The Treatment of Typhoid Fever by Vaccines with special reference to Autogenous Living Vaccines

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The treatment of typhoid fever by vaccines has not yet shown the high percentage of distinct cure good results which vaccines have shown in some other diseases. There are, however, a sufficient number of definite, sometimes startling, cases directly attributable to vaccine treatment to justify the belief that with greater knowledge of improved vaccines this line of treatment may yet come to be of general use to the medical profession.

During the war, when on duty with a military hospital, I had the opportunity of treating several cases of typhoid. I tried this method, using autogenous living vaccines, and although I had neither sufficient material nor facilities for carrying my investigations to a logical conclusion, yet in conjunction with the work of others, these experiments
may help to add evidence to a subject in which much work yet remains to be done.

I will endeavour first to explain my own methods and cases before touching on the work of others.

It has been shown in work on plague that the strain of organism used is of great importance, and that antigen is a very delicate substance. Any physical method used to kill the bacillus will presumably act deleteriously on the continued antigen, and on this supposition it was suggested that if dead vaccines had proved of benefit, living vaccines would prove to be even more effective. This would be especially so if the patients own strains of organism were used.

Other workers working with various vaccines have shown only a very slight benefit of living over dead vaccines and the dangers of their
general use probably outweigh this slight disadvantage. Some workers, whom I will quote later, have had equally good if not better results using mixed vaccines of various strains of organisms, others by marked emphasis on the importance of a percentage of B. coli along with the B. Typhosus.

The following cases are given in full as they occurred. Here is no attempt at hiding what may appear to be negative results. They merely go to prove that there is "something in it." What that "something" is has yet to be worked out.

The cases were soldiers, and as they occurred in the first few months of the war they had not been previously inoculated. Diagnosis of all cases was checked by blood culture as well as by the
Bidal test.

Preparation of Vaccine

5 ccm. of blood was drawn from the arm with the usual aseptic precautions and were transferred immediately to a 1% solution of sodium thiosulphate. A broth culture was prepared from this and the growth was seeded by agglutination & sugar fermentation tests. The culture was inoculated into other tubes of broth which themselves constituted the vaccine used. The number of bacilli in the culture was obtained by direct count, on the method of the late Major C. Brodie, R.T.M., & whom most of the bacteriological work was done.

The doses given varied from 60 to 350 million.
Method of Injection

The injection was made subcutaneously and was followed by a marked general reaction. Within a few hours there were one or more rigors and the temperature rose. Within 24 hours the temperature fell of a marked crisis accompanied by profuse sweating, the tongue cleared of the general appearance of the patient was much improved.

The local reaction was surprisingly slight, not so much as is obtained of the typhoid or inoculation which later became general throughout the army.

Although no blood count was made in the cases mentioned here, late work has shown that the injection is followed by a leucopenia of several hours duration followed again by a leucocytosis polymorph in character. The fall changed from 5,000 down to 1,000 rising to 20,000 cells in 24 hours.
agar, to 6 or 8:000. The serum also shows an increase of agglutinating property denoting the development of some substance antagonistic to B. Typhosus. It is on these blood changes that Wright has based his obscuric work dealing with the spacing of the doses, with the object of giving the second and subsequent doses at the moment when the blood is at the height of its obscuric index. Unfortunately, when these cases were treated in the past, was known of Wright's work on the subject and little were no facilities of obtaining access to relevant literature. 'The spacing of the doses, a most important point in treatment, was thus done purely experimentally.'
Case 1
Pt. J. M. - Royal Welsh Fus. 23 years.

Not been inoculated for typhoid.

Nov 30th
Headache & feeling out of sorts.

Dec 1st
Fell out of parade & reported sick.

Dec 2nd
Admitted to hospital. On examination:
- Patient appeared tired & listless, pupils large,
- Tongue dry, glazed, brown fur, tannin stains,
- Considerable tongue - slight expectoration,
- Breath fetid - Abdomen no tenderness, abdomen
- No peristalsis, - reflexes diminished.
- A few petechial spots on abdomen. Marked
- Diarrhoea, with considerable vomiting
- after milk. Often enlarged lymph nodes, 
- Exanerated - Start-locating - last
- Milk rales all over, no sputum.
- Had the general appearance of a
- Moderately severe case.

Dec 3rd
Blood culture positive
Abdomen more taut - spots on
Vaccine 100 milli. at noon.

6th
Slight local reaction - almost gone
- Slight headache - abdomen tender - more spots
-
Dec 8th

Felt much better - slept well.

Vaccine 100 mill.

9th

Reactions as before - skin starting rise in temp. & blanched fall. T. Debo much better.

11th

Vaccine 100 mill. Temp remained normal.

13th

More local reaction than with previous injection. Much easier generally was able to read newspapers.

18th

Convalescent - got up for two hours.

This case reached normal convalescence on his tenth day in hospital (with a history of several days ptomaine illness dating from his first symptoms of headache). After what appeared to be a fairly severe attack of fever, the interval was tried at three days between doses.
Case 2  Sep 1  24  R.I. Rg. 25 yr.

Never been inoculated.


Abdomen tender. Distended & tympanitic.

Many rose spots. Spleen enlarged.

Dec 23  Blood culture positive

Vaccine 100 mill. Slight local reaction.

Rigors & sweating.

24th. Patient feels much better & looks brighter.

Vaccine 100 mill. Complains of pain in left fossa temporis. Inc.

Passed a good night & feels better. Pain gone. New rash of rose spots. Tongue still coated & tremulous but less than on admission.

31st. Vaccine 100 mill.

Jan 1st. Patient sweated freely and is in much better spirits.

Vaccine 100 mill. Some reaction. Tongue clean. No abdominal tenderness, slight he nervous felt well.
This case appeared very toxic on admission and though his temperature did not come down as suddenly as the first case his condition each morning after his vaccine proved a considerable improvement, quite apart from the rise of his temperature chart. It was the general appearance, the clearing of the skin, the mental brightness, the improved sleep and general vigor of the patient that I encountered has to continue with the treatment in other cases.

He became convalescent on his eighteenth day in hospital. The interval between doses was increased to four days.
Case 3

Sergeant A - ASC - 30 years.

Dec. 10th. Sudden attack of shivering, malaise, pain in back & headache.

11th. Admitted. Tongue thick white fur, turning brown. General condition brighter than would be expected. Area double of Lt. middle lobe in lung. Abdomen rose spots, some tenderness, but no pain or quivering. Suggest blood culture positive.

14th. Vaccine 200 million followed by the usual general reactions.

18th. No marked improvement - no more spot appeared.

20th. 250 mill vaccine followed by para-teriacin.


23rd. 1/100 million vaccine.

29th. Patient much more cheerful & intelligent.

Jan 3rd. Vaccine 100 mill.

Jan 6th. Somnolent.
In this case the dose was increased to 200 mill., but he did not seem to respond as well as the two previous cases at 100 mill., and therefore it was reduced. The two later doses did produce a more marked improvement in his general condition, but as he was still rather ill this cannot be claimed as being due to the reduced dose.

The interval was again kept at four days.
Case 

**Mr. T. B. Asst. 30 years.**

**21st.** General malaise & headache.

Admitted - flushed, tired, restless, severe headache, pain in back & legs. Bronchitis with some sputum that up some blood - complain of thirst.

Eye sunken, breath pasted, tongue dry, furred & tremulous - no epistaxis.

Shellass & slight delirium.

**22nd.** Pulse 108 soft & diastolic. Spleen not obviously enlarged - no rose spots.

No abdominal pain but tenderness & loss of abdominal reflexes. Blood culture positive.

Vaccine 200 mill. subcutaneously.

**28th.** Slight local reaction - no general reaction but no great improvement.

**29th.** Sleepless & delirious, incontinence of urine.

**30th.** Slightly better. Stools still watery & mind still clouded.
Dec 2nd
- 200 mill. Vaccine

3rd
- Distinct improvement.

1st
- Heavy & dull, tongue tremulous & cough still bad.

6th
- Greatly improved. Incontinence of urine & feces stopped.

7th
- Difficulty in passing water, but pond filled up as usual. Catheter passed 2 ½ pints, drained 77.
- Vaccine 300 mill.

8th
- More general reaction than usual. Last pulse did not alter.
- Mind now clear.

9th
- Bowels open normally, stools more solid - catheter passed owing to old structure which frequently gives him trouble. No signs of hectic.

11th
- 300 mill. Vaccine. Nothing to account for last night's temperature.

15th
- Convalescent.

18th
- Rise of temp. following a meal of solid food.
Case 2...

This case promised to be very severe. The man was delirious, delirious, suffered from constant severe cough, incontinence of urine, fever, followed by failure of Pers. His chart showed no very marked improvement after each injection, but there was considerable improvement in symptoms after the second and subsequent doses. The general conclusion of the attacks was better than one would have expected from the severity of the case judging by the chief symptoms. The interval between the doses was five days, and the doses were thought were too large.

Although the temperature jumped so considerably, the pulse remained almost unaltered throughout the course of the disease.
accepted with reservation

very few observations -
maintly a review of literature
but reveals an attempt -
- independent work

[Signature]
Case 5

Pt. M. ASC, 25 years.

12th Headache & general malaise

14th Admitted. Burns dull & listless

Fever dry. Sore & purulent & tremulous.

Slight Irregular respiration.

15th Blood culture positive.

18th Vaccine 200 milli.

21st Vaccine 200 milli.

22nd Shows considerable general

improvement. More than his chart

would indicate. Still some cough.

25th Vaccine 200 mill. Sense

reactions & feels better after it

30th Burns better, tongue moist &

clean, no abdominal symptoms.

Feels hungry. Is

bright & cheerful.
Case 5

This seemed a straightforward case of moderate severity. There was no marked drop in temp. after each dose as in case 1, but he made a steady improvement & touched normal on the 17th day in hospital.

There is no real reason to suppose that this improvement was due to the vaccine. Such a claim would be impossible without taking a large number of cases, with an equally large number of controls, treated similarly, except for the administration of vaccine.

Although there was no eviis after each dose the chart does thus a series of steps, the temperature coming down one degree after each dose & remaining there for three days.
Case 6

Pt: A.S. 1st binculus 19 years

Dec 23rd. Reported sick with headache, abdominal pain & diarrhea which had lasted for some days.

26th. Admitted. Very debry & bitter

unable to sleep. Throat dry & furred
white turning brown, abdomen
distended & tympanitic. Tender
in ileo region & over the spleen

A few red spots

Blood culture positive - Paratyphoid

28th. Very drowsy

29th. Fitted 60 million vaccine.

30th. Very marked improvement.

broad & tongue clean & not mo.
tumulous. Stools are typically
enteric. local reaction was more
than usual.

31st. Vaccine 60 milk.

Jan 1st. General improvement - diarrhea

stools have ceased - A fresh crop

of rose spots have come out

Tongue clean & no tremor.
Jan 6th 60 mill. Vaccine given.
   Focal rise in temp. and
   Some local reaction.
8th   Much improved.
9th   Convalescent.

In this case the long period before
entering hospital rather spoils any
calculation as to length of state.
After the first two injections this
temperature not only came down
but his general condition improved
strikingly.

By this time we were favouring
smaller doses at shorter intervals, and
had military exigencies not integrat
with the discontinuance of the series.
Further work would have been done
with smaller doses at shorter
intervals.

The gap after the second dose was
left to see if the temp. would drop if
its own accord which it did not do.
Conclusion on these cases.

These cases are too few in number to justify any dogmatic statement on the value of vaccines, but they go to prove that:

1. Living autogenous vaccines can be given with safety.
2. That the patient, however ill, shows a response, in most cases for the better, in no case for the worse.

In opposition to these results there is the very exhaustive work of Capt. Blantingston (Harris 1916), working at the same time but in a different hospital. He took 500 cases divided into 5 groups according to the severity of the symptoms. Each group was again divided carefully into two, one half being used as a control, the other being inoculated with
dead vaccine of the Army "stock" type as used for prophylactic inoculation before the T.A.B. vaccine came into use.

His cases were treated by several different M.O. s. in different wards of the hospital, and this concluded, were as follows:

"Vaccinia treatment by Army stock vaccine is disappointing in severe cases; there is no definite improvement in mild cases, and there are reasons to suspect an increased liability to haemorrhage and other complications. In conclusion, the treatment is not to be recommended."

His work was thorough & the large number of controls prevented the natural temptation of laying credit to the vaccine for what was only a natural good result. But on the other hand he used doses of 250 million to 600 million at 20
three day intervals and his poor results may be accounted for by that fact alone apart from the actual vaccine used.

Other workers using different vaccines and methods came to different conclusions, some being very enthusiastic, others not so. Against this, of course, it always has to be remembered that those who got the best results will probably short order, and many of those who found vaccine harmful, if they, have not published their work at all.

Ichikawa working in Osaka published in a German publication in 1914 the results of treatment of 82 cases. He used an intravenous injection of vaccine sensitized with serum from convalescent cases with the addition of 3% of borax acid.
He claims that 89% were definitely cured by crisis following the inoculation. The crisis occurred within 1.8 hours of the dose, and he claims that 90% of the cases entered convalescence on the third day after the first injection.

These results would appear extraordinary, and we can only conclude that they are due to the actual nature of the vaccine used. The cases all occurred during one epidemic when presumably one strain of organism was dominant in all cases. His mortality was high, 12%, but in his controls the mortality was 30%, which merely goes to prove the severity of the epidemic.

Magliove at Buenos Ayres (5/15/1916) treated 131 cases with a mixed vaccine containing 110 different strains of B. Typhosus from a 48 hour gas
agar culture and gave up to 8 doses at 2 to 3 day intervals. He says that the average duration of cases so treated was 14 days in hospital, while his average for the last 4 years was 31 days in hospital.

He also notes the liability to haemorrhage, and had bad results with alcoholic and tuberculous cases. He notes the rigors, sweating, and fall of temperature which we got, in those which are remarked on in almost all writers.

Kranz in the Argentine (Wien klin. 1924) gives similar results working with a vaccine killed with ether and giving doses of 50 to 100 million.

A number of German investigators have published their results in several German medical publications, principally the Wien klin. With all claiming good
results using different varieties of vaccines while Italian writers have also their work on war cases.

Fagioli (Bull 1916) claims success with killed vaccines of 100-300 million.

Pearson (S. F. Med Rec. 1918) claims more frequent cases and fewer complications than previously by using Bourn's Wellcome Vaccine while Prazzini & Senay (Bull 1918) gives similar results with doses of 250 to 1,000 million. They, however, lay emphasis not so much on sudden cures of crisis as to the fact that the average length of the fever is shortened.

Pernicata & Maloeri (Med Soc. Pavia 1918) give some interesting results. Giving small doses substantially they say that 70% showed no effect, but that in 20 cases 10 were cured by crisis in three days. This latter goes
To suggest that these 10 cases happened to be suffering from the exact strain of organism used in the vaccine.

They also state however that when they increased the dose to 200 units they got 63% cases. There seems to have been little very real progress in recent years, for as far back as 1902 Pletsko (Pletsko 1902) describes a method of treatment & a killed vaccine which he called "tyskorn". He stated that it was of benefit with mild cases, but not with severe cases, or in the presence of complications. This rather nullifies the use of the treatment, as it is just in these bad cases when it is most required. Breslau (Breslau 1905) tried living vaccines, but therapeutically satisfactorily, and although he claims good results in both he lays principal stress on the benefit from
the latter. Thus he approaches the more recent work of his Alewirth bright who has brought his prophylactic vaccine into a high state of perfection, as is seen in the inoculation results during the present war. He argued on purely theoretical grounds that vaccines would prove of greater service as a preventive than as a cure, and results have borne this out.

Still, though treatment may possibly swing in favour of sedums such as that of Chantemesse who published his results in the Prise Medecale - Paris 1903, there is no reason to condemn vaccines which are only emerging from their infancy. In passing, it may be noted that the failure of many serums put on the market seems to be due to the fact that they are
antibacterial and not antitoxic, as was the original serum prepared
with great difficulty by Blumenthal. He had a case mortality of 3% 
compared with that 7 70% for the
rest of Paris in 1902.

In comparing the results of these
many writers one is struck with
the high case mortality admitted
amongst many of the cases treated
with vaccine. This in itself is
values as a basis on which
to estimate the value of treatment,
unless compared with the mortality
rate of controls treated under
similar conditions.

What is of value, however, is
to study the deaths which are
directly attributed to the use
of vaccine. I have only been able
to find reference to five such
cases, all by French writers.
They all state the cause of death
as haemorrhage of one sort or another. This seems to corroborate the statements of many others who say that vaccine treatment is contraindicated in cases of haemorrhage, without quoting actual cases of death. This finding is unfortunate as haemorrhage usually occurs late in the disease while vaccine treatment is most effective when given early.

Many different kinds of vaccines seem to have been used, but after considering some 500 cases reported in recent literature, there does not seem to be a very great advantage of any one over the other. A small advantage does seem to be obtained by those using living vaccines but the difference is not marked. What is noticeable however is that many observers
while getting on an average only slightly better results with vaccine than without, to quote individual cases where the improvement was noticeably marked. This is perhaps the case in my own records in the case marked I.

Only one finding is common to all observers, and that is the immediate reaction, both general and local, to the inoculation.

There is no uniform conclusion as to the importance of the size of the dose. Some advocate doses to 500 millii and more, others doses of only several millii. This may be partially due to the great difference in power of response shown by the different cases. One can only hope that when the subject is better understood, that a more uniform dose will be established, such as simplified the prophylactic inoculation of the Army to be considerably.
Spacing of doses

As to the spacing of doses much work has been done by Sir
Almroth Wright who has shown by repeatedly taking the opsonic index
of cases under examination that when second and subsequent doses
are given during the negative phase the general responsive power of the
patient is gradually lessened, or definite harm is done. When the
interval is too long, i.e. when the
positive phase has returned to
normal, the patient will react
successfully to each dose, but
his general resistance will
remain about the same. The
ideal is to give the subsequent
doses after the negative phase has
passed when the positive phase
is at the highest point of its
rise and before it begins to fall
again to normal. By this the
resistance of the patient is
steadily increased. In the inocula-
of healthy persons this seems to average about every 10th day, but in cases where the disease is already present the 3rd or 4th day seems to be about the average.

Method of inoculation

Most workers seem to favour the intracutaneous method using very much smaller doses than subcutaneously. This certainly gets rid of the local reaction which, if great, and if the dose have to be repeated often, may cause great discomfort on the part of the patient.

Mixed Vaccines

Of recent years the theory has been professed that most infectious diseases are caused, not by one, but by several organisms, of which one plays the major part.
The other, non-pathogenic under normal circumstances and when present in certain proportions, may assume pathogenic characteristics when the balance of nature has been upset.

This multiplicity of organisms is well known in that affecting if this theory is correct in cases where the meso-plasma is the main seat of the disease there is no reason why it should not also apply to disease, affecting primarily other parts of the body.

It has been suggested that complications are frequently due to these secondary organisms. Several authors among them Dr. W. M. Grotan (Therapeutic Immunisation 1918) have suggested that B. coli is a necessary addition to all curative typhoid vaccine. There is great reason to believe that
this is so. B. coli, present so universally, or rather the many unknown strains of the B3. coli group, seems under certain circumstances to be able to assume a violently pathological character, as for instance when present in the peritoneum. It is reasonable to believe that in a disease like typhoid where the intestinal canal is so intimately affected, that the B. coli may again assume a pathological character. Crofton insists that its presence is essential and that several strains of B. Typhosus should be used. Magliocca at Buenos Ayres as already quoted uses a vaccine containing 10 different strains of B. Typhosus.
Of recent years Parker, Fair & Co. have put on the market a preparation which they name "phylaegen." This they claim gives better results than a pure Typhoid vaccine. The preparation is called a serum vaccine & is named from the antitoxic substance found in the blood of immunised animals by Henkin & which he called "phylaein."

The preparation is the product of a large number of different organisms, of different strains of the same organism. Staphylococci, Streptococci, Pneumococci, B. pyogenicus, B. coli, and others, are grown on media, samples of different strains are collected mixed, transferred to an aqueous solution, incubated, & filtered through porcelain. The resulting substance is their "stock mixed phylaegen." This is mixed with an equal quantity of a similar preparation made from Bacini strains of B. typhosus & Paratyphosus.
The resulting mixture is specially advocated for the treatment of typhoid. I have not had an opportunity of testing the preparation, and the only literature on the subject I can find is that produced by the manufacturer. They appear, however, to have made an honest attempt to obtain the unbiased opinion of various medical men unconnected with the firm, whom they have supplied with the preparation for experimental purposes. The results published are undoubtedly good, though naturally we have no record of the unpublished results which may not be so favourable.

Recent investigations have shown that typhoid is no longer the single disease it was once thought to be, but that many similar but different organisms such as the paratyphoids may cause a disease which is outwardly identical.

On these grounds there is
much to be said in favour of a mixed vaccine, though it has not to beproved that there is any gain by adding the large number of 
sabarid organisms contained in the "stable mixed phlegm" 
incorporated in all other.

The final test of the argument however can only be by carefully 
observed results.

Professor Nont of Basel University 
has tried the preparation on 25 cases. 
He reported that it was a distinct 
benefit in a safe line of treatment.
His cases had an average stay in 
sanatorium of disease of 616 days 
and a stay in hospital of 290 days 
which was a great improvement 
on the cases treated by ordinary 
methods.

He found that the best method 
was to start with a subcutaneous dose 
of 1 c.c. to test the amount of reaction 
given by each individual patient.
Second & subsequent doses were given intravenously using a much smaller dose, i.e., gradually being increased.

As a rule the dose was repeated each 24 hours for 4 or 5 days provided that the reaction from each dose had died down before the next was given. After each injection there was little usual rigor, sweating, rise & fall of temperature.

He found that out of his 25 cases, 2 were in remission & died, 8 recovered & a rapid fall of temperature almost approaching a crisis & directly attributable to the vaccine, 10 gave a rapid fall followed by a slow rise, & one of these & the alcoholic died finally. After having at first responded well to the treatment, the remaining 2 showed little response for 16 days, when the temp. of one suddenly fell & continued to remain down, the other ran a
lung course of 29 days but showed 
signs of pulmonary tuberculosis.

The cases were treated by varied 
doses & intervals to find out the best 
method. The better results were all 
obtained by the intravenous method 
at about a 24 hour interval. It 
was noticeable that those cases which 
made least response were those treated 
substantially. There were comparatively 
no complications & these were probably 
due to stopping the injections too soon.

It was recommended therefore that 
treatment should be continued for 
several days after the temperature 
reached normal.

As a general conclusion be found 
that the average duration of disease 
was 16 days which was much better 
than his previous results.
Conclusions

From these it may be concluded that in several hundred cases of typhoid treated by vaccine, most observers report that over 60% show definite improvement, the direct result of the treatment.

Only a few bad results are reported, and these are worthy of mention.

Up to the present no special type of vaccine appears to be outstandingly superior, but opinion seems to be turning in favor of mixed vaccines of one sort or another.

Recent work in the differentiation of various varieties of B. Typhosus & B. Paratyphosus perhaps explains many of the failures of the past, when a pure culture of one variety was used to treat all cases alike, many of whom must have been suffering from the effects of other, other organisms.
The effect of treatment is shown in
most cases as a considerable shortening
of the disease as well as the amelioration
of symptoms.

A few cases enter on convalescence
by crisis within a few days of the
first injection. Many more improve by
lysis reaching normal within 16 days.
If these the fall in temperature is
shown to be steadily affected by each
dose of vaccine.

Almost all patients, however ill,
show a definite reaction after each
dose. This is shown by rigor, sweating,
and rapid rise and fall of temperature.
During these reactions the pulse
rate does quicken but not so much
as would be expected from the
rise in temperature.

The blood after each injection
shows a temporary leucocytosis followed
within a few hours by a leucocytopenia
polymerphic in character.

The opsonic index after a
Temporary fall also rises reaching its maximum in a few days. If not affected by a second infection it falls steadily to normal.

The general improvement in the patient is usually greater than the fall in temperature would indicate.

Antigenous living vaccines, judging by the very few cases treated by myself, do not appear to give much better results than killed vaccines.

The difficulty of their preparation the case required, and the necessary delay before they can be administered are a distinct disadvantage, and are sufficient to prevent their universal use.

All new methods have been received with adverse public opinion until almost fully perfected.

Typhoid antitoxins, at first condemned,
has now won its place as an accepted fact.

Much work remains to be done before vaccines in the treatment of typhoid become established as a safe and reliable cure, but there is sufficient evidence to show that a large number of undoubted cures have already resulted from their use.

It is to be hoped that with greater knowledge our present lessons will be overcome and the vaccine treatment of typhoid will take its place as another example of the victory of science over disease.
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