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Typhoid Vaccine Studies*

Investigation of Virulence and Antigenic Properties of Selected Strains of the Typhoid Organism

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THE use of typhoid vaccine for individual prophylaxis was first introduced into the United States on a large scale by General F. F. Russell, of the U. S. Army. The preliminary studies were made by him at the Army Medical School, in Washington, D. C., and, after thorough investigation of such work in England and Germany, production of vaccine was begun in 1908. The following year vaccination was commenced in the Army as a voluntary measure; it became applicable to all military personnel in 1912.

The strain of the typhoid bacillus selected for the preparation of the vaccine was the well known Rawlings strain isolated by Wright in 1900 and used by Leishman for the preparation of the British Army vaccine. The original technic of preparation here combined the German saline suspension of agar cultures with the British method of counting, of killing at a relatively low temperature, and of preserving with cresol. Although minor changes have been made occasionally, the technical procedures have remained essentially the same throughout the years. The Rawlings strain is still in use.

From time to time suggestions have been made to the effect that a change in technic, such as: that the use of formalin for killing and preserving would reduce reactions and preserve the original antigenic qualities of the vaccine, or that the use of a different strain—a freshly isolated strain, or several strains—of the typhoid bacillus would improve the immunizing potency of the vaccine. Such suggestions have always received serious consideration, as evidenced by the recent thorough discussion of the subject by Hawley and Simmons.

That the vaccine as it has been prepared, using the Rawlings strain, is efficiently immunogenic has been amply demonstrated by the trend of typhoid fever in the U. S. Army and the U. S.

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Navy following its introduction as a preventive measure. With the record achieved, it is obvious that any change in the method of preparation of the vaccine or in the strain of bacillus used must await thorough study of all factors involved. Before any modification can be considered seriously there must be ample proof, gained by a dependable method, that through it the vaccine will be no less protective than it has been in the past. The development and production of the Army typhoid vaccine is a major function of the Army Medical School. It is, therefore, in conformity with this duty that the investigations now under way were undertaken. They relate to studies of selected strains of the typhoid bacillus, the purpose in view being the utilization of all recent developments in bacteriology and in immunology to determine when, and how, it may eventually be practicable to improve still further the protective qualities of the typhoid vaccine prepared for and used by the Army, Navy, and other government bureaus as a protective measure.

Great credit must be given to Grinnell for his originality in applying to the direct evaluation of virulence and immunogenic potency of vaccine strains a method which has been at our disposal for many years. He used the intraperitoneal injection of mice to study the relation of the killing power of various strains of the typhoid bacillus to their immunizing activity, and correlated these factors with their colonial and antigenic structural characteristics. In this work he brought together and used to a practical end those recent developments in the study of bacteriology which might otherwise have remained nothing more than intensely interesting and possibly controversial research phenomena. The result of Grinnell's work is that we now have an experimental method which may give us an approach to the standardization of typhoid vaccine.

THE STRAINS OF EBERTHELLA TYPHOSA CONCERNED

From the numerous strains available 7 were finally selected for this work. Each of them is representative of the group to which it belongs; together they include the types of typhoid bacilli most under discussion at present.

1(I)

This is the Army Medical School culture of the English Rawlings strain which was brought to the United States by General F. F. Russell in 1908. Since 1910, it has been used in the preparation of typhoid vaccine at the Army Medical School. Subsequent to the observations of Arkwright it has been considered an intermediate form, being neither completely rough nor typically smooth. The colonies grow rapidly, are round or nearly so, with smooth edges sloping upward to a slightly raised center. Under 5X magnification colonies have a slightly roughened appearance. In consistency, they are moist and homogeneous. When grown in broth a uniform turbidity is produced; the growth on agar is easily made into a stable uniform suspension in saline. It is actively motile. The majority of the bacilli are of average size with the variations usually seen in old stock cultures—individuals vary from short, almost coccal or oval to long, curved forms.

The average lethal dose* (a.l.d.) for mice is approximately 400 million organisms in Ringer's solution suspension. In mucin suspension the m.l.d. is approximately 100 million in Swiss mice.

1(R)

This is a typical rough variant of 1(I) obtained from the agar transplant

* Average lethal dose (a.l.d.) is defined as the number of bacilli which have been found to kill 50 per cent of the mice injected; m.l.d. is that which kills 100 per cent. In this work mature, white mice weighing 18 to 20 gm. have been used. The observation period is up to and including 72 hours.

of a 17 day old infusion broth culture of the latter. The colonies are rapidly growing, flattened, with irregular margins, and roughened surfaces. In consistency, they are dry and granular. Growth in broth is luxuriant, with pellicle formation and sedimentation, the intervening medium being clear or only slightly clouded. While growth on agar is abundant, a uniformly turbid suspension of it in saline is made only with difficulty. The suspension agglutinates spontaneously forming flakes of varying size. In hanging drop the bacilli are seen to be actively motile; stained preparations show atypical forms, many of them being large, thick, curved rods. The young organisms, while typical bacilli in form, are larger than those of the same age of the parent strain.

The a.l.d. for mice is approximately 400 million organisms in Ringer's solution suspension.

1(s)

A typical smooth form of 1(I) obtained from the agar transplant of a 17 day old infusion broth culture of the parent organism (isolated in 1931). The colonies grow slowly and are considerably smaller than 1(I) colonies. They are round, with even margins and smooth surfaces, characterized by a heaped center giving the colony the geometrical appearance of a half-sphere. In consistency they are moist and homogeneous. Growth in broth produces uniform turbidity, and the growth on agar is easily suspended in saline. The bacilli are actively motile; in stained smears they are indistinguishable from those of the parent culture.

The a.l.d. for mice is approximately 400 million organisms in Ringer's solution suspension.

53

Isolated from the blood of a mild case of typhoid fever, at Walter Reed General Hospital, in May, 1932. The blood serum of the patient contained both flagellar and somatic agglutinins. Colonies are round, of medium size, have raised centers, and slightly irregular margins from which ridges begin, converging to the center. The consistency of the colonies is moist and homogeneous. This strain produces uniform turbidity in broth; the growth on agar is easily suspended in saline. It is actively motile; there is nothing characteristic on a stained film.

The a.l.d. for mice is approximately 300 million organisms in Ringer's fluid suspension.

36

Isolated in October, 1933, from the blood of a patient at Walter Reed General Hospital. Clinically a very toxic type of infection. No flagellar and little if any somatic agglutinins could be demonstrated in the patient's serum. Moreover, the latter failed to agglutinate this organism. It was an O inagglutinable strain.

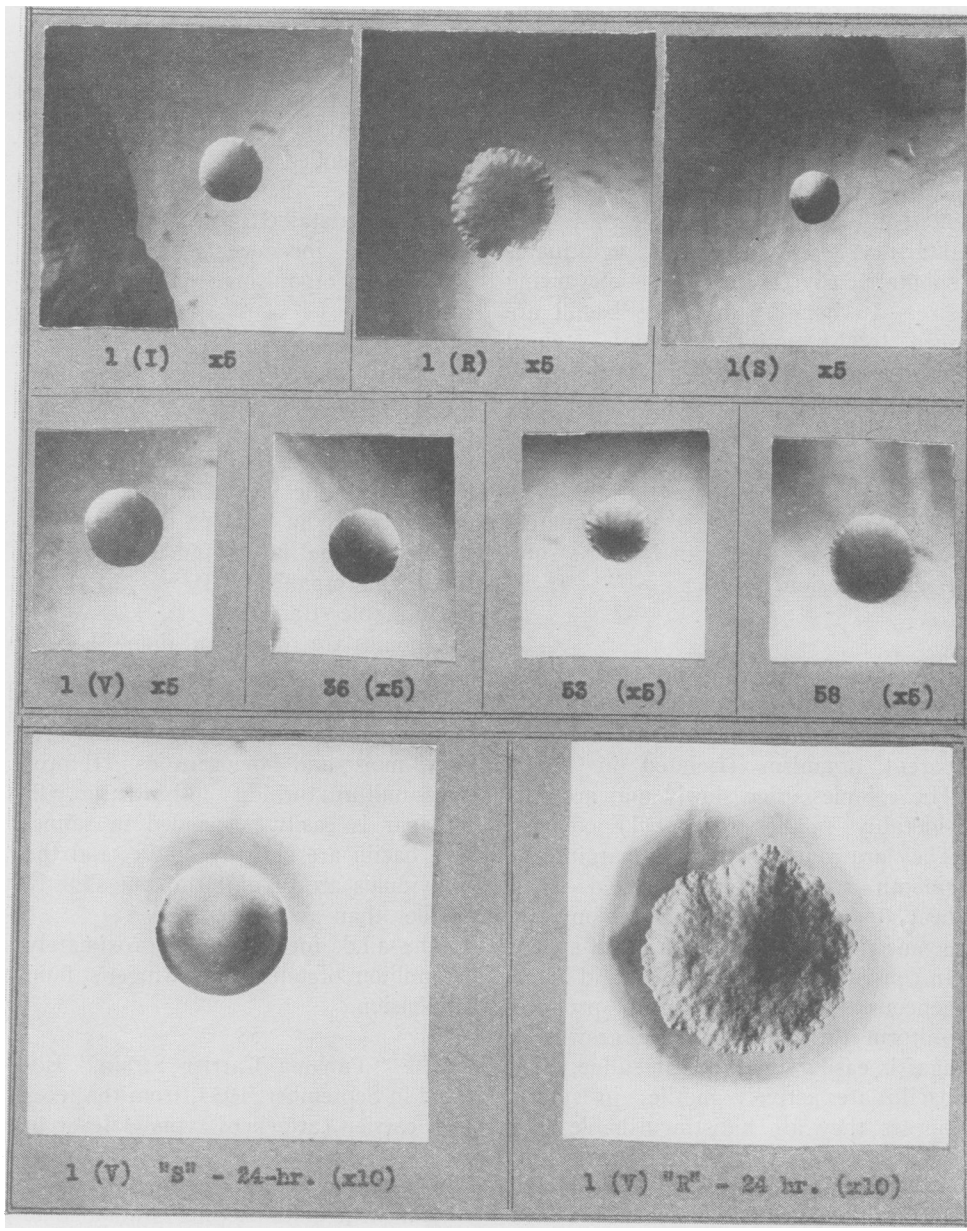
Colonies are round and dome-shaped, with smooth margins and surfaces, of medium size, and characterized by a translucent brownish center. Consistency, moist and homogeneous. It produces uniform turbidity in broth; growth on agar is easily suspended in saline. The bacilli are actively motile, and the individuals are of uniform, but slightly smaller than average size.

The a.l.d. for mice is approximately 75 million organisms in Ringer's fluid suspension.

58

The "Panama Carrier Strain," isolated in September, 1934, from the feces of a carrier (attack of typhoid fever in 1913) in Panama, by Dr. L. B. Bates. The colonies are larger than average, round, with sides sloping gradually to raised, flat centers; the margins are slightly crinkled; the consistency is moist and homogeneous. Growth in broth produces uniform turbidity; growth on agar is easily suspended in saline. The bacilli are actively motile;

TYPICAL COLONIES OF STRAINS OF E. TYPHOSA USED IN THIS WORK



NOTE: Colonies in upper block, 1(I) to 58, 18 hours old.

a stained preparation shows them to be small, short rods, uniform in size.

The a.l.d. for mice is approximately 100 million organisms in Ringer's solution suspension. In mucin suspension the m.l.d. is 100 bacilli, in Swiss mice.

1(v)

Rawlings-Bensted. A rejuvenated (by mouse-passage) race of the Rawlings strain, obtained from Colonel Perry of the R.A.M.C., Netley, England, in October, 1934. The colonies produced by this culture grow rapidly, they are large, round, and perfectly smooth. Growth in broth produces uniform turbidity; the moist and homogeneous growth on agar is easily made into a uniform and stable suspension in saline. The bacilli are actively motile, although non-motile colonies have been encountered in this study. A stained preparation shows them to be small rods, uniform in size.

The a.l.d. for mice is approximately 75 million organisms in Ringer's solution suspension.

PRESERVATION OF STRAINS

In order that strains shall remain without change, at least, until the completion of these studies, special measures have been taken to provide against the differences likely to occur in routine cultivation. In January of this year, prior to the commencement of the virulence tests, each strain was frozen and dried by the method of Flosdorf and Mudd. The growth from agar cultures after suspension in veal infusion, peptone broth (pH 7.4) was distributed into sterile, pyrex ampules. The am-

TABLE I

PRELIMINARY TOXICITY TEST

JAN. 23, 1935

		Dose in Millions of Organisms								
Strains	*Time Period*	*50*	*100*	*200*	*400*	*600*	*800*	*1,000*	*1,200*	*1,400*
1(I)	24-hr.			1/5	2/5	3/5	4/5	5/5		
	48-hr.			nc	nc	nc	1/5			
	72-hr.			nc	nc	nc				
	Total			1/5	2/5	3/5	5/5	5/5		
1(S)	24-hr.			0/5	3/5	5/5	5/5	4/5		
	48-hr			nc	nc			1/5		
	72-hr.			nc	nc					
	Total			0/5	3/5	5/5	5/5	5/5		
53	24-hr			2/5	5/5	5/5	5/5	4/5		
	48-hr.			1/5				1/5		
	72-hr			nc						
	Total			3/5	5/5	5/5	5/5	5/5		
1(R)	24-hr.					1/5	3/5	5/5	5/5	5/5
	48-hr.					nc	1/5			
	72-hr.					nc	nc			
	Total					1/5	4/5	5/5	5/5	5/5
36	24-hr.	1/5	4/5	5/5	4/5	4/5				
	48-hr.	nc	1/5		(*)	nc				
	72-hr.	nc				1/5				
	Total	1/5	5/5	5/5	4/5	5/5				
58	24-hr.	3/5	3/5	4/5	5/5	4/5				
	48-hr.	2/5	1/5	1/5		(*)				
	72-hr.		nc							
	Total	5/5	4/5	5/5	5/5	4/5				
1(V)	24-hr.	1/5	4/5	4/5	5/5	5/5				
	48-hr	2/5	1/5	1/5						
	72-hr.	nc								
	Total	3/5	5/5	5/5	5/5	5/5				

Explanation: Denominator represents number of mice injected; numerator indicates number of mice dead within respective period; " nc " denotes no change; (*) signifies one mouse missing from cage.

pules were immersed in alcohol chilled to about −78° C. by means of CO_2 snow, then they were attached to the manifold and suction applied by means of a vacuum pump. Drying of the suspension was effected without thawing. After 5 to 6 hours, during which time a high vacuum was maintained, the ampules were sealed off in a blow pipe flame—without breaking the vacuum. They were stored in a refrigerator whose temperature is about 5.0° C. Up to the present no change of any kind has been detected in the strains preserved in this way.

TESTS FOR TOXICITY OR VIRULENCE

These tests were carefully planned in order that the bacteria of the various strains would be of the same age at the time of their injection. This required the coöperation of the entire technical staff of the Army Medical School. To insure thorough understanding on the part of everyone a " dry run " was enacted the day before the first series of tests was made.

The cultures, grown exactly as for the production of typhoid vaccine, were suspended in buffered Ringer's solution when they were from 18 to 20 hours old. The suspensions were then counted in a Helber counting chamber; the average of at least 3 counts was considered as giving the greatest accuracy obtainable.

The suspensions were then diluted to the desired strength with buffered Ringer's solution. The dose for a mouse was adjusted so that in every instance it was contained in 0.5 c.c. of fluid. This amount was injected intraperitoneally, the skin of the mouse being first touched by a cotton swab moistened with alcohol. Tuberculin syringes of 1.0 c.c. capacity were used; these carried a 5/8" −25 gauge needle. Great care was taken to see that the injected mice were properly fed and watered.

Two sets of tests were made—a preliminary and a final. In the preliminary test, lots of 5 mice each received the same dose. Five different doses were injected for each strain. The information desired was the a.l.d. for each strain. This is the number of bacilli which will kill 50 per cent of the mice. Table I shows the results of the preliminary tests.

The information gained was used in estimating the range of dosage for the final tests. In this, 5 different amounts were injected. The amounts were adjusted so that the a.l.d. might fall at the middle dose. For the lowest and the highest doses 10 mice were injected and 30 for each of the 3 intermediate doses. The counting and method of injecting were identical with those of the preliminary tests. The results are shown in Table II.

VACCINE PROTECTION TESTS

Having determined the a.l.d. for each of the 7 strains the next point was to use this information to determine the relative protective value of vaccines made from them. The tests were planned so that the protective potency of the vaccine of each strain would be ascertained not only for itself but for each one of the other strains. In other words, cross-protection tests were made in all directions. Furthermore, the extent of the protection was ascertained by testing against not only one, but also against multiples of the a.l.d. In this, as in the virulence tests, there were a preliminary and a final series of tests.

The vaccines were made exactly as the regular typhoid vaccine is made, routinely, in the Army Medical School. They were standardized so that the first dose was 100 million, the second and the third 200 million typhoid bacilli. These amounts were contained in 0.25 c.c. of the vaccine. Injections were made intraperitoneally at weekly intervals. Two weeks subsequent to the final dose the test injections were given as in the virulence tests. The results of the prelim-

TABLE II

FINAL TOXICITY TEST

JAN. 31, 1935

Strain of E. typhosa	Time Period	Dose in Millions of Organisms									
		12.5	25	50	100	200	400	600	800	1,000	1,200
1(I)	24-hr.					0/10	1/30	7/30	8/30	9/10	
	48-hr.					nc	nc	nc	6/30	1/10	
	72-hr.					nc	nc	nc	nc		
	Total					0/10	1/30	7/30	14/30	10/10	
1(R)	24-hr.						5/10	27/30	27/30	29/30	10/10
	48-hr.						1/10	nc	1/30	nc	nc
	72-hr.						nc	nc	nc	nc	nc
	Total						6/10	27/30	28/30	29/30	10/10
1(S)	24-hr.				0/10	6/30	10/30	27/30	8/10		
	48-hr.				nc	2/30	8/30	nc	1/10		
	72-hr.				nc	nc	1/30	nc	nc		
	Total				0/10	8/30	19/30	27/30	9/10		
53	24-hr.			0/10	2/30	6/30	25/30	8/10			
	48-hr.			nc	1/30	nc	2/30	2/10			
	72-hr.			nc	nc	nc	nc	nc			
	Total			0/10	3/30	6/30	27/30	10/10			
36	24-hr.	1/10	4/30	7/30	25/30	10/10					
	48-hr.	nc	4/30	1/30	3/30	nc					
	72-hr.	nc	nc	nc	nc	nc					
	Total	1/10	8/30	8/30	28/30	10/10					
58	24-hr.	0/10	1/30	4/30	20/30	8/10					
	48-hr.	nc	1/30	1/30	3/30	1/10					
	72-hr.	nc	nc	nc	nc	nc					
	Total	0/10	2/30	5/30	23/30	9/10					
1(V)	24-hr.	0/10	10/30	15/30	25/30	10/10					
	48-hr.	nc	4/30	8/30	nc	nc					
	72-hr.	nc	nc	nc	nc	nc					
	Total	0/10	14/30	23/30	25/30	10/10					

Explanation: Denominator represents number of mice injected; numerator expresses number of mice dead within indicated period; "nc" denotes no change.

inary immunization test are shown in Table III.

This may be considered a satisfactory result. The first dose for each strain in the protection test was estimated to be one-half the a.l.d. In other words, it was the intention to have for each group of 5 vaccinated mice an amount below that expected to kill more than 2 of them. That things did not turn out exactly according to the plan is merely one more illustration of the wide limits of accuracy, resulting from several uncontrollable factors, attainable in such work. On the other hand, a high percentage of the control mice died and a high percentage of the vaccinated mice lived. Furthermore, the indication is clear that vaccines made from strains 58, 36, and 1(V) afforded better protection than did the others.

Another interesting factor suggested by this series is that mice which received living bacilli belonging to strains 1(I), 1(R), 1(S), and 53 were not protected so well as those which received as their test dose bacilli of strains 36, 58, and 1(V). One explanation for this is immediately apparent when we note the enormous numbers of bacilli it was necessary to inject when testing with members of the avirulent group.

The information gained from careful study and discussion of these preliminary cross-immunity tests was used in planning the final one. In this the conditions were identical with those of former tests. Planting of cultures on the day prior to the injection of the test doses of living organisms, was so timed as to make the whole chronological set-up uniform. The injections were

TABLE III

TEST FOR IMMUNITY AND CROSS IMMUNITY

MARCH 14, 1935

Injections of Live Organisms		*Percentage of Deaths Among Lots of Five Mice, Each Lot Immunized, Respectively, with the Following Vaccines 14 Days Previously*							
Strain	*Numbers (in millions)*	*1(I)*	*1(R)*	*1(S)*	*36*	*53*	*58*	*1(V)*	*None—Normal Controls*
1(I)	800	40	0	0	0	20	20	0	100
	1,600	100	80	60	100	100	20	60	100
	3,200	80	100	100	100	100	80	100	100
	6,400	100	100	100	100	100	100	100	100
	12,800	100	80	100	100	100	100	100	100
1(R)	500	20	0	0	0	0	0	0	80
	1,000	20	40	60	20	40	0	40	100
	2,000	100	80	100	80	100	100	100	100
	4,000	80	80	100	80	100	80	80	100
	8,000	100	100	100	100	100	100	100	100
1(S)	400	0	0	0	0	0	0	0	20
	800	0	20	0	0	0	20	0	100
	1,600	40	60	40	80	60	40	40	100
	3,200	80	100	100	100	100	80	80	100
	6,400	100	100	100	80	100	100	100	100
36	75	20	0	20	0	0	0	0	20
	150	0	0	20	0	20	0	0	100
	300	80	80	80	20	80	0	0	100
	600	100	60	100	20	100	0	0	100
	1,200	100	100	100	80	80	0	60	100
53	300	0	0	20	0	0	20	0	40
	600	0	20	20	0	0	0	0	100
	1,200	80	80	60	80	100	60	60	100
	2,400	100	60	80	100	80	80	80	80
	4,800	100	100	100	80	100	100	100	100
58	75	20	0	0	0	40	0	0	0
	150	60	0	20	0	20	0	0	60
	300	80	60	80	20	40	0	0	100
	600	80	80	100	0	60	0	0	100
	1,200	100	100	100	60	100	20	40	100
1(V)	25	0	0	0	0	40	0	0	20
	50	40	0	40	0	0	0	0	20
	100	60	20	60	0	40	0	0	100
	200	80	60	80	0	60	0	0	100
	400	100	80	80	20	60	0	20	100

90.5% of the deaths among the vaccinated mice occurred during the first 24 hrs.
9.5% . . . . . 2nd 24 hrs.
97.7% of the deaths among the normal mice occurred during the first 24 hrs.
The remainder, or 2.3% were dead at the end of 48 hours.

made by a uniform technic, and the mice were cared for subsequently as were those of the previous lots. The total number of mice used in this series was 6,200, and they were all injected between 8:00 A.M. and 3:00 P.M. The results are shown in Table IV.

Examination of this table gives in probably a more satisfactory and conclusive manner the same information as that gained from the preliminary cross-protection tests. The death rate among the controls was closer to the ideal. In the case of 58 and 1(V) the results might have been even more convincing if the dosage had been somewhat higher.

It is quite clear that we are dealing with two different groups of strains so far as virulence is concerned. In the tests with living bacilli of the relatively avirulent group it appears that the dosage was so high that differences in protective value of the vaccines were almost obliterated. When we examine the results among the groups which received as their test doses bacilli of the

TABLE IV

FINAL IMMUNIZATION TEST

MARCH 27, 1935–APRIL 24, 1935

Injections of Live Organisms		*Percentage of Deaths Among Lots of Mice, Each Lot Immunized, Respectively, with the Following Vaccines 14 Days Previously*							
Strain	*Numbers (in millions)*	*1(I)*	*1(R)*	*1(S)*	*36*	*53*	*58*	*1(V)*	*Controls*
1(I)	400	0	0	20	0	0	0	0	40
	800	16	13	13	10	3	4	10	80
	1,600	67	60	69	63	82	53	79	100
	3,200	96	96	96	86	96	100	86	100
	6,400	90	80	100	90	100	90	100	100
1(R)	400	0	0	0	0	0	0	0	20
	800	10	0	16	10	20	3	16	80
	1,600	56	43	30	43	79	30	67	100
	3,200	82	82	92	97	100	90	92	100
	6,400	90	90	90	100	100	80	100	100
1(S)	400	0	10	0	0	0	10	0	20
	800	43	36	36	20	46	14	13	80
	1,600	79	82	79	36	89	63	89	100
	3,200	96	89	100	100	96	82	96	100
	6,400	100	90	90	90	100	100	100	100
36	75	0	10	0	0	0	0	0	40
	150	43	0	33	0	30	0	0	100
	300	53	30	76	0	82	16	0	100
	600	92	86	79	0	92	3	3	100
	1,200	90	90	70	30	100	10	40	100
	2,400	90	100	100	50	100	80	70	100
53	300	0	10	0	0	10	0	0	0
	600	7	13	10	0	7	7	7	60
	1,200	60	76	56	3	53	30	20	100
	2,400	86	92	86	92	92	82	86	100
	4,800	100	100	90	80	100	100	90	100
58	75	0	0	0	0	10	0	0	20
	150	7	0	10	0	0	0	0	40
	300	10	3	43	0	13	0	0	80
	600	46	13	60	0	82	0	0	80
	1,200	80	50	80	0	90	10	20	100
	2,400	100	90	80	10	100	0	20	100
1(V)	25	20	0	10	0	10	0	0	0
	50	10	0	13	0	10	0	0	0
	100	13	3	26	0	20	3	0	0
	200	36	16	30	3	56	0	0	20
	400	60	40	60	0	40	0	0	80
	800	100	100	100	30	100	0	20	100

more virulent strains, however, wide differences in the protective value of the vaccines are apparent. Here again the strains are clearly grouped. The strains 36, 58, and 1(V) are more efficiently immunogenic than are 1(I), 1(R), 1(S), and 53.

DISCUSSION

In such work as this one is constantly seeking to differentiate between toxicity and virulence and between these terms and invasiveness. The last, it is believed, should be restricted to cases in which the animal species concerned is susceptible to natural infection by the organism concerned; to cases in which, by some means, the microörganism gains access to the tissue for which it has a special predilection and develops there eventually causing morbidity and possibly mortality. The sickness most frequently exhibits a characteristic clinical picture. The type of clinical syndrome usually depends upon the characteristic metabolic products of the infectious process.

It is not so easy to separate virulence from toxicity. In any case, toxicity is not a good word to be employed in so vague a manner. Ehrlich defined the

word toxin so clearly and definitely that its use in any other sense is really not admissible. The trouble is that we have no other term to express the idea here. In the injection of enormous doses of relatively avirulent typhoid bacilli we have almost overwhelmed the mice by a mass of noxious or "toxic" material which gives their acquired vaccinogenic immunity no chance to demonstrate its existence. The differences in immunity which we do discover are the result of combinations of noxiousness or "toxicity" and virulence in which the former is not sufficient to overwhelm the animal. On the other hand, it acts somewhat like an "aggressin" and prepares the mouse for a result dependent upon whatever virulence the particular strain of relatively avirulent bacilli may have.

CONCLUSIONS

There seems to be some indication in these results that immunogenic properties of typhoid organisms are associated with their virulence. The virulent organisms used in this experiment, when used as a heat-killed tricresol preserved vaccine in the number of mice tested, gave better protection than that afforded by the avirulent group under similar circumstances.

Laws, Dealer's Insurance

. . . Instead of protesting against health legislation, the informed milk dealer is one of its most ardent advocates. Aside from his interest as a citizen, he is concerned in a selfish way with the maintenance of standards which will guard the milk supply from any suspicion of being a carrier of disease. Let him think for a moment what it would mean to him if an epidemic were traced to the milk supply of even some small unimportant peddler, to say nothing of what it would mean if one of the large milk concerns were implicated. Attach the stigma of milk-borne infection to even the smallest route and the whole milk industry in that area suffers. Orders are cancelled by the thousands and it is no easy task to convince frightened mothers that their children are safe if they drink the milk of a concern which is not involved in the outbreak. Why, health laws are the best insurance the milk trade can have!

. . . Most large milk distributors, for a purely selfish reason, leave nothing undone to safeguard the purity of their product. But sometimes the small concern or the producer-distributor might not be so careful since, having less investment in the business, he has less to lose and might be more willing to take a chance. Rigidly enforced milk regulations prevent him from taking that chance and thus serve as a safeguard not only to the public health but to every other farmer who produces milk in that area, and every other man who distributes it. There may be laws which seem to serve no worthy purpose but they are comparatively few in number and the burdens they inflict are offset a hundred times over by the value of the good ones. If public health authorities were to announce tomorrow that every regulation governing the sale of milk were to be removed, not 10 days would elapse before leading dealers would be attempting to do, voluntarily, what the laws now require them to do. The only difference is that they could not do the job half so well.—Editorial, *The Dairy Record,* Jan. 8, 1936.