ON IMMUNITY AGAINST INFECTIOUS DISEASE,

WITH SPECIAL REFERENCE TO

ANTI-TYPHOID INOCULATION.

By E. J. McWeeney, M.A., M.D., D.P.H., F.R.C.P.I.
(Professor of Pathology, University College, Dublin).

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In a recent Address entitled "Bacilli and Bullets," Sir Wm. Osler[1] says that he cannot look upon a group of recruits marching to the depôt without asking himself what proportion of these fine fellows will die legitimate and honourable deaths from wounds, and what percentage will perish miserably from neglect of ordinary sanitary precautions. "It is bitter," Sir William goes on to say, "to lose thousands of the best of our young men in a hideous war, but it adds terribly to the tragedy to think that more than half the losses may be due to preventable disease." Formerly typhus and cholera, and still further back, bubonic plague, were the principal enemies to the health of armies in the field. In the more recent wars, however, Typhoid has assumed the proportions of a formidable pestilence. Success in a modern war depends on the intelligence with which it is waged—on the utilisation of every weapon which modern science places in our hands not merely for destroying the enemy but for the protection of our own men. We cannot afford, therefore, to neglect any method that may enable us to ward off the danger of Typhoid from our troops. Protective Inoculation is such a method, and it is therefore with pleasure that I now comply with a request conveyed to me at the last Council Meeting of the Statistical Society, and come forward with an account of the method, its underlying principles, and the results that have been attained by its use. Premising that my hearers do not, for the most part, belong to the medical profession, I shall find it necessary to begin by explaining some points connected with the modern doctrine of Immunity, a knowledge of which might otherwise be taken for granted. The same fact absolves me from entering into the details of the preparation of the several varieties of vaccine, and the discussion of their relative merits, with the fulness that a medical audience might expect.

I propose to deal with the subject matter under the following heads:—

I.—The Nature, Causes and Kinds of Immunity against Infectious Disease, with special reference to Typhoid [Enteric] Fever.
II.—Incidence of Typhoid on the General Population.
III.—Incidence of Typhoid on Troops in the Field.
IV.—History of the Method of preventing Typhoid by protective Inoculation, and the Results that have been achieved.
V.—Duration of the Immunity conferred by Inoculation.
VI.—Reaction caused by the Inoculation.
VII.—Classes of the Population that should be inoculated.
VIII.—Kinds of Vaccine in Use.

I.—Nature, Causes and Kinds of Immunity.

It is a well-known fact that second attacks of infectious diseases are, with few exceptions, rare. In withstanding the first attack the patient has acquired immunity against further onslaughts of the same disease-germ. Examination of the blood of such a person, moreover, affords evidence of the presence in it of substances that exercise a deleterious influence on the germ—may, indeed, kill it. These substances are spoken of as being "*anti,*" that is opposed to, the germ causing the disease from which the patient has recovered. Their presence in the blood of the convalescent patient is only a particular case of a general law which may be thus stated:—*The entrance of foreign albuminous matter (protein) into the system, evokes the production of specific anti-bodies.* We now call the foreign or intrusive protein "antigen." Ehrlich explains the action of the antigen by supposing that its molecules combine with the receptors or nutritive side-chains of the body-cells. Should the antigen be poisonous or occupy too many of the side-chains the cell may be killed. But if it survives it reacts by producing fresh combining-links or receptors, which, being discharged into the blood, constitute the anti-body.

[*Diagrams illustrating Ehrlich's Theory of Side-Chains were here projected on the screen.*]

I must expressly state that the side-chains or receptors with their supposed capacities for combining, etc., have never been seen and may possibly not exist. They have been imagined and enable us to visualise a certain concept of how immunity is brought about. That concept may not be right—may not correspond to facts in all particulars. But it certainly does so to a very large extent, and, what is

very important, the theory has proved itself a genuinely heuristic one in the sense that inferences based upon it have been found justified by the test of actual experiment. Under the influence of this theory, Immunity has become a vast and highly specialised department of Research, and has yielded practical results of the highest importance, with one of which we are this evening concerned.

With regard to Antibodies there are two points deserving special notice.

In the first place they are only produced when the antigen is introduced par-enterally, that is, otherwise than by way of the Alimentary Canal. Our food consists in a large measure of substances endowed with antigenic properties—of foreign proteins. During their passage through the Alimentary Canal the food-stuffs are subjected to the action of various ferments (enzymes) which break up the molecules of foreign protein, and thus deprive them of their characteristic foreign architecture. The foreign molecules are broken up and the fragments, so to speak, rounded off and made capable of being built up into the new edifice of which they are now to form part. On the other hand when the foreign molecules gain entrance par-enterally, that is, *not* through the alimentary canal but by being injected under the skin or directly into the blood, they come into direct contact with the receptors of the cells and (usually) combine with some of them, the result being (as I have already mentioned) the reproduction of the blocked receptors in excessive number and their discharge into the serum, where they constitute the anti-body.

The second point is that Anti-bodies are specific, that is, will only combine or react with the Antigen that produced them*—just in the same way as a lock of complex construction can only be opened by a key specially made to fit it. Recovery from one disease will not protect against another.

We term the poisons produced by microbes "toxins." They behave as antigens.

As an example of a simple sort of Antibody we may take an Antitoxin. Antitoxins are identical with cast-off cell-receptors and possess only one capacity—that of combining with the toxin that evoked them, and so preventing that toxin from combining with the cells and thus injuring or killing them.

A second and more complex type of antibody is an "Agglutinin," viz., one which has the power of causing the micro-organisms that evoked it to adhere together in masses which are often large enough to be visible with the

* The question as to the so-called "group-reactions" is here passed over.

unaided eye, and tend to fall as a sediment to the bottom of the containing vessel, instead of remaining in suspension. A *Precipitin* has much the same power but exercises it upon yet smaller particles—the molecules of the protein which gave rise to it. This type of antibody exercises two functions—one that of combining with, and the other that of agglutinating, its antigen. The entrance of the Typhoid Bacillus, which is powerfully antigenic, into the blood, evokes the production of agglutinins, the demonstration of which in the serum is an easy matter, and constitutes a most reliable method of diagnosis—that associated with the name of Widal.

Yet another sort of Antibody was discovered by Wright and named by him "Opsonin." Its function is to act upon the intrusive micro-organism by rendering it palatable to the leucocytes or white blood-cells, and thus increasing the tendency of these cells to take up and digest the micro-organism.

There are yet other antibodies—those called "Amboceptors," because they have two combining-links, by one of which they attach themselves to the Antigen, whilst with the other they combine with a powerful enzyme or ferment normally present in the blood and now usually termed "Complement." The effect of linking up the complement with the Antigen is that the former exercises its solvent, or, as we say, "lytic" effect on the latter. Antigens such as micro-organisms that are laden with their corresponding amboceptors are said to be *sensitised* and at once undergo solution when injected into a normal animal or man. This principle underlies the use of one variety of Anti-Typhoid vaccine (Besredka's).

From the foregoing brief exposition we have, I trust, learnt enough to appreciate what takes place during a non-fatal attack of an infectious disease such as Typhoid. The Bacilli, consisting as they do, of foreign protein, are powerfully antigenic and stimulate the cells of the individual attacked, with the result that a crop of anti-bodies is produced, specifically directed against the intrusive micro-organisms.

Thus there are found—

(1) Opsonins that lead to the ingestion and destruction of the germs by the white blood-cells.
(2) Antitoxins that combine with and neutralise its poisons.
(3) Agglutinins that cause the bacilli to adhere together and doubtless assist in their destruction; and
(4) Bacteriolytic Amboceptors that focus upon the Bacillus the powerful ferments contained in the blood and thus bring about its dissolution.

The consequence is that the attack is foiled. The disease-germ is suppressed and got rid of. The patient recovers, and for a time retains in his blood enough of the specific anti-substances to render any further attack from the same quarter impossible. Such a patient is said to be immunised or protected. The duration of such protection varies within wide limits. In the case of some of the acute eruptive fevers such as small-pox, scarlatina, measles, it is often life-long. In other diseases, such as pneumonia, erysipelas, influenza, bronchial catarrh, it may only last a few weeks. In a given case, by testing the serum at intervals for anti-bodies, we can form an idea of the length of time it lasts. But even should the result of the test be negative, should anti-bodies be no longer demonstrated, there still remains a state of hypersensitiveness or "allergy," as it is now termed, by virtue of which the defensive mechanisms, as the result of their previous experience of the micro-organism in question, respond to its re-appearance more quickly and more vigorously than would have been the case had they now known it for the first time. They overwhelm the unwelcome visitor with an array of rapidly mobilised antibodies.

Immunity may be *natural* or *acquired*. In natural immunity the man or animal is congenitally incapable of becoming infected owing to the absence from his body-cells of receptors capable of combining with the germs or their toxins. Thus birds possess natural immunity against tetanus. Acquired immunity may be the result of—

(1) An accidental, involuntary attack of the disease contracted in the ordinary way, or
(2) the deliberate introduction of the antigen, or the corresponding antibodies by the par-enteral path.

This is artificial Immunity.

Artificial Immunity may be (1) active or (2) passive. Passive immunity is obtained by the introduction into the subject of antibodies ready made. The antibodies are contained in the serum of an actively immunised animal, and this "anti-serum" as it is called is injected. This procedure does not further concern us here and we will dismiss it with the remark that it has proved of remarkable service against two formidable maladies—diphtheria and tetanus. Active immunity, on the other hand, is brought about by the reactive forces of the individual himself, elicited by the entrance of the specific micro-organism. It may be induced by the introduction of the disease germ

(1) in its primitive unaltered condition, or
(2) modified in various ways.

(1) Artificial introduction of the germ in the living state and of full virulence is, of course, a dangerous procedure, as the attack so induced may prove fatal. Inoculation with small-pox virus is an example of this practice and was extensively carried out before the introduction of Vaccination by the immortal Jenner. It was abandoned for the reason just mentioned.

(2) The following are the chief modes of modifying the virus of a disease so as to render it suitable for protective inoculation.

(*a*) It may be passed through the system of a more or less insusceptible animal. This is what happens in the only kind of protective inoculation hitherto universally practised—that directed against small-pox. The procedure derives its name from *vacca*, a cow, the animal employed for the purpose.

(*b*) The virulence of the micro-organism may be diminished by heat or antiseptics. This is called attenuating the virus and was first employed by Pasteur against the splenic fever of sheep and the cholera of fowls.

(*c*) The virus may be slowly dried outside the body. In this way Pasteur succeeded in attenuating the virulence of the unseen micro-organism of Rabies and thus converting it into a harmless vaccine which has saved thousands from a painful death.

(*d*) The disease-germs may be killed by heat or antiseptics. Their dead bodies constitute the vaccine. This is the method most usually employed as against Typhoid and is consequently that which chiefly interests us this evening. It has also been found to work well as against Paratyphoid, Cholera, Plague, and Dysentery.

(*e*) The germ itself may be got rid of by filtration and only its products or toxins may be introduced. This plan only works when the toxins are excreted into the culture fluid, as happens in the case of Diphtheria and Tetanus. When the poisons remain locked up in the body of the micro-organism—as they do in the case of Typhoid—this plan is not applicable. The bodies of the Bacilli may, however, be allowed to dissolve (undergo autolysis) or they may be pulverised at the temperature of liquid air, or they may be forced by enormous pressure to yield up their toxins, which may then be used for inoculation.

Having thus striven to give some idea of the principles underlying the modern practice of immunisation, I shall now turn to its application in the case of Typhoid Fever.

II.—Incidence of Typhoid on the General Population.

Before considering the need for a new method of combatting a disease, it is proper to ask ourselves how the disease has been influenced by the ordinary sanitary measures prescribed by the State or adopted by up-to-date units of sanitary administration.

When we come to do this in the case of Typhoid we find that there has been of late years a remarkable reduction in the incidence of that disease. In Great Britain twenty years ago, the death-rate per million, from this cause, was over 300; in 1912 it had fallen to 44—the lowest recorded. In Ireland there was also a fall, though not so pronounced. In 1903 the deaths numbered 480, and in 1913 289, the average for the past 10 years being 371. The rate per million dropped from 109 in 1903 to 53 in 1912, the average for the 10 years being 84. In many of our great cities the same thing has occurred. Thus in Liverpool in 1894 there were 1,350 cases with 248 deaths, whilst in 1913 there were only 153 cases with 33 deaths. In Glasgow the case-rate per 100,000 was 138·6 in 1891, and the death-rate 21·8. In 1913 the former had sunk to 23·2 and the latter to 0·36. In other cities the fall is not so great. In Manchester, for example, there were in 1899 381 cases with 73 deaths, and in 1913 292 cases with 47 deaths, the death-rate per 100,000 falling during the 15 years from 13 to 6. In our own City of Dublin the cases 20 years ago numbered 813 and the deaths 104. Last year the cases had fallen to 287 and the deaths to 33. This latter figure corresponds to a death-rate of 11 per 100,000, the average for the previous 10 years being 16.

These figures afford convincing proof of the fact that under ordinary civil conditions of life, general sanitary measures, such as pure water, good methods of sewage disposal, attention to the food supply (supervision of shell-fish, of milk), and certain specialised measures such as the discovery and isolation or cure of "carrier"-cases, have proved effective in diminishing the prevalence of Typhoid.

III.—Incidence of Typhoid on Troops in the Field.

Experience has shown that when men are huddled together in camps or trenches or in beleagured towns under war conditions, Typhoid tends inevitably to break out amongst them and speedily becomes a regular pestilence.

Table I. sets forth the figures for Typhoid in some recent campaigns.

TABLE I. (2).—Losses caused by Typhoid in some modern Wars.

War.	Strength.	Typhoid Cases.	Typhoid Deaths.	Killed in in Action Died of Wounds.	Died of Disease.
Franco-German, 1870-71, German Army.	—	73,393	6,965	28,269	15,240
Spanish-American, 1898, American Army.	107,973	20,738	1,580	243	2,565
Boer War, 1899-02, British Army.	380,605.	57,684	8,022	7,702	13,250.
Russo-Japanese, 1904-5, Russian Army.	—	17,033	—	34,000	9,300

From this we see that during our war with the Boers we suffered greater losses from Typhoid Bacilli than from the bullets of the enemy. The reason for the terrible ravages of this disease during war-time is the greater difficulty there is in disposing of the germ-laden excretions of the human body under the conditions then prevailing. Typhoid in military encampments is not, as a rule, water-borne. The specific germs are introduced by mild, undiagnosed cases, and by germ-carriers. The latrines and trenches thus become infected and the bacilli are widely spread through the agency of "the three F's—Food, Flies, and Fingers," so that all are brought in contact with the germs of the disease, and all that are susceptible take it.

IV.—History of the Method of Checking the Spread of Typhoid by Protective Inoculation—and the Results so achieved.

For such exceptional conditions as those just referred to, exceptional measures are obviously called for. It is to the labours of our gifted fellow-countryman Sir Almroth Wright that we are indebted for the introduction of a method that has now proved itself to be an effective weapon against the spread of Typhoid. In his praiseworthy endeavours, Wright has been most ably seconded by Colonel Sir Wm. B. Leishman, R.A.M.C., whose untiring industry

has placed the procedure on a sound basis of experiment and observation, and thus powerfully contributed to its now well-nigh universal adoption in the armies of all the leading countries.

Wright's first steps in this matter were taken so far back as 1896, when he was Professor of Pathology at the Army Medical School at Netley, and are recorded in a paper(3) which was concerned with a totally different subject. In this paper he speaks of two men and an animal (horse) as having received inoculations of dead Typhoid Bacilli. Early in the following year(4) he describes the changes in the blood of 17 persons similarly inoculated. Meanwhile, it is only fair to state, the subject was being energetically worked at in Germany by Pfeiffer and Kolle, who published(5) an account of their systematically conducted experiments a few months before Wright's first paper appeared. Wright's work was, however, quite independent of theirs, and the development of the method in this country under Wright and Leishman was quite original and not in any way due to German influence.

In 1898 Wright availed himself of his presence in India, where he was serving on the Plague Commission, to inoculate 4,000 men of the Indian Army.(6) Shortly afterwards came the first instance of the application of the new method in civil life, at the Barming Asylum, where there was a serious outbreak of Typhoid, and one hundred of the attendants were inoculated, not one of whom contracted the disease.(7)

As early as 1900 the method, still in its infancy, was tried here in Dublin at the Richmond Asylum, which was at that time suffering from a severe visitation of Typhoid. At the instance of that able administrator, the late Dr. Connolly Norman, Professor Wright was invited to make a trial of his method, and the work of carrying out the inoculations —the first of their kind in Ireland—was intrusted to the Assistant Medical Officer, the late Dr. Henry M. Cullinan, who recorded his experiences in the *Dublin Journal of Medical Science*.(8) It is interesting to note that Dr. Cullinan describes the inoculation as an "operation." We have progressed since then!

Among the un-inoculated, 114 in number (all nurses), there were 17 cases with 4 deaths. Among the inoculated, 500 in number (all patients), there were 7 cases with one death. Of the 7 cases, three were already infected at the time of inoculation, and must be left out of account. The case-incidence per cent. was therefore 14·9 among the un-inoculated, as compared with ·8 among the inoculated, and the death-rate 3·5 as compared with ·2—a highly satis-

factory result.* Only one inoculation was given and the reactions were severe, necessitating the patients staying in bed for three or four days. A few months later Wright discussed this case very fully in a paper(9) in which he seems to under—rather than over—estimate the favourable nature of the results observed as the result of the new prophylactic.

The Boer War of 1899-02 afforded the first opportunity of testing the new method on a really large scale. Its use was sanctioned by the War Office but was left optional with the individual. Some 400,000 doses were sent out by Wright and Leishman, but it is believed that only about 100,000 men received one or more.(10) Some were inoculated on the way out, some on arrival, many did not receive more than one dose, and the statistical results are incomplete. I reproduce Wright's figures.

TABLE II.—Boer War, British Troops.†

—	Number.	Cases.	Rate per 1,000.	Deaths.	Rate per 1,000.
Inoculated ..	19,069	226	11·84	39	2·04
Not Inoculated	150,231	3,739	24·88	(?)	(?)

TABLE III.—Results at Ladysmith and Modder River.

—	Number.	Morbidity.	Mortality.
		per cent.	per cent.
LADYSMITH—			
Inoculated ..	1,705	35 =2·05	8 =0·47
Not Inoculated ..	10,529	1,489 =14·14	329 =3·13
MODDER RIVER—			
Inoculated ..	2,335	26 =1·11	(?)
Not Inoculated ..	10,981	257 =2·34	(?)

It will be noted that Wright claims to have diminished the case incidence by more than one-half and the mortality

* The fact that all the inoculated were patients and all the non-inoculated nurses, does not invalidate the favourable inference but rather strengthens it. See Cullinan, *loc. cit.*

† The tables are taken from Russell (11), the original publication not being available.

in still greater proportion. I feel certain that the method did not on this occasion obtain a fair trial. The unpleasant fact remains that out of a total strength of about 381,000 there were during that campaign nearly 58,000 cases of Typhoid with over 8,000 deaths. Some observers reported favourably of the method, such as Tooth[12], Marsden[13], Boyd[14], Osborn[15], and Cayley[16]. But others were not able to agree as to its value (Elliot and Washbourn[17], and Melville[18], whilst yet others[19] went so far as to assert that the number of cases and deaths was increased by the inoculation. The *ad interim* verdict at the time was "not proven." The War Office suspended the practice for the time being, and appointed a Commission to report upon it. This Commission, which was presided over by Dr. C. J. Martin, F.R.S., now Director of the Lister Institute of Preventive Medicine, entrusted the experimental part of the work to Colonel (now Sir W. B. Leishman.

By direction of the Commission, inoculations were again taken up amongst the *personnel* of a number of selected units serving abroad, chiefly in India. Under the skilful guidance of Leishman the procedure was carried through in the most thorough-going and systematic manner. Careful attention was paid to the incidence of Typhoid upon the units under observation, the most modern methods of diagnosis being employed by medical officers specially trained for the purpose. An *ad-interim* Report appeared in 1904 which I have not yet been able to consult, but I reproduce the main results as reported by Sir Wm. Leishman to Section XX. of the XVII. International Medical Congress, held in London in August, 1913, and subsequently published by him.[20] The observations were made on 24 selected Test Units. The period covered extended from December, 1904, to June, 1909.

TABLE IV.—Results of Anti-Typhoid Inoculation among Troops on Foreign Service (Leishman).

—	Total Strength.	Cases.	Rate per 1,000.	Deaths.	Rate per 1,000.	Case Mortality.
						per cent.
Not Inoculated	8,936	272	30·4	46	5·14	16·9
Inoculated	10,378	56	5·4	5	0·47	8·9

In another Table Leishman sets forth the Typhoid incidence and mortality in India for the past 23 years, but it will suffice, for our present purpose, to confine our attention to the last 11 years, beginning in 1902 and ending in 1912.

TABLE V.—Typhoid Fever in India from 1902 to 1912 (Leishman).

Year.	Admissions.	Deaths.	Admissions per 1,000 of strength.	Case Mortality per cent.
1902 ..	1,012	260	16·7	25·69
1903 ..	1,366	292	19·6	21·38
1904 ..	1,384	265	19·7	19·15
1995 ..	1,146	213	16·1	18·59
1906 ..	1,095	224	15·6	20·46
1907 ..	910	192	13·1	21·10
1908 ..	998	191	14·6	19·14
1909 ..	616	112	8·0	18·18
1910 ..	296	45	4·1	15·20
1911 ..	170	22	2·3	12·9
1912 ..	118	26*	1·7	19·0

It will be remarked that this remarkable fall is not evenly distributed over the period covered. It is most rapid in 1909 and the following years. Now, the practice of inoculation was re-introduced in the year 1905, but it was not until 1909 that the number of men inoculated was large enough to influence the general statistics. "From that year," says Leishman, "there has been a steady and very remarkable decline, the figures for each successive year constituting a fresh low record until in 1912 we find that there have been only 118 cases in the whole of the British Army in India—a gratifying contrast to the large figures recorded in the past." (In 1897 there were 2,050 and in the following year, 2,375 cases.) Leishman then proceeds to disclaim the view that this great diminution is exclusively attributable to the inoculations. "Improvements," he says, "in general sanitation, improved methods of diagnosis, the detection and isolation of 'carriers,' have undoubtedly all played a part; but my strong personal conviction, shared, I am glad to know, by many of my brother officers, is that the reduction is in the main due to the extended employment of anti-typhoid vaccine."

* This number has, I understand, been reduced to 3 during 1913.

History of the Method in America.—The remarkable results that have been achieved in the American Army by the use of the method are mainly due to the energy and perseverance of Major F. F. Russell, M.D., Professor of Bacteriology in the U.S. Army Medical School, Washington, D.C., who has recorded his experiences in a valuable paper(2) to which I am much indebted. The fearful havoc wrought by Typhoid among the American troops during the war with Spain called imperatively for active measures, and in 1908 Major Russell was directed by his Chief, Surg.-Genl. O'Reilly, to proceed to Europe and familiarise himself with the technique of the preparation of the vaccine. Russell accordingly betook himself to London, where he worked under Leishman and his assistants, and brought home the necessary experience and the special strain of Typhoid (Rawlings) used in the preparation of the British Army vaccine. The following year Russell began by inoculating his own laboratory staff. The news spread, and practically all the medical officers in and about Washington volunteered and sent their wives, children, friends, and servants. Then the corps of hospital attendants came in, and by the end of 1909 there had been vaccinated 1,887 persons. The following year 16,073 people were done. During 1911 the influx of volunteers still continued, and the Authorities, fortified by the experience of 20,000 vaccinations without a mishap, felt justified in making it compulsory upon all that were to participate in the manœuvres on the Mexican Frontier. The order was issued in March, 1911. The results achieved fully justified the step taken. Major Russell refers to the three divisional camps near the border, each camp being in full occupation for four months. At the Galveston (Texas) Camp there were 4,500 men, at San Diego (California), 3,000, and at San Antonio, 13,000. At Galveston, though there were 192 cases of Typhoid amongst the civil population (with whom the soldiers mixed freely) *there were no cases amongst the troops.* From San Diego, only two cases were reported, one of which was doubtful. Major Russell draws an interesting comparison between the experience at the San Antonio camp in 1911 and that at Jacksonville (Florida) in 1898 These two camps, each of approximately equal size, were maintained for the same length of time. They were situated in the same latitude, and each had artesian well-water of excellent quality. Yet in 1898 there were over 2,500 cases of Typhoid at Jacksonville, with 248 deaths, on a strength of 10,759 men, whilst at San Antonio in 1911, on a strength of 12,801 men, there were only two cases with no fatality.

Nor was the possibility of infection lacking, for, during the duration of the camp, there were 47 cases of Typhoid

with 19 deaths reported among the civil population, with whom the military freely mixed. Every allowance being made for improved sanitary measures and the fact that the 1898 camp was in war-time, whilst peace prevailed in 1911, the results must be looked upon as the signal evidence of the power of inoculation to save encamped troops from this disease.

TABLE VI.—1898, Spanish-American War.—Camp at Jacksonville, Florida. (Russell.)

Strength.	Cases of Typhoid certain.	Certain and probable.	Deaths from Typhoid.	All Deaths.
10,759	1,729	2,693	248	281
1911, Camp at San Antonio, Texas.				
12,801	2	—	0	11

The next step in the American campaign against typhoid was the extension of the vaccination order to all recruits. This was done on June 7th, 1911. Vaccination against smallpox is carried out at the same time. "If the Vaccinia be severe," says Major Russell, "the second dose of Typhoid-prophylactic is postponed a few days, but in no other way has it been found necessary to deviate from this routine of simultaneous vaccination against the two diseases. The two vaccinations are completed by the time the man has been twenty days in the service. Re-vaccination against both diseases is carried out, according to the present regulations at the beginning of each 4-year period of enlistment. This is not because the immunity has by that time disappeared, for its duration is not yet known. It, no doubt, diminishes gradually, as is the case with that from smallpox, yet in the service it is desirable to maintain the army in a maximum state of protection against infection at all times, and it does not seem advisable to omit vaccination until an outbreak of typhoid shows the disappearance of all immunity. Smallpox has been almost entirely suppressed; there were only five cases among the American troops in 1911, with no fatalities, and typhoid has ceased

to be the scourge of former times." I have thought it well to quote this passage from Major Russell's paper in view of its applicability to the situation created in our armies by the present war. I am clearly of opinion that only by making the inoculation compulsory shall we be able to get the best results from it, and I venture to express the hope that our Military Authorities, uninfluenced by the protests of "faddists," may, before long, see their way to follow in the footsteps of the Americans.

On September 30th, 1911, compulsory prophylaxis was extended to all persons in the American Army under 45. The results are set forth in three Tables which I reproduce.

TABLE VII.—Typhoid Fever (United States) among Enlisted American Troops. (Russell.)

Year.	Mean Strength.	Cases.	Deaths.	Cases per 1,000.	Deaths per 1,000.
1901 ..	26,515	250	17	9·43	·64
1902 ..	39,736	341	34	8·58	·86
1903 ..	42,264	246	12	5·82	·28
1904 ..	43,940	247	12	5·62	·27
1905 ..	42,834	153	13	3·57	·30
1906 ..	40,621	230	12	5·66	·28
1907 ..	35,132	124	7	3·53	·19
1908 ..	46,316	136	11	2·94	·23
1909 ..	57,124	173	16	3·03	·28
1910 ..	55,680	129	9	2·32	·16
1911 ..	55,240	44	6	0·80	·11
1912 ..	58,119	15	2	0·26	·03

TABLE VIII.—Showing the Number and Proportion of Typhoid Fever Cases contracted before Enlistment, and among the Protected Officers and Enlisted Men (United States Proper only). (Russell.)

Year.	Total Cases.	Total Deaths.	Infected prior to Enlistment.	Among the Vaccinated.	
				Cases.	Deaths.
1909 ..	173	16	(?)	1	
1910 ..	129	9	(?)	4	
1911 ..	44	6	(?)	7	
1912 ..	18	3	5	6	

TABLE IX.—Typhoid Fever, 1901 to 1912, for the Whole Army, Officers and Men, at Home and Abroad. (Russell.)

Year.	Mean Strength	Cases.		Deaths.		Occurring among the Vaccinated.	
		Number	Ratio per 1,000.	Number	Rate per 1,000.	Cases.	Deaths.
1901 ..	81,885	552	6·74	74	·88	–	–
1902 ..	80,778	565	6·74	69	·85	–	–
1903 ..	67,643	348	5·14	30	·44	–	–
1904 ..	67,311	293	4·35	23	·33	–	–
1905 ..	65,688	206	3·14	20	·30	–	–
1906 ..	65,159	373	5·72	18	·27	–	–
1907 ..	62,523	237	3·79	19	·30	–	–
1908 ..	74,692	239	3·20	24	·31	–	–
1909 ..	84,077	282	3·35	22	·26	1	0
1910 ..	81,434	198	2·43	14	·17	7	0
1911 ..	82,802	70	·85	8	·10	11	1
1912 ..	88,478	27	·31	4	·044	8	0

From Table VII. it will be gathered that the case-rate per 1,000, which was 3·03 in 1909 and 2·32 in 1910, fell in 1911, coincidently with the widespread adoption of vaccination in that year, to ·80, and in 1912, the first year it was compulsory, to 0·26. Remarkable as are these results, they are surpassed by those of 1913, for the first nine months of which figures were available. The following Table shows the monthly case-incidence for the past six years. It will be seen that the cases during the first nine months of the last four years show a fall from 92, to 39, then 13, and none at all in the year 1913. During the period in question there was no change of importance in the general sanitary administration, and nothing to account for the disappearance of Typhoid save the introduction of prophylaxis by inoculation. This result must surely claim attention as a remarkable example of the annihilation of disease by the weapons which bacteriological research has placed in our hands.

[TABLE X

TABLE X.—Monthly Incidence of Typhoid amongst U.S. Officers and Men. (Russell.)

Year.	Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total for 9 months.
VOLUNTARY—													
1908 ..	5	6	4	2	3	11	14	31	25	26	12	8	101
1909 ..	4	10	6	4	11	15	26	14	16	45	20	6	106
1910 ..	8	11	1	4	2	6	12	27	21	16	20	11	92
1911 ..	3	3	3	7	4	4	4	7	4	4	1	0	39
COMPULSORY—													
1912 ..	1	2	2	0	0	3	1	3	1	4	0	1	13
1913 ..	0	0	0	0	0	0	0	0	0	–	–	–	0*

* I understand that 1 case occurred during the last quarter of 1913.

Experience of other Countries.—Although the American figures may be regarded as affording conclusive evidence of the value of the inoculation method, it may not be amiss to briefly set forth what has been accomplished by this means in other countries—more especially as the mode of preparing the vaccine is not everywhere the same.

French Experience.—According to Chantemesse[21] there have been roughly 66,000 cases of Typhoid in the French Army during the past 20 years, with about 10,000 deaths. Amongst 30,325 inoculated troops no cases have occurred, whilst among the non-inoculated the case mortality was 2·22 per 1,000 of the troops in the Métropolitaine area (Morocco), and 6·34 of those on colonial services. In the Navy, 4,700 persons were inoculated between April, 1912, and December, 1913. No case has occurred among them, whereas the average case-incidence amongst the non-inoculated during the same observation-period was 1 in 120.

A very instructive example of the value of the method is that afforded by the garrison at Avignon.[22] From 1892 to 1912 there were 1,263 cases of Typhoid, requiring 44,133 days of invalidity. In 1912 there was an outbreak in the garrison, which numbered 2,053, of whom 1,366 were inoculated and 687 were unprotected. Both sets of men lived under precisely similar conditions as regards food, lodging, and hygiene. Amongst the uninoculated minority of 657 there were no fewer than 155 cases with 21 deaths, whilst there was not a single case amongst the protected majority, which, had the inoculation made no difference, ought to have furnished 308 cases with 41 deaths.

Amongst the civil population excellent results have also been recorded. According to Chantemesse[23] 14,000 civilians that were inoculated have as yet shown no case of typhoid.

Senez and Rouque (of Marseilles) report that they have used over 4,000 doses of anti-typhoid vaccine (iodised). Despite the fact that the disease was raging with epidemic virulence at the time, one in every ten of the population being affected, not one of their cases had, up to the time of writing, become affected. The same authors refer to a silk-works where there were on an average 8 to 12 cases yearly amongst the employés. No case occurred during the year after the staff were all vaccinated.

As the result of these experiences anti-typhoid vaccination has been made compulsory in the French Army by Law passed on March 28th, 1914.

Belgian Experience.—This is recounted by Professor Malvoz,(24) and is highly favourable.

Roumanian Experience.—An interesting case of inoculation of soldiers, in which some were injected with living sensitised Typhoid Bacilli according to Besredka's method, whilst others were treated with a vaccine killed at 60° C., is reported by Cuica, Combriscu, and Bolterna.(25)

Italian Experience.—This is to be learnt from a paper by Santoliquido,(27) who tells us that the vaccinations were begun in August, 1912, among the troops in Tripoli and Cyrenœa, that two sorts of vaccine were used, one prepared in the German manner, and the other on the plan devised in France by Vincent. Nearly 28,000 men were vaccinated and the severity of the reactions was carefully noted. The following Table sets forth the results:—

TABLE XI.—Result of Anti-Typhoid Inoculation amongst Italian Troops in Africa.

	Cases per 1,000.	Deaths per 1,000.
Uninoculated	35·3	7·01
Inoculated with Kolle-Pfeiffer Vaccine ..	1·0	0
Inoculated with Vincent's Vaccine ..	0·3	0

Japanese Experience.—Kabeshima(26) reports some interesting results achieved by the use of a mixed vaccine consisting of the Typhoid Bacillus together with the organisms that cause the two forms known as "A" and "B" of Paratyphoid Fever. His paper does not lend itself to condensation, but it may be said that on the Japanese Naval Hospital Ships among the inoculated, the incidence of Typhoid was only one-fourth, and of Paratyphoid "A" one-third of what it was amongst the unprotected. The case mortality amongst the unprotected was double that amongst the vaccinated in the case of Typhoid and Paratyphoid "B," whilst there was no difference in the case of Paratyphoid "A."

Canadian Experience.—The following table speaks for itself:—

TABLE XII.—Results of Anti-typhoid Inoculation in Railway-Camps in Alberta (Canada).

Year.	Uninoculated Strength.	Inoculated Strength.	Uninoculated Cases.	Inoculated Cases.
1911	4,500	5,500	220 =48·8 per 1,000.	2 =·36 per 1,000.
1912	2,000	8,400	76 =38 per 1,000.	1* =·114 per 1,000.

The significance of these results is unmistakable. They show that an even higher protection can be attained by means of anti-typhoid inoculation than has been reached by what has hitherto been looked upon as the model for all these procedures—vaccination against small-pox.

This paper has reached such dimensions that I must cut short the consideration of the remaining points, which, however, appeal rather to a medical audience than to those whom I have the honour of addressing this evening.

V.—Duration of the Immunity Conferred.

This has not yet been determined with certainty. According to Leishman,[20] the average duration of the protection afforded by the British Army Vaccine is two years, and after that time, the individual, if still exposed to the danger of infection, should be re-vaccinated. It seems to me possible that by increasing the number of doses (we give two, the Americans, three) a higher and more durable immunity might be conferred. Individuals differ greatly in their capacity for immunisation and the length of time they retain the impress so conferred.

VI.—Reaction caused by the Inoculation.

This is generally slight. Russell (*loc. cit.*) says 200,000 men have been inoculated with the American vaccine without a single fatality or serious complication. The Surgeon-General of the United States Navy states in his Annual

* This case is supposed to have been already infected at the time of inoculation.

Report for 1912 that "the inoculation of practically the entire Naval personnel has been completed without a single serious result or casualty. Only a small fraction of 1 per cent. had reactions necessitating rest in bed, and but a small percentage of individuals required to be excused from duty."

That serious illness does, now and then, supervene on inoculation is undeniable, and attention has been called to several such cases that have occurred in our Army since the war began. It would take too long to go into these cases individually, and this is not the place to do it. In considering the rôle played by the inoculation in these cases there are two points that have to be kept in view.

Firstly, when such large numbers are inoculated, it would be very extraordinary if some few did not happen, just at that time, to be in the incubation stage of some infection which might, even without the inoculation, run a serious or even a fatal course. The two cases of Pneumonia reported by Professor Boyd and referred to by Sir Wm. Osler[28] are clearly of this kind.

Secondly, we must bear in mind that hundreds of other men, inoculated at the same time with the same batch of vaccine were completely unaffected. This shows that not the vaccine but something peculiar to the individual was responsible for the severe illness.

The question has been raised as to whether the inoculation can actually produce Typhoid. Quite a number of cases have occurred in which Typhoid came on shortly after the inoculation. It must be remembered, however, that when inoculations are carried out amongst a population already stricken with Typhoid, some are sure to be incubating the malady when vaccinated. Moreover, the incubation period of Typhoid is a long one, extending to 21 days and even longer. This fact alone invalidates most of the instances in which Typhoid has been attributed to the Vaccine. Again, we must not lose sight of the fact that typhoid vaccine has come largely into use for the *treatment* of the fever and has yielded excellent results in many hands. In conclusion, I do not think it has been proved that Typhoid Fever can be set up by the inoculation as we conduct it in this country, and I agree with Sir Wm. Osler when he says that "reports of death as the result of the inoculation are false."

The general reaction after inoculation comes on in about 8 hours and lasts 24 to 48 hours. It consists of chilly sensations, restlessness, "all-overish" feeling, and a rise of temperature to 101 or 102°. Locally there is some redness and swelling with tenderness. In order to get over these

discomforts as easily as possible, the vaccination should be done in the late afternoon and the patient should lie up if at all possible next day, and, above all things, avoid chill. He should also abstain from alcohol.

VII.—Classes of the Population that should be Inoculated.

(1) Soldiers and naval men.

(2) Persons working in places where there is no organised system of sewage-disposal, such as engineers and operators on railway and canal works, mining villages, etc.

(3) Inmates of lunatic asylums.

(4) Young persons going on vacation to the country.

(5) Above all, nurses and hospital attendants, the liability of whom to contract Typhoid is much greater than that of the population at large. (Hachtel and Stoner[29] found the incidence among the nurses and attendants in six Baltimore hospitals to be 12 to 20 times greater than the rate for the city, and Joslin and Overlander in Boston found the incidence of Typhoid amongst nurses 8 times as high as that of the State at large.)

VIII.—The Various Vaccines that have been employed for Immunisation against Typhoid may be classified as folows:—

(1) Vaccines consisting of living Bacilli. (Castellani, Besredka, Broughton-Alcock.)

(2) Those consisting of killed Bacilli. (Wright, Leishman, Russell, Chantemesse, Vincent, Pfeiffer-Kolle.)

(3) Those consisting of extracts of Bacilli. (Bassenge and Meyer, MacFadyen and Rowland, Vincent.)

To enter upon the description of these several forms of vaccine would unduly overload this paper, and I will, therefore content myself with referring anyone who seeks further details to a paper in the *Office International d'Hygiène Publique* for September, 1913, in which the

literature of the subject will be found. Suffice it to say that our British Vaccine as prepared at the Royal Army Medical College and at St. Mary's Hospital consists of broth-cultures of a certain strain of Typhoid Bacilli, killed at 53° C. and containing a certain percentage of antiseptic sufficient to maintain sterility. The germ-content is standardised so that each cubic centimetre of the liquid contains 500 millions for the first dose and 1,000 millions for the second, which is injected 10 days after the first. My own experience with this vaccine, for specimens of which I have to thank Colonel Sir Wm. Leishman, has been most satisfactory. The reactions were slight to moderate in intensity and the agglutinative power of the patients' serum reached the titre 1 : 1000 ten days after the first injection. Unfortunately I have not been able to test how much higher it went after the second dose.

I have been prevented by consideration of space and time from dealing with the question as to the greater efficacity of polyvalent vaccines (Vincent) and of combined vaccines (Castellani). It seems quite possible that improvements, in the shape of longer duration of immunity and less severe reactions may yet be achieved. But I think I have said enough to show that the modern study of Immunity has enabled us to score some triumphs over disease and death, and promises to accomplish yet more in the future.

Addendum made when correcting for Press.

Since writing the above, I have been favoured with the Report of the Army Sanitary Committee on Enteric Fever in the British Expeditionary Force, from which I subjoin the following figures:—The total cases in the British Expeditionary Force numbered 212; with 22 deaths. *Of the 212 cases 173, or 81·5 per cent., and all the deaths occurred amongst the uninoculated.* Of the 39 cases that occurred among the inoculated 28 occurred amongst those who had received only one dose, or who had been inoculated more than two years ago, whilst only 11 occurred amongst the fully vaccinated.

(Convincing as are these results, they would be still more so did we but know the actual numbers of the two classes, inoculated and uninoculated. It would then be seen that the vast majority of the cases (81·5 per cent.) occurred amongst the comparatively few unprotected men.)

REFERENCES

1. *British Med. Jl.*, 1914, Vol. II., p. 569.
2. Russell, *Am. Jl. Med. Sci.*, Vol. 146, 1913, p. 817.
3. Wright, "On the Association of Serous Hæmorrhages with Conditions of Defective Blood-coagulability," *Lancet*, 1896, Vol. II., p. 807.
4. *B. M. J.*, 1897, Vol. I., p. 807.
5. *Deutsche med. Wochenschrift*, 1896, p. 735.
6. *Lancet*, 1902, Vol. II., p. 654.
7. Leishman, Harben Lecture, *Jl. Stat. Med.*, Sept., 1910.
8. *Dublin Journal of Medical Science*, July, 1901.
9. *B. M. J.*, 1901, Vol. II., p. 1226.
10. Russell, *loc. cit.*, p. 804.
11. *Ib.*, p. 805.
12. Ref. in D. med. Woch., 1901, No. 17.
13. *Lancet*, 1900, Vol. II.
14. *Scot. Med. and Surg. Jl.*, 1901.
15. *Lancet*, 1900, Vol. I.
16. Cayley, *B. M. J.*, No. 2089.
17. *Med. Soc., Lond.*, 28th October, 1901.
18. *B. M. J.*, 1901, Vol. I.
19. Crombie, *Lancet*, 1902, Vol. I., p. 1201, and 1902, Vol. II., p. 436.
20. *Jl. R.A.M.C.*, April, 1914.
21. Paper read before the Paris Academy of Medicine, 3rd March, 1914. Ref. in *Sém. méd.*, 1914, No. 9, p. 104.
22. Simon: La Fièvre Typhoïde dans la garnison et la population d'Avignon de 1892 a 1912 (Arch. de Méd. et de Ph. Militaires, av. 1913). Ref. in Office Internal d'Hygiène Publique. T. V., 1913, p. 1577.
23. *Loc. cit.*
24. Acad. Med. Belge, May 30th and June 27th, 1914. Ref. in *Sém. méd.*, 1914, p. 312.
25. *Ibid.*, 1914, p. 239.
26. *Centralbl. f. Bakt.*, June, 1914.
27. Office Internat. d'Hyg., publ., Nov., 1914, p. 1844.
28. *B. M. J.*, 1914. II., p. 911.
29. Ref. in Russell, *loc cit.*, p. 830.