Spotted Fever Immunization:

Results and Recommendations*

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CONSEQUENT upon a widening area of distribution and upon the increasing population within the areas that have become endemically affected, the spotted fever of the Rocky Mountains has become of enhancing importance as a public health problem.[218, 223] Of this fact, cognisance has been taken by state and local health officers, by regional and inter-state conferences, by private practitioners, and by the increasing coöperation of the Federal Government. The coöperation of the latter has taken the form chiefly of conducting epidemiologic and ecologic studies in the field, of carrying out laboratory investigations on the virus, and of the manufacture, in annually increasing quantities, of a preventive vaccine of proven, and we might add, great value.[209, 225]

The vaccine, as originated by R. R. Spencer and R. R. Parker has an important place in any control program, but is particularly necessary for use in localities where tick control measures can not be conducted economically, due either to the character of the terrain, the sparseness of the population, or the very occasional character of the menace from spotted fever. Where, however, it has been found profitable to maintain tick control procedures, there is not yet justification for diminishing the tick control activities because of the recent introduction of a preventive vaccine.[224]

This paper will be limited to a study of the production, distribution, and efficacy of the spotted fever vaccine as originated by R. R. Spencer and R. R. Parker; the value of the vaccine as compared with other spotted fever control measures being given only incidental consideration inasmuch as this aspect has lately been elsewhere considered in detail by the author.[231]

The need for a preventive serum or vaccine was early apparent in the study of possible prophylactic measures against spotted fever, as the disease is of great economic importance in the areas where it is most prevalent; as also in areas where it is of (consistently) great virulence.[36,47,97] P. G. Heinemann and J. J. Moore[76,84] attacked the problem from the aspect of passive immunity. They showed that passive immunization offered virtually no prospect for effective prevention or therapy. It was H. T. Ricketts[49,56,75] and associates[61,69], and later Noguchi[142,143,144] who conducted the first studies on active immunization against spotted fever. Subsequent studies of related nature were reported by Conner[147,148], by Breinl[163], by Kuczynski[166], and by Otto[177]. It was not, however, until the experiments of R. R. Spencer and R.

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R. Parker resulted in the production of an attenuated virus, in sufficient concentration, that a practical vaccine became available.[150,153] This vaccine was first released for distribution in 1925.

The Nature of the Vaccine

The vaccine is the spotted fever virus obtained from infected ticks ("tick virus") rather than from the blood of infected animals ("blood virus"); its virulency is attenuated by chemical means. It is standardized for approximate potency by biologic (guinea pig) assay. Each dose (2 c.c.) equals the attenuation of approximately 20,000 minimum infectious doses for a guinea pig. Two such doses at five day intervals have constituted the standard course, which requires being repeated annually.

Although most vaccines are prepared by heating the organisms to 56° C. it has been found necessary to obtain attenuation by means of a chemical, as the protective quality of spotted fever virus is entirely destroyed at the temperature of 56° C.

Manufacture of the Vaccine

Wild adult ticks, collected in the field, are permitted to feed on infected guinea pigs after the onset of the fever, placing about 75 ticks in a wire gauze capsule fastened to each animal. After two days of feeding the ticks are removed and placed at room temperature over moist sand, where they may be kept for several months. Before being used for making vaccine these ticks are again fed, this time on normal animals, for five or six days. This second feeding produces a tremendous increase in the number of minimal infectious doses of the virus per tick. For routine purposes it is not necessary to determine this dosage by the graded injections of the live tick-virus suspensions, as was formerly done.

The partly engorged ticks (male and female) are now ground in a mechanically operated porcelain mortar and pestle with fine quartz sand and a small quantity of physiological salt solution which contains 1.6 per cent phenol and 0.4 per cent formalin. After thorough grinding the whole mass is transferred to a large stock bottle, and an additional amount of the salt solution and preservative is added until the concentration reaches, but does not exceed, four ticks per cubic centimeter. After standing for 48 hours, during which time the preservatives will precipitate most of the protein, an equal volume of physiological salt solution is added. This dilutes the preservatives to 0.8 per cent phenol and 0.2 per cent formalin. At this stage the material is kept for seven days at room temperature. This has been found a sufficient period to kill most extraneous organisms, including sporebearers.

The suspension is then diluted once more by again adding an equal volume of salt solution. This final dilution will contain 0.4 per cent phenol, 0.1 per cent formalin, and the killed virus equivalent of one tick per cubic centimeter. The sand, chitin, and precipitated protein is now removed by centrifugation and the remaining clear amber-colored supernatant fluid is ready for the final containers. Occasionally some precipitate forms afterwards. This can be disregarded, for it does no harm when injected, and besides has protective value. In fact, the discarded heavy precipitates from potent lots may be combined and resuspended in sterile salt solution, again cleared by centrifugation, and the clear supernatant fluid still found to possess high protective value. A number of such lots have been so made and used in human vaccination.[199]

Test for Potency and Sterility. Each lot is tested for potency by inoculating six guinea pigs subcutaneously with one cubic centimeter each. After twelve days the animals are given intraperitoneally a test dose of one cubic centimeter of guinea pig blood virus. If four of the six animals do not show symptoms of spotted fever the vaccine is considered suitable for human use. An arbitrary standard of potency of this kind admits the operation of several variables. The potency of any two lots of vaccine is only approximately the same.

Sterility tests are made in accordance

with the hygienic laboratory procedure for biologic products.

Keeping Quality. The vaccine is fairly stable at ice box and room temperature. Ice box preserved vaccine protected guinea pigs invariably up to 200 days and 6 out of 9 pigs at 576 to 597 days. Vaccine kept at room temperature protected 8 of 9 pigs up to 108 days and one-half of 10 pigs at 215 days, the remainder dying of spotted fever.

Distribution of the Vaccine

The vaccine is produced solely by the U. S. Public Health Service at Hamilton, Montana. It is distributed to physicians without charge and it is expected that only a nominal charge will be made for administering the vaccine. Application for the vaccine should be made to the Officer in Charge, U. S. Public Health Service, Hamilton, Montana.

Each year there has been an increasing demand for the vaccine. The heaviest calls are from Montana, Wyoming, Idaho, and Oregon, the last named state using the most in 1930. There is a moderate demand from South Dakota, Nebraska, Colorado, Nevada, and Washington.

The amounts that have been distributed are as follows:

Year	C.C.	Number of Doses	Number of Courses
1925	372	186	93
1926	3,412	1,706	856
1927	6,284	3,064*	1,532
1928	6,500	3,250	1,625
1929	16,600	7,786	3,893
1930	32,000	16,000	8,000
1931	64,000	32,000	16,000

*Includes 312 doses at 2.5 c.c. per dose.

Method of Administration

Equally good protection has been effected by the subcutaneous, intravenous, intramuscular, and intraperitoneal routes, the latter employed in guinea pigs only. Ordinarily the vaccine is administered subcutaneously. Attempts to vaccinate animals by forcing them to swallow the vaccine have produced immunity in only a few instances, and failed in the great majority of cases.

Reactions

Less than five per cent of four thousand persons have complained of constitutional symptoms. These have included malaise, slight fever, nausea, and aching joints or muscles. Protein reactions with urticaria and edema have occurred in about one per cent of those vaccinated, the symptoms usually appearing very shortly or within a few hours after the injection, but in one instance were delayed ten days. The symptoms last from a few hours to several days, but in one man the urticarial rash persisted somewhat for nine months, finally disappearing following infection with spotted fever. About one-half of those who have reacted after the first injection do not do so on subsequent injections, whereas a few react more violently. Marked collapse occurred in one person who, the next day, felt normal except for weakness.[201]

Local reactions have mostly been inconsequential and limited usually to local redness, swelling and itching about the site of injection. Swelling sometimes extends below the elbow and occasionally to the hand. Itching, the most common complaint, either disappears or becomes scarcely noticeable in persons who have been vaccinated several times.

Duration of Immunity

Data from the Bitter Root Valley test indicate that the duration of protection in the average individual does not exceed one tick season. The period varies in individuals, however, and for some may be quite short. Vaccination annually is therefore desirable.

While effective immunity does not last longer than one year, there is evidence that a residual immunity persists for a much longer time.

Populations Immunized

Immunization has included the vaccination of three accurately controlled experimental groups, and a dispersive, not accurately controlled distribution of the vaccine. The general distribution, not available for accurate comparative statistics was as follows:

In	No. of Individuals to Jan. 1, 1930	No. of Individuals to Jan. 1, 1932 (Approximately)
Montana (excluding Bitter Root Valley test group)	401	2,600
(including test group)	(3,231)	(7,100)
Idaho (excluding test group)	203	1,400
(including test group)	(396)	(1,593)
Wyoming	863	2,900
Oregon	30	3,300
Nevada	5	300
Colorado	3	275
Utah, Dakotas and Nebraska	2	275
Washington and California	0	250
General distribution	1,507	8,300
Total distribution	4,530	16,000

The three test or controlled groups were the following: the U. S. Public Health Service workers (including state control employees); the Idaho Test Group, and the Bitter Root Valley Test Group. The Idaho Test Group included 94 persons in 1926 and 99 in 1927 (none thereafter), a second annual vaccination not being offered in 1927 to those vaccinated in 1926. The number of inoculations administered to the Public Health Service (including state control) employees is included in the following statistics concerning the Bitter Root Valley Group.

The following table (table I) shows the number of individuals who, in each year, had received the number of vaccinations and revaccinations as indicated by the integers on the course line.

Table I

Courses received:	1	2	3	4	5	6	7	Total
1925	34							34
1926	624	30						654
1927	846	339	112					1,296
1928	1,469	430	141	11				2,051
1929	2,067	491	191	71	10			2,830
1930	2,550	555	257	143	64	9		3,578
1931*	2,720	800	550	265	150	10	5	4,500

*Estimate by the author, official records not yet compiled for publication.

Results

From the results of a two year test (1926 and 1927) made in southern Idaho (Snake River Valley) against the mildest type of the disease, and another test against the most virulent type, which has been in progress for seven years in the Bitter Root Valley, the following conclusions are justified —that against the milder types of infection the vaccine usually affords full or nearly full protection, while against the highly virulent type the degree of protection is usually sufficient to cause a marked amelioration of the customary very severe symptoms, and to predispose to the recovery of most cases.

In southern Idaho infection is very prevalent among persons handling sheep on the range, and the test was therefore confined to that industry. During the two seasons of 1926 and 1927, 193 sheep herders were vaccinated, and 364 non-immunes served as controls. A single case only occurred among the vaccinated men (1 in 193). This man had refused the second injection. Among the 364 control individuals there were 22 cases, or one in every 16.55 men.

The Bitter Root Valley case mortality for the twelve years, 1917 to 1928, was 53 deaths out of 69 cases, a rate of 76.81 per cent. In six of these twelve years the mortality for adults was 100 per cent. During the period of the four years under consideration (1925-1929) there were, including the non-vaccinated control group, a total of 18 cases with 15 deaths, a case mortality rate of 83.3 per cent, among the non-vaccinated persons living in the Bitter Root Valley.

The results of the test against the malignant Bitter Root Valley strain yield the following statistics for the period 1925 to 1931, inclusive:

	Vaccinated Group	Non-vaccinated, Control Group
Number of individuals in group	3,578	about 8,700
Approximate ratio to whole population	30%	70%
Number of cases in group	16	30
Case incidence	1:223*	1:290
Died	2	22
Death rate	12.5%	73.32%
(Parker-Spencer series	9.09%	90.91%

*The slightly greater incidence rate in the vaccinated group was due to the fact that vaccination was first carried out to proportionately greater degree in a "well defined dangerous zone on the west side of the valley", where of 1,208 persons, 496 were vaccinated, letting the remainder, 712 in number, serve as controls. Considering only the group of 1208 in the dangerous zone on the west side of the valley, there were during the four years (1926-1929) three cases (1 in 165) among the members of the vaccinated group, none of which was fatal, while there were nine cases (1 in 79) among the non-vaccinated group, seven of which proved fatal, a case mortality rate of 77.7 per cent.

A composition of the Public Health Service (Group A) cases, seven in number (with one death), the Bitter Root Valley cases, 16 in number (with two deaths) and the experience of Dr. E. L. Jewell with two cases (both recovered) each with the equally fatal Kirby Creek strain of spotted fever, gives a total of only three deaths in twenty-five cases of almost fatal virulency, a mortality rate of 12 per cent against the twelve year average of 85 per cent.

Parker and Spencer, writing of their initial series, have been able to say "Considering only adult cases in the Bitter Root Valley as a whole, the recovery of 10 of 11 vaccinated adults, 7 of Group A and 4 of Group B (90.91 per cent recovery) during the four year test period offers vivid contrast, first with the death of 10 of 11 non-vaccinated adults (90.91 per cent mortality) during the same period, and second, with death of 9 of every 11 non-vaccinated adult cases (84.91 per cent mortality) during the past twelve years."[201]

Prospects

Having passed the experimental stage, the prospects for the adequate employment of the vaccine have to do with problems of distribution, and of coördinating the use of the vaccine with other control measures, according to the relative economic positions of the measures available. Maximum distribution requires suitable publicity and organization of distributing channels—matters of routine.

The evaluation of the vaccine's economic position is not definitely established, there appearing to be a tendency to undervalue it (compared with other measures) even by those reasonably conversant with the situation. This we believe is a great mistake.

The limited supply, the high cost of manufacture, the disposition of many persons to refuse to submit to any sort of vaccination, the necessity for annual reinoculations, and the popular appeal of other more visibly tangible control measures, such as tick destruction and rodent destruction, all serve to restrict the use of the vaccine to a greater degree than they should.

While it is evident that other control measures can not be diminished the slightest, in areas of great malignancy or tick concentration, on account of the introduction of the vaccine, the great fallibility of these measures renders imperative the systematic use of the vaccine in all dangerous areas, despite the additional cost. In areas of lesser danger the use of the vaccine is equally imperative, as in most such localities the liberal use of tick destruction and rodent destruction measures are economically infeasible. Particularly requiring the vaccine are transient visitors to dangerous areas, and residents of remote or sparsely settled localities in the infected areas. It is particularly the latter class of persons that present serious problems in the matter of distribution.

In final analysis it is apparent that the prospects for the use of the vaccine are predominatingly in the hands of the medical men serving in the localities affected; if they energetically sponsor the use of the vaccine they will be supported by the proper persons for obtaining the necessary publicity; if they are negligent the popular appeal will eventually foster an increasing use of the vaccine, but never perhaps to a sufficient degree unless actively supported by the medical profession. Certainly, however, there is no reason to infer that physicians will be remiss in this matter, as the initial response of the profession has been exceedingly gratifying. Nevertheless, to facilitate distribution, various regional organizations and standards need to be created; these are matters of administration, largely being developed at the present time, and will be dealt with as recommendations.

Recommendations

Current problems have to do with methods of manufacture and standardization, means of distribution, educational programs, and plans of inoculation.

The progressively increasing demand for the vaccine will undoubtedly be met adequately by the U. S. Public Health Service for years to come. It may, however, become necessary to require some reallocations in the manner of defraying the cost of manufacture, as the production of the vaccine is exceptionally costly due to the high labor charge for field work in obtaining the ticks, and for the laboratory work needed to infect them and rear them. Methods of manufacture are, however, being studied from the aspect of reducing unit cost and of increasing potency. A better method for assaying and standardizing potency is desirable.

Distribution through the medical profession should continue as the main avenue of release. In controlled areas and other highly malignant localities, the vaccination should be under the immediate supervision of the statistician in charge. For reaching men on remote sheep ranges, the state sheep inspectors, veterinarians, and other intelligent persons of the locality should be trained to give the vaccine and to keep the records.

As maximum distribution can not be obtained without persistent publicity of the proper sort, it is recommended that newspaper editors, ministers, school teachers, district supervisors, and educators in the higher grades be officially requested to publish the facts concerning spotted fever vaccination, and to give such information of local interest as will facilitate obtaining the inoculations. For this publicity the school and civic exercises of Washington's birthday should be utilized systematically to the end that the date of February 22 shall become firmly associated in the public mind with the need for obtaining the first of the year's spotted fever inoculations. Similarly in areas of great malignancy the same custom should also become identified with May Day, May 1st, for the single mid-season injection. On the other hand, in areas where one injection of the year is the optimum dosage, this fact should be made known to relieve the public mind and to discourage the needless waste of the vaccine.

Regarding dosage and plan of administration, in view of the need of economy and maximum general efficiency, it is recognized that collectively better results will be obtained by so employing the vaccine as to depart from the present standard dosage (two injections of 2 c.c. each, at five day intervals) wherever local requirements, particularly the greater or less local virulency of the disease, indicate the advisability of establishing an optimum dosage for the locality concerned. Thus a single mid-season injection (about May 1st) in addition to two pre-season injections, is decidedly to be recommended for persons exposed in areas of great malignancy. On the other hand, in certain localities a single annual injection of 2.5 c.c., before the commencement of the tick season, should be considered optimal, according to local conditions. In areas of intermediate virulence the optimum dosage appears to consist of two injections of 2 c.c. each, or possibly the first of 1.5 c.c. and the second of 2.5 c.c., the interval of five days being permissibly lengthened to seven days where local conditions seem to make the latter interval more feasible.

Regarding organization of the distributing channels it is recommendable that state health boards shall (to assist them and the Federal authorities) appoint non-salaried, resident district supervisors among the regular medical practitioners of their State, with view to surveying local requirements, obtaining and supervising proper publicity, keeping records, rendering reports, and otherwise assisting in the distribution of the vaccine, with consideration to apportioning it where it is most needed.

Summary

Six years' experience with the Spencer-Parker spotted fever vaccine, a chemically attenuated form of the virus, has demonstrated it, by several controlled experiments, to be of great and dependable value in preventing the occurrence of the mild type of spotted fever, and of great value in mitigating the severity of the highly fatal type of the disease, the mortality of the latter being reduced from the twelve year average of eighty-five per cent to approximately ten per cent (nine to twelve per cent).

As the protective action of the vaccine lasts only one season (four to twelve months), annual reinoculations are necessary before the commencement of each tick season. Since the introduction of the vaccine in 1925 to the year 1931, inclusive, between 25,000 and 30,000 persons have been vaccinated; and many of them revaccinated annually from two to six times.

The demonstrated value of the vaccine, and the great need for it in endemic areas, has created an increasing demand for it from the medical profession and the laity, a demand that will continue to be met gratis by the U. S. Public Health Service Laboratory at Helena, Montana, despite unusual difficulties of manufacture and distribution.

While it is recognized that tick destruction and rodent control measures can not be safely diminished on account of the introduction of the vaccine, it is of great importance that the vaccine be used adequately and systematically in all endemic areas, as in most areas it is the only preventive measure available that is both dependable and economically feasible. To effect better distribution and economy, several recommendations are made concerning organization, publicity, and modification of dosage with respect to local requirements, according to the virulency of the local strain.

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