flury), after passages in the brain of chicks, and then in chick embryos, became non-pathogenic for dogs by intramuscular inoculation and it is this strain which is used to prepare the “chicken embryo” canine vaccine which was so successful during 1952-53 in the eradication of rabies from Malaya. Previously, a less successful vaccine prepared from calf brains in the same way as human Semple-type vaccine, was used for dogs.

PATHOLOGY

Central nervous system: Gross appearances.—General congestion of the meninges associated with some degree of cerebral oedema is usual. The cut surface of the brain is congested. When the bite is in an extremity the cut surface of the spinal cord frequently shows unilateral pinkish-grey discoloration and obliteration of the normal markings, most marked in the posterior horn. It can be seen microscopically that these changes involve the tracts of Goll and Burdach and the posterior funiculus.

Microscopic appearances.—There is general congestion and may be perivascular haemorrhages especially in the thalamus and beneath the ependyma. Severe damage to nerve cells is widespread—usually most marked in the medulla and midbrain but also in the cortex of cerebrum and cerebellum and in the spinal cord. When changes are present in the spinal cord they are found also in the corresponding posterior root ganglia. No lesions can be found in the root ganglia in neuroparalytic accidents, a fact which may be of assistance in distinguishing them from paralytic rabies. A variable degree of demyelination is common. Interstitial round cell infiltration and perivascular cuffing vary in degree with the duration of the disease. There may be round cell infiltration of the meninges.

Negri bodies.—These are the only characteristic findings and are absolutely diagnostic of rabies when seen. They vary greatly in numbers however and cannot always be found. About ten per cent. of suspect brains in which Negri bodies cannot be demonstrated can be shown to contain rabies virus by animal inoculation. Negri bodies are round or oval eosinophil inclusions found in the cytoplasm of nerve cells. There may be several in one cell and they vary in size. The characteristic internal structure which confirms the nature of the inclusions can be seen in the larger bodies. This consists of a central granule or a ring of granules which show as vacuoles with some staining.
methods. When present, Negri bodies are usually most numerous in the hippocampal gyrus but common also in the pyramidal cells of the cortex generally and in the Purkinje cells of the cerebellum. They are also found in the basal ganglia, cranial nerve nuclei and in the spinal cord.

Salivary glands.—There is usually degeneration of the acinar cells and interstitial lymphocytic infiltration.

**PROPHYLACTIC TREATMENT**

**IMMEDIATE MEASURES**

**Essential information about the responsible animal.**—When a patient seeks treatment for any animal bite careful enquiries should be made about the attacking animal.

1. *If the responsible animal can be identified and is alive* it is important that it should be captured and taken to the veterinary authorities for observation: the killing of dogs which have bitten should be avoided if at all possible. The doctor must keep in close contact with the Veterinary Officer so that he may start and stop vaccine treatment at the earliest possible moment.

2. *When the responsible animal is dead or has escaped* enquiries should be made about its behaviour and, if there is any suggestion of rabies, the patient treated as if bitten by a rabid dog. The brain of a dead dog should be sent to the laboratory for examination (see Appendices A & B). A dog killed too early in the disease may not have developed Negri bodies in the brain: isolation of the virus in mice may, however, be possible. If there is a definite bite and a real suspicion of rabies, treatment should be started, and stopped only if the doctor feels that negative laboratory findings in any particular case are significant. The decision will, of course, be influenced by the absence or prevalence of the disease in the vicinity in recent months or years.

3. *Where the dog is known to have been vaccinated with chicken embryo vaccine* (see page 24), rabies is unlikely, although in a mass vaccination campaign failures cannot be absolutely excluded. A tag on the neck gives no certainty that a dog has been vaccinated: it may have been stolen.

A Veterinary Department ear-tattoo, if present, may prove that the dog had been vaccinated with chicken embryo vaccine not more than three years previously. Rabies in that case would be unlikely.

**First aid treatment of dog bites.**—The wound should be washed out immediately with as much water as possible to remove saliva. Remember that the saliva in the wound is infectious. Soap may be used but vigorous scrubbing and any probing or cutting of the wound should be avoided. Detergents such as patent washing powders or shampoos are better than soap. A dry dressing should then be applied and the patient taken to a doctor or hospital as soon as possible.

**Local treatment of the wound.**—Early efficient washing of infected saliva from the wound is probably the most important protective measure which can be taken. The wounds should be thoroughly cleaned with soap and water or, better, 1 per cent. CTAB (Cetyltrimethylammonium bromide)*. Large volumes of water should be used and a jet of water directed into the wound. Soap and CTAB should not be used together as soap inactivates the latter. Lépine (1954) recommends 20 per cent. concentrated soap. Vigorous scrubbing so as to open up tissue planes should be avoided. Cauterisation is of doubtful value and can cause very disfiguring scars: it should probably be reserved for deep puncture wounds which cannot be readily cleaned.

When hyperimmune serum is to be given it is probably best to administer this first (see page 11) and then clean the wound which should not be interfered with surgically

* CTAB is the standard detergent most readily obtainable in Malayan hospitals. Any other detergent will do equally well, e.g., 1 per cent. Zephiran is recommended by Shaughnessy and Zichis (1954).
until the antibodies administered have had time to reach the circulation. Infiltration of the vicinity of the wound with hyperimmune serum is valuable before surgical interference.

In general, the less the wounds are interfered with surgically the better as there is danger of disseminating the infection by opening up tissue planes which may have been sealed against the virus by inflammatory reaction. There are, however, occasions when some débridement or suture will be necessary to avoid disfigurement and in these cases normal surgical measures should be used with the above precautions. Antibiotics have no effect on the rabies virus but may be indicated, as may be antitetanic serum, etc., on general grounds.

**Vaccine Treatment**

**Indications**

Before administering antirabic vaccine treatment to any patient, the following three questions must be answered:

1. Is there evidence that the biting animal was rabid and infectious at the time of contact?
2. If so, is there reason to believe that its saliva had opportunity to infect the patient?
3. Is the risk of rabies greater than the risk of paralytic accident when all the information is carefully considered?

To help Medical Officers to answer these questions they are considered in that order.

1. **Is there evidence that the biting animal was rabid and infectious at the time of contact?**

Vaccine treatment should be considered only where there is reason to believe the biting animal to be rabid.

Even if the Veterinary Officer thinks that the animal has rabies on clinical grounds this should be accepted as final whether Negri bodies are subsequently found in its brain or not.

(a) If the animal is captured and placed under observation treatment should be started as soon as the Veterinary Officer says that he considers that the animal has symptoms of rabies, but not before.

(b) If the dog becomes ill or dies under observation treatment should be given but may be stopped if the brain is reported to have no Negri bodies and the Veterinary Officer agrees that the cause of death was not rabies; otherwise treatment should be continued. If the animal shows no symptoms ten days after biting there is no danger of rabies.

(c) If the animal escapes or is killed immediately after attacking and there is reason to believe that rabies is enzootic in the area, treatment should be given if indicated. Any animal which bites without provocation should be regarded as possibly rabid and if it has been killed immediately the absence of Negri bodies in its brain does not exclude rabies. It is in this type of case that much unnecessary treatment can be avoided if the animal is captured and observed. It is evident that the closest co-operation between the doctor and the Veterinary Officer is of paramount importance.

2. **If so, is there reason to believe that its saliva had opportunity to infect the patient?**

Even if the animal is believed to have rabies, vaccine treatment is indicated only:

(a) When a bite has penetrated skin or mucous membrane.

(b) When previous open and raw wounds are contaminated with saliva.