Typhoid Vaccine Studies IX

Intracutaneous versus Subcutaneous Vaccination for Initial Immunization

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IN 1939, Siler and Dunham [1] published a preliminary report on the re-immunizing effect of 0.1 ml. of vaccine intracutaneously administered. During the following year, Longfellow and Luippold [2] reported results on an extension of the preceding work.

Since this time, it has been asked why the intracutaneous route for the establishment of *initial* immunity has not been adopted, inasmuch as it had been recommended for revaccination. The answer, of course, is that, although there is a mass of clinical and experimental data on the effectiveness of subcutaneous vaccination, there are no comparable data on the efficacy of vaccination by the intracutaneous method. Realizing the capacity of the skin to produce antibodies, an investigation of dosage and routes of administration of typhoid vaccine was begun here early in 1940, but this study was interrupted by the intervention of other and more urgent work, and was postponed until time and material again became available.

Meanwhile, we had made an observation on a diminutive-scale comparison of these two methods of vaccination. During the latter part of 1942, we received specimens of serum from Morgan [3] as control material on other sera included in an investigation being conducted by him at that time. Eight of the control sera were from persons who had been inoculated intracutaneously with 0.05, 0.1, and 0.1 ml. of commercial T.A.B. vaccine, while 7 were from individuals who had received 0.5, 1.0, and 1.0 ml. of the same vaccine subcutaneously. The sera of these 15 persons were titrated for protective substances [4] active against *Eberthella typhosa*. Results of these titrations have been recorded in Table 1.

TABLE 1

Results of Serum Protection Tests on Small Groups of Individuals Vaccinated, Respectively, With an Intracutaneous Course of T.A.B. Vaccine Consisting of 0.05, 0.1 and 0.1 ml., and with a Subcutaneous Course of 0.5, 1.0, and 1.0 ml.

Minimal Lethal Doses of Test Organism (E. typhosa)	Number and Per cent of Persons Whose Sera, in 0.1 ml. Amounts, Protected Groups of 4 Mice Against the Doses of Test Organisms Listed in Column on left			
	Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent
100,000	..	....	2	28.5
10,000	..	....	3	43.0
1,000	2	25.0	..	....
100	4	50.0	2	28.5
10	2	25.0	..	....
Totals	8	100.0	7	100.0

If these results were any indication of what would happen in large groups of individuals, it was plain that intracutaneous vaccination is definitely inferior to the subcutaneous method—*in the dosages used.* Morgan and his

associates [3] commented on this observation as follows: "The intradermal administration of bacterial vaccines was found less effective than the subcutaneous route." As will be shown later, dosage is an important factor; and to have added "in the dosages used" would have been a desirable qualification.

Meanwhile, also, we were aware of an increasing tendency toward intracutaneous administration of typhoid vaccine by many agencies, for the establishment of initial immunity. The most interesting report of this activity appeared under the heading of "Vaccination: Wholesale," in which Fennel [5] wrote of the widespread practice of intracutaneous vaccination of the civilian population of Hawaii by the local health authorities. This incident in Hawaii has also been revealed in the introduction to a paper by Tilden and Arnold.[15] The popularity of the intradermal method of antityphoid vaccination in Cuba has been commented upon by Curbelo,[17] and more fully expounded in a paper by Argudin.[16]

We were also aware of the many reported studies on the comparative effectiveness of intracutaneous and subcutaneous vaccination; but all of these, with the single exception noted below, were evaluated on the basis of agglutinative titers, whereas we desired an evaluation based upon the production of demonstrable protective substances in the blood serum.

Tuft [6] (1931) advocated as a routine procedure the intracutaneous administration of 4 doses of triple typhoid vaccine (0.05, 0.1, 0.15, and 0.2 ml.) spaced by an interval of from 5 to 7 days. At this time, his conclusions were based on the results of agglutinin titrations; but in 1940, Tuft [7] reported the results of mouse protection tests with pooled sera from 9 individuals who had been vaccinated intracutaneously with 3 doses of typhoid vaccine (0.1, 0.15, and 0.2 ml.) at weekly intervals. The protective titer of this pooled serum was reported to be somewhat higher than that of a pooled sample of serum from 19 subjects who had received 0.5, 1.0, and 1.0 ml. of the vaccine subcutaneously. Tuft then recommended the 3 intracutaneous injections cited above as routine procedure.

Valentine, Park, Falk, and McGuire [8] (1935) reported on the agglutinin response produced by intracutaneous and subcutaneous vaccination, concluding that the intracutaneous doses employed were as effective as five times the amount of vaccine subcutaneously administered, but that one-tenth of the subcutaneous dose intracutaneously administered "produced slightly less response."

Perry [9] (1937) employed a course of T.A.B. vaccine consisting of 3 intracutaneous doses (0.05, 0.1, and 0.1 ml.) administered at weekly intervals; and, for the control group, subcutaneous doses of 0.5, 0.8, and 1.0 ml. He stated that these procedures were equally effective in the production of "H" and "O" agglutinins.

Wyandt, Bayliss, Tollman, and Gunderson [10] (1938) used intracutaneous doses of 0.05, 0.1, and 0.1 ml., and subcutaneous doses of 0.5, 1.0, and 1.0 ml. of T.A.B. vaccine. In both courses of vaccination, the doses were spaced by 1 week. These workers reported that the subcutaneous course produced approximately twice the antibody [agglutinin] response of that produced by the intracutaneous doses.

Van Gelder and Fisher [11] (1941) reported on a large group of children in whom they found an equal degree of response to "H" antigens by the intracutaneous and subcutaneous methods, but the latter produced a higher average "O" titer. Despite the inferior production of "O" agglutinins produced by the intracutaneous doses of 0.05, 0.1, and 0.15 ml., these workers recom-

mended this course for subjects weighing 120 lb. or more, in preference to the usual dosage administered subcutaneously.

Naumer and Nerb [12] (1943) vaccinated respective groups of children intracutaneously (0.1, 0.2, 0.3, and 0.4 ml.) and subcutaneously (0.5, 0.75, and 1.0 ml.). They reported that "The intracutaneous injections were followed by a slightly higher ["H" and "O"] titer formation although the difference is hardly significant."

Leibovitz [13] (1943) reported that higher "H" and "O" titers were produced in girls vaccinated intracutaneously with 0.05, 0.1, and 0.1 ml. of T.A.B. vaccine, than in boys vaccinated subcutaneously with ten times this dosage; and that "O" agglutinins disappeared more rapidly from the blood serum of the subcutaneously vaccinated boys during a period of 13 months, implying that intracutaneous vaccination favored persistence of "O" agglutinins.

Kamp [14] (1943) vaccinated a total of 946 children with an intradermal course of 0.1, 0.15, and 0.2 ml. of T.A.B. vaccine, and concluded, on the basis of previous work and on his own findings of economy and marked absence of general reactions, and a minimum of discomfort associated with the local reactions, that "Sufficient work has been done to warrant using this method as a means of initial typhoid fever immunization."

Thus, it will be seen that the production of agglutinins has been quite generally accepted as an index to the production of protective substances, or as a criterion for appraising the relative effectiveness of intracutaneous and subcutaneous vaccination. This paper reports a direct determination of protective antibodies, as demonstrated by mouse protection tests, produced by each of the two methods of immunization under discussion; and a comparative evaluation of these methods on the basis of demonstrable protective substances in the blood serum. Typhoid "H" and "O" agglutinative titers have also been determined as a matter of interest only.

THE PRESENT INVESTIGATION

Subjects—These were medical students, first and second year, recruited from six major universities. Only those students whose histories were negative for typhoid fever and for antityphoid vaccination were included in this study.

The Vaccine—Triple typhoid (T.A.B.) vaccine [18] prepared in the Division of Biologic Products of the Army Medical School was used exclusively.

Dosages of Vaccine—A review of the literature, and of unpublished work brought to the author's attention by advocates of the intradermal method, indicate that three courses of vaccine have chiefly been used and recommended for intracutaneous vaccination: (a) 0.05, 0.1, and 0.1 ml., (b) 0.1, 0.15, and 0.2 ml., and (c) 0.1, 0.2, and 0.2 ml. It appears that 0.2 ml. represents the maximum amount of material that can be injected intracutaneously without producing undue physical destruction of tissue, or leakage into subcutaneous tissues. To those individuals in the control groups, the standard course (0.5, 1.0, and 1.0 ml.) of vaccine was administered subcutaneously. The interval between doses was, in all instances, 7 days.

Collection of Serum—All subjects were bled from 1 to 7 days prior to the administration of the first dose of vaccine, and again 14 days following the last dose. The serum was separated aseptically, and stored in the refrigerator without the addition of a preservative.

Instructions to Group Leaders at Medical Schools—In order to standardize the procedures as nearly as practicable at the six medical schools participating in this investigation, the following instructions (altered slightly)

TABLE 2

Comparison of Typhoid Protective Titers Produced by 0.05, 0.1, and 0.1 ml. of T.A.B. Vaccine Intracutaneously Administered, With Those Titers Produced in the Control Subjects by the Standard Subcutaneous Course of 0.5, 1.0, and 1.0 ml.

Number and Per cent of Persons Whose Sera, Before and After Vaccination, Protected Mice Against the Doses of Test Organism Listed in Column on Left

Minimal Lethal Doses of Test Organism	Before Vaccination				After Vaccination			
	Intracutaneous Group		Subcutaneous Group		Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent
10,000	..	..	..	..	3	15	9	45
1,000	..	..	..	..	11	55	10	50
100	..	..	1	5	6	30	..	..
10	2	10	..	..	..	..	1	5
1	6	30	5	25	..	..	..	..
Failed against 1	12	60	14	70	..	..	..	..
Totals	20	100	20	100	20	100	20	100

TABLE 3

Comparison of Typhoid Protective Titers Produced by 0.1, 0.15 (or 0.2), and 0.2 ml. of T.A.B. Vaccine Intracutaneously Administered, With Those Titers Produced in the Control Subjects by the Standard Subcutaneous Course of 0.5, 1.0 and 1.0 ml.

Number and Per cent of Persons Whose Sera, Before and After Vaccination, Protected Mice Against the Doses of Test Organism Listed in Column on Left

Minimal Lethal Doses of Test Organism	Before Vaccination *				After Vaccination			
	Intracutaneous Group		Subcutaneous Group		Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent
100,000	..	....	..	....	..	....	6	6.0
10,000	..	....	..	....	21	21.0	33	33.3
1,000	..	....	..	....	35	35.0	31	31.3
100	1	1.0	..	....	29	29.0	21	21.2
10	5	5.3	5	5.3	11	11.0	3	3.0
1	17	17.8	16	16.7	4	4.0	5	5.0
Failed against 1	72	75.8	74	77.8	..	....	..	....
Totals	95	99.9	95	99.8	100	100.0	99	99.8

* 9 specimens lost in transit

TABLE 4

SUMMARY: *Comparison of Typhoid Protective Titers Produced in All Persons Intracutaneously Vaccinated in This Study With Those Titers Produced in Control Subjects Receiving the Standard Subcutaneous Course of Vaccine*

Number and Per cent of Persons Whose Sera, Before and After Vaccination, Protected Mice Against the Doses of Test Organism Listed in Column on Left

Minimal Lethal Doses of Test Organism	Before Vaccination *				After Vaccination			
	Intracutaneous Group		Subcutaneous Group		Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent
100,000	..	....	..	....	..	....	6	5.0
10,000	..	....	..	....	24	20.0	42	35.3
1,000	..	....	..	....	46	38.3	41	34.4
100	1	0.9	1	0.9	35	29.2	21	17.7
10	7	6.0	5	4.3	11	9.1	4	3.3
1	23	20.0	21	18.2	4	3.3	5	4.2
Failed against 1	84	73.0	88	76.5	..	....	..	....
Totals	115	99.9	115	99.9	120	99.9	119	99.9

* 9 specimens lost in transit

were circularized among the group leaders:

"This comparison of the immunogenic effectiveness of intracutaneous and subcutaneous administration of triple typhoid vaccine will be based on the results of serum protection tests. However, both 'H' and 'O' agglutinative titers of the sera will also be determined. It is requested that the following outlined procedures be adhered to as closely as practicable in order that this and similarly treated groups may be considered jointly as one large group.

"1. Only primary cases should be chosen. Histories of previous antityphoid immunization and of typhoid and paratyphoid fevers should be negative. . . .

"2. Groups (classes) should be divided, as nearly as possible, into two subgroups of equal numbers—one to receive vaccine intracutaneously, the other to be vaccinated subcutaneously.

"3. Triple typhoid vaccine, prepared at the Army Medical School, will be used. This is the stock 'Army T.A.B.' product, and will be supplied in adequate amounts.

"4. Recommended Dosage: Intracutaneously, one of the following: (a) 0.05 cc., 0.1 cc., and 0.1 cc., (b) 0.1 cc., 0.15 cc., and 0.2 cc., (c) 0.1 cc., 0.2 cc., and 0.2 cc. Subcutaneously, 0.5 cc., 1.0 cc., and 1.0 cc. In each instance, the interval between doses should be one week.

"4. a. Site of Injection: (Separate communication. The area described as the inser-

TABLE 5

Comparison of Paratyphoid A Protective Titers Produced by 0.05, 0.1, and 0.1 ml. (in 20 Persons) or More (in 45 persons) of T.A.B. Vaccine Intracutaneously Administered With Those Titers Produced in the Control Subjects by the Standard Subcutaneous Course of Vaccine

Minimal Lethal Doses of Test Organism	Number and Per cent of Persons Whose Sera, Before and After Vaccination, Protected Mice Against the Doses of Test Organism Listed in Column on Left							
	Before Vaccination				After Vaccination			
	Intracutaneous Group		Subcutaneous Group		Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent
1,000	..	....	..	....	..	....	1	1.5
100	..	....	..	....	4	6.1	18	27.7
10	2	3.0	1	1.5	32	49.2	30	46.2
1	6	9.2	10	15.4	22	33.8	14	21.5
Failed against 1	57	87.7	54	83.0	7	10.8	2	3.0
Totals	65	99.9	65	99.9	65	99.9	65	99.9

TABLE 6

Comparison of Paratyphoid B Protective Titers Produced by 0.05, 0.1, and 0.1 ml. (in 20 Persons) or More (in 50 Persons) of T.A.B. Vaccine Intracutaneously Administered, With Those Titers Produced in the Control Subjects by the Standard Subcutaneous Course of Vaccine

Minimal Lethal Doses of Test Organism	Number and Per cent of Persons Whose Sera, Before and After Vaccination, Protected Mice Against the Doses of Test Organism Listed in Column on Left							
	Before Vaccination				After Vaccination			
	Intracutaneous Group		Subcutaneous Group		Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent	No. of Persons	Per cent
100,000	..	....	..	....	14	20.0	31	44.3
10,000	..	....	..	....	34	48.6	22	31.4
1,000	3	4.3	1	1.4	20	28.5	15	21.4
100	15	21.4	11	15.7	2	2.8	2	2.8
10	14	20.0	16	22.9	..	....	..	....
1	12	17.1	13	18.5	..	....	..	....
Failed against 1	26	37.1	29	41.4	..	....	..	....
Totals	70	99.9	70	99.9	70	99.9	70	99.9

TABLE 7

Comparison of Typhoid "H" and "O" Agglutinin Titers Produced in 20 Subjects by a Course of 0.05, 0.1, and 0.1 ml. of T.A.B. Vaccine Intracutaneously Administered, With Those Titers Produced in 20 Control Subjects by the Standard Subcutaneous Course of Vaccine

Method of Vaccination	Type of Agglutinin	Numbers of Individuals Whose Sera, After Vaccination, Agglutinated the Respective Antigens Completely in the Dilutions Set Forth Below									Average
		1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	
Intracut.	"H"	..	1	..	4	3	4	2	6	..	1:1,106
Subcut.	"H"	..	..	1	..	3	4	5	4	3	1:1,780
Intracut.	"O"	2	3	9	5	1	..	..	..	..	1:100
Subcut.	"O"	..	2	7	5	3	2	1	..	..	1:248

TABLE 8

Comparison of Typhoid "H" and "O" Agglutinin Titers Produced in 95 Subjects by a Course of 0.1, 0.15 (or 0.2), and 0.2 ml. of T.A.B. Vaccine Intracutaneously Administered, With Those Titers Produced in 95 Control Subjects by the Standard Subcutaneous Course of Vaccine

Method of Vaccination	Type of Agglutinin	Numbers of Individuals Whose Sera, After Vaccination, Agglutinated the Respective Antigens Completely in the Dilutions Set Forth Below									Average
		1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	
Intracut.	"H"	..	..	6	11	18	22	22	12	4	1:1,068
Subcut.	"H"	..	..	3	13	11	25	21	16	6	1:1,267
Intracut.	"O"	13	10	32	32	6	2	..	..	..	1:122
Subcut.	"O"	3	17	26	30	14	5	..	..	..	1:161

TABLE 9

SUMMARY: *Comparison of Typhoid "H" and "O" Agglutinin Titers Produced in All Persons Intracutaneously Vaccinated in This Study, With Those Titers of the Subcutaneously Vaccinated Control Subjects*

Method of Vaccination	Type of Agglutinin	Numbers of Individuals Whose Sera, After Vaccination, Agglutinated the Respective Antigens Completely in the Dilutions Set Forth Below									Average
		1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	1:5,120	
Intracut.	"H"	..	1	6	15	21	26	24	18	4	1:1,074
Subcut.	"H"	..	..	4	13	14	29	26	20	9	1:1,356
Intracut.	"O"	15	13	41	37	7	2	..	..	..	1:118
Subcut.	"O"	3	19	33	35	17	7	1	..	..	1:176

tion of deltoid muscle was chosen by all group leaders for both methods of administration.)

* * *

"6. Specimens of Serum: A 30 cc. specimen of blood should be drawn from each person just prior to the administration of the first dose of vaccine, and again on the 14th day following the last dose. The serum should be aseptically separated and bottled (or tubed), and plainly labeled with the person's name and the date on which the specimen was collected . . ."

PROTECTIVE TITERS

Serum protection tests[4] were performed on all sera to determine the extent of production of typhoid protective substances, but protective titers for *Salmonella paratyphi* and *Salmonella schottmuelleri* were determined on only a limited number of sera. Typhoid protective titers have been recorded in Tables 2 and 3, and summarized in Table 4. Since the disparity between the two intracutaneous courses consisting of the larger doses is not significant (0.05 ml.), the titers of individuals receiving these courses have been combined in Table 3. Para A and B protective titers have been recorded in Tables 5 and 6 respectively.

AGGLUTINATIVE TITERS

Typhoid "H" and "O" agglutinative titers were determined by the familiar test-tube titration method with standard "H" (formalinized H–901)

and "O" (alcohol-treated O–901) antigens. These titers have been recorded in Tables 7, 8, and 9.

DURATION OF PROTECTIVE AND AGGLUTINATIVE ANTIBODIES

Leibovitz [13] reported a more substantial duration of agglutinins in intracutaneously inoculated children than in their subcutaneously vaccinated controls. In view of this finding, it was thought desirable to study this factor of duration in respect to protective substances before concluding our investigation. Sera from the participants of the original vaccination experiment who were still available and eligible * for follow-up tests were obtained through the coöperation of group leaders at three of the participating medical schools. However, a total of only 18 sera representative of each vaccinated group were received. These were titrated for agglutinative and protective antibodies for whatever information they would provide. Results of these titrations have been recorded in Tables 10 and 11.

* Some of the participants had been inducted into the Army or Navy and revaccinated before the expiration of one year.

REACTIONS

Data on reactions were collected by a method somewhat different from any that has hitherto been used. At the time of administering the first dose of vaccine, each student was given a blank form (illustrated below) on which he was requested to record his reactions. Instructions to group leaders who supervised the procedures at their respective schools read as follows:

"Reactions: These should be recorded by the individuals themselves, in their own words and with a minimum of coaching or warning of manifestations to be anticipated. The attached form, copies of which will be supplied, is suggested for the use of each individual."

TABLE 10

Comparison of Typhoid Protective Titers Persisting One Year After Vaccination in 18 Persons Who Received an Intracutaneous Course of 0.05, 0.1, and 0.1 ml. (or More) of T.A.B. Vaccine, and in 18 Persons Who Received the Standard Subcutaneous Course

Minimal Lethal Doses of Test Organism	Number and Per cent of Persons Whose Sera, One Year After Vaccination, Protected Mice Against the Doses of Test Organism Listed in Column on Left			
	Intracutaneous Group		Subcutaneous Group	
	No. of Persons	Per cent	No. of Persons	Per cent
10,000	..	....	3	16.6
1,000	5	27.7	6	33.3
100	3	16.6	3	16.6
10	6	33.3	3	16.6
1	4	22.2	3	16.6
Totals	18	99.8	18	99.7

TABLE 11

Comparison of Typhoid "H" and "O" Agglutinin Titers Persisting One Year After Vaccination in 18 Persons Who Received an Intracutaneous Course of 0.05, 0.1, and 0.1 ml. (or More) of T.A.B. Vaccine, With Those Titers Produced in 18 Persons Vaccinated With a Standard Subcutaneous Course

Method of Vaccination	Type of Agglutinin	Numbers of Individuals Whose Sera, One Year After Vaccination, Agglutinated the Respective Antigens Completely in the Dilutions Set Forth Below							
		1:10	1:20	1:40	1:80	1:160	1:320	1:640	Average
Intracut.	"H"	1	1	5	4	6	1	..	1:102
Subcut.	"H"	..	..	2	7	8	1	..	1:124
Intracut.	"O"	7	2	4	4	1	..	..	1:42
Subcut.	"O"	3	3	3	7	2	..	..	1:61

Data on Reactions Following Vaccination With T.A.B. Vaccine

NAME: _____ GRADE CLASS _____ ORG. SCHOOL _____

HISTORY OF TYPHOID OR PARATYPHOID FEVER: _____

PREVIOUS ANTITYPHOID VACCINATION: Number of Courses: _____

Date of last course: _____

METHOD OF ADMINISTRATION, THIS COURSE: (Check one) Intracutaneous
Subcutaneous

Dose	TIME OF READING	AREA OF HYPEREMIA		LYMPHATIC INVOLVEMENT	SYSTEMIC MANIFESTATIONS
		Size (in sq. cm.)	Degree of Tenderness		
1st	24 hrs.				
	48 hrs.				
2nd	24 hrs.				
	48 hrs.				
3rd	24 hrs.				
	48 hrs.				

This method is admittedly not without its faults, but it does possess certain advantages: Although it stimulates an anticipation of some ensuing reaction, there is an absence of suggestion of specific manifestations; a convenient form is available for recording the reactions at or soon after the time they occur, so that there are no blanks nor vagaries due to lapse of memory; and the records are made in a uniform manner, thus facilitating tabulation of data.

TABLE 12

Summary of Local and Systemic Reactions Following Subcutaneous Injections of the Standard Dosage (0.5, 1.0, and 1.0 ml.) and Intracutaneous Injections of One-tenth to One-fifth of this Dosage (115 Persons in Each Group)

			Local								Systemic								
				Degree of Tenderness				Lymphatic Involvement											
Method of Vaccination	Dose of Vaccine		Average Area of Hyperemia (Cm²)	None	Slight	Moderate	Severe	None	Cervical	Axillary	None	Headache	Chills	Fever	Lassitude	Muscular Pains	Malaise	Nausea	Urticaria
Intracut.	1st		19	6	69	33	7	70	2	44	94	6	1	2	5	0	7	2	0
Subcut.	1st		51	0	35	51	29	56	3	57	67	22	6	11	17	8	10	1	0
Intracut.	2nd		24	2	58	41	14	67	1	46	92	7	1	4	6	0	7	3	2
Subcut.	2nd		65	0	30	46	39	58	1	56	67	15	4	12	16	12	15	1	1
Intracut.	3rd		23	12	72	26	5	90	0	25	101	7	0	1	4	1	4	1	0
Subcut.	3rd		45	5	76	24	10	80	0	35	99	7	2	3	5	4	4	0	0
Total intracut.				20	199	100	26	227	3	115	287	20	2	7	15	1	18	6	2
Total subcut.				5	141	121	78	194	4	148	233	44	12	26	38	24	29	2	1

It is believed that these students were sufficiently advanced and trained to observe intelligently and record accurately the simple manifestations likely to be evoked by T.A.B. vaccination.

A summary of the individual reports received from the students has been entered in Table 12. There was one minor alteration: remarks such as "drowsiness," "felt tired," "muscular weakness," "not hungry," "faint feeling," "sluggishness," and others having similar implications, were grouped under the general heading of *lassitude*. When entries under the 24 hour and 48 hour periods differed, that entry indicating the more severe reaction was chosen for inclusion in the tabulated data.

DISCUSSION

Protective Titers—It appears that the intracutaneous course of 0.05, 0.1, and 0.1 ml. of T.A.B. vaccine is not as effective in the production of typhoid, paratyphoid A, and paratyphoid B protective substances as is the course consisting of 0.1, 0.2, and 0.2 ml.; also, that the latter is, in general, not as effective in respect to protective titers as is the standard subcutaneous course of 0.5, 1.0, and 1.0 ml. of vaccine. It is true that the differences in the latter comparison do not loom up as widely separated values, but it is believed that they are significant in view of the constant tendency in each of the six groups to favor the standard subcutaneous course.

Agglutinative Titers—As stated earlier in this paper, typhoid agglutinative titers were included only as a matter of interest. The "H" and "O" titers produced by the standard subcutaneous vaccination were, in general, higher than were those produced by any of the intracutaneous courses.

Duration of Protective and Agglutinative Antibodies—Unfortunately, we are dealing with too insignificant numbers of subjects to arrive at any definite conclusions. Leibovitz [13] vaccinated 41 girls (average age 10) intracutaneously with 0.05, 0.1, and 0.1 ml. of Lederle's T.A.B. vaccine, and 44 boys (average age 10) with a subcutaneous course of 0.5, 1.0, and 1.0 ml. of the same vaccine. He reported that the greater percentage of subjects with the higher "O" agglutinative titers were in the group vaccinated intradermally, on determinations made 13 months after vaccination, using the rapid slide agglutination technic of Welch and Stuart.[19]

We, on the other hand, vaccinated 18 young adult males intracutaneously with a course of 0.05, 0.1, and 0.1 ml. (or more) of Army T.A.B. vaccine, and a comparable group of persons subcutaneously with 0.5, 1.0, and 1.0 ml. of the same vaccine. At the end of 1 year, we found that both agglutinative and protective titers were higher, on an average, in the subcutaneously vaccinated individuals. Our agglutinative titers were determined by means of the commonly used tube titration method.

In summation, there was no suggestion in our results that these antibodies persisted longer in the blood serum of intracutaneously vaccinated persons than they did in persons vaccinated subcutaneously. Considering the fact that the titers for both types of antibodies were initially (14 days) higher in those individuals comprising the subcutaneous group, there was neither any evidence that persistence of antibodies is a special attribute of the subcutaneous administration of T.A.B. vaccine.

Reactions—A casual inspection of Table 12 reveals that, in general, both local and systemic reactions were appreciably less frequent and severe following intracutaneous injections of vaccine. This is in agreement with all reported studies cited elsewhere in this paper.

However, it was interesting to observe disparities between reactions among some of these vaccinated groups. At one school, for example, lymphadenitis

was much more frequent and pronounced among intracutaneously vaccinated individuals than among their subcutaneously vaccinated controls. At a different school, another irregularity noted was the almost indistinguishable rate of frequency and degree of severity of systemic reactions among intracutaneously and subcutaneously vaccinated persons. In fact, the third dose was not given to two persons in the intracutaneous group because of the severity of reactions, described as (1) " Very ill, chills, fever 104°," and (2) " Severe rash (Hives) with confluent wheals." At this same school, the third dose was also omitted in the case of one person in the subcutaneous group because of " Hives over entire body, swollen face, temp. 102°." In each instance, these reactions were reported to have occurred within 24 hours following the administration of the second dose of vaccine. The group leader at this school, in commenting upon reactions, remarked that he was " rather surprised at the slight difference between the groups." In general, however, there is little doubt of the relatively fewer and milder reactions evoked by the intracutaneous injections of the small doses of T.A.B. vaccine employed in this investigation.

Although we have not had an opportunity to observe late granulomatous reactions following intracutaneous injection of vaccine in individuals comprising this study, we have noted chronic granulomas in other intracutaneously inoculated persons. Tilden and Arnold[15] have reported their observations of this late reaction in the Hawaiian population reported by Fennel[5] to have been vaccinated chiefly by the intradermal method.

In the full awareness of the occurrence of occasional undesirable symptoms attributable to the subcutaneous dosage of T.A.B. vaccine, it is thought that too much weight has probably been given to reactions as a criterion for appraising methods of vaccination. While it is unquestionably desirable that reactions be reduced in frequency and severity (if this reduction can be accomplished without a reduction of immunological response), we do not agree with Van Gelder and Fisher[11] who stated: " It is this difference in reactions that renders the intradermal method superior to the subcutaneous method for typhoid immunization." After all, these are *immunizing* procedures; and, since neither is dangerous to life or injurious to health, superiority of one method over another must be based upon the degree of *immunological response,* not on the degree of freedom from annoyance.

Other Observations—The value of a combination of six group studies conducted according to a uniform set of stipulations, rather than the study of a single group, was made apparent in many ways. As an example, assuming that only the one school cited above (whose intracutaneously and subcutaneously vaccinated groups manifested almost the same rates and degrees of systemic reactions) had been observed, the relative innocuousness of intradermal injection of T.A.B. vaccine, quite evident in the other five schools, would not have been confirmed. In another instance, the protective titers produced by the two methods of administering vaccine, although slightly in favor of the subcutaneous method, were not significantly so as they were in the other five comparative groups. In still another instance, typhoid " H " and " O " titers were so nearly equal that, from this single comparison one would be forced to conclude that the two routes and the dosages employed were equally productive of agglutinin titers. In short, if it were not for the five other comparative groups acting as a counterbalance on some one observation made of a single group, it is easy to discern at least three conclusions that

would be divergent from those that have been set forth below.

CONCLUSIONS

1. The standard subcutaneous course of T.A.B. vaccine consisting of 0.5, 1.0, and 1.0 ml., is more effective in the production of typhoid, paratyphoid A, and paratyphoid B protective substances than is one-tenth to one-fifth of this dosage intracutaneously administered.

2. The standard subcutaneous course of T.A.B. vaccine is more effective in the production of typhoid "H" and "O" agglutinins than is one-tenth to one-fifth of this dosage intracutaneously administered.

3. In small experimental groups, there was found no evidence that persistence of agglutinative or protective antibodies, at the end of 1 year, is a special attribute of either intracutaneous or subcutaneous administration of T.A.B. vaccine.

4. Although local and systemic reactions are more frequent and pronounced following administration of the standard subcutaneous doses of T.A.B. vaccine than following the intracutaneous injection of one-tenth or one-fifth of these doses, it is not felt that we can risk any lowering of protection for the questionable reward of milder reactions. Under the best of conditions of immunological response to artificial immunization, we cannot expect our standard method of vaccination to be adequate at all times in the field to the challenge of infecting organisms. Adoption of the intracutaneous administration of reduced doses of T.A.B. vaccine would seem to increase this inadequacy.

5. It is not to be inferred from these conclusions that the intracutaneous administration of T.A.B. vaccine for the establishment of initial immunity is indiscriminately condemned. On the contrary, intracutaneous vaccination has a definite usefulness in its application to elderly persons and to allergic individuals, in whom severe or serious disturbances may be avoided by the administration of reduced doses, intradermally placed.

6. It is neither to be inferred that we consider the standard subcutaneous course of T.A.B. vaccination as the ultimate in antityphoid vaccination procedures. Intervals between doses, and the doses themselves, would bear investigation. Preliminary studies on these questions are now in progress.

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Institute on Rural Youth Migration

The Annual Meeting of the Institute on War and Postwar Problems of Rural Youth Migration was recently held in Washington, D. C., including a section on Rural Health Conditions under the Chairmanship of C. L. Williams, Jr., M.D., of the States Relations Division, U. S. Public Health Service. Other members of the section interested in public health included Anna Heisler, R.N., U. S. Public Health Service, Fred Mott, M.D., U. S. Public Health Service and Chief Medical Officer of the Farm Security Administration, and Arthur J. Lesser, M.D., Regional Medical Consultant, U. S. Children's Bureau.

It is reported that there was agreement at the Institute that health and medical services are important contributing factors to community morale. It was realized that such services are distributed among the population with more regard to the ability to pay than to actual need. It was concluded that the availability of health and medical services in rural areas should be regarded as a right rather than a luxury dependent upon individual or community purchasing power. Specific recommendations included:

(a) The further extension of existing public health services, with special emphasis on the local level, was urged. The system of public health districts developed by the Committee on Administrative Practice of the American Public Health Association and based upon population and area was approved in principle and its acceptance urged.

(b) The further extension of existing medical, dental, and nursing services including hospitals and clinic services was favored. Medical and Hospital facilities should be made available to all people regardless of their place of residence or their financial status. The war has shown a need for more physicians, especially in rural areas. Accordingly, provisions should be made for additional training facilities to meet the war and the anticipated postwar demand for medical care.