Bull. Org. mond. Santé } 1954, 10, 845-866
Bull. Wld. Hlth Org. }

CAN MAN BE PROTECTED AGAINST RABIES ?

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SYNOPSIS

The literature dealing with the protection of man against rabies over the past 70 years in many parts of the world is reviewed, and the salient problems of our present state of knowledge analysed. The author discusses the measures currently in use for eliminating canine rabies by quarantine, regulation of the dog population, and—in particular—mass vaccination of dogs, with a detailed survey of the questions of immunological research which this method raises. Measures for suppressing the disease in other vectors are also described. It is concluded that, given effective education of the public and the widespread use of canine mass vaccination, human rabies is a preventable disease.

The question " Can man be protected against rabies ? " has, with varying intensity, engaged the minds of those who are brought into contact with this malady, one of the oldest known diseases of animals. Man has always been concerned with protecting himself against hydrophobia. Vivid accounts describe the hysteria of the populace when rabid wolves invaded the towns in the Middle Ages, attacking people, flocks, and herds. Frantic efforts to protect themselves led the people to brutal acts against human victims suspected of exposure to this terrifying disease; murder was a not uncommon death for individuals suffering from rabies.

A new, more rational, era in the control of this disease was ushered in by Pasteur when he demonstrated that its infective agent can be transferred from one dog to another, elucidating the spread of rabies. Pasteur learned that rabies in man can be prevented by treating persons bitten by rabid animals and by eliminating rabies from dogs and other carnivores. Through the ensuing 70 years of experimentation, the search for an effective therapeutic vaccine, and appraisal of the efficacy of those produced, doubts have recurred concerning the merits of postinfectional antirabies treatment. In recent years, under the influence of what has been learned of neurotropic viruses, the data annually collected to evaluate the relative efficiency of the diverse methods of postinfectional vaccination have been critically re-analysed. This has revealed that the traditional strong belief in the efficacy of antirabies treatment is unfortunately based on some general assumptions and on only a few controlled series, for example those reported by Cornwall.[7]

This author carefully observed a group of treated and untreated persons bitten by a presumably rabid dog and came to the conclusion that postinfectional antirabies treatment saved one out of every two of the individuals who had been bitten and who would otherwise have developed hydrophobia. Similar observations make it appear that antirabies treatment reduces the mortality-rate to half that in the untreated. Remlinger, one of the greatest living authorities on rabies, has repeatedly emphasized the value of treatment impressively shown in connexion with wolf bites (Remlinger & Bailly [39]). These carnivores seldom bite unless they are rabid, and the mortality-rate among persons bitten by rabid wolves and not treated is generally believed to be about 75%, at least not less than 60%. The mortality-rate from rabies in those treated after wolf bites is reported by Remlinger to be not more than 15%. Nikolic [33] reported that the mortality-rate among 256 persons bitten by wolves and receiving Pasteurian treatment was 27%, and in the presence of head injuries reached 45%. The Hempt etherized virus was given in five injections. According to Gremliza,[14] 15 of 32 persons bitten by the same wolf died from proven rabies. More impressive are the data when the sites of the bite-wound are analysed. Ten out of 17 with bites on the head and face, two out of three with bites on the neck and mandible, and three out of eight with bites on the upper extremities, succumbed to rabies.

Discounting the emotions provoked by those who wish to cast suspicion on the value of postinfectional antirabies treatment of persons bitten by rabid animals, one sees the present position of this preventive measure as follows : (*a*) postinfectional antirabies treatment does help to prevent the development of rabies in man, but it is urgent that (*b*) the factors in the acquisition of an immunity effective against rabies in the bitten individual be more clearly understood, and (*c*) passive immunization be carefully compared with active immunization. The value of both potent immune antirabies sera and improved vaccines must be determined by comparing the incidence of disease in treated persons with the incidence in those exposed to the same risk who, for some reason, have not been treated.

Other aspects are worthy of attention. No consideration is given in this condensed statement to the economic implications; it fails to reflect the anxiety which the bite-victim, his medical adviser, and his relatives endure while he undergoes postinfectional vaccine treatment that may be complicated by post-Pasteurian paralysis. The knowledge that rabies is invariably fatal once it develops makes it one of the most notorious and feared of human diseases. It is therefore particularly puzzling that only in the face of epizootics among foxes, coyotes, skunks, or other carnivores, which create losses among livestock, is the population sufficiently aroused to demand effective action. They object not at all to the annual heavy expenditure on postinfectional immunization, which could be eliminated if rabies were to be effectively suppressed or eradicated. There is a paradoxical lack of awareness that the investigation of animal bites, quarantine measures, stray-animal services, and laboratory and administrative services may absorb large sums, sometimes millions of dollars, from taxpayers' funds.

Under the impact of postwar experience with epizootics and of the energetic drive of veterinary public-health services, serious consideration is now being given to the second step in the control of rabies : elimination of the reservoirs of rabies. No clairvoyance is needed to predict that this action will go much further towards preventing rabies in man than will treatment after he has been bitten by a rabid carnivore.

According to the description by Johnson,[19] two epidemiologic types of rabies are now generally recognized : (1) the disease in the natural reservoir in wild animals—the localized sylvatic and campestral types—and (2) the disease in the world-wide domestic-animal reservoir—the urban type—maintained in densely populated regions where the love for pets creates a complex, partly domesticated-dog and partly wild-dog reservoir. The specific measures for controlling the spread of rabies will vary according to the ecological interrelations between the reservoirs and man, and consequently it is advisable to discuss the principles of control in separate sections.

Measures for the Elimination of Rabies from Dogs

Every international conference, regional meeting, or discussion on rabies has stressed, and continues to stress, that rabies must be eradicated from domestic dogs and that this is the most urgent, most challenging problem to be solved within the foreseeable future. There is ample historical evidence to support the concept that dogs acquired rabies from the enzootic reservoir in wild animals. Once established in the domestic dog, rabies followed the wanderings of man to the towns and villages he built. All densely settled regions throughout the world sooner or later became focal areas in which intimate contact with dogs led to outbreaks of human rabies in epidemic proportions. It is equally well known that epizootics are distributed by the mass migration of people during unrest, particularly during wars. In any area where rabies smoulders in suitable hosts and vectors, dogs accompanying their masters to these areas become the spreaders of the rabies virus. Efforts made during the latter half of the 18th century and then in the middle of the 19th century, before the nature of the infection was understood, to combat and eradicate epizootics of canine and feline rabies by means of laws and regulations merely relieved the situation temporarily. One fact was fully recognized : that the combating of rabies on a large scale is successful only when the legal regulations are properly, fearlessly, and inflexibly applied for a period covering the longest latency of the disease. For more than 100 years the aim has been to prevent any dog from biting another. The traditional veterinary police-measures attempt to eliminate the disease among dogs by quarantine and restraint. There is no need to detail the procedures and specific measures recommended at previous conferences. They are generally known and are well described in a number of valuable publications (van Rooyen & Rhodes,[41] World Health Organization,[53] Tierkel,[46] Vittoz,[50]). However, the wide variety of measures often face unsurmountable difficulties in enforcement, because of social or religious attitudes of the populations whose co-operation is so essential in the success of the undertaking. In general, dog owners refuse to accept responsibility for their own protection, for the protection of those who may come into contact with their dogs, and even for the pets themselves. Consequently, the only feasible approach is through the public, who must be educated before any of the necessary specific measures can be applied with any assurance of success.

Education of the public

As a rule, the population of an area where rabies suddenly appears is not prepared to grasp the seriousness of the problems the public-health officer and the public-health veterinarian face. Rumours and misinformation are freely spread by the ignorant, who rebel against any attempts to regulate the free movement of animals which may be their pets, or their food supply, or which may be held sacred according to their religious beliefs. Such prejudicial attitudes must be prevented from developing or must be attacked through mass education, using all the techniques of public-health guidance which will prove effective in the region or country concerned—the work must be meticulously adapted to local conditions.

This task should be undertaken only after the appointment by the health authority of an advisory committee on which the more enlightened and influential citizens and representatives of the health agencies serve; such a group must be chosen carefully, because it is most important that every citizen have full confidence in its decisions and actions. The first step of this group is to secure the co-operation of the local press, to induce it to agree to faithful reporting of the facts, and to detailed coverage of the first mass meeting. Those responsible for this meeting must stimulate wide and genuine interest in it and must be prepared to satisfy and perpetuate this interest. It should be held in any hall, or perhaps in any open area, that will accommodate every interested person. At such a meeting the public must be taught accurately, in terms they can understand, the basic facts of the epidemiology of rabies. The forum technique, led by an experienced moderator assisted by experts, should be freely supplemented by visual educational materials. There is urgent need for the careful preparation of audiovisual film material which refutes popular misconception and misinformation. The reasons why certain actions, for example the registration, licensing, taxation, and leashing of owned dogs, and the elimination of stray dogs, are insisted upon must be simply, directly, and forcefully explained.

Subsequently the press, radio, or other means of mass communication must be used to continue the interest and to distribute further information. The advantages of mass vaccination of dogs must be widely advertised by citing concrete examples of its success; the facts supporting the claims should be selected by an international group of experts, and made readily available to those in charge of control. The strategy and tactics of a planned control programme depend on the confidence the public develops as a result of the educational campaign. Its whole-hearted co-operation will grow as the day-by-day reporting of every incident and observation made by competent veterinarians and health officials creates confidence in the programme.

Every antirabies campaign in one area should be co-ordinated with similar efforts being made in other areas. Control measures should preferably be carried out on a national scale; they should unquestionably operate on a regional basis in all the infected areas. International experience, now scattered through many invaluable publications and official reports, should be pooled, analysed, and freely distributed by an international organization, perhaps the World Health Organization. Short articles, written so that they can be readily understood by the laity, should be published in popular magazines read by owners of dogs and livestock, and sportsmen. Since programmes to educate the public frequently lack a deep-rooted appeal to social conscience and responsibility, the urgent necessity for control is not recognized, and the measures adopted are not understood, becoming progressively more unpopular. This is particularly true in preparing the public for the mass vaccination of dogs; on such occasions too much distorted misinformation has been disseminated.

The time has also arrived to insist that a group of international experts agree, on the basis of results now available, on the principles of vaccination and on the type of vaccines to be used in mass immunization. As soon as scientific knowledge can be converted into public information, a demand for public action will follow. Constant and competent education of the public is the inexhaustible source of strength and energy in a rabies control programme. With a few laudable exceptions, the stage has simply not been properly set; groups in charge have not been prepared to act on public demand, and consequently the eradication of canine rabies has not progressed as rapidly as available knowledge would justify.

Quarantine of dogs

Probably no general measure has proved as effective as quarantine. This practice has prevented the establishment of rabies in many islands—Australia and Hawaii, for example. A six-months observation period of dogs to be imported, rigorously enforced in the British Isles, the Scandinavian countries, and Canada, has, with rare interruptions, eliminated the disease. There is ample proof that quarantine for six months is justified. During a period of 21 years, 16 dogs held in quarantine developed rabies four or more months after importation into England (Galloway [10]). In this connexion it is interesting that in a recent book, *The control of communicable diseases* (Paul [35]), in the section on the British Isles no chapter dealing with rabies can be found.

Regulation of dog population

This includes, aside from the very important registration and licensing of dogs, the unpleasant tasks of impounding or destroying ownerless stray dogs, isolating and observing animals bitten by rabid animals, and leashing and muzzling all owned dogs, while a control campaign is under way. In considering the advisability of these activities, it is quite often not appreciated that many of them cannot be planned with any degree of efficiency until the density of the dog population in the affected area is known. Dog-licence figures are of little value in gauging dog populations; a more accurate method of taking the dog census must be devised (Fredrickson et al.[9]). Without an accurate census the magnitude of the control task cannot be estimated, nor can the public be informed of the expenditures required to accomplish the desired goal.

To safeguard the human community it is imperative that the dangerous rabies carrier, the stray dog, be eliminated. Even the most vigorously enforced mass vaccination will not reach the ownerless dog. Consequently the elimination of stray dogs will always remain an important specific measure in a control programme. One potential pitfall should be anticipated : the net that gathers and renders harmless the stray dog in large cities sooner or later collects some pet animals. These unwanted victims of the control procedures—which must, to repeat, be ruthlessly administered—sometimes serve as a starting point for numerous controversies. Animal-lovers and humane societies, supported by an inadequately informed press and its readers, enhanced by the inherent human aversion to destruction of pets, sooner or later puncture the most carefully planned campaign, or at least add an exceedingly troublesome snarl. Political intrigue and machination influencing the enforcing agency may render police measures ineffective. An attempt to free the Federation of Malaya from rabies by shooting stray dogs without a licence or muzzle proved temporarily effective (Vittoz [50]). However, Wells (see page 731) has clearly shown that compulsory vaccination is essential. Experience and a thorough knowledge of local conditions at the time must be used to determine the best and most humane manner of accomplishing the task. Neither precedent nor information collected by others from previous experiences can serve as a dependable guide.

Many communities, aroused by fatal cases of human rabies, have demonstrated the efficacy of a vigorously and fearlessly enforced elimination of the stray dog, supported by the traditional measures of restraint of owned dogs.

Immunobiological Control

In view of the difficulties inherent in regulating the dog population, in fact the admitted complete failure in certain countries, due to lack of the required powers of enforcement by local rather than by central authority, health officials have for many years advocated mass vaccination of dogs, and even of other animals (Irr [17]). The persistent recurrence of rabies indicates that control of this communicable disease by the classical procedures which prevent transmission of the infective agent has not succeeded. This type of control, exposition prophylaxis, does not suppress disease when crowding and intimate contact with latently infected animals cannot be prevented; the protection of the susceptible is therefore essential. This second form of prophylaxis, disposition prophylaxis, is known as immunobiological control. Before this method of protecting man against rabies is considered, a brief critical appraisal of protective immunization in general appears justified.

Those familiar with the general field, among them Remlinger & Bailly,[40] are disturbed by the dogmatism or doctrinism particularly prevalent among groups of workers who wish to promote and support a particular immunization procedure, and to protect it against attacks. Until quite recently, empiricism led investigators to ignore the theoretical experimental basis of the procedures and to accept only results obtained by mass immunization. In fact, experimental study of the process quite often trailed its practical application, and the latter was not founded on the former, as should always be the case. As some astute worker pointedly expressed it, more science and less practice was needed to secure a solid foundation on which to formulate sound immunobiologic prophylaxis.

The general principles, now fully recognized to be the guiding ones, are as follows : Immunization must be harmless, without pathological consequences. However, the primum non nocere should not overshadow the efficacy of the method. Procedures of vaccination that produce no reactions and are relatively harmless have frequently been observed to have little or no immunogenic power; facultative or obligatory use of such procedures is not justified. If, on the other hand, a procedure confers intense and durable protection, immunisatory reactions must be kept at a minimum and then accepted as inevitable—always provided that the risk is quantitatively and qualitatively heavily counterbalanced by the danger that the omission might entail.

The purpose of all immunization is (*a*) to protect those immunized against the manifest symptoms of the infectious processes ; (*b*) to modify the course of the disease ; or (*c*) to reduce the fatality-rate. All the procedures are directed against the pathogenic effect, not against the infection per se. In fact, a great deal can be achieved if immunization transforms the infection into a subacute or abortive process. Observations during the past 30 years have shown that recovery from certain viral infections leaves a relatively dependable, permanent, specific protection against re-infection. Furthermore, since mild abortive infections confer a more durable protection than does immunization with antigens, attention has been focused on immunogenic agents that induce a highly attenuated infection. Immunization by producing mild infections is theoretically sound. Immunization with antigens consisting of inactivated or killed infective viral agents leaves a great deal to be desired. The magnitude of the immunogenic response can be greatly enhanced by the spacing of the doses of antigen or killed agents, and by the supplementing of the primary basic one-dose immunization with a second, or even a third, stimulus, with " booster " or " recall " inoculations. Observations in support of these principles are now impressive, and assume the position of scientific facts.

Before any procedure of immunization is used it must be tested, through extensive animal experiments, in two steps : (1) by inoculating the immunogenic agent, and (2) by determining the refractoriness of the inoculated. Immunity can be evaluated by intentional infection, by intentional exposure to a natural infection, by permitting the prevailing epidemiological chances to act freely, and by studying the manifestations of immunity in the inoculated—for example the humoral antibodies. All four procedures have been used in evaluating the methods of immunization against rabies.

It appears profitable to evaluate now the merits of the various methods employed in the pre-infectional prophylactic antirabies treatment of animals in order to prevent the spread of the disease. In the classical review prepared by Gautier [11] it is made quite obvious that during the period he covers the laboratory evaluation of canine-rabies vaccines recommended for and used in mass inoculations had not received the attention it deserved. Vaccines of different antigenicities prepared from living fixed virus attenuated to varying degrees, and the chemically inactivated or killed infective brain suspensions, had been tested ; it is not surprising that differences were noted in their antigenic value—indeed, even a single type of vaccine produced divergent results when attempts were made to immunize by a single injection of the preparation. As a whole, the laboratory evaluation tests were inconclusive, but the practical application, the vaccination of millions of dogs, at times brought very striking results.

These contradictions could not be explained until Webster [51] introduced the use of the mouse as an experimental animal and thus established better means of measuring the antigenic content of vaccines. This procedure demonstrated that a considerable number of the vaccines produced by institutes or commercial firms exerted only very slight immunizing activity. This revelation was promptly followed by an improvement in the quality of the old vaccines and by the development of new and very effective vaccines, among them the UV-irradiated vaccines. Assaying the immunogenic potency of an antirabies preparation today is a standard prerequisite, and the minimal requirement of an efficient vaccine is that it should protect white mice against 1,000 median lethal doses (LD_{50}) of a standard highly active virus (Habel & Wright [16]).

Finally, these newer methods of testing the immunity disclosed the diversity of the viruses used for producing vaccines. A wide range in immunizing ability of fixed virus strains was disclosed (Habel [15]). Apparently, a high immunizing potency against a heterologous test virus is not an inherent characteristic of a strain, but it can be altered by transfer. There is, however, general agreement that the classical Paris strain is the best immunizing strain. All these researches clearly set forth that the ultimate aim should be the manufacture of a uniform stable virus of marked immunizing properties to replace the fixed-virus brain emulsions. There is encouraging evidence that this goal may be reached (Koprowski & Cox [26]). Adaptation of the rabies virus to the chick embryo, in particular of the Flury strain, has yielded, at various stages of adaptation, a living viral agent of excellent immunogenic properties. Although this strain is still slightly pathogenic on intraneural inoculation, the pathogenicity has gradually diminished through passage. There are indications that further adaptation may further decrease the virulence of this strain, or may even render it avirulent. More significant are the observations that rehydrated supernatant aqueous extracts of chick embryos infected with the Flury strain, when 2-5 ml is inoculated intramuscularly into dogs, produce no signs of systemic reaction. These favourable findings led to the evaluation of this strain as an immunizing agent for dogs. Its immunizing power proved to be excellent. In a series of 7,000 dogs it was possible to observe 422 carefully, and among these there was no abscess at the site of injection and no postvaccinal paralysis. None of the vaccinated animals contracted rabies, nor did any of them die as the result of vaccination (Starr et al.[43]).

Since the days of Pasteur, dogs have been employed for estimating the refractoriness conferred on an animal by a vaccine (Worthington [54]). The vaccine has been administered and then the immunity has been challenged. The severity of such tests has varied greatly in the nature and the dose of test virus and in the method of its introduction. There was a tendency to use the street virus and to inject it intracerebrally or intraocularly so as to obtain a 100% mortality among control animals. This method was not satisfactory ; its excessive severity conveyed the impression that neither living fixed virus nor phenol- or chloroform-inactivated vaccine could immunize dogs. There is another paradox here : the value of Semple phenol-inactivated vaccines for human postinfectional rabies treatment was never questioned, whereas the same type of vaccine for the pre-infectional immunization of dogs was severely criticized. It was not appreciated in the pre-neurotropic-virus period that an extremely sound immunity is required to afford protection against subdural infection. In view of the inherent variable susceptibility of the dog to fatal rabies, most experiments suffered from the realization that it is necessary to use many animals to rule out chance errors (Leach [28]).

When the test virus was later introduced by the extraneural route, however—a method used by numerous workers (Fermi,[8] Remlinger,[37] Kelser,[22] and others)—vaccinated animals resisted the challenge. Hence it was proposed to reject the tests being employed for estimating the resistance as a sequel to vaccination and to use the intramuscular method, in general equivalent to the usual risk of infection as the result of a bite. In recent protection tests the challenging street virus, obtained from the salivary glands of experimentally infected dogs, is injected in standardized amounts into the masseter muscles 30-60 days after vaccination (Tierkel et al.,[48] Koprowski & Black [24]).

Under these conditions from 50% to 66% of the unvaccinated control dogs die of rabies. Thus it is reasonable to surmise that the general susceptibility of the average mongrel to fatal rabies is around 50% ; in fact, in a recent test (Koprowski & Black [25]) it was as high as 91%. Consequently comparison of different vaccines must be conducted on not less than 10-20 dogs. Since the dogs must be held under observation for up to five or six months, the cost of maintenance in suitable quarters is considerable. It would be advantageous if, by international agreement, some central veterinary institute could be chosen to conduct the testing of vaccines and methods of immunization of dogs against rabies. All the necessary elements for a quantitative assay of canine vaccines and for expressing the challenge infection in LD_{50} mouse doses are now available. Certain other aspects must be refined further. For many years it has been known that antibodies with rabicidal properties appear in the serum of animals treated with live or inactivated vaccines. There is, however, still a divergence of opinion as to whether rabicidal substances indicate resistance to infection or not. Fatal infections have occurred in animals with highly rabicidal serum ; although immune bodies and resistance usually develop together, there may be lack of correlation (Casals [5, 6]). Although the virus-neutralizing power of the serum cannot for the present be regarded as a reliable test of the degree of immunization, it is imperative to learn the nature of this discrepancy.

To all intents and purposes, the interpretation of the serological findings is based on an analogy deduction. The following question must be answered : Are the antibodies merely auxiliary phenomena or are they absolute and essential conditions of favourably changed susceptibility ? In recent experimental studies on the protective value of four different antirabies vaccines, neutralization tests with the serum of the vaccinated dogs were made. Because of the unusually large number of serum samples to be tested, preliminary abbreviated screening tests were carried out. All the animals, irrespective of the vaccine used, reacted with formation of antibodies that persisted for from 21 to 60 days. Although it proved difficult to correlate the serological evidence and the resistance of the dogs to experimental infection, among 32 vaccinated dogs two succumbed to challenge (Tierkel et al.[48]). Regardless of the type of vaccine used, homologous antibodies appeared in the serum ; the decrease in level ran parallel to the length of time after vaccination. Of the seven control dogs that resisted infection, the antibody level of five was either low or not demonstrable at all. Until the nature of the antirabies immunity is more clearly understood it is probably premature to consider the measurable antibodies merely as auxiliary phenomena in immunity. At this stage of laboratory investigation of the potency and efficacy of antirabies vaccine, it is probably sound experimental procedure to study in various ways the serological response in the vaccinated, and to explore the possibility of measuring the tissue-neutralizing substances which, on theoretical grounds, may be concerned with destroying the virus introduced into an immunized animal.

In summary, the laboratory investigations to appraise prophylactic pre-infectional antirabies treatment on a large series of dogs have proved that chloroform-treated vaccines in a single subcutaneous dose of 5 ml confer a high degree of resistance (85% to 94% survivors) against an intramuscular challenge (Leach & Johnson [29]). However, in accordance with the principles of repeated and proper dosage, three doses given once a week for three weeks induced a greater degree of resistance than one-dose immunization. In the experience of the US War Department with dogs used by the Armed Forces during the second World War, only one dog developed rabies among 19,050 dogs injected and 9,261 re-injected with multiple inoculations of commercial vaccine (New York Academy of Medicine [32]). In other series still in progress, two vaccine preparations —the egg-adapted Flury strain and the rabbit-brain fixed virus, both living— in a single dose of 5 ml intramuscularly protected completely against an infection that proved fatal to 53% of the control dogs. Another egg-adapted rabies virus and a phenolized vaccine conferred strong resistance, but two vaccinated dogs succumbed to rabies after challenge with the street virus.

Results of these reliable assessments lend irrefutable support to the extensive observations on immunization of dogs in many countries during the past 30 years. They substantially support the trend towards wide use of canine vaccination as one of the most important methods in the control of rabies and the protection of man against this disease. Much of the vaccination work in the past was done with completely ineffectual vaccine preparations, and the efficacy of a vaccination procedure could rarely be evaluated by numerical data. It is very difficult to ascertain the ratio between vaccinated and nonvaccinated dogs because the size of the canine population, particularly stray dogs, is merely estimated. For the same reason it is impossible to compare with any degree of accuracy the morbidity in the vaccinated dogs with that in the nonvaccinated. Using merely the owned group, which can be kept under supervision, a comparison would be facilitated. However, in such a group the prevailing epidemiologic chances greatly diminish the natural infection, which acts more freely in dogs free to wander at large. To measure the value of preventive canine vaccination by the number of persons applying for Pasteur treatment before and after introduction of the measure is also uncertain. Spontaneous decline of an epizootic, or more drastic enforcement of sanitary measures by police, may bring about fluctuations in the reported figures. The proportion of actually infective bites from proven infected dogs cannot be determined with certainty.

Recently Korns & Zeissig [27] attempted a comparison of rabies attack-rates in vaccinated and unvaccinated dog populations in an area where at least 60,647 of the 77,758 dogs had been vaccinated at least once. The enumerated population had remained remarkably constant over a period of years. Vaccination failures were defined as the occurrence of rabies in dogs 1-18 months after vaccination. The total of such failures was 15. No obvious explanation other than inadequacy of immunity in the dog could be discovered. On further analysis of the results, introducing time as a factor, in 867,603 months—the length of time accumulated in vaccinated dogs beginning 1 month after the completion of each regional vaccination programme—the attack-rate in presumably protected animals was 1.7 per 100,000 months. On the other hand, 101 unvaccinated dogs became rabid during the same period in the same area in 368,614 months, a rate of 27.4 per 100,000 months. Thus the attack-rate in the unvaccinated was 15.8 times that in the vaccinated. When the analysis was made using only licensed dogs, the attack-rate in the unvaccinated was still 13.5 times that in the vaccinated. The figures are in keeping with those reported for Birmingham, Alabama, in the USA, where the attack-rate among the unimmunized was 8 times that in the immunized. This is the first appraisal of preventive canine-vaccination by statistical analysis. With this noteworthy exception, the results are merely recorded as facts.

What are some of the more recent significant data ? After the first World War, on the European continent Hungary was the country most severely infected with rabies. Following an experimental mass-vaccination test on 17,000 dogs with a one-dose, glycerol-phenolized emulsion of fixed virus originally isolated by Högyer from a Hungarian street virus and manufactured from sheep brain, which proved favourable, the immunization of sheep-dogs was made obligatory. Subsequently the dogs of Budapest and other districts were taken into the vaccination-net and by 1939 canine vaccination was made obligatory. A total of 752,000 dogs were treated. The success was without parallel; throughout the country rabies had for practical purposes been eradicated. Unfortunately the war-year 1945 brought an interruption of the vaccination activities. The incidence of rabies rose in 1946, and by 1947, 252 Negri-positive animals had been observed. Canine vaccination was again, step by step, vigorously enforced. In September 1948, no cases of rabies were reported; in October there was only one, and the dog in this case had been brought into the area from outside. By 1950 the dog population of the entire country had again been vaccinated. In the total of 7,000,000 vaccinated dogs, 0.2 per 1,000 suffered from vaccination injuries—abscess or skin necrosis followed by sepsis; postvaccinal paralysis resulted in 0.037% of the cases, and a third of these were fatal. On the basis of these remarkable achievements, attributable to prophylactic mass-vaccination of dogs, the delegates to a rabies conference in Budapest recommended that the authorities of the countries plagued by rabies follow the example set by Hungary (Kaiser & Puntigam [21]).

In adjacent Yugoslavia, where wolves from Romania had introduced rabies, the epizootic involving 1,417 animals, the disease was controlled by compulsory vaccination. The usual police measures and destruction of ownerless dogs proved inadequate. Compulsory vaccination of 1,585,559 dogs with three different vaccines between 1946 and 1950 brought about a steady decrease of rabies in animals and man. Strikingly, the persistence and incidence of the disease was greatest in those regions where least vaccination had been carried out (Kodrnja [23]). Canine vaccination was available optionally by 1940. Without charge to their owners, 12,419 dogs were given a single inoculation.

Before the second World War, Poland was never enthusiastically in favour of vaccination; only 652 dogs were inoculated between 1925 and 1935. Yet that country now reports that in 1949 alone 702,209 dogs were given pre-infection treatment. Moreover, postinfection therapy with Semple vaccine was being practised (Zebrowski [55]). In the course of the mass vaccination of the dog population, postvaccinal accidents in the form of paralysis (594 cases, 0.08%) and even deaths (387, 0.05%) were attributed to the presence of living fixed virus in the vaccine preparations (Stryszak,[44] Janowski [18]). It is unnecessary to dwell on the repugnance that arises against canine vaccination when the vaccines used possess a certain degree of virulence.

Numerous publications by Remlinger, and more recently by Bailly,[2] emphasize that inactivated virus, particularly the phenolized fixed-virus vaccine, has reduced the accidents to a negligible level. Production of the fixed virus using the brain of infected goats requires no elaborate facilities; the prices are low and the procedure is simple. The successes following the use of this vaccine in Corsica, Morocco, and Tangier are invariably reported as satisfactory, although the documentation leaves a great deal to be desired.

In the USA successful organized canine vaccinations have invariably been inaugurated after traditional quarantine and restraint measures alone have failed to control the disease (Bruckner,[3] Korns & Zeissig [27]). Aside from experiences in New York already discussed, the promising results in Alabama must be noted. The most impressive large-scale vaccination of dogs was tried in 1951 in St. Louis, Missouri, where the long-range history of epizootics recurring over a period of 20 years had been carefully recorded. After immunization of 58,000 dogs with phenolized vaccines prepared by three commercial manufacturers, rabies was virtually eradicated within 9 months. This significant accomplishment is contrasted with previous epizootics which lasted several years. Instead of a gradual reduction in the number of rabid dogs (the normal course), vaccination abruptly terminated the epizootic in the area which undertook a determined control programme, while the communities closely surrounding the metropolitan area of St. Louis continued to remain infected. This decline of rabies was not a mere coincidence; it can be attributed to mass inoculation of a type of antirabies vaccine which has, at times, been considered ineffective (Fredrickson et al.[9]).

The few random examples of the practical application of canine antirabies vaccination lend support to recent laboratory studies. The efficacy of inactivated fixed-virus vaccines, provided they are of proven immunogenicity, is clearly indicated. In fact, one cannot escape the impression that, as a whole, dogs can be immunized relatively readily with one dose of vaccine. This violates all modern concepts of immunology. All published studies and field observations rarely progress beyond a one-year period. The duration of the immunity established by a single injection remains unknown. On theoretical grounds it is reasonable to think that the protection conferred by inactivated vaccine lasts only a short time, and consequently the recommendation of repeated, or at least annual, vaccination is scientifically sound. How to meet this prerequisite administratively, if the immunity should last for several years, requires further investigation. Again, comparative analogic deductions favour a vaccine that creates not only a strong, but also a long, refractoriness. Living viruses as a rule do this, and if they are innocuous, particularly if they are free from paralytogenic properties, they should ultimately be selected as the vaccines to be used. There is encouraging evidence that some strains of avianized or egg-adapted living rabies virus may meet these requirements.

In summary, the time has arrived when, with candour, confidence, and frankness, the supporters and the opponents of preventive pre-infection canine antirabies vaccination should reach an understanding concerning the application of the principles and facts now available. As a supplementary tool to the traditional method, mass vaccination of dogs assumes a key position in eradicating urban rabies and protecting man against this disease. One can share with Vittoz [50] the firm belief that mass vaccination of dogs should be regarded as a general method of prophylaxis and should be integrated with the police-enforced sanitary measures throughout the countries of the Middle and Far East particularly—in fact wherever rabies is a problem. The urgency of the problems requires local, national, and international understanding and planning.

Measures for the Suppression of Vectors of Rabies other than Dogs

Rabies in wild animals, long recognized, apparently rarely becomes epizootic. The fox, the principal wild-animal vector in western Europe, perpetuated seven major migrating epizootics which ultimately established the disease in dogs, during the period between 1803 and 1925. Since 1945, epizootics of fox rabies in Austria, introduced from Yugoslavia (Schoop [42]), have been menacing Germany. The wolf is an important host in Romania, Turkey, Iran, and the USSR. The jackal plays an important role in Israel (Goor [13]), and is the principal host and vector in India. The mongoose in India is also occasionally found to be infected with rabies. On the African continent the disease is enzootic among jackals in the Anglo-Egyptian Sudan. Small rodents are suspected as vectors in West Africa. In South Africa the rabies virus has completely adapted itself to small carnivores, most of which are included in the family *Viverridae*. The yellow bushy-tailed mongoose (*Cynictis penicillata*) has been responsible for human cases and for outbreaks of rabies among cattle. The small spotted genet (*Genetta felina*), the lesser grey mongoose (*Myonax pulver ulentus*), and the meerkat (*Suricata suricata*) have also been proved vectors. Wild members of the *Sciuridae* (ground squirrel, *Geosciurus capensis*), *Mustelidae* (skunk, *Ictonyx*, and honey-ratel, *Mellivora capensis*), *Proteleidae* (grey jackal, *Protelus cristatus*), *Felidae* (black-footed cat, *Microfelis negripes*, and wild cat, *Felix ocreata*), and *Canidae* (silver fox, *Cyana lopex chama*) have acted as vectors under natural conditions. This exceedingly interesting ecological interrelationship is by no means understood. Rabies remains more or less enzootic in its relation to the *Viverridae* : when domestic animals are bitten, the infection, in spite of the complete absence of any control measures, dies out. Furthermore, it remains more or less restricted to certain well-defined areas where conditions apparently favour the survival of the vectors. This South African reservoir was responsible for 410 reported cases of disease in man and animals from 1916 to August, 1947 (Neitz et al.[31]).

Turning to the continent of America, starting in the north, the Arctic fox and wolf have been proved to be infected in three widely separated areas of the northwest. This focus constitutes a reservoir from which dogs, affected by the so-called Arctic-dog disease, and other animals, including man, may be infected. There appears to be some relation between the migration of lemmings (*Dicrostomyx* sp.) and outbreaks of rabies in Arctic foxes (Plummer [36]). During an epizootic in dogs in 1945-1947 it was proved that rabies is well established in Alaska in a reservoir consisting principally of foxes (*Alopex* and *Vulpes* spp.) (Williams [52]).

In the USA, serious epizootics of rabies in foxes (*Urocyon cinereoargenteus* and *Vulpus fulva*) have been recognized since 1872. Skunk rabies in Kansas and Arizona, coyote rabies on the west coast and in New Mexico, and timber-wolf rabies in eastern North America have all played important roles in the history of this disease in North America. Since 1944 the problem of fox rabies has become increasingly serious in the Appalachian area of the eastern States. Fox rabies extends from northern central New York through Pennsylvania, Virginia, the length of the Appalachian Range to north-western Georgia, westward across Alabama, Mississippi, and Louisiana, and into east Texas. The magnitude of the problem may be judged from some of the reported figures. In Alabama and New York during 1946, 267 and 308 fox brains respectively were proved Negri-positive. Texas, with the highest incidence of rabies of any State in the Union, lists, for 1948, a total of 1,200 laboratory diagnoses of rabies in animals. Georgia in 1946 reported the loss from rabies of 864 cattle, 151 horses and mules, 131 hogs, and 16 goats. A total value of $138,678 was ascribed to these animals. In New York at least 432 head of cattle were lost during the grazing season through the transmission of rabies from foxes. So far as has been determined from available reports and records, few human deaths due to rabies were traceable to foxes. Hundreds of pelts have been handled by trappers and fur dealers with no ill effects to the handlers. Occurrence of rabies in other wild animals is not so common, but bobcats (*Lynx rufus emericus*) and skunks (*Mephitinae*) are involved in nearly every rabies epizootic. Mountain lions (*Lynx rufus* spp.), raccoons (*Procyon lotor*), and opossums (*Didelphys virginiana*) have been suspected of having rabies, but the disease apparently does not become epizootic among them. How rabies is maintained in the fox population and why it assumes epizootic dispersion has not been satisfactorily explained. Nothing is known concerning the virulence of the viral agents isolated from the various species of animals involved. Some strains apparently have a low pathogenicity for dogs when administered extraneurally (Gier [12]).

The discovery that vampire bats (*Desmodus rotundus murinus*) are infected with rabies in some sections of Mexico and South America has disclosed the existence of symptomless transmitters. A paralytic disease of cattle known for many years, called mal de caderas in Brazil, Paraguay, Uruguay, Argentina, and Venezuela, and derriengue in the Pacific Coast States of Mexico, is actually rabies transmitted by vampire bats (Johnson [20]). During warm weather the bats may fly above parallel 30°, so that infected bats may enter the USA. These cause sporadic cases of rabies among animals (Malaga-Alba [30]) and are now of growing interest. Ever since a rabies virus resembling the vampire-bat strain was isolated from the brain of a horse in San Diego, California, in 1950, suspicions have been gathering that bats in the USA might be infected. In July 1953 they were precipitated when the rabies virus was found in the nerve tissue of a common Florida yellow bat (*Dasyptcrus floridanus*) that had bitten a 9-year-old child in the Tampa area. Rabies in raccoons and dogs in this area is by no means uncommon.

Quite recently a major outbreak of rabies due to an epizootic in the mongoose (*Herpestes javanicus*) population of Puerto Rico spread to dogs, cats, cattle, goats, and swine. Not native to the islands of the Caribbean, the mongoose was imported from India in an effort to destroy the rats that were causing economic losses in the cane-fields. The mongoose has little value in rat control and becomes a liability to be eliminated by an effective rabies control programme (Tierkel et al.[47]). There is weighty suspicion that the importation of ferrets (*Mungus bismanicus*) for the same purpose into Cuba has greatly increased rabies on that island (Calvó-Fonseca [4]).

In this sketchy account of rabies in wild animals, decidedly difficult problems become apparent. Eradication of the vast natural reservoirs cannot be attempted until the ecological interrelations are more clearly understood. By analogy with other infectious diseases in nature, confined to well-defined areas or pockets where they are enzootic, it is most important to determine the relationship of primary- to secondary-reservoir hosts. Although carnivores appear to be predominant vectors, the role of other species, particularly of rodents, deserves detailed ecological appraisal. Suffice it merely to indicate now that the importance of the rat has attracted attention through the observations of Remlinger.[38] Now that it has been discovered that rabies may remain asymptomatic and latent in at least one animal, the vampire bat, the problem of the ecology of rabies has entered an entirely new phase. It will be the task of experienced mammalogists, working in close co-operation with virologists, to study the habits and migration range of the species involved. Certainly the viral agents isolated from animals comprising the known reservoirs must be studied more thoroughly by modern immunological technique, especially their pathogenicity and virulence for different species of animals. A virus with a broad infection-spectrum must indeed possess a wide range of adaptation.

While these inquiries are in progress, man, and particularly his welfare in relation to losses he sustains through rabies in his livestock, must be protected. Three methods have been followed : (1) self-eradication of the disease by permitting it to run its course in the wild, decimating the reservoir animals; (2) indiscriminate killing of susceptible wildlife to reduce the possibility of the disease being spread from animal to animal; (3) prophylactic pre-infection inoculation of livestock and of the dog population exposed to wild-reservoir hosts.

The first is nature's way. It has, at least temporarily, effectively eliminated the disease, as experiences in Sweden, Switzerland, and England by the turn of the 18th century fully prove (Babès [1]). It progressed in foxes and skunks in the 19th century, and repeats itself in the 20th century in the USA.

The second method was first employed against the coyote-rabies outbreaks in California and Nevada in 1915-20, and it has been used with great intensity since 1940. The fox population is being reduced to combat fox rabies on both the North American and the European continents. The numbers of the hosts and vectors are being drastically reduced by hunting, trapping, and poisoning within—and, more important, around—the centres of infection in order to diminish the slow radial spread of the disease. Such activities must be carefully planned and executed by highly-trained and experienced personnel under a central authority. Artificial reduction of the wildlife population is not so wasteful as is unhampered self-eradication, and is less dangerous to man and domesticated animals. In the future it should be possible to prevent the occurrence of rabies in foxes by an adequate and continuous census-taking of the animals, by control of habitats, and then controlled reduction of each species as a necessary means of preventing extreme overcrowding. Destruction of jackals in Israel is carried out simultaneously with the removal of stray dogs (Zlotnik,[56] Goor [13]). To reduce various species of small carnivores and the ground squirrel (*Geosciurius*) at the Grootfontein College of Agriculture in South Africa, trapping, poisoning, and gassing of burrows with Cyanogas were used. The campaign would not have been successful without the use of strychnine poison baits in clearing an area of over 2,000 cases (Sutton & Marais [45]). As a rule, mass trapping is followed by poisoning.

Neither of these methods has been adequately evaluated. They are not satisfactory without the important supplementary support of preventive vaccination. There is noteworthy unanimity that prophylactic rabies vaccination of the dog population in the regions with epizootics of rabies in the wild is an essential measure to build a barrier against the spread of the infection. The control of cattle and horse rabies by vaccination, although practised on a large scale in regions where vampire bats are prevalent, has not been thoroughly evaluated. It is claimed that it is highly effective in reducing livestock losses. One aspect, the cost of this procedure, which, if carried out over a wide area, assumes prohibitive proportions, may frequently deter authorities from its application. Moreover, until the vaccines to be selected, and their method and frequency of administration for adequate protection of cattle and horses against bites of wild animals, have been scientifically evaluated, it is premature to offer binding recommendations. Such statements as that paralytic rabies in Venezuela is now well controlled and has ceased to be a problem because of preventive mass vaccination of all susceptible animals with a local Bolivar fixed virus, is encouraging (Novicky [34]). It would gain in significance if controlled laboratory tests were available. Worth mentioning is the undisputed fact that combined control measures, bat-proofing of homes and stables, destruction of vampire bats, and vaccination of livestock, have proved successful in eliminating the disease from Trinidad. No outbreaks have occurred since these measures were taken (de Verteuil & Urich [49]).

Conclusions

This incomplete review has attempted to assemble evidence which would permit of a hopeful answer to the question : Can man be protected against rabies? The evidence answers the question; in particular, it is pointed out that the traditional control measures frequently prove inadequate and difficult to enforce, and that without the adjunct of canine mass vaccination the principal source of human rabies cannot be eradicated. Improved methods of preparing safe vaccines of proven high immunogenic efficacy and conferring prolonged durable immunity, have been introduced. The results, both in the laboratory and in the field, are impressive and encouraging. With the eradication of urban rabies, most human beings will be protected against the disease. All this knowledge will remain of little value until more effective educational programmes implement the control measures being instituted to protect the life and welfare of the dog lover. Rabies is a preventable disease, and all present-day scientific and administrative knowledge must be marshalled to erase the blot on 20th-century civilization which the continued existence of the rabies problem represents.

RÉSUMÉ

Cherchant à répondre à la question : « L'homme peut-il être protégé contre la rage ? », l'auteur rappelle d'abord les étapes principales de la lutte antirabique depuis Pasteur, puis il montre que cette lutte doit maintenant franchir un nouveau pas et viser à l'élimination des animaux réservoirs de la maladie. Du point de vue épidémiologique, ces derniers constituent deux groupes : les animaux sauvages (rage sylvatique ou champêtre) et les animaux domestiques (rage urbaine). Les mesures à prendre, dans l'un et l'autre cas, dépendent des relations écologiques entre le réservoir d'infection et l'homme.

La lutte contre la rage chez les chiens implique, de la part des propriétaires de ces animaux et de la population en général, une compréhension de la gravité des risques encourus. Aussi l'éducation du public en est-elle un des fondements. Elle doit être entreprise par tous les moyens disponibles et à l'échelle nationale, si possible. Sauf dans quelques cas exceptionnels, les réalisations pratiques n'ont pas suivi le développement des connaissances scientifiques, faute d'une instruction suffisante des populations intéressées. La quarantaine des chiens — observation durant six mois des animaux destinés à l'importation — a été sans doute, jusqu'ici, la mesure la plus efficace. L'enregistrement des chiens, le muselage et la garde des chiens à l'attache, l'élimination des chiens errants — qu'aucun programme de vaccination ne peut atteindre — demeurent des éléments essentiels de la lutte antirabique. Toutefois, ces mesures ne peuvent être appliquées

partout de façon rigoureuse. Dans certains pays, elles ont même totalement échoué. Les sujets réceptifs à l'infection doivent alors être protégés: la lutte immunobiologique entre en jeu.

Après avoir rappelé les principes fondamentaux de l'immunobiologie et les conditions que doivent remplir les agents immunisants, l'auteur passe en revue et évalue les diverses méthodes de prophylaxie antirabique appliquées à l'animal, afin d'éviter la propagation de la maladie et il énumère les tests qui, au laboratoire, en permettent le contrôle.

Toutes les expériences pratiques et les recherches indiquent que le but final doit être la mise au point d'un virus stable et uniforme, ayant un pouvoir immunogène élevé, qui pourrait remplacer, dans la vaccination, les suspensions cérébrales de virus fixe. L'adaptation du virus, et en particulier de la souche Flury, à l'embryon de poulet, a rapproché les chercheurs de ce but. D'autre part, la découverte du pouvoir immunisant pour les chiens de la partie surnageante de l'extrait aqueux d'embryon de poulet infecté par le virus Flury est, elle aussi, très prometteuse.

La sérologie de la rage est encore obscure sur certains points. Les opinions divergent quant au rôle des anticorps dans la résistance. Sont-ils seulement des auxiliaires ou sont-ils déterminants dans l'apparition de la résistance ? On n'a pas pu établir de relation constante entre le taux des anticorps dans le sérum et le degré de protection acquise. En évaluant la vaccination prophylactique, il est nécessaire d'étudier, sous ses divers aspects, la réponse sérologique des animaux vaccinés et de chercher les moyens de mesurer les substances qui, dans les tissus, peuvent contribuer à la destruction des virus introduits dans l'organisme animal.

Les expériences de vaccination des chiens, effectuées dans divers pays, sont nettement en faveur de cette méthode de lutte. Tant sur le terrain qu'en laboratoire, on a pu établir que le virus fixe inactivé peut être efficace, à condition que son pouvoir immunogène soit éprouvé. L'impression qui se dégage de ces observations est que, d'une façon générale, les chiens peuvent être rapidement immunisés par une seule dose de vaccin. La durée de l'immunité ainsi provoquée est inconnue. Il est probable qu'elle est de courte durée, aussi est-il justifié de recommander des vaccinations répétées, au moins annuellement. Il paraît souhaitable que l'on puisse disposer d'un vaccin qui crée à la fois une immunité élevée et de longue durée. Les vaccins vivants possèdent ces qualités, et, s'ils sont inoffensifs et dépourvus de facteur paralysant, ils pourront, à l'avenir, être choisis. Certaines souches de virus adaptées à l'œuf donnent actuellement bon espoir.

Le moment est venu où partisans et adversaires de la vaccination prophylactique des chiens devraient arriver à une entente, sur la base des faits actuels. La vaccination est une méthode qui complète les mesures traditionelles de lutte et prend une importance-clé dans les mesures envisagées pour supprimer la rage et protéger l'homme. Elle devrait être intégrée dans les mesures générales d'hygiène publique dans tous les pays du Proche-Orient et de l'Extrême-Orient, où la rage pose de graves problèmes.

Quant aux animaux autres que les chiens, impliqués dans la transmission de la rage, ils varient selon les pays. Ce sont les renards, les loups, les chacals, de petits rongeurs et de petits carnassiers, les viverridés en particulier, et enfin les vampires hématophages. La découverte, relativement récente, que, chez ces derniers, la rage pouvait exister à l'état latent ou asymptomatique, a ouvert de nouveaux horizons à l'écologie de la rage. Les virus isolés des animaux sauvages doivent être étudiés à fond au moyen des nouvelles techniques immunologiques, et en particulier leur pathogénicité et leur virulence pour différents animaux. Un virus ayant une gamme d'infectivité étendue possède certainement un grand pouvoir d'adaptation.

En attendant que ces recherches aient donné des résultats susceptibles d'application, l'homme doit être protégé, ainsi que les animaux de l'élevage desquels il vit. Trois méthodes ont été appliquées dans ce but : *a*) laisser la maladie évoluer et s'éteindre parmi les animaux sauvages qu'elle décime; *b*) détruire les animaux sauvages sensibles à la rage, afin de réduire la transmission; *c*) vacciner préventivement le bétail et les chiens exposés à être infectés par les animaux sauvages.

La première de ces méthodes est celle de la nature. Elle a donné d'excellents résultats en divers pays à diverses époques. La deuxième, appliquée pour la première fois contre le coyote en 1915-20, a été dirigée avec intensité contre le renard depuis 1940, soit dans le continent nord-américain, soit en Europe. Les pièges, le poison et les fumigations de terriers ont été employés pour la destruction des animaux sauvages. Mais ces mesures seules ne suffisent pas. La troisième méthode doit intervenir pour créer, par la vaccination des chiens, une barrière de protection entre animaux sauvages et domestiques. La vaccination des troupeaux doit être appliquée aussi, afin de diminuer les pertes, dans le cas où la rage est transmise par les vampires au bétail.

En conclusion, les faits répondent affirmativement à la question posée au début. L'homme peut être protégé contre la rage grâce à l'application de l'ensemble des méthodes qui viennent d'être mentionnées.

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