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Rabies

Suggested Indications for Treatment of Exposed Persons

GEORGE L. HUMPHREY, D.V.M., M.P.H., *Berkeley*

THE RECOMMENDATIONS made here for the treatment of persons exposed to rabies have been prepared by the California State Department of Public Health and were endorsed by the California Conference of Local Health Officers 29 October 1966.

The recommendations are based on those of the World Health Organization Expert Committee on Rabies, Fifth Report,[80] with modification and addenda apropos the occurrence of the disease in California. The document constitutes a revision of the previous recommendations published by the Department in 1960[17] and in a *Manual for the Control of Communicable Diseases in California.*[2]

The most important revisions incorporated in the present document concern: (1) local treatment of bite wounds, (2) information on the comparative efficacy of duck-embryo (D-E) rabies vaccine and nerve-tissue Semple type (N-T) vaccine, (3) pre-exposure immunization of man against rabies, and (4) up-dating of information on the disease in California.

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Reprint requests to: Veterinary Public Health Section, Bureau of Communicable Diseases, California Department of Public Health, 2151 Berkeley Way, Berkeley 94704.

Recent experimental trials in animals have strongly indicated that prompt and adequate local treatment of bite wounds is of primary importance in preventing rabies infection, and presumably this would apply also to humans. The work done on local wound treatment strongly suggests that certain agents be used and, more important, that a precise method be followed in using them.

The rationale suggested by current knowledge is to:

1. Swab and flush the bite wound vigorously and repeatedly with either soap *or* quarternary ammonium solution* (preferably benzalkonium chloride).

2. Apply topically to the wound hyperimmune antirabies serum (optional in instances of mild exposure, recommended for severe exposure).

3. Infiltrate under the wound itself with hyperimmune antirabies serum (hereinafter referred to simply as antirabies serum) where feasible to do so in all instances of severe exposure.

4. Administer the recommended systemic antirabic treatment, using either rabies vaccine alone for mild exposure or combined antirabies serum and vaccine for severe exposure (See *Outline Guide of Suggested Treatment,* Table 4.)

*Soap and the quarternary ammonium compounds are chemically incompatible.

The systemic use of antirabies serum is reserved for instances of severe exposure (multiple bites; face, head, finger or neck bites; or bites by certain wild species), due to the frequent occurrence of delayed serum sickness type reactions.

TABLE 1.—*Known Infectious (Virus in Saliva) Periods for Rabies in Various Animal Species*

Species	Maximum Periods that Rabies Virus Has Been Isolated from Saliva or Salivary Glands: Before Onset of Overt Disease*†	Before Death†
Dog	5 days[35,68]	12 days[36,68]
Cat	1 day[70]	6 days[70]
Skunk	5 days[64]	18 days[51]
Fox	3 days[64,68]	17 days[42,66,68]
Bats (Insectivorous)	Some individuals may be in the early stages of the disease. Data of the type obtained for the carnivores are not available for bats[13,66,68,69]	
Other Species	Information not available	

*Classic signs of rabies or paralysis. Prodromal signs such as fever, irritability and various types of abnormal behavior will be present preceding the onset of overt signs of clinical illness. During the early stages of the disease, abnormal behavior may not be constantly present but be exhibited in cycles.[36]

†Reference numbers quoted refer to those listed at the end of the paper.

Both N-T† and D-E‡ type rabies vaccines are commercially available in the United States. The N-T product may occasionally cause neurologic complications, D-E vaccine less frequently. Duck-embryo rabies vaccine is the type now most commonly used in the United States but is clearly less potent than N-T vaccine.

Duck-embryo vaccine is the present product of choice for pre-exposure immunization of persons at high risk of exposure but N-T vaccine is probably the best choice for post-exposure treatment, particularly when combined antirabies serum and rabies vaccine are administered to severely exposed persons.

The attending physician must exercise judgment which will logically result in variation in therapeutic procedure for individual patients based on the circumstances under which exposure occurs and the clinical status of the patient. The variable factors with reference to authoritative knowledge and the circumstances surrounding a particular situation

†National Drug Company, Philadelphia.
‡Eli Lilly and Company, Indianapolis.

TABLE 2a. — *Frequency of Positive Results for Rabies by Species in Animals Examined by the California Department of Public Health, 1950-1963*

Species	Examined	Positive for Rabies*: No.‡	Per Cent†	Species	Examined	Positive for Rabies*: No.‡	Per Cent†
Skunk	1,988	1,028	51.7	Weasel	89	....	....
Bovine	373	101	27.1	Deer	26	....	....
Badger	10	2	20.0	Chinchilla	13	....	....
Bobcat	62	12	19.4	Mink	12	....	....
Equine	96	14	14.6	Vole	9	....	....
Fox	598	83	13.9	Hawk[e]	9	....	....
Bat	1,071	138	12.9	Pig[f]	8	....	....
Goat	9	1	11.1	Ocelot	8	....	....
Coyote	93	7	7.5	Bear	7	....	....
Sheep	19	1	5.3	Owl[e]	6	....	....
Dog	6,054	232	3.8	Porcupine	5	....	....
Racoon	285	7	2.5	Mountain lion	3	....	....
Monkey	153	2	1.3	Gibbons ape	3	....	....
Cat[a]	4,730	24	0.5	Prairie dog	3	....	....
Gopher	1,412	....	....	Beaver	2	....	....
Squirrel[b]	1,358	....	....	Coatimundi	2	....	....
Rat	1,090	....	....	Chicken[e]	2	....	....
Mouse[c]	942	....	....	Ferret	1	....	....
Hamster	639	....	....	Wolf	1	....	....
Rabbit[d]	319	....	....	Nutria	1	....	....
Chipmunk	262	....	....	Tapir	1	....	....
Muskrat	129	....	....	Kinkajou	1	....	....
Opossum	128	....	....	Pheasant[e]	1	....	....
Guinea pig	113	....	....	Parakeet[e]	1	....	....
Mole	92	....	....	Unknown[g]	130	1	..
				TOTALS	22,369	1,653	7.4

*Positive for rabies by microscopic examination for Negri bodies, mouse inoculation or fluorescent rabies antibody (FRA).
†Percentage calculated to nearest one-tenth per cent.
‡Of the total of 1131 specimens reported positive during the 11-year period, 1950-1960, 627 were positive by mouse inoculation.
a—Includes both domestic and feral house cats.
b—Includes both tree and ground squirrels.
c—Includes field and house mice and pet white mice.
d—Includes both domestic and wild rabbits.
e—Avian species are not considered to play any role in rabies.
f—One hog reported positive for rabies by the Los Angeles County Health Department in 1956.
g—Species not stated or unknown.
SOURCE: State of California Department of Public Health Laboratory Report Records.

can be expected to influence the pattern of prophylaxis to be followed. The recommendations made here have been prepared with a view to providing information which will be of assistance to persons involved with decision for the administration of human antirabic treatment in California. The date of final preparation of these recommendations is October 1966.

The Decision to Treat

Utilization of Veterinary Clinical Judgment. The first problem arising in any medical situation concerning rabies is basically a veterinary one—that is, determination of the health status of the biting animal. This question is important in that specific antirabic treatment of the bitten person is not necessary if the exposure has not involved rabies virus.[30] In many instances, decision to administer treatment will depend upon the health status of a biting animal which is available for observation. The use of veterinary clinical judgment as to the health status of a biting animal can often be helpful in deciding the need for initiating systemic antirabic treatment.

It is seldom necessary to initiate systemic treatment as long as the biting animal remains normal (an exception is bats, for sometimes apparently normal bats may be in the early stages of the disease). Where decision to initiate treatment of a bitten person may hinge upon determination of the health status of an available suspect animal, the services of a veterinarian should be used if available. Under California law, only a veterinarian is legally qualified to render clinical judgment of rabies infection in animals.

The Infectious Period. In determining the need for systemic antirabic treatment of a bitten person, the period of time during which rabies virus may be present in the saliva of a rabid animal is important, in particular that period preceding the onset of frank overt signs of a disease—classical signs of rabies or paralysis.

Rabies virus invades the salivary glands and may be present in the saliva of a variable proportion of naturally infected animals. In most infected animals, rabies virus does not occur in the saliva until after the onset of frank clinical signs of the disease; in a few the occurrence of virus in the saliva will precede overt clinical signs by a variable period.

It is almost impossible to define any overt sign or symptom in the pathogenesis of the disease other than paralysis or death for use as a "landmark" in saying that rabies virus would not have been present in the saliva more than a specified number of days before the landmark appeared.

It is doubtful, however, that rabies virus will be present in the saliva of an infected animal before the initial onset of fever.[36] In addition, one or more prodromal signs such as hyperactivity, irritability, change in disposition, diminution of corneal reflex, abnormal appetite (eating of wood, dirt, stones, feces, bedding, etc.) will be apparent to an informed observer. Early in the clinical course of infection, such subjective signs as abnormal behavior or activity are not always constantly present but may occur in increasingly frequent cycles as the disease progresses.

In rabid wild animals—skunks, foxes, coyotes, racoons, bobcats and weasels, for example—such abnormal behavior as daytime appearance, loss of fear of humans and human habitation or attacks upon man, domestic pets or livestock, all carry an extremely high order of suspicion of rabies. Also, taking young wild animals found abroad during daytime in areas where rabies exists in wildlife may result in exposure to rabies. The very young of any species are extremely susceptible to rabies. Rabid mother skunks, for example, may infect their entire litter before dying of the disease. In young skunks thus infected rabies may not develop until several months later, long after they may have been taken into the home as pets. An incubation period as long as 177 days has been reported in skunks.[51]

The information available on the infectious period for rabies in different species is included in Table 1. The information in this table can be useful from the standpoint that if a biting animal, a cat for example, remains healthy (without fever or signs of abnormal behavior) for two or more days after it has bitten someone, one may presume that the cat was not infectious at the time of biting.

Relative Risk of Rabies Infection. In weighing the question of systemic antirabic treatment of a person bitten by an animal or otherwise exposed, consideration should be given to the risk of incurring serious reaction to treatment as against the risk of incurring rabies. The risk associated with antirabic treatment is fairly well known and reaction rates have been reported by various authorities (see section on Systemic Antirabic Treatment, page 370). On the other hand, the risk of incurring rabies infection from a particular exposure oftentimes cannot be so well established.

Certain data are available, however—for exam-

ple, the relative frequency of positive findings for rabies in various species of animals examined in California—which permit some degree of evaluation as to the relative risk of exposure to rabies infection from various species of animals. Certain species have never been found rabid despite numerous laboratory examinations extending over many years. The data available provide a basis of experience as to the relative frequency of positive findings in laboratory examinations, by species, in animals examined by the State Department of Public Health during the 14-year period 1950-1963 (Table 2a) and in California as a whole during 1964-1965 (Table 2b).

High Risk Species. Bites inflicted by such species as the striped skunk, spotted skunk (civet or "Phobey cat"), bobcat, fox, badget, bat and coyote (in descending order of risk), should be considered to carry a relatively high risk of exposure to rabies unless proved otherwise.

Bites from such species as the dog, racoon and cat carry a lesser degree of risk (less than five per cent of biting animals submitted for examination found positive) than the preceding group of animals (Tables 2a and b).

Exposure to cattle—as, for example, in administration of medication or the like to an ill animal which later comes under suspicion of being rabid —also carries a high risk (27 per cent of such animals submitted for examination were found rabid. See Table 2a).

Low Risk Species. Bites inflicted by such species as gophers, various squirrels, wild rats, pet white rats, wild mice, pet white mice, hamsters, wild and domestic rabbits, chipmunks, muskrats, opossums, guinea pigs, moles and chinchillas and others, are considered to carry an extremely low order of risk of rabies infection[54] and seldom if ever should necessitate systemic antirabic treatment of the bitten person (Tables 2a and b).

Pet white rats and white mice, hamsters, domestic rabbits, pet chipmunks and squirrels, guinea pigs, etc., can be further evaluated from the standpoint of where these pets have been kept and what animals they have had contact with in the period preceding infliction of the bite. In the absence of contact with a rabid animal—and such contact is extremely unlikely in the environment that such pets are usually kept—the possibility of rabies can often be excluded on the basis of the history of the animal involved.

Current Situation. In evaluating the degree of

TABLE 2b. — *Frequency of Positive Examinations for Rabies by Species in Animals Examined in California, 1964-1965 (Consolidated State and Local Examinations)*

Species	Examined	Positive for Rabies* Number	Per Cent
Skunk†	1,118	323	28.9
Equine	31	8	22.6
Bovine	98	23	23.6
Bobcat	28	3	10.7
Bat	1,118	117	10.5
Badger	12	1	8.3
Fox	277	14	5.1
Coyote	42	2	4.8
Dog	2,976	65	2.2
Opossum	99	1	1.0
Racoon	146	1	0.7
Cat	4,097	3	0.1
Gopher	1,679	....	....
Hamster	1,515	....	....
Mouse‡	1,280	....	....
Rat§	900	....	....
Squirrel		....	....
Ground	572	....	....
Tree	100	....	....
Kind not stated	169	....	....
Rabbit	346	....	....
Guinea pig	231	....	....
Chipmunk	198	....	....
Monkey	135	....	....
Weasel	81	....	....
Muskrat	65	....	....
Mole	64	....	....
Rodent, kind not stated	17	....	....
Ocelot	12	....	....
Sheep	9	....	....
Deer	9	....	....
Mink	9	....	....
Seal	8	....	....
Pig	6	....	....
Goat	5	....	....
Leopard	3	....	....
Owl	3	....	....
Species not listed above	30	....	....
TOTALS	17,488	560	3.2

*Positive for rabies by microscopic examination for Negri bodies, mouse inoculation or fluorescent rabies antibody (FRA).
†Skunk (including spotted skunk).
‡Mouse (including house and field mouse and vole).
§Rat (including kangaroo rat).
SOURCE: State of California, Department of Public Health, Laboratory Records.

TABLE 3. — *Frequency of Negri Positive Specimens by Species in Rabid Animals Examined by the California State Department of Public Health, 1950-1960*

Species	Confirmed by Mouse Inoculation	With Negri Bodies Number	Per Cent
Skunk	343	187	55
Dog	110	32	29
Fox	55	14	25
Bovine	54	11	20
Bat	30	5	17
Cat	13	2	15
Bobcat	8	1	13
Equine	6	....	0
Racoon	5	1	20
Goat	1	....	....
Sheep	1	....	....
TOTAL	626	253	41

SOURCE: State of California Department of Public Health, Laboratory Records.

TABLE 4.—*Outline Guide of Suggested Treatment of Persons Exposed to Rabies, California State Department of Public Health, 1966*

A. LOCAL TREATMENT

1. *First-aid Treatment*
   Immediate washing and flushing with copious soap and water, detergent and water or water alone as soon as possible. (Warning: See footnote a.)
2. *Treatment by a Physician*
   a. Thorough cleansing by vigorous swabbing and flushing with 20 per cent green soap solution or 0.1 per cent (1:1000) or 1.0 per cent (1:100) quarternary ammonium compound. (Warning: See footnotes a and b.)
   b. Topical application of hyperimmune antirabies serum by vigorous swabbing and flushing (optional in instances of mild exposure but definitely recommended in all instances of severe exposure).
   c. Immediate suturing of the wounds is not recommended.
   d. Infiltration of hyperimmune antirabies serum around and under the wound where feasible is recommended in all instances of severe exposure.

B. SPECIFIC SYSTEMIC TREATMENT

Nature of Exposure	*Health Status of Biting Animal*		*Suggested Systemic Treatment (rabies vaccine, antirabies serum)*
	At Time of Exposure	*During Observ. Period of 10 Days*	
I. No lesion; indirect contact only	Rabid	....	None
II. Licks of:			
(1) Unabraded skin	Rabid	....	None
(2) Abraded skin, scratches and unabraded or abraded mucosa	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid (laboratory)	Start vaccine at first signs of rabies in the biting animal.[c]
	(c) Signs suggestive of rabies	Healthy	Start vac. immed.: stop treatment if animal is normal on 5th day after exposure.
	(d) Rabid, escaped, killed or unknown	....	Start vaccine immediately.[c]
III. Bites:			
(1) Mild exposure (other than multiple bites or face, head, finger or neck bites).	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid (laboratory)	Start vaccine at first signs of rabies in the biting animal.[c]
	(c) Signs suggestive of rabies	Healthy	Start vac. immed.: stop treatment if animal is normal on 5th day after exposure.
	(d) Rabid, escaped, killed or unknown	....	Start vaccine immediately.[c]
	(e) Wild (skunk, bobcat, fox, bat, etc.)	....	Serum immediately, followed by vaccine.[d]
(2) Severe exposure (multiple bites or face, head, finger or neck bites).	(a) Healthy	Healthy	Serum immed.; no vac. as long as animal remains normal.
	(b) Healthy	Clinical signs of rabies or proved rabid (laboratory)	Serum immediately, start vaccine[d] at first sign of rabies in the biting animal.
	(c) Signs suggestive of rabies	Healthy	Serum immediately, followed by vaccine. Vaccine may be stopped if animal is normal on 5th day after exposure.
	(d) Rabid, escaped, killed or unknown	....	Serum immediately, followed by vaccine.[d]
	(e) Wild (skunk, bobcat, fox, bat, etc.)	....	Serum immediately, followed by vaccine.[d]

a—Where soap has been used, all traces of it should be removed before application of quarternary ammonium compounds because the latter are neutralized by soap.

b—Quarternary ammonium compounds: (1) *ZEPHIRAN*—Winthrop Laboratories, New York, N. Y.—high molecular alkl-dimethyl benzalkonium chloride. Available as a 17 per cent buffered aqueous stock solution and diluted 1:17 in distilled water to yield a 1.0 per cent (1:100) concentration and 1:170 for a 0.1 per cent (1:1000) concentration for bite wound treatment. (2) *PHEMEROL*—Parke Davis and Co., Detroit, Mich.—high molecular alklamine hydrochloride (benzethonium chloride). Available as a 3.0 per cent aqueous stock solution containing added amber dye to mark the area of topical application. It should be noted that in a 1.0 per cent concentration, the quarternary ammonium compounds will have some deleterious effect on tissues. Care should be exercised to avoid retention in puncture wounds. A concentration of 0.1 per cent while less effective in experimental rabies prevention should have no deleterious effect on tissues. The 1.0 and 0.1 per cent concentrations should not be used on mucous membranes or near the eyes.

c—The course of rabies vaccine should consist of a minimum of 14 doses (one per day) followed by booster injections at 10 and 20 days following the last dose. Booster injections are especially indicated where combined hyperimmune antirabies serum and vaccine have been used.

d—In all cases of severe exposure and in all cases of unprovoked bites by wild animals, e.g., skunks, bats, foxes, bobcats, racoons in California, hyperimmune antirabies serum together with 14 doses of vaccine and booster injections at 10 and 20 days following the 14 dose course should be given.

NOTE: This table is similar to but differs in minor respects from the guide contained in the WHO Expert Committee on Rabies, Fifth Report, World Health Organization, Technical Report Series, No. 321, 1966, pp. 34-35.

risk associated with a particular exposure, it should be kept in mind that the relative frequency of rabies infection in animals examined for rabies originating from a specific area may vary widely from far below to far above the composite percentages shown in Tables 2a and b. Local health officers, however, can supply specific information on the current rabies situation within their respective areas and should be consulted in this connection.

Saliva Contact

Unabraded Skin. The exposure of intact skin to saliva of a rabid animal should not warrant systemic antirabic treatment. All available evidence supports the concept that infection is dependent upon the implantation of an infective dose of rabies virus in or near nerve tissue.

Abraded Skin or Scratches. Systemic antirabic treatment should be considered a necessity if abraded skin or scratches without eschar or less than 24 hours old are contaminated with saliva of a rabid animal. If the abrasions or scratches do have eschar or are more than 24 hours old, the contamination may be considered as contamination of intact skin, and not necessitating system antirabic treatment.[60,80]

Abrasions or Scratches Inflicted by Claws. Abrasions or scratches of skin inflicted by the claws of an animal suspected of rabies should be considered as a possible exposure to infection. At times, such injuries may be quite severe. The possibility of exposure to rabies arises because if an animal were rabid and virus were present in the saliva, the claws might have been contaminated by the animal licking them just before inflicting the abrasions or scratches. Hence, decisions regarding systemic antirabic treatment of a person incurring injuries inflicted by the claws of a cat should be guided by the same considerations as for bite injuries, that is, the degree and location of the wounds and the health status of the cat at the time of inflicting the injury and during the period of observation afterward.

Severity of Exposure. Bite wounds inflicted on the head, face and neck regions and fingers and multiple bites in other areas carry an increased risk of rabies infection. The transmission of rabies is dependent upon the implantation of an infective dose of virus in or near nerve tissue. The more dense concentration of sensory nerve endings in the head, face, neck and finger regions probably accounts for the greater risk of infection observed with exposure in these areas. Similarly, the more extensive the bite wounds inflicted, the greater the risk of infection due to the greater chance of exposing nerve tissue to an infective dose of rabies virus. Such exposures are considered severe and warrant the best treatment available — adequate local treatment, infiltration of antirabies serum under the wound, systemic administration of antirabies serum and a full 14-dose course of rabies vaccine with two booster injections as outlined hereinafter.

Local Antirabic Treatment of Bite Wounds

The primary importance of early adequate local treatment of bite wounds was stated in the previously mentioned 1960 recommendations for antirabic treatment.[2,17] However, recent experiments in animals[20,39,53,76] have explored new approaches to local treatment, the effectiveness of which recommend the use of certain agents and suggest that a certain method be followed in using them.

It has been shown that rabies virus inoculated intramuscularly in animals can persist at the site of inoculation for 24 hours and in some instances up to 72 to 96 hours.[29,43,58] However, the virus level drops sharply following injection.[58] The objective of local treatment of bite wounds is to reduce the amount of rabies virus implanted in the wound to below the infective dose level. The level of virus may be reduced through dilution (swabbing and flushing), virucidal action of the agent used or a combination of both.

Experiments in animals have demonstrated such agents as tap water and soap, 20 per cent green soap solution, quarternary ammonium compound,*† nitric acid or antirabies serum to be effective in preventing rabies when used locally at the site of exposure. Soap, quarternary ammonium compound, nitric acid and antirabies serum all possess virucidal ability. Nitric acid is corrosive and will produce a high degree of local tissue reaction as compared with either soap or antirabies serum. Benzalkonium chloride in 1.0 per cent concentration has been shown to be effective in the local treatment of wounds in guinea pigs infected with

*Soap and the quarternary ammonium compounds are chemically incompatible.

†Quarternary ammonium compounds:

(1) High molecular alkl-dimethyl benzalkonium chloride. *ZEPHIRAN®*—Winthrop Laboratories, New York, N.Y. Available as a 17 per cent buffered aqueus stock solution. The 17 per cent stock solution is diluted 1:17 to yield a 1.0 per cent (1:100) concentration and 1:170 for a 0.1 per cent (1:1000) concentration for bite wound treatment. See discussion above regarding corrosive nature of 1.0 per cent solution upon tissue.

(2) High molecular alklamine hydrochloride (benzethonium chloride). *PHEMEROL®*—Parke Davis and Co., Detroit, Michigan. Available as a 3.0 per cent aqueous stock solution containing added amber dye to mark the area of application.

rabies virus, but in a 1.0 per cent concentration benzalkonium chloride will also have a deleterious effect upon tissues.[80] Shaughnessy and Zichis,[63] however, report that 1.0 per cent benzalkonium chloride did not cause burns or scarring or interfere with wound healing.* The 0.1 and 1.0 per cent concentrations of the quarternary ammonium compounds should not be used on mucous membranes or about the eyes, however. The fact that 1.0 per cent benzalkonium chloride has proved more efficacious than a concentration of 0.1 per cent or than 20 per cent soap solution would recommend the use of 1.0 per cent benzalkonium chloride as the agent of choice for local treatment of bite wounds.

The literature cited include local treatment of superficial wounds but some is primarily concerned with the local treatment of deep puncture wounds which are difficult to treat satisfactorily.[20,39]

First Aid Treatment. The effectiveness of such simple and widely available agents as tap water and soap in preventing rabies in experimental animals with superficial non-puncture wounds suggests that such treatment should be applied when other agents are not available or there is delay in reaching a physician.[20] Often exposures are scratches and minor lacerations or bites. In such cases, first aid treatment using soap and water pending more adequate care by a physician will materially reduce the risk of rabies infection.

Superficial Wound Treatment. Agents effective experimentally in antirabic treatment of superficial wounds in animals were tap water, Ivory soap and water, Ivory soap and water followed by topically applied antirabies serum, 20 per cent green soap solution, and 1.0 per cent aqueous benzalkonium chloride.[20] All the foregoing agents provided significant protection when applied within three hours after exposure by vigorous scrubbing and flushing of the wounds, using cotton pledgets.[20]

Treatment of Puncture Wounds

Swabbing and Flushing. Repeated swabbing and flushing with 20 per cent green soap solution,[39] aqueous benzalkonium chloride,[20,39] antirabies serum[20] or combinations thereof[20] in deep puncture wounds reduced the degree of infection (but here again the warning that soap and the quarternary ammonium compounds are chemically incompatible. Hence, any residual traces of either should be flushed away before the other is used).

The method of treatment suggested by recent investigations[20,39] is that repeated vigorous swabbing (twirling) of the wound depths should be carried out, using six tightly twisted cotton-tipped applicators twirled four times each after they have been dipped in the agent being used, combined with deep flushing by use of a blunted hypodermic needle attached to a 5 to 20 ml syringe inserted into the depths of the wound. It should be emphasized that the above method of application is more important than the nature of the agent used.[39] In experimental animal trials with less vigorous methods of treatment, the mortality rate was higher.[20,39]

Vigorous swabbing and flushing with benzalkonium chloride within 12 hours after exposure, and with serum within six hours, gave significant protection.[20] Similar treatment using 20 per cent green soap solution within one hour provided significant protection.[39]

Swabbing and flushing with antirabies serum is optional in instances of mild exposure and is recommended in all instances of severe exposure.

Possible sensitivity to antirabies serum should be determined in all instances before topical use is made of serum (see section on Systemic Antirabic Treatment).

Infiltration of Antirabies Serum Under Wound. There is sufficient experimental evidence to show that infiltration of antirabies serum under the wound itself is effective in preventing rabies infection in animals.[20,39,40,53] Presumably this is true also in humans, although clinical evidence on this point is lacking. The dose of serum used for local infiltration will be dictated chiefly by the site of the bite wound. However, where possible, not less than 5 ml is recommended. Sensitivity to antirabies serum should be determined before it is used (see section on Systemic Antirabic Treatment). Infiltration under the wound is recommended in all instances of severe exposure.[80]

Nitric Acid. The specific value of nitric acid applied locally to bite wounds is clear. There is no evidence that nitric acid is more effective than 1.0 per cent benzalkonium chloride or 20 per cent green soap solution.[80] Moreover, the use of nitric acid is probably more subject to variables in method or degree of treatment in the course of normal medical practice than would be the use of 1.0 per cent benzalkonium chloride or green soap solution. This fact as well as the caustic nature of nitric acid suggests limited use of this chemical in

*Care should be exerted to flush residual traces of the drugs in such concentrations from the depths of puncture wounds.

local wound therapy for the prevention of rabies.[39,53,62,63]

Suturing of Bite Wounds. It is recommended that bite wounds not be immediately sutured, in light of evidence that early closure can be a contributing factor to the development of rabies infection.[11,80]

Antiseptics and Antibiotics. The application of ordinary antiseptics and the local use of antibiotics, while they have no prophylactic value against rabies, may follow local treatment to combat bacterial infection.[80] However, the thorough cleansing and debridement recommended for bite wounds would suggest that antibiotics should not be necessary as a routine procedure.

Systemic Antirabic Treatment

Relative Efficacy of Various Treatment Regimens. Systemic antirabic treatment is based upon the administration of rabies vaccine alone or vaccine in combination with intramuscular injection of antirabies serum. It is generally conceded that combined serum and rabies vaccine provides the best protection in post-exposure treatment.[80] In descending order of efficacy: (a) combined serum and vaccine, (b) vaccine alone and (c) serum alone are the available methods of systemic post-exposure treatment.

The general principles upon which the *Outline Guide of Suggested Indications for Treatment* is based is that with mild exposures a course of rabies vaccine following the recommended local treatment is sufficient, whereas with severe exposure the combined use of antirabies serum and rabies vaccine should be employed.[80]

Rabies vaccine should be administered in all instances as a course of 14 doses (one dose daily) plus booster injections of vaccine at 10 and 20 days after completion of the basic 14 dose course. Booster injections at 10 and 20 days following the basic course are particularly important when antirabies serum has been administered, due to interference of antirabies serum with the immune response to rabies vaccine.[80]

Systemic Use of Antirabies Serum. While the use of rabies serum alone apparently exerts some saving effect, experimental results indicate that the chief effect of systemically administered serum is a definite prolongation of the incubation period.[44,72,73] The greatest use for the serum is in conjunction with rabies vaccine for cases of severe exposure to rabies, in which the incubation period is most likely to be very short.

Time Limit on Use. Experimental results in animals clearly indicate that the sooner antirabies serum is administered after exposure the better.[58,77] The effectiveness in animals decreases rapidly when serum is administered more than 72 hours after exposure.[44,72,77] While early use of antirabies serum is recommended, there is no time limit beyond which administration of serum is contra-indicated.[80] When antirabies serum is combined with rabies vaccine treatment, however, certain recommendations relative to administration should be noted due to an interference phenomenon on the part of antirabies serum with antibody response to the course of vaccine[9,80] (see following paragraph).

Administration of Combined Antirabies Serum and Rabies Vaccine. If passive (serum) antibodies are maintained for too long a period by repeated systemic doses of antirabies serum or if less than a complete course of vaccine (14 doses plus booster injections at 10 and 20 days) is given after the single intramuscular dose of antirabies serum recommended, there occurs a definite interference phenomenon on the part of passive serum antibodies with the antigenic response to rabies vaccine as measured by neutralizing antibody titer.* In animals this interference phenomenon has also been confirmed by subsequent virus challenge.[31,78] Doses of rabies vaccine given toward the end of the series, that is, after the 10th day, together with booster injections at 10 and 20 days following completion of the basic course, are active in overcoming such interference.[81,80]

Recommendations for the combined use of antirabies serum and rabies vaccine, therefore, are that only a single administration of serum be given (minimum dosage, 40 international units (IU) per kilogram of body weight inoculated intramuscularly in the buttocks) followed by a course of 14 doses (one dose daily) of vaccine plus booster injections of vaccine at 10 and 20 days following completion of the basic 14-dose course.[80] Vaccine can be started at the time of administration of antirabies serum. The two booster inoculations of rabies vaccine are essential if the interference phenomenon is to be overcome. Antibody response to booster doses of rabies vaccine has been observed within three days following injection.[80]

Reactions to Antirabies Serum and Sensitivity Testing. Reactions to antirabies serum, even though

*Reference Nos. 8, 9, 10, 78, 80.

concentrated and purified, occur approximately to the same degree as with other sera of equine origin. Reactions can be of the immediate anaphylactic type or the delayed serum sickness type. Serum sickness occurs in about 15 to 25 per cent of persons given serum of equine origin.[80] The incidence is less in children below 15 years of age.[80]

An immediate reaction of anaphylactic type to antirabies serum can usually be avoided by the routine use of an intradermal or ophthalmic test for sensitivity.[80] Skin tests should not be administered unless a syringe containing one ml of 1:1000 epinephrine is available for immediate use.[19] In the event of a positive reaction to a sensitivity test, the usual precautions of desensitization should be followed in administration of the serum.[80]

While skin or ophthalmic tests are useful in anticipating possible anaphylactic type reactions, a negative test result does not preclude the presence of sensitivity and the subsequent development of delayed serum sickness reaction. Such reactions may have onset as much as 12 days[68] after administration of serum. The incidence and severity of reactions to antirabies serum can be reduced by the administration of an antihistamine drug.[80] It is recommended that an antihistamine be given daily for 10 to 12 days following administration of serum.

Treatment of Reactions to Antirabies Serum

1. *Epinephrine.* One ml of 1:1000 epinephrine should be available for immediate use in carrying out sensitivity tests or in topical or systemic administration of antirabies serum as a safeguard in the event of reaction of anaphylactic type.[19]

2. *Antihistamines.* The administration of an antihistamine for 10 to 12 days after injection of serum can reduce the incidence of serum sickness following the use of antirabies serum.

3. *Cortisone and Corticotropin* (ACTH). These agents are extremely effective in controlling reactions to serum (serum sickness)[14] and the neuroparalytic reactions associated with the use of nerve-tissue Semple type vaccine.[12,25,37,49] Although the foregoing products are effective in controlling reactions, evidence exists that they interfere with the development of active immunity elicited by vaccine[14] and may possibly reactivate rabies infection in an exposed individual.[65]

Experimental work in rabbits suggests that corticotropin (ACTH) may interfere less with production of active neutralizing antibody than does cortisone.[14] However, neither product appears to affect adversely the persistence of passive immunity induced through administration of antirabies serum.[14] In instances of severe reaction, use of these agents should not be rigidly withheld, but they should be avoided if possible.

Post-Exposure Rabies Vaccine Treatment

Types of Vaccine Available. Semple type nerve-tissue (N-T) and duck-embryo (D-E) vaccine are the two types of human antirabic vaccine commercially available in the United States.

While the efficacy of human post-exposure antirabic treatment with vaccine is difficult to document, that treatment using various types of rabies vaccine does have a saving effect is generally accepted, based upon observation of extensive use throughout the world since vaccine was first administered by Pasteur 80 years ago.

In a group of 465 persons bitten in India by rabid animals which were proved capable of transmitting the virus (one or more of the persons or animals bitten died of rabies), 316 persons were given a complete series of treatment using Semple type nerve-tissue rabies vaccine and 106 persons received no treatment. In the treated group, 28 or 8.9 per cent died of rabies whereas 51 or 48.1 per cent of the untreated group died of the disease.[71] Twenty-nine of the group of 465 persons cited above did not receive complete courses of Semple vaccine treatment, five or 17.2 per cent of whom died of rabies; and 14 other persons who died during the course of vaccine treatment are excluded from the relative mortality figures quoted for the completely treated and untreated groups.

Actively induced serum neutralizing antibodies resulting from daily inoculations of rabies vaccine are not detectable in many persons, however, until the tenth to the fifteenth day.[10,23] In severely exposed persons, that is, those in which the incubation period is likely to be very short, antirabies serum should be used in combination with vaccine treatment,[80] as previously described.

Comparative Efficacy of Nerve-Tissue and Duck-Embryo Rabies Vaccines

The D-E product is the most commonly used of the two types of rabies vaccines now available, probably well in excess of 60 per cent of the total amount of vaccine used in California during recent years.[15] The D-E vaccine has been commercially available since early in 1957.

Following its introduction, the California Department of Public Health was asked by local health officers to comment upon the efficacy of

D-E vaccine as compared with N-T vaccine. While recognizing that D-E vaccine probably carried less risk of neuroparalytic accident than did N-T vaccine, the Department felt that the question of efficacy of the D-E product as compared with N-T vaccine could not be answered with the information then available. Adequate data for making such a comparison still was lacking in 1960 when the previously mentioned recommendations for antirabic treatment were published.[2,17] Experimental work carried out since 1961, however has shown that D-E vaccine is clearly less potent than N-T vaccine.[21,74]

In tests conducted in the New York State Department of Health Laboratories,[21] 13 (72.2 per cent) of 18 lots of commercial D-E rabies vaccine obtained on the open market in 1961 did not meet minimal Habel-test standards; the other five lots passed marginally. Six lots of D-E vaccine evaluated for potency by the National Institutes of Health (NIH) method failed to meet minimal standards established by the NIH for vaccines containing inactivated virus. The results of the foregoing work with D-E vaccine provided the impetus behind a 10-fold increase in duck-embryo tissue concentration made in the commercial product in 1962.[21]

In another report, post-infection treatment of guinea pigs with D-E vaccine in a dosage corresponding to that recommended for human treatment was shown to give very poor results whether the vaccine was used alone or in combination with antirabies serum.[74] Even when the dosage of D-E rabies vaccine was raised to the same level as that recommended for pooled Semple type N-T rabies vaccine, the results obtained with D-E vaccine given alone or in combination with different doses of serum were inferior to those obtained with N-T vaccine given under identical conditions. The investigators concluded from the results of their work that, on the basis of relative weights of the experimental animals and humans, the dosage of D-E rabies vaccine recommended for human post-exposure treatment is inadequate.[74]

Dean,[19] in summarizing his opinion regarding D-E vaccine, said: " . . . there is evidence in animals that duck-embryo vaccine is less antigenic than nerve-tissue vaccine. Properly produced, nerve-tissue vaccines readily pass the Habel and NIH tests for potency whereas duck-embryo vaccine customarily either passes such tests marginally or fails. Preference for duck-embryo vaccine is apparently justified largely because of its greater freedom from postvaccinal neurologic complications."

Reactions to Rabies Vaccine Treatment

Nerve-Tissue Vaccine. It is recognized that N-T antirabies vaccines occasionally produce so-called neuroparalytic accidents.[34] The incidence of serious paralytic reactions to N-T vaccine varies with different reports but appears to approximate one per 4,000 persons treated.[7,33,50,55,60]

One study produced evidence also that approximately 14 per cent of persons treated with N-T vaccine had electroencephalographic abnormalities during immunization, whereas persons receiving D-E vaccine in the same study did not.[26]

The neurological complications occurring with the use of N-T rabies vaccine usually do not begin until after completion of the vaccine course. When symptoms such as chills, fever, headache, nausea, vomiting and generalized lymphadenopathy develop during rabies vaccine treatment, vaccine should be immediately discontinued.[7,32,35] The neurological reactions to N-T rabies vaccine can be classified as: (a) peripheral neuritis, (b) dorsolumbar myelitis and (c) ascending paralysis (Landry's type).[35] Reactions of paralytic type seldom develop until after the sixth dose of N-T rabies vaccine, and they may occur as late as two weeks after completion of treatment.[35]

Cortisone and corticotropin (ACTH) have been successfully used in controlling reactions to both serum and N-T rabies vaccine.[12,25,37,49] Evidence indicates, however, that these agents interfere with the development of active immunity[14] and additionally may possibly reactivate rabies infection.[65]

Duck-Embryo Vaccine. While D-E rabies vaccine carries less risk of neuroparalytic accident than does N-T rabies vaccine, the D-E product is not devoid of the paralytic factor. MacFarlane and Culbertson[46] reported that encephalomyelitis developed in two (2.4 per cent) of 83 guinea pigs injected subcutaneously with D-E vaccine suspended in Freund's adjuvants, compared with 21 (or 87.5 per cent) of 24 guinea pigs after injection similarly with rabbit brain suspensions.[46]

A number of severe reactions in man have also been reported in association with use of duck-embryo rabies vaccine.[3-6,24,41] It is clear, therefore, that D-E vaccine is less hazardous of neuroparalytic accident than is N-T vaccine but that N-T vaccine will evoke the higher degree of protection against rabies infection. When D-E rabies vaccine is used, its lesser effectiveness should be kept in

mind and not fewer than 14 doses, with booster injections* after 10 and 20 days, should be administered.

When antirabies serum is used, N-T vaccine is probably the vaccine of choice and should also be followed with booster injections† after 10 and 20 days.

Care should be exercised in administration of D-E vaccine to persons known to be sensitive to egg material.[80] In instances where persons incur severe reaction to D-E vaccine, a change to N-T vaccine may permit continuation of the course of treatment.

Pre-Exposure Immunization

From recent studies, it is clear that any of the rabies vaccines used—for example, chick-embryo Flury strain high egg passage (HEP),‡ duck-embryo (D-E)[1,8,22,59,67] and nerve-tissue (N-T)[8,10,23]—are capable of eliciting antibody response in treated persons and thereby sensitizing them or preparing them for prompt response to booster injections.

The Flury strain HEP rabies vaccine which was used in numerous pre-exposure immunization studies, was used experimentally only and is no longer available. Only D-E and N-T rabies vaccines are available now. Of the two currently available products, D-E vaccine, while less potent than N-T, will elicit an immune response and thus sensitize or prepare a person for quick response to future booster injections.[1,8,22,59,67] Since D-E vaccine carries less risk of neuroparalytic complications than N-T vaccine,[46] the former is probably the rabies vaccine of choice for pre-exposure use in persons at high occupational risk of exposure to rabies.[80]

In most studies on pre-exposure immunization, rabies vaccine has been injected intradermally.§ However, wide variations in response, from approximately 30 to 95 per cent of those inoculated responding, have been noted by various workers using the intradermal route.¶ These variations in response were apparently largely due to variations in the administration of intradermal injections.[52] As a result, injecting larger doses subcutaneously is the method now recommended.[38,52,80]

The WHO Expert Committee on Rabies, Fifth Report, recommended that a short primary course of two to three inoculations of 1 ml of reconstituted D-E rabies vaccine be administered deep subcutaneously in the upper arm at one month intervals. The primary course should be followed by a single booster inoculation six months later.[80]

Since individuals vary in their response to primary immunization it is desirable that a serum specimen (5 to 10 ml) be collected 30 days after the booster injection and submitted to a laboratory for a serum neutralization test to determine the level of antibody response. If antibody response has not been elicited, booster inoculations should be continued until response is obtained. The submission of serum for neutralizing titer determination should be arranged for in advance through the local county health department and the California State Department of Public Health.

The WHO Expert Committee on Rabies, Fifth Report, recommended that booster inoculations be given at one- to three-year intervals as long as the individual remains at risk.[80] Not enough information is available to provide a basis for firm recommendations as to the best procedure to follow when an immunized person who has demonstrated immune response in the past is exposed to rabies. The WHO Expert Committee on Rabies, Fifth Report, however, suggested that on mild exposure one dose of rabies vaccine be given and that on severe exposure five doses be given, followed by a booster dose 20 days later.[80] Observed antibody response to booster injections has been prompt—significant rise in titer within four to eight days in persons who have had previous antibody response to rabies immunization.[8]

Re-treatment

It has been found that a single dose of potent rabies vaccine given to persons who have received a course of rabies vaccine as long as 15 to 25 years previously, results in prompt and significant antibody rise[8,22,23,52] within four to eight days.[8] The questions here of course are those of verification of previous rabies vaccine treatment, the potency of the vaccine used for previous treatment and the antigenic response of the individual thereto.

Until 1939 there was no practical method of testing rabies vaccines for potency.[30] When standard test procedures were developed,[30,75] it was found that most rabies vaccines produced in the United States lacked potency.[30] A similar situation existed with regard to low potency of D-E rabies vaccine when tested by Dean and Sherman in 1962.[21] It should also be noted that if combined

*When D-E rabies vaccine is used for the basic course, use of N-T rabies vaccine for booster injections at 10 and 20 days may reduce the risk of allergic reaction.

†WHO Expert Committee on Rabies, Fourth Report (1960)[79] recommended use of D-E vaccine for booster injections when N-T vaccine is used for the basic course of treatment.

‡Reference Nos. 8, 10, 23, 56, 57, 59, 61, 67.

§Reference Nos. 1, 8, 10, 22, 23, 56, 59, 61, 67.

¶Reference Nos. 1, 8, 10, 22, 52, 56, 59, 61, 67.

antirabies serum and rabies vaccine were used, the antigenic response of the individual might be impaired in some degree, particularly if unusually large doses or multiple doses of serum were administered or if less than 14 doses of vaccine plus booster injections (recommended at 10 and 20 days after completion of the 14 dose series) were administered.

If, however, an individual has demonstrated proved immune response to post-exposure treatment or a pre-exposure course of immunization within the past two to three years, the WHO Expert Committee on Rabies, Fifth Report, suggested that in the event of a mild exposure one booster dose should suffice, and for several exposures five doses with a booster dose 20 days later.[80]

Laboratory Diagnosis of Rabies

Fluorescent Rabies Antibody (FRA) *Test.* This test is a new and important development in rabies diagnosis.[27,28,45,47] In an experienced laboratory it is fast (overnight as used in the California Department of Public Health laboratory) and the reliability of the test is such that a negative report can be expected to weigh heavily for a decision not to treat a person who has been bitten.[47,80]

In the California Department of Public Health laboratory over 4,230 specimens routinely submitted for rabies examination between October 1959 and September 1962 were comparatively examined, using the FRA test, microscopic examination for Negri bodies and mouse inoculation test.[48] Of the total number, 363 were reported positive for rabies, 361 (99.4 per cent) being FRA positive, 357 (98.3 per cent) mouse positive and 239 (65.8 per cent) Negri body positive. Six specimens positive to the FRA test, including four in which Negri bodies were demonstrated, were negative on mouse inoculation. Two specimens initially reported negative to the FRA test were positive on mouse inoculation. On careful reexamination of additional slides from the foregoing two specimens, using the FRA test, a few scattered foci of specific fluorescence were found.[45,48]

The FRA test was adopted as the standard examination procedure for rabies by the California Department of Public Health in January 1963.[16,45] From January 1963 through October 1964, nearly 4,000 additional specimens were examined by the FRA test. Of this number, only two specimens initially reported negative to the FRA test were found positive on mouse inoculation. Reexamination of multiple smears of these two specimens (from a dog and a horse) by FRA revealed trace amounts of specific fluorescence.[45]

In the light of nearly five years of experience in California Department of Public Health laboratory, the FRA test is considered to be highly (99.95 per cent) reliable. The examination results can be reported by that laboratory within 24 hours. The presence or absence of Negri bodies in the specimen is no longer of concern and it is no longer necessary to withhold a final laboratory report for two weeks or longer while awaiting the results of mouse inoculation. The FRA test results, be they positive or negative,* may be used by physicians and public health officials to determine promptly the need for antirabic treatment of persons exposed to an animal suspected to have rabies.[47]

The FRA test is reliable with fresh, frozen or glycerinated specimens and may also be used to examine salivary gland material.[18,27,28] The efficiency of the test on salivary gland material is still under investigation, however.

Microscopic Examination for Negri Bodies. This examination procedure is rapidly being supplanted by the FRA test in local health laboratories in California (22 of a total of 41 local health department laboratories in California were utilizing the FRA test as of 31 December 1965).

The presence of Negri bodies is pathognomonic of rabies infection. The absence of Negri bodies, however, does not rule out rabies infection. Wide variations occur in the relative frequency of Negri bodies found in the various species of rabid animals. The variations in the frequency of Negri-positive specimens examined by the California Department of Public Health during the 11-year period 1950-1960 are shown in Table 3.

The microscopic examination has been replaced by the FRA test as the routine diagnostic procedure in the California Department of Public Health laboratory.[16]

Mouse Inoculation Test. This test was previously performed by the California Department of Public Health laboratory routinely on all specimens in which Negri bodies could not be found or on which examination could not be satisfactorily performed due to the unsuitable condition of the specimen. Its use has ben supplanted by the FRA

*In making decision *not to initiate* or to *stop* antirabic treatment in an exposed person based upon a negative FRA test, consideration should be given to the volume of positive rabies material being seen by the laboratory and the frequency of positive specimens missed by the laboratory in the past. In the case of small laboratories, local public health laboratories where relatively few positive specimens are seen—it is suggested that, where possible, material be forwarded to the California Department of Public Health for confirmation.

test.[16] Mouse inoculation will usually be attempted, however, in instances where the condition of specimen precludes reliable testing by the FRA procedure.

The incubation period in inoculated mice developing rabies may range from five to twenty-three days. The average incubation period in the California Department of Public Health laboratory has been approximately 12 to 14 days.* Inoculated mice are routinely observed for 28 days before a negative report is rendered.

Serum-Virus Neutralization Test. This test is used to identify rabies virus. It has been used in the California Department of Public Health laboratory in instances where typical Negri bodies could not be demonstrated in inoculated mice which were dying, to establish if the pathogenic agent were rabies virus. Its use has largely been replaced by the FRA test.[16]

The technique, however, is currently used to determine the development of specific neutralizing antibody titer in persons administered pre-exposure or primary courses of rabies vaccine using serum drawn from the individual 30 days following administration of the booster inoculation (See section on Pre-Exposure Immunization).

*Observed range of incubation periods in inoculated mice in the California Department of Public Health laboratory during the period 1950-1962. The preponderance of positive specimens were from wild species or domestic species originating from wildlife rabies affected areas. Positive canine specimens originating from urban areas where dog to dog transmission has been prevalent have exhibited the more usual classic characteristics on mouse inoculation, however.

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CORRECTION

In the article, "Acute Myocardial Infarction in Los Angeles County," by L. Julian Haywood, the figures for the Centinella Valley Community Hospital were incorrectly reported in Table 1. The correct data are as follows:

TABLE 1.—*Data From Myocardial Infarction Survey—Hospitals of 95 or More Beds in Los Angeles County*

		Data on Infarction and Coronary Insufficiency				*Data on Special Care Units*		
Hospital	*No. of Beds*	*Condition*	*Total Cases*	*Deaths*	*Mortality (Per Cent)*	*Beds In ICU*	*Has CCU*	*Planning CCU?*
Centinella Valley Comm. Hosp.	150	AI	218	29				
		ACI	128	9				
		Total	346	38	10.9	6	No	No

AI = Acute infarction (definite or probable)
ACI = Acute coronary insufficiency
ICU = Intensive care unit
CCU = Coronary care unit

This would also change the figure for the total deaths reported for all the hospitals included in the survey to 2,261 instead of 2,441.