An anthrax vaccine was evaluated clinically and epidemiologically in an exposed, susceptible, and supervised population. Findings are reported and the authors suggest exposed populations for whom the vaccine is recommended.

FIELD EVALUATION OF A HUMAN ANTHRAX VACCINE

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IN A SERIES of papers published from 1951-1955,[1-6] Wright and colleagues, reported on the development of an anthrax vaccine. This vaccine was shown to be an effective immunizing agent for laboratory animals and its safety for human use was demonstrated by the successful injection of 600 scientific personnel at Fort Detrick. Its value for human immunization could be established through a field study of a susceptible industrial population known to be chronically exposed to anthrax. This communication reports the data collected in such a study over a four-year period.

Material—Methods

The necessary requirements of a well defined, exposed, susceptible population among whom cases of anthrax were reported with some regularity could only be met, in this country, in an industrial area; and, thus, epidemiological studies were conducted in various mills where Bacillus anthracis-contaminated raw materials were handled and clinical infections occurred. Four mills located in northeastern United States qualified for inclusion in the evaluation program. All processed raw imported goat hair into a hair cloth interlining used in suit coats. The average yearly incidence of anthrax per 100 employees for these mills was 1.2 cases with a range of from 0.6 to 1.8 as shown in Table 1.

The vaccine was supplied by Dr. G. G. Wright and associates of the U. S. Army Chemical Corps, Fort Detrick, Frederick, Md. It was produced by growth of the Rl-NP strain in 599 medium. Rl-NP is a nonencapsulated, nonproteolytic mutant of the Vollum strain of B. anthracis. Protective antigen in the sterile culture filtrates was precipitated and concentrated by addition of 0.1 per cent aluminum potassium sulfate (alum). The immunizing properties of various lots of antigen were established by immunization and challenge of rabbits; lots with poor activity were not used in the human evaluation. Details of methods for preparation and testing of the antigen have been presented by Wright, et al.[5]

The employees who had not had anthrax were divided into two numerically equal groups according to their length of employment, age, the department in which they were employed, and the specific job performed. One group received the antigenic material and the other a placebo that consisted of 0.1 per cent alum. The employees were not told which material they received. Voluntary cooperation of the employees was solicited and those who refused

were removed from the lists. Refusals were distributed in approximately equal proportions among the two groups so that of those initially cooperating, 48 per cent were in the vaccine group and 52 per cent in the placebo control group.

The immunization schedule used was based upon the results of animal immunization studies. Inoculations consisted of 0.5 ml of either vaccine or placebo given subcutaneously in the deltoid area. The initial series of inoculations consisted of three injections given at two-week intervals, followed by three 0.5 ml booster doses given at six-month intervals. Thereafter, booster inoculations were given at yearly intervals.

The employees of two mills were examined at 24 and 48 hours after each inoculation, and evidence of local or systemic reactions were noted.

A close surveillance was maintained at each mill by means of routine visits and regular environmental sampling programs throughout the study period. The management at each mill was aware of the advantage of a reduced incidence of anthrax infections so that they had an incentive to report all suspicious cases as they occurred. In spite of this close surveillance, one probable case of cutaneous anthrax in a placebo inoculated individual did occur that was not reported. This case is not included in this analysis.

Results

Population

The total populations at the four mills were divided into high- and low-risk groups as defined by the degree of contact with the raw materials. It has been shown that the incidence of cutaneous anthrax is highest in the bale opening department and gradually decreases through successive departments.[7] The total eligible population at the initiation of the program in each mill was 1,249 individuals, with 47 per cent working in high-risk areas and 53 per cent working in low-risk areas (Table 2).

The total eligible population continuing through successive inoculations is summarized in Table 3, and shows an initial marked decrease (61 per cent) between the intial series and the first booster inoculation. Most of this decrease was the result of the termination of the program at the largest mill (A) midway between the initial series and the first booster, because of an outbreak of inhalation anthrax. All employees were then immunized, which removed from the controlled study 49 per

Table 1—Incidence of Anthrax in Four Mills Prior to Initiation of Vaccination Program

Mill	Average Total Employment	Cases of Anthrax, 1948 to Initiation of Study*	Cases per 100 Mill Employees Per Year
A	655	63	1.0
M	227	23	1.4
P	148	6	0.6
S	300	38	1.0
	1,330	130	1.2

* Mill A, May, 1957 Mill P, May, 1956
Mill M, June, 1955 Mill S, Feb., 1955

Table 2—Participation of Employees in Anthrax Vaccine Evaluation Program

Mill	High Risk					Low Risk					Total				
	Inoculated					Inoculated					Inoculated				
	Vacc.*	Plac.*	Inc.*	Refusal	Total	Vacc.	Plac.	Inc.	Refusal	Total	Vacc.	Plac.	Inc.	Refusal	Total
A	59	60	11	70	200	90	104	24	214	432	149	164	35	284	632
M	42	49	8	8	107	31	42	4	16	93	73	91	12	24	200
P	19	22	15	10	66	22	22	13	21	78	41	44	28	31	144
S	89	95	31	1	216	27	20	10	–	57	116	115	41	1	273
Total	209	226	65	89	589	170	188	51	251	660	379	414	116	340	1,249

* Vaccinated—Placebo—Incomplete

cent of the total eligible population. Subsequently there was a gradual decline (13 per cent to 20 per cent) following each successive booster inoculation, partly because of the changing nature of the textile business and partly because of the withdrawal of some of the employees from the program. Since the mills entered the program at different times, the respective personnel had received varied numbers of inoculations when the program was terminated at the end of four years.

The inoculees referred to as complete include all those employees who received the prescribed inoculations at the scheduled times; incomplete inoculees include those who missed one or more of the scheduled inoculations, whether placebo or vaccine.

Clinical Data

A total of 26 cases of anthrax were reported among the employees of the four mills during the evaluation program. The occurrence of the cases by month for each mill is summarized in Figure 1. In mills M, P, and S, the cases were reported essentially throughout the entire evaluation period. At mill A, the occurrence of nine cases during a ten-week period clearly indicates an epidemic.[8,9]

Twenty-one of the cases were cutaneous, and five were of the inhalation type; four of the latter were fatal. The cases are individually summarized in Table 4. Three of these cases occurred among individuals who had received the vaccine, and the remaining 23 cases occurred among individuals who either had received the placebo inoculations or had not received any inoculations at all (Table 5). Seventeen of these unvaccinated cases received the alum control inoculations and are referred to as placebo control cases, and six were uninoculated employees.

The diagnoses of anthrax were based on clinical, bacteriological, pathological,

and epidemiological data and are summarized in Table 6. Subcultures of recovered B. anthracis organisms were studied and confirmed in the Anthrax Investigations Unit Laboratory.

Three cases of cutaneous anthrax without bacteriological confirmation are included because in each case the clinical diagnosis was made by a physician who had previously diagnosed many cases which were subsequently confirmed by bacteriological methods. The single case of fatal inhalation anthrax without laboratory confirmation is a patient whose clinical course paralleled that of three other confirmed cases of fatal inhalation anthrax that occurred at the same time at the same mill.[8,9]

The clinical courses, age distributions, sex ratio, length of employment prior to developing anthrax, location of lesions, and over-all departmental attack rates reflect human industrial anthrax as seen in this country.[7,10,11] Twenty-three of the cases occurred among individuals who worked in the high-risk areas, and three occurred in individuals in the low-risk areas.

The immunization histories of the 26 patients are summarized in Table 7. The "complete" vaccinated case was a 33-year-old female spinner who developed a mild cutaneous lesion five months after receiving the last inoculation of the initial series and just before the regularly scheduled first booster inoculation was due. A smear and culture from the lesion were positive for B. anthracis. Her clinical course was not different from many others previously seen among employees of this mill.

One of the "incomplete" vaccinated cases developed a "typical" cutaneous anthrax a day or two before the scheduled third inoculation of the initial series. A smear and culture were positive for B. anthracis. Since this employee had not received the full complement of the initial series, the failure in protection cannot be charged to the vaccine, therefore, the case is considered to represent an "incomplete" vaccinated case.

The other "incomplete" vaccinated case, a 25-year-old male, had received his initial series in proper order but had not received any subsequent booster inoculations and developed a "typical" cutaneous lesion 13 months after his initial series. A smear and culture from his lesion were positive for B. anthracis.

Two "incomplete" placebo individuals developed anthrax: A 62-year-old female who worked in the drawing department

Table 3—The Population Remaining in the Evaluation Program Following Successive Inoculations

	Inoculations					
	Complete		Incomplete	None	Total Eligible	
	No.	Per cent Decrease			No.	Per cent Decrease
Primary Series	793		116	340	1,249	
		51				61
Booster: 1	390		56	47	493	
		16				16
2	327		65	23	415	
		19				13
3	265		69	24	358	
		28				20
4	190		73	24	287	

Table 4—Summary of Cases of Anthrax in the Evaluation Population

	Date of Onset	Name	Age	Employer	Department	Length of Employment (Years)	Vaccine Status*	Site of Lesion
1.	3-14-55	A.C.	24	S	Spinning	4½	V-I	hand
2.	3-30-55	J.K.	36	S	Carding	4	P-C	nose
3.	5-19-55	G.W.	30	S	Spinning	4	P-C	finger
4.	5-27-55	V.V.	48	S	Spinning	16	P-C	hand
5.	9-4-55	M.S.	33	S	Spinning	9½	V-C	leg
6.	11-1-55	E.S.	27	S	Spinning	3	P-C	forearm
7.	11-18-55	M.G.	53	S	Spinning	10	P-C	cheek
8.	1-31-56	M.V.	33	S	Spinning	4	U	finger
9.	6-15-56	H.K.	38	S	Carding	6	P-C	wrist
10.	8-10-56	C.P.	55	M	Spinning	8½	P-C	finger
11.	12-18-56	E.S.	43	S	Spinning	7	P-C	forearm
12.	2-15-57	N.J.	40	S	Carding	6	P-C	neck
13.	2-18-57	S.W.	62	P	Drawing	†	P-I	arm
14.	5-20-57	A.I.	63	P	Carding	†	P-C	cheek
15.	8-27-57	T.T.	60	A	Carding	6	U	inhalation
16.	9-1-57	A.J.	49	A	Carding	1½	U	inhalation
17.	9-2-57	E.C.	65	A	Weaving	11	P-C	inhalation
18.	9-9-57	L.L.	46	A	Carding	2	P-C	inhalation
19.	10-3-57	V.K.	64	A	Weaving	7	P-C	finger
20.	10-10-57	H.T.	35	A	Carding	7	U	forehead
21.	10-15-57	R.P.	50	A	Weaving	2	P-I	wrist
22.	10-30-57	A.L.	33	A	Carding	(2½ mo)	U	inhalation
23.	11-5-57	C.S.	61	A	Carding	(2½ mo)	U	chest
24.	11-11-58	M.G.	55	M	Combing	5	P-C	cheek
25.	3-31-59	D.J.	39	M	Spinning	6	P-C	forearm
26.	3-27-59	J.W.	25	P	Picking	1½	V-I	forearm
Median			45			5½		

* P—placebo
V—vaccine
U—uninoculated
C—complete
I—incomplete

† Not known

developed her lesion eight months after receiving the last inoculation of her initial series, and a 50-year-old female weaver developed anthrax three months after the last inoculation of an "incomplete" initial series.

The "complete" inoculated placebo cases (15) occurred at all stages of vaccination in decreasing numbers, reflecting the decreasing population for successive inoculations. No cases of anthrax occurred in individuals known to have recovered from a previously confirmed anthrax infection.

The statistical analysis was performed by Dr. R. E. Serfling, chief of the Statistics Section, Epidemiology Branch, Communicable Disease Center. It consisted of calculating the person-months exposure by inoculation status, for each mill, for both the high- and low-risk groups, including only those with "complete" inoculations. The cases of anthrax that occurred in the "complete"

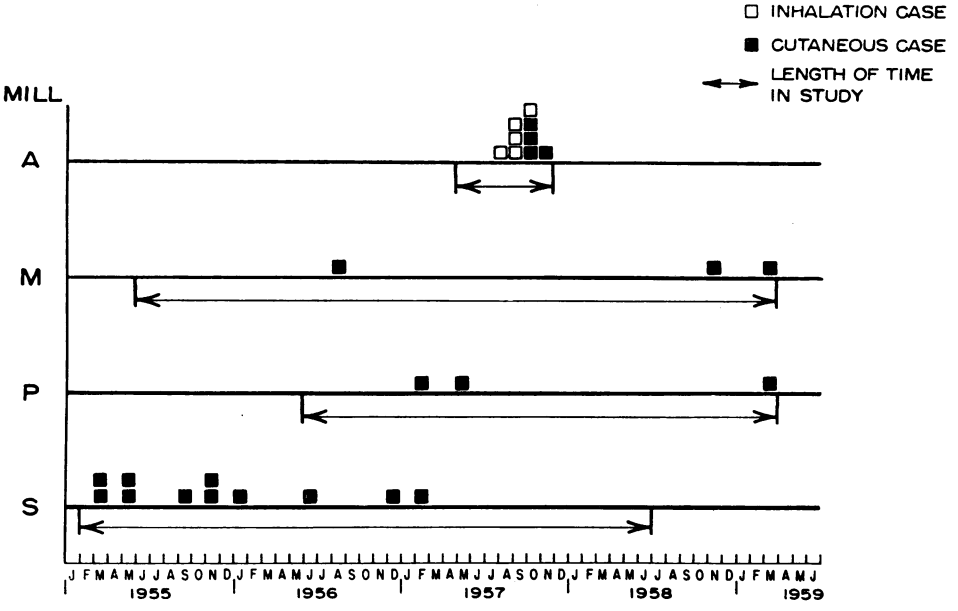

Figure 1—Occurrence of Cases of Anthrax in Four Mills During Vaccine Evaluation Studies, January, 1955-March, 1959

inoculated group only were grouped in a similar manner, and the attack rates calculated per 1,000 person-months. Using the attack rates in the placebo groups, the expected numbers of cases in the vaccinated groups were calculated. The total expected cases for the entire vaccinated group was 13.35. Considering that only one case was actually observed, the effectiveness of the vaccine is calculated to be 92.5 per cent $(13.35-1) \div (13.35)$ (Table 8).

"Determination of the confidence limit for the estimated effectiveness involved the following computations. Allowing π_i, $^{v}_{i}$ to represent, respectively, the risk of infection and the number of person-months exposure in the i^{th} (plant, risk-group, time-period) subgroup, and letting ρ represent the relative risk of infection if vaccinated, the expected number of vaccinated cases over all subgroups will equal $\rho\Sigma\pi_i{}^{v}_{i}$. Taking the sum of expected cases in

Table 5—Cases of Anthrax Occurring at Each Mill During Evaluation Program

Mill	Complete Inoculations		Incomplete Inoculations		No Inoculations	Total
	Vaccine	Placebo	Vaccine	Placebo		
A	–	3	–	1	5	9
M	–	3	–	–	–	3
P	–	1	1	1	–	3
S	1	8	1	–	1	11
Total	1	15	2	2	6	26

Table 6—Diagnostic Criteria for the 26 Cases of Anthrax that Occurred During the Evaluation Period

	Clinical Data	Smear	Culture	Pathology
Vaccinated Cases: (3)				
Cutaneous				
Complete 1	+	+	+	
Incomplete 2	+	+	+	
Placebo Control Cases: (17)				
Cutaneous (15)				
12	+	+	+	
3	+	ND	ND	
Inhalation (2)				
Fatal 1	+	ND	ND	ND
Recovery 1	+[a]	−	−	
Uninoculated Control Cases (6)				
Cutaneous (3)				
2	+	−	−	
1	+	+	+	
Inhalation (all fatal)				
2	+	+	+	+
1	+	−	−	+

\+ Positive
− Negative
ND Not done
[a] Serological data also positive

the vaccinated as calculated from the data to be an estimate of $\rho\Sigma\pi_i{}^{v}{}_i$ with $\rho=1$, and considering the observed cases in the vaccinated to be a Poisson variable, the probability of obtaining at least as many vaccinated cases as were observed may be calculated for various values of ρ." This procedure leads to an estimate of 65 per cent as a lower 95 per cent confidence limit for effectiveness of the vaccine.[17]

A similar analysis of 81 individuals in the study population who had previously had anthrax was made. By calculating the person-months exposure during the evaluation period and utilizing the attack rates observed for the placebo group (Table 8), 5.73 cases would have been expected in this group; however, no cases were observed. This data suggests that a previous anthrax infection provides some protection against a second anthrax infection.

Reactions

Objective criteria for evaluation of local reactions are summarized in Table 9. These consisted of the determination of two indexes based upon observations following inoculations of employees at two of the mills. The first index is the erythema value based upon the measured area of local erythema observed, and the second is the reaction index based upon all objective findings, including erythema, induration, and edema.

The average erythema value and the average reaction index for all vaccinated persons, following successive inoculations is summarized in Figure 2 and shows that both values gradually rose through the fifth inoculation and then declined. This decline was not related to the withdrawal from the program of those who had the more severe local reactions.

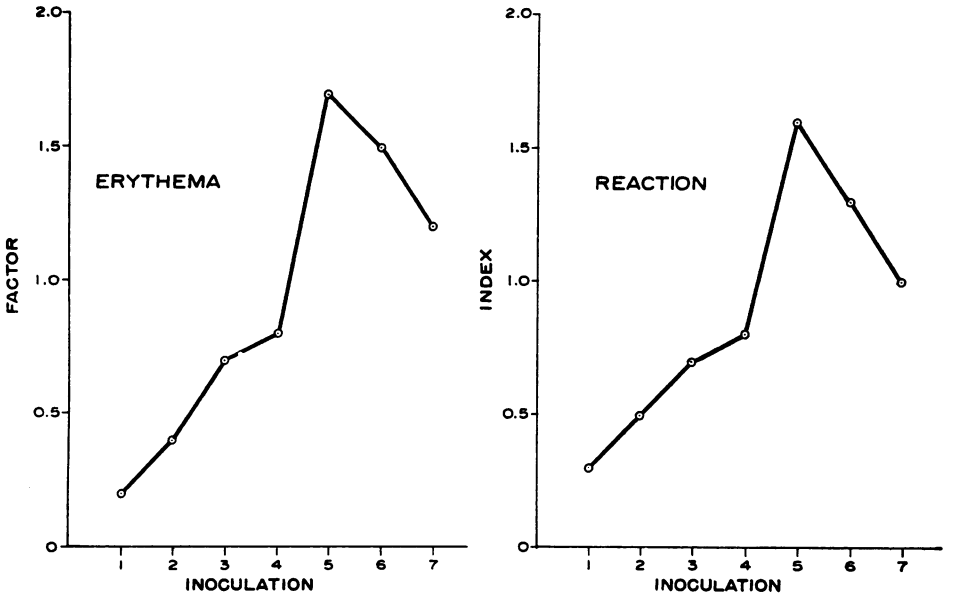

Figure 2—Average Erythema Factor and Reaction Index per Person Following Anthrax Vaccination

The typical reaction was mild and did not cause any interruption of work. A small ring of erythema 1 to 2 cm in diameter, with slight local tenderness, was noted commonly within 24 hours after vaccination. In general, all signs and symptoms disappeared within the next 24 to 48 hours. In many of the cases, this minimal degree of local reaction would not have been noticed by the inoculee had not his arm been examined at 24 and 48 hours after inoculation. In a few instances, the area of erythema increased between 24 and 48 hours to an area of from 3 to 5 cm in diameter which then disappeared. Pruritus and a small area of induration were the next most common local reaction. More severe local reactions were characterized by edema, erythema

Table 7—Occurrence of Anthrax Cases During the Evaluation Program by Immunization Status

	Complete Inoculations		Incomplete Inoculations		No Inoculations*
	Vaccine	Placebo	Vaccine	Placebo	
1st Series	1	6	2	2	5
1st Booster	–	4	–	–	1
2nd Booster	–	1	–	–	–
3rd Booster	–	2	–	–	–
4th Booster	–	2	–	–	–
Total	1	15	2	2	6

* Listed according to what their inoculation status would have been, had they entered the inoculation program.

greater than 5 x 5 cm, induration, and considerable local warmth, tenderness, and pruritus. A few inoculees developed small, firm, painless nodules at the site of injections which persisted for several weeks. It was our impression that antihistamines were effective in giving relief from the symptoms, especially pruritus.

The total incidence of the more moderate local reactions is summarized in Figure 3. The most prominent local reactions were those associated with the development of local edema (4+). Figure 3 shows that 21 individuals experienced 29 such reactions. None of these reactions were noted following the first inoculation but 4 per cent of the vaccinees developed this degree of reaction after the second inoculation. Following a decline, the incidence rose to a peak of 7 per cent after the sixth inoculation, and then fell to 2 per cent after the seventh inoculation.

Half of these edema-producing reactions were maximum at 24 hours, and the remainder at 48 hours. Three individuals experienced edema extending from the deltoid to the mid-forearm and, in one case, to the wrist, with a definite collection of fluid in the bursa of the elbow. This extensive edema disappeared within three to five days. Once an in-

Table 8—Calculation of Effectiveness of the Anthrax Vaccine

Period Number*	Risk Group	Length of Exposure (Months)	Person-Months Exposure by Vaccine Status and Mill: Vaccinated Mill A	Mill M	Mill P	Mill S	Sub-Total	Not Vaccinated (Placebo) Mill A	Mill M	Mill P	Mill S	Sub-Total
1	High	6	372	231	99	483	1,185	384	270	120	513	1,287
2		6	–	189	63	423	675	–	237	87	429	753
3		6	–	150	42	381	573	–	216	54	366	636
4		12	–	240	42	588	870	–	390	42	588	1,020
5		12	–	204	–	306	510	–	306	–	306	612
	Subtotal		372	1,014	246	2,181	3,813	384	1,419	303	2,202	4,308
1	Low	6	450	177	120	144	891	534	243	114	96	987
2		6	–	156	84	117	357	–	219	75	72	366
3		6	–	138	54	87	279	–	186	39	63	288
4		12	–	234	48	132	414	–	312	24	90	426
5		12	–	180	–	120	300	–	264	–	66	330
	Subtotal		450	885	306	600	2,241	534	1,224	252	387	2,397
	Grand Total		822	1,899	552	2,781	6,054	918	2,643	555	2,589	6,705

			Anthrax Cases by Vaccine Status and Mill: Vaccinated Mill A	Mill M	Mill P	Mill S	Sub-Total	Not Vaccinated (Placebo) Mill A	Mill M	Mill P	Mill S	Sub-Total
1	High	6	–	–	–	1	1	1	–	–	3	4
2		6	–	–	–	–	–	–	1	1	2	4
3		6	–	–	–	–	–	–	–	–	1	1
4		12	–	–	–	–	–	–	–	–	2	2
5		12	–	–	–	–	–	–	2	–	–	2
	Subtotal		–	–	–	1	1	1	3	1	8	13
1	Low	6	–	–	–	–	–	2	–	–	–	2
2		6	–	–	–	–	–	–	–	–	–	–
3		6	–	–	–	–	–	–	–	–	–	–
4		12	–	–	–	–	–	–	–	–	–	–
5		12	–	–	–	–	–	–	–	–	–	–
	Subtotal		–	–	–	–	–	2	–	–	–	2
	Grand Total		–	–	–	1	1	3	3	1	8	15

* Represents sequential periods of exposure between inoculations except that period 5 is the 12-month interval following the last inoculation.

Table 8—(Continued)

Period Number	Risk Group	Length of Exposure (Months)	Attack Rate per 1,000 Person-Months by Vaccine Status and Mill: Vaccinated Mill A	Vaccinated Mill M	Vaccinated Mill P	Vaccinated Mill S	Not Vaccinated (Placebo) Mill A	Not Vaccinated (Placebo) Mill M	Not Vaccinated (Placebo) Mill P	Not Vaccinated (Placebo) Mill S
1	High	6	–	–	–	2.07	2.60	–	–	5.85
2		6	–	–	–	–	–	4.22	11.49	4.66
3		6	–	–	–	–	–	–	–	2.73
4		12	–	–	–	–	–	–	–	3.40
5		12	–	–	–	–	–	6.54	–	–
1	Low	6	–	–	–	–	3.75	–	–	–
2		6	–	–	–	–	–	–	–	–
3		6	–	–	–	–	–	–	–	–
4		12	–	–	–	–	–	–	–	–
5		12	–	–	–	–	–	–	–	–

Period Number	Risk Group	Length of Exposure (Months)	Expected Cases in Vaccinated by Comparison Group and Mill: Not Vaccinated Mill A	Not Vaccinated Mill M	Not Vaccinated Mill P	Not Vaccinated Mill S	Not Vaccinated Sub-Total
1	High	6	0.97	–	–	2.83	3.80
2		6	–	0.80	0.72	1.97	3.49
3		6	–	–	–	1.04	1.04
4		12	–	–	–	2.00	2.00
5		12	–	1.33	–	–	1.33
Subtotal			0.97	2.13	0.72	7.84	11.66
1	Low	6	1.69	–	–	–	1.69
2		6	–	–	–	–	–
3		6	–	–	–	–	–
4		12	–	–	–	–	–
5		12	–	–	–	–	–
Subtotal			1.69	–	–	–	1.69
Grand Total			2.66	2.13	0.72	7.84	13.35

$$\text{Estimated effectiveness} = \frac{\text{Expected Cases Minus Observed Cases}}{\text{Expected Cases}}$$

High-risk group only $\frac{11.66-1}{11.66} = 91.4\%$

Low-risk group only $\frac{1.69-0}{1.69} = 100\%$

High-risk and low-risk groups combined $\frac{13.35-1}{13.35} = 92.5\%$

dividual had an edema-producing local reaction, he had an 88 per cent chance of having a less severe reaction following subsequent inoculations. These individuals were scattered throughout all departments in the mill and had worked for varying periods of time before being immunized. A total of six working days were lost as a result of these edema-producing reactions.

Confirmed systemic reactions were not seen except for two individuals who experienced, along with the edema-producing local reactions, some malaise of 24 hours' duration. Reactions to the alum material were seen in three individuals. These reactions, however, were mild as compared to the edema-producing reactions in vaccinated individuals.

The development of local reactions was not related to the particular batch of vaccine used or to the length of employment of the individual, the depart-

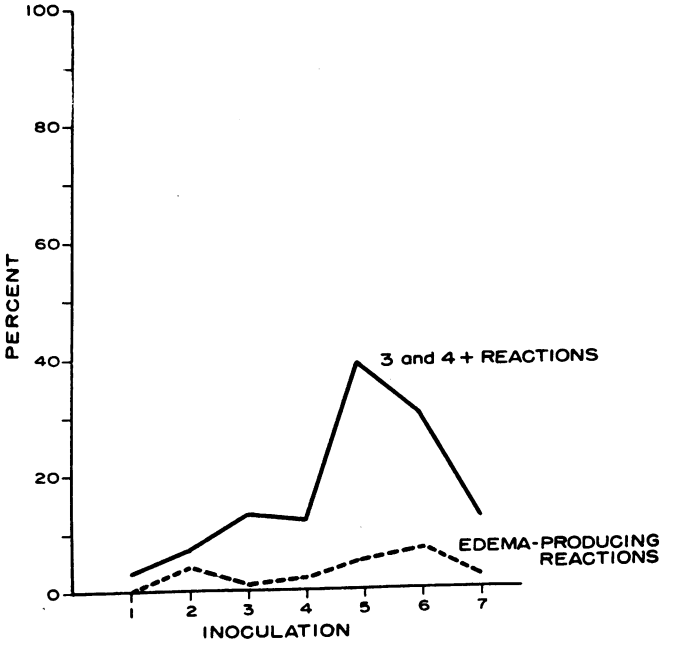

Figure 3—Per cent of Immunized Persons Who Had Significant Reactions Following Inoculations

ment in which he was employed, or the type of work in which he engaged. There were two individuals who inadvertently received the first injection of the vaccine, even though they had had clinical cutaneous anthrax 7 and 14 years previously. Both of these individuals experienced severe local reactions at 24 and 48 hours, with edema, induration, erythema, and pruritus. They received no further inoculations. The patient in mill A who had inhalation anthrax and recovered was vaccinated several months later without any untoward reaction. These are the only three individuals in this series who received the vaccine following a clinical anthrax infection.

Discussion

In 1946, Gladstone reviewed the literature on the characterization of immunizing antigens extracted from Bacillus anthracis cultures or anthrax lesions.[12] He described the elaboration of the protective antigen from B. anthracis organisms grown in serum. In 1947, Watson, et al., reported on the separation of two factors from the edema fluid of anthrax lesions; one of these factors was used for successful immunization of animals.[13] Heckly and Goldwasser (1949) and Boor (1955) recovered the protective antigen after incubation of B. anthracis in special culture media.[14,15] All of these preparations of the protective antigen were used to successfully immunize laboratory animals (including sheep).

Wright's protective antigen was elaborated by the growth of a selected B. anthracis strain in a chemically defined medium. Darlow, Belton, and Henderson reported the development of a similar vaccine in 1956.[16]

The evaluation of the Wright vaccine demanded a susceptible population that was exposed to B. anthracis and that was under adequate medical supervi-

sion. These criteria were satisfied in the four goat hair processing mills selected for this study. The statistical analysis of the data indicates that the vaccine was effective in protecting against cutaneous anthrax infections. When inhalation anthrax is considered, the limited experience with this form of the disease makes the data less significant in showing effectiveness of the vaccine.

The occurrence of the single vaccinated case five months after the initial series may indicate that the immunity resulting from the initial three inoculations had fallen significantly by that time. This possibility is further substantiated by a report that the only cases of anthrax among the immunized people in the Biological Laboratories of the U. S. Army Chemical Corps at Fort Detrick occurred in two employees, five months after the initial series.[18] It appears that a booster response occurs after the first booster inoculation, raising immunity to protective levels which are stable for at least six months. The single case in the incompletely immunized individual, 13 months after the initial series, further supports the importance of the first booster inoculations in securing adequate protective levels. Serological investigations of antibody titers utilizing the agar-gel precipitin method are currently in progress.[19] Darlow and colleagues, using their own vaccine, immunized human subjects by giving two subcutaneous inoculations ten days apart followed by a booster inoculation one year later.[16] They then demonstrated a booster response by using the rabbit-skin toxin-neutralization method.

Systemic or local reactions following vaccination were a minor problem. The incidence of 0.2 per cent systemic reactions, representing malaise in two individuals, compares favorably with that found by Wright[5] and Darlow.[16]

The detection of local reactions was overemphasized because of the close surveillance maintained for 48 hours after vaccination. A gradual increase in the severity of local reactions was noted through the fifth inoculation followed by a decline. The edema reaction, however, peaked after the sixth inoculation and then decreased in incidence. The total incidence of all local reactions from the mildest to the most severe was 35 per cent; however, the most severe or edema-producing local reactions occurred in only 2.8 per cent of the vaccinations. The latter figure corresponds to that reported by Wright. Although Wright noted some increased reactivity associated with certain lots of vaccine, the same correlation could not be made in this study.

In Darlow's series, the reactions seen were mild with an over-all reaction rate of 20 per cent. Darlow states that six different batches of vaccine were used without evidence of variation in potency or reactivity among them. Darlow also

Table 9—Criteria for Evaluation of Local Reactions

Erythema Value	
1(+)—1 to 99	$\frac{\quad}{mm^2}$
2(+)—101 to 399	$\frac{\quad}{mm^2}$
3(+)—400 to 1,599	$\frac{\quad}{mm^2}$
4(+)—1,600+	$\frac{\quad}{mm^2}$

Reaction Index*	
0—No reaction	
1—1-2 (+) E or I alone	Minimal
2—3-4 (+) E or 1-2+E & I	Mild
3—3-4 (+) E & I or Ed	Moderate
4—3-4 (+) E & I & Ed	Marked reaction

* E—Erythema
I—Induration
Ed—Edema

noted the development of lymphadenopathy and lymphangitis in several individuals, signs that were not encountered in our series. He also described the development of small, painless persistent nodules, of doubtful significance, at the site of inoculation. Similar nodules were noted in some of the inoculees in this series but were not recorded.

The increase in incidence and severity of the local reactions indicates an allergic component. Wright and Darlow came to the same conclusion. Treatment of the severe local reactions, especially of pruritus, with antihistamines was followed by fairly prompt relief. The decline in reactivity following the sixth and seventh inoculations may indicate some desensitization of the recipients. Darlow also noted in some people the development of mild local reactions at the site of a previous inoculation even though given in the opposite arm; we did not encounter this phenomenon.

There are various occupational groups in whom use of the vaccine is indicated. In this country immunization should be recommended for people who work with imported wool, hair (especially goat hair), bristles, hides, bone meal, and any materials reclaimed from animal products industries. Anthrax is rare among stevedores and truckers who have brief and sporadic but intimate contact with these materials. The cases that do occur, however, are not uncommonly quite severe, so that immunization of these groups is desirable but would be more difficult to accomplish. Veterinarians practicing in certain "anthrax districts" in this country should be vaccinated just as they recommend vaccination of cattle in these areas. Laboratory workers who have contact with B. anthracis should also be protected by vaccination.

The world incidence of human anthrax has recently been estimated to range from 20,000 to 100,000 cases annually.[20] The majority of these cases are agriculturally associated, and are reported from southern European, African, and Asian countries. It would be difficult to vaccinate the rural susceptibles in many of these countries because of the prevalent nomadic conditions and the inadequate medical facilities available. The necessity of giving multiple inoculations is also a factor that would contribute to the difficulties of implementing an anthrax vaccination program. Currently, an improved vaccine prepared by Dr. Wright is being evaluated through serological testing and by use in an exposed, susceptible population. If the new vaccine should prove more potent, a less strenuous immunization schedule may be applicable.

Summary

An anthrax vaccine was clinically and epidemiologically evaluated in an exposed, susceptible, supervised population. Twenty-six cases occurred among the population during the evaluation period. Four cases occurred in individuals who had incomplete inoculations. Of the remaining 22 cases, 15 occurred in placebo-inoculated employees, six in uninoculated employees, and one in a vaccine-inoculated employee. The data indicate that the vaccine has an effectiveness of 92.5 per cent with a lower 95 per cent confidence limit of 65 per cent.

Individual reactions to the vaccine was a relatively minor problem. Edema-producing local reactions occurred following 2.8 per cent of all inoculations. There was evidence that the local reactions had an allergic basis, with reactivity increasing through the fifth inoculation, following which they decreased. Systemic reactions were rare with only 0.2 per cent of inoculations followed by noticeable symptoms.

There are various exposed population groups in whom use of the vaccine is recommended. Specifically, these include persons who handle imported hair, wool, hides, or bone meal, in addition to veterinarians in "anthrax districts." Selected use in other countries is also recommended, though implementation would be difficult.

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