THE CAUSATION AND PREVENTION OF ENTERIC FEVER IN MILITARY SERVICE.

WITH SPECIAL REFERENCE TO THE IMPORTANCE OF CARRIERS.¹

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(Continued from p. 665, Vol. XX.)

PART II.—THE TYPHOID CARRIER STATE AND PREVENTION OF ENTERIC FEVER.

HAVING dealt, in the preceding paragraphs, with the causation of enteric fever, it now remains to discuss its prevention in military service, with special reference to germ carriers.

This requires a consideration of the "typhoid carrier state," both in its acute and chronic manifestations, as well as of the means at our disposal for the detection and, if possible, the cure of these conditions; so that any subsequent recommendations may be made as a logical sequence to the conception we have formed of the nature of the problems involved.

Pathogenesis of the "Acute Typhoid Carrier" State.

The pathogenesis of the typhoid carrier state can only be adequately discussed in association with the question of the pathogenesis of typhoid fever, a question which still requires very careful examination. It was at one time assumed that typhoid fever was an intestinal disease. Sanarelli ² was, we believe, the first to oppose this view, and Houston ³ also expressed the opinion that the disease was a septicemia. We regard this view as now proved, but, while an adequate expression of the nature of the disease, it does not deal with the question of its pathogenesis. The latter problem is by no means settled, and until further experimental work is carried out we must retain an open mind on the subject. Certain points deserve special attention in this connexion.

1) Of a number of persons equally exposed to infection, only a certain number manifest the clinical phenomena of typhoid fever.

2) Apart from those who exhibit the disease in an acute form,
certain persons are infected with the bacilli and yet do not develop the clinical features of typhoid fever.

(3) The incidence of the acute disease is much higher amongst persons under 25 years than in persons over that age.

(4) In communities, such as regiments, exposed to infection, the incidence is greater where previous exposure to infection has been slight, less where previous exposure to infection has been considerable.

(5) The incubation period of the disease is quite clearly marked out from that of the zymotic diseases, properly so called, in that it varies within wide limits instead of being practically constant. It may be said to lie between seven and forty-five days.

(6) In practically all post-mortem examinations of persons dying of typhoid fever, the bacillus is found in the gall-bladder, either in the bile or in the wall of the organ, or in both situations.

(7) B. typhosus can be isolated from the blood of cases, practically constantly, at all periods previous to the formation of agglutinins in appreciable quantity, that is to say, up to the seventh day in ordinary cases, until much later in severe cases with retarded production of antibodies, and during relapses where the agglutinins undergo a temporary decrease.

(8) Coincident with the production of a high titre of agglutinins in the blood, B. typhosus disappears from the general circulation and is deposited in large quantities in the internal organs, especially the adenoid structures, the spleen, Peyer’s patches and the mesenteric glands.

(9) B. typhosus can be isolated from the faeces frequently during the incubation period (G. Mayer,¹ Conradi²) and in the early days of the disease, with difficulty during the height of the attack (probably owing to the enormous growth of other bacteria in the inflamed and abnormal intestine), and in a large number of cases during convalescence. It is unusual to find the bacillus in the urine in the early stages of the attack, but it can be isolated without difficulty from this source in over 30 per cent of cases from the end of the second week and onwards into convalescence.

Bearing these facts in mind, we submit the following as a tenable conception of the pathogenesis of the disease.

INCUBATION STAGE.

The organism after ingestion reaches the alimentary canal and gains the portal circulation through the intestinal wall and reaches the liver, whence such individual germs as escape phagocytosis and destruction gain access to the bile. Here they are safe from the action of the body-fluids, owing to the complement-fixing properties of the bile salts, and are able to multiply to some extent, passing with the bile into the duodenum, and thus again reaching the portal system and leading to fresh infection of the bile via the liver, until they attain sufficient numbers to compete successfully with the intestinal bacteria and reach the outside world in the feces (Precocious Carriers). One of two things may now happen.

INVASION.

(1) The vicious circle of increasing infection of the intestine from the gall-bladder, with reinfection of the gall-bladder from the intestine, via the liver, may outstrip the gradual production of antibodies, which has probably been initiated by the entry of the germs from the intestine into the portal circulation, in which case a typhoid septicemia will result and an acute attack of typhoid fever be produced; or

(2) The production of immune bodies may outstrip the increase of typhoid bacilli, in which case the infection will be gradually overcome. In this event, especially where there are slight structural lesions of the wall of the gall-bladder, due to calculi or some other cause, the B. typhosus, protected by the anti-bactericidal action of the bile, may establish itself in the gall-bladder without any successful invasion of the general circulation (thus producing the so-called Paradoxical Carrier), this condition being most likely to occur in later life, when the susceptibility to acute typhoid fever is lessened and the probability of the presence of calculi or structural lesions of the gall-bladder epithelium is increased.

In the cases of infection which pass into an acute attack of typhoid fever, the body will be called upon for a very high production of antibodies if recovery is to take place. As, however, the body has now to deal not only with an invasion of bacteria but also with the solution products of their body substance (toxins) it will be necessary to form not only antibacterial substances, such as opsonins and agglutinins, but also antitoxic substances. It is conceivable

1 Cummins, Journal of Hygiene, October, 1911.
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that the production of the latter class of substance may be in excess of that of the former, leading to a clinical recovery from symptoms without a complete elimination of the infective bacteria from the organs. This is probably the mechanism of the “relapse” which is so common in typhoid fever; but the same conception may help to throw light on the typhoid carrier state. One thing is certain that with the deposit of typhoid bacilli in the internal organs, which is coincident with the successful production of agglutinins and the clearing of the general circulation of germs, there commonly occurs an excretion of bacilli from the kidneys and intestine, which may last well on into and after convalescence (Temporary Carriers). Apart from the direct excretion from infected foci it is possible also that some cases of “temporary carrying” may be conditioned by a passage of bacilli from the spleen, through the splenic and portal veins, to the liver and thus to the bile, the latter being in this way kept infected as long as the spleen contains germs.

We may recall the fact that the above summary of the conditions which we believe to underlie the pathogenesis of typhoid fever, and to explain the various phases of “acute carrying” of the \( B. \) typhosus, although it covers the known facts, and is founded on conceptions that have been thoroughly established, is still a hypothesis only, but it forms a useful basis for the further consideration of the “chronic carrier” state which we now proceed to discuss.

**Pathogenesis of the “Chronic Typhoid Carrier” State.**

When the conception of the “chronic intestinal carrier” was first enunciated, it appears to have been assumed by many that “the infective germs might lead a saprophytic existence in the intestinal tract” just as \( B. \) coli is assumed to do; and this idea underlies some of the methods of treatment at first suggested for the condition. We may pause for a moment to consider to what extent the normal intestinal existence of \( B. \) coli may be compared to the abnormal presence of \( B. \) typhosus in the intestinal tract of man. In experiments, already recorded, on the viability of \( B. \) typhosus in food it may be noted that the milk used in two experiments was found, on examination, to contain large numbers of \( B. \) coli, and that a sample of liver and bacon, although cooked and examined just as it had been served at table, was found on incubation to contain \( B. \) coli, which subsequently grew out in large numbers. In fact this organism is constantly being reinforced in the intestines from the ingested food. Further, it finds in the intestine the
### S. L. Cummins

**FEEDING EXPERIMENTS.**

**Series I.**—White Rats on “Human” Diet.

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Time after the “75 million” feed</th>
<th>Stomach</th>
<th>Upper small intestine</th>
<th>Lower small intestine</th>
<th>Cecum</th>
<th>Heart blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat I</td>
<td>1½ hours</td>
<td>Numerous B. coli and B. typhosus</td>
<td>3 colonies of B. coli</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>II</td>
<td>5 &quot;</td>
<td>B. coli, B. typhosus</td>
<td>Sterile ..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>III</td>
<td>28 &quot;</td>
<td>Only 1 colony (B. coli) on agar slope. Plate sterile. Broth sterile.</td>
<td>B. coli (many), 4 small clear colonies. Not B. typhosus</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>IV</td>
<td>5 days</td>
<td>No colonies ..</td>
<td>B. coli (many), A few clear non-lactose fermenting colonies</td>
<td>Nearly a pure culture of a non-lactose fermenter. Not B. typhosus</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>V</td>
<td>Control (no B. typhosus given in food)</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>VI</td>
<td>“</td>
<td>6 clear non-lactose fermenting colonies (no typhoid)</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>Pure culture of non-lactose fermenters. Not B. typhosus</td>
</tr>
</tbody>
</table>

**Series II.**—White Rats on “Human” Diet.

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Time after “500 million” feed</th>
<th>Stomach</th>
<th>Upper small intestine</th>
<th>Lower small intestine</th>
<th>Cecum</th>
<th>Heart blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat VII</td>
<td>4½ hours</td>
<td>(1) Streptococcus, (2) Non-lactose fermenting colonies. Not B. typhosus</td>
<td>Streptococcus. B. typhosus</td>
<td>Small non-lactose fermenter, Not B. typhosus</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>VIII</td>
<td>28 &quot;</td>
<td>B. coli, Streptococcus</td>
<td>B. coli, Streptococcus</td>
<td>B. coli, Clear non-lactose fermenters. Not B. typhosus</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>IX</td>
<td>45 &quot;</td>
<td>B. coli (many)</td>
<td>A few coli, a few non-lactose fermenters. Not B. typhosus</td>
<td>A few coli, Some non-lactose fermenters. Not B. typhosus</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>X (Very ill)</td>
<td>1 week</td>
<td>B. coli, Streptothrix-like rod</td>
<td>Nocelli, Streptothrix</td>
<td>(1) B. coli, Colony Streptothrix non-lactose fermenter (Fluoresc.) Not B. typhosus</td>
<td>..</td>
<td>..</td>
</tr>
</tbody>
</table>

In Series I, 75,000,000 typhoid bacilli were mixed with the “feed” given to each rat. The animals were chloroformed and their intestinal contents examined by “plating” at varying intervals after the “feed.” In Series II, a larger dose, 500,000,000 bacilli, was given. In no case were the bacilli to be recovered later than five hours after the “feed.”
conditions natural to its growth and multiplication. Is this so with the *B. typhosus*? It certainly is not constantly reinforced by fresh contingents of germs ingested with food, and the experiments already detailed clearly show that the intestinal flora, especially *B. coli*, are definitely antagonistic to the survival of *B. typhosus* in the lower bowel. Even in the upper reaches of the small intestine, where the presence of bile is a great aid to the survival of this organism, there would appear to be strong antibacterial agencies at work. The experiments appended demonstrate that in the intestines of rats fed with emulsions of *B. typhosus* the organism is rapidly killed off, and cannot be isolated after eighteen hours, though recovered from various situations up to five hours after feeding. In these experiments, rats were chosen as resembling human beings in their varied diet, and the animals used were fed on "human" diet for a week before the experiment commenced in order to bring about an approximation to "human" intestinal conditions. The tendency of the stomach and small intestine to be sterile, or to contain only a few bacteria is to be noted and is quite in line with the known facts about the human alimentary tract. The large bowel is invariably teeming with bacteria, and appears to constitute a very efficient "septic tank" for the overgrowth and elimination of organisms such as *B. typhosus*, which are a source of danger when passed in the feces. We consider, then, that there is no analogy between the presence of *B. coli* in the intestines of normal persons and the existence of *B. typhosus* in the feces of typhoid carriers, and we believe that the word "saprophytic" in the latter connexion is misleading. We may, then, enunciate the proposition that in the typhoid carrier, whether intestinal or urinary, the *B. typhosus* leads a parasitic existence in infective foci in the tissues, and that the feces and the urine are merely vehicles for its transmission to the outer world.

The evidence in support of this proposition may be summarized under the following headings:

(1) Post-mortem and operation findings.
(2) Animal experiments.
(3) "Content" of the body-fluids in immune substances.
(4) Focal reactions following the inoculation of typhoid vaccine.
(5) Studies of the varying degrees of "excretion" by "carriers."

(1) Post-mortem and Operation Findings.

These are not yet sufficiently numerous to be regarded as final. On no occasion, as far as we can ascertain, have typhoid bacilli been
found in tissue lesions of the intestinal wall of chronic carriers, but
they are often found in the bile and frequently in the liver and in
the wall of the gall-bladder. They are also found in the small
intestine contents which they have obviously reached with the bile.
Ledingham quotes the results of three post-mortems (recorded by
Loele, Kamm and Gray) which all point to the biliary tract as the
site of the infection. In a recently recorded post-mortem on a
chronic intestinal carrier by K. Bernhuber1 the organism was
recovered from the liver and gall-bladder as well as from the
intestine. Here the wall of the gall-bladder is stated to have
been atrophied and the liver congested. The same phenomena
have been found constantly at operations, chiefly performed for the
relief of gall-stones. In operative procedures on urinary carriers, of
which several are on record, the condition has always been found
associated with tissue lesions, in the shape of small abscesses in
the kidney or ulcers of the urinary bladder; and in one kidney case
(Greaves),2 a phosphatic calculus was present.

(2) Animal Experiments.

Blachstein,3 Doerr,4 Forster and Keyser,5 Hailer and Rimpau,6
Morgan,7 and others have ascertained that, following the intra-
venous inoculation of living typhoid bacilli in rabbits, a condition
analogous to the typhoid carrier state may be initiated. The
arrestment and growth of the B. typhosus in the biliary tract seems
to be an almost constant sequence to the intravenous injection
of typhoid bacilli in rabbits.

Doerr was able to recover the bacillus from the gall-bladders of
animals so treated in nine out of ten experiments, from the 4th
up to the 120th day after injection. J. A. Johnston,8 in a recent
paper of the highest interest, recovered the organism from the
gall-bladder of rabbits similarly treated in ten out of eleven

1 "Typhusbazillenträgerin in einem Erziehungsinstitut," Münch. med.
Woch., February 13, 1912.
2 Calculus in Connection with Urinary Carrier." Greaves (1907), British
Medical Journal, ii, 1907, p. 75.
6 Hailer u. Rimpau, Arbeit. a. d. Kaiserl. Gesundheitsamt, Bd. xxxvi,
p. 407.
8 "Research on the Experimental Typhoid-Carrier State in the Rabbit,"
Journal of Medical Research, vol. xxvii, No. 5, p. 177.
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animals. The latter observer was also able to show that a secondary typhoid septicemia lasting for a considerable time (to 30th day) developed in about seven days after the intravenous inoculation. These facts point very distinctly to the gall-bladder as the site of multiplication of the *B. typhosus* in acute infections, and appear to favour the hypothesis as to the pathogenesis of the disease previously enunciated, but they might be taken to have a greater bearing on the "acute" and "temporary" carrier state than on the chronic type. Johnston, however, in the paper above quoted, makes the very important observation that while "the bile contains *B. typhosus* up to from thirty to sixty days after inoculation," the bacillus "would then appear to become attached to the gall-bladder wall." Now, J. Koch (1909—quoted by Ledingham 1) in investigating the histology of the gall-bladder in a fatal case of typhoid fever, reported that "the mucosa of the gall-bladder was very much corrugated and papillated, and near the extremities of the papillae typhoid nests were found with necrotic areas in their vicinity. The superficial epithelium had completely disappeared and there was a marked inflammatory proliferation of the submucosal folds. A conspicuous feature was the close relationship of these typhoid nests to the minute end-capillaries of the submucosal papillae, suggesting that the bacilli had reached this situation solely by way of the blood-vessels."

Has this any bearing on the work of Johnston? Why is it that after the bacilli have ceased to be found free in the bile of the experimental rabbits, they appear to "attach themselves to the wall of the gall-bladder"? And why does this occur from about the thirtieth day after inoculation and onwards? We shall return to this point, but we may here say that we believe these experimental infections of tissue to be of extreme significance as bearing on the evolution of the chronic carrier.

(3) "Content" of the Body-Fluids of Carriers in Immune Substances.

Various observers (Gaehtgens, 2 Ledingham, 3 Kennedy 4 and others) have recorded high opsonic indices in carriers, and both

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2 Gaehtgens (1910), Arch. f. Hyg., Bd. 72, p. 233.
3 Ledingham, J. C. G. (1908), British Medical Journal, 1908 ii, p. 1173.
agglutinins and bactericidins are also noted as being increased. Here the time-factor has to be taken into account as it is known that the immune substances resulting from an ordinary attack of the disease remain in decreasing quantities for many months. There is no doubt, however, that they tend gradually to disappear and that it is unusual to find them in high degree after from six months to a year from the attack. In our own experience, while the agglutinins usually fall to a low level, the opsonic index remains abnormal for protracted periods in the case of most of the carriers whose sera have been examined (vide pp. 59 and 61). There is, however, the undoubted fact that, in the case of one of the fecal carriers, even the opsonic index could not be claimed as abnormal on one of the occasions when it was worked out (Carrier F. C., on February 7, 1911), while the agglutinins had quite disappeared, although the patient was still excreting large numbers of bacilli. We regard this as merely the expression of the rule that where foci of bacterial infection are almost entirely cut off from the circulation antibodies tend to diminish. The fact that in the great majority of the cases investigated, and in all the urinary cases, the opsonic index was decidedly raised at periods amounting to years after the original attack, is very strong evidence that the *B. typhosus* exists, in these cases, as a parasite in the tissues, and not as a saprophyte in the cavities of the body.

(4) Focal Reactions to Inoculation of Typhoid Vaccines.

Irwin and Houston¹ and later Clemens and Dawson² have called attention to the focal pain and general disturbance following inoculation of "carriers" with vaccine for purposes of treatment. In a series of observations on Urinary Carrier F. I. (vide vol. xx, p. 647, Part D), we have noted that large inoculations of vaccine caused local pain and an increased excretion of urine, as well as tending to lead to a temporary increase in the excretion of germs. We would submit that these very definite focal phenomena following the inoculation of the specific germ point to a focal infection by that germ and are inconsistent with the saprophytic theory.

(5) Studies of the Varying Degrees of Excretion by Different Carriers.

If the *B. typhosus* existed as a saprophyte in the human intestine, it would be natural to expect that men living under identical

² Clemens and Dawson, *Journal of the Royal Army Medical Corps*, April, 1911.
conditions as to food, housing, exercise, and so on, would excrete
the bacillus in almost equal degree. A reference to Chart I
(Part I) will show that such is not the case. Taking the two
faecal carriers, S. and F. C., kept in the same ward and on the
same diet, living lives as closely similar as the organization of
a military hospital can make them, we find that Carrier S. gave
counts that amounted to hundreds of millions on fifteen out of
twenty observations, his average excretion amounting to about
250 million per gramme of faeces. In the case of Carrier F. C. the
counts were in millions or in tens of millions on eighteen out of
twenty observations, only twice attaining to hundreds of millions;
with an average of thirty-six millions per gramme. In short, the
excretion by Carrier F. C. was on a definitely lower scale than that
by Carrier S. The excretion by two other faecal carriers under
observation at the same time was very markedly intermittent, the
*B. typhosus* being isolated on one occasion only during three
months of constant observation of Carrier P., while there were
intermissions up to five weeks in duration in the case of Carrier L.
These differences in quantitative output of germs are easily ex­
plained on a basis of tissue infection of greater or lesser extent,
but it is almost impossible to explain them on the "saprophytic"
assumption.

*We conclude then that in faecal as in urinary cases, the typhoid
carrier state depends on focal infection of the tissues.*

**DETERMINING CAUSES OF THE "CHRONIC CARRIER" STATE.**

Before examining this subject in detail, we would bring forward
certain points which must be explained by any theory which is
intended to explain the state of chronic typhoid carrying.

(1) The work of Klinger (quoted by Ledingham)\(^1\) has shown
that "whereas amongst transitory carriers young persons form the
majority, among the chronic carriers, persons in middle age
and advanced life predominate markedly."

(2) The *B. typhosus* is not only present in the bile and in the
gall-bladder wall, but also has frequently been found in the interior
of gall-stones.

(3) There appears to be a very close association between the
carrier state and gall-stones. Gall-stone troubles were diagnosed in
13.6 per cent. of Klinger's chronic carriers.

\(^1\) "Report to the Local Government Board on the Enteric Fever Carrier,"
Dr. J. C. G. Ledingham, 1910.
There is a great preponderance of females to males amongst chronic typhoid carriers.

The association of gall-stones with the typhoid bacillus and with chronic carriers being so marked, it has been suggested that the gall-stones result from the action of the typhoid bacillus, an idea which appears to gain support from the fact that this organism can be isolated with great frequency from the interior of gall-stones. On the other hand there is the view, perhaps rather implied than expressed in the literature of the subject, that the presence of gall-stones initiates the chronic carrier state, but against this there is post-mortem evidence that some chronic carriers at least are free from gall-stones. It is significant that the conditions of age and sex associated with a preponderance of chronic carriers are just those associated with gall-stone formation. Schröder, who examined all patients dying in the Strassburg Hospital, found gall-stones in 12 per cent of all cases. There were only 2-4 per cent in patients under 20 years, the number gradually mounting until no less than 25-2 per cent were found in persons over 60 years old; 20-6 per cent of female bodies contained gall-stones as compared with 4-4 per cent of males, or nearly five to one, the proportion being highest amongst women who had borne children.

Now old age and "chronic carrying" are undoubtedly associated, while, in Klinger's research, there were found 183 female carriers to thirty-eight male, or nearly five to one—a figure that corresponds exactly with Schröder's sex-incidence of gall-stones. Much experimental work has been done as to the connexion between B. typhosus and gall-stones. It has been shown that the organism appears to penetrate into gall-stones allowed to remain in broth cultures of the germ (Gilbert and Fournier), and that B. typhosus can bring about a precipitate of cholesterin when grown in filtered bile (Bacmeister). That gall-stones can be, and are, produced by the vegetation of B. typhosus in the gall-bladder can hardly be doubted, but it seems clear that gall-stones can result from other causes than the B. typhosus. The connexion between the two seems, however, to be a very close one, and must be borne in mind in considering the pathogenesis of the carrier state.

We have already expressed the view that the B. typhosus uses
the bile as a medium in which to increase during the incubation stage of an acute attack. We have also mentioned the probability that when, during the attack, the organisms are collected in the spleen and abdominal lymphoid tissues, as well as in the small intestine itself, a passage of germs may take place from these sites along the splenic and portal veins to the liver and thus once more to the gall-bladder. None of these cases involve tissue lesions of the walls of the bile passages, but merely the collection and growth of the bacillus in the bile, where it is safe from the lytic action of the body fluids. But in speaking of the experiments of Johnston, which showed that in rabbits intravenously inoculated with typhoid emulsions, the bacilli "seemed to become attached to the gall-bladder wall" from the thirtieth to the sixtieth day after the inoculation, we laid stress upon the fact that at this stage a tissue-invasion had apparently taken place. To show that similar tissue invasions take place in typhoid cases, we cited the observation of J. Koch, who found, in an autopsy on a fatal case, that there were typhoid nests near the extremities of the submucosal papilla, in close association with the minute end capillaries, and suggesting that the bacilli had reached this situation through the blood-stream. We consider that when agglutinins have been formed in the course of typhoid fever, there is every chance that clumps of agglutinated bacilli may be arrested at this situation, being unable to pass the end-points of the minute capillaries. Such clumps are to be found in the spleen, lymphoid tissues and other internal organs at the same stage of the disease. In Johnston's experimental rabbits, the septicemia came to an end as a rule about the thirtieth day after inoculation, i.e., just at the time when the bacilli "seemed to become attached" to the gall-bladder wall. We think it probable that the gall-bladder wall, in these rabbits, was infected direct through its own vessels and not from the bile.1 Now the B. typhosus is not an organism that frequently tends to form pus. Nothing is more remarkable than the way in which the spleen and other heavily infected organs clear up after an attack without any suppuration. In the case of the gall-bladder wall, however, as in the case of the intestinal lymphoid tissue or of the renal epithelium,

1 More recent and not yet published experiments by the author lead him to think that this "attachment" of the bacilli to the gall-bladder wall is unconnected with infection through the blood-vessels, as he was able to demonstrate it in two rabbits on the thirty-fifth day after infection although there was no secondary septicemia in either animal, as proved by frequent negative blood culture.
the deposits are not really internal, but on the inner surface of a hollow organ. We regard the suppuration of Peyer’s patches as due to invasion of the congested tissue by intestinal organisms other than the typhoid bacillus. In the case of the gall-bladder wall and the renal epithelium, the sites of typhoid deposits may or may not be subject to mechanical irritation on the surface directed towards the cavity. Let it be noted that, in both situations, there is a tendency to lithiasis, liable to be increased in the course of typhoid fever by the deposit of cholesterol as a result of the presence of typhoid germs in the bile, or by the highly concentrated urine of pyrexia in the case of kidney infection. Or again, especially in the later periods of life, there may be pre-existing lesions in the walls of the gall-bladder or of the tubules and pelvis of the kidneys, which would permit of direct infection. Under these circumstances, it is not hard to understand that focal infections of the bile-area or in the kidneys must frequently occur in the course of typhoid fever. Such focal infections will be all the more common where mechanical irritation is supplied by the presence of biliary or urinary gravel or stones, or where there is pre-existing loss of surface in the walls of the cavities concerned—in other words, the determining factors for focal deposits are much more common in middle life and advanced age.

Again, the tendency to healing of such deposits will be greater where a good circulation of blood and a high vascularity of the tissues co-exist with an absence of local irritants such as lithic deposits. In other words, the tendency of youth and adolescence will be to temporary infections only, of middle life and old age to the formation of chronic foci of the typhoid bacillus; while the stasis of circulation of blood and the slowing of the passage of bile by tight-lacing, and in some cases the pressure of an enlarged uterus, will tend to make the female sex more liable than the male both to cholelithiasis and typhoid infections of the biliary area.

The extreme chronicity of these foci, however, and their obstinacy in the face of treatment, even where, as in vaccine-therapy, it can be demonstrated to have resulted in an increase of immune substances in the blood, marks them out from other chronic infections, and requires to be explained. We may find the explanation, perhaps, in the case of infections of the hepatic area and gall-bladder, in the anti-bactericidal action of the bile-salts while, in the case of the kidney, the effects of acid secretions in inhibiting the action of opsonins must be borne in mind as a possible explanation. This action of acids has been well shown by
Irwin and Houston and we have found support of their work in our own experiments. Once established, these foci probably tend to become so shut off from the circulation that there is the further factor of mechanical obstruction to the access of bacteriotropic substances, while the "aggressive" action of chronic purulent collections, recently laid stress on by Dudgeon may be yet another possible protection to the typhoid bacilli in the foci of infection.

As to the connexion of "chronic carrying" with gall-stones, we consider that the same conditions which lead to gall-stone formation also favour the formation of chronic foci of typhoid infection in cases where the specific germ happens to be present. The previous presence of gall-stones, leading to the mechanical production of loss of substance in the walls of the gall-bladder, will certainly favour the direct infection of these sites by bacilli present in the bile and may explain the origin of those chronic carriers who have never experienced an acute attack of the disease—the "paradoxical carriers" as they are called by Saquépéé. On the other hand, it is almost certain that typhoid infection of the bile may produce gall-stones, which in their turn will tend to make chronic the acute infections of the tissue of the gall-bladder wall arising, via the blood-stream, during acute attacks of the disease. So much for the bile. It must be remembered, in speaking of chronic carriers, that focal deposits of the bacillus can, and do sometimes, arise in sites other than the bile-area or the kidneys. The irregular distribution of these deposits makes it difficult to deal with them, but it is the case that they are generally in close connexion with bone or periosteum, in situations, that is, where the impact of bruises or blows is most resisted and therefore most effective in causing injury. It seems unlikely that such tissue-infections would be so, as it were, accidental in position unless there were some accidental basis for their development, such as the congestive after-effects of traumatic or other injuries.

To sum up, then, we regard the focal lesions in "chronic carriers" as due to the invasion, by the typhoid bacilli, of sites rendered vulnerable by some ancillary cause, either pre-existent or coincident with the typhoid infection. Such causes are most likely to occur in middle life or old age, are especially liable to be present in the bile-areas and in the kidneys, owing to the tendency, in these situations,

1 Lancet, January 30, 1909.
INTERMITTENCY OF EXCRETION.

Typhoid foci, like tubercle foci, may be described as "open" or "closed." Those carriers whose lesions take the form of periosteal deposits are quite harmless unless the abscess be opened for drainage. We have heard of a case in which such a "carrier," harmless for sixteen years after his acute attack, caused a fatal infection of his wife, who dressed the abscess after surgical interference. The majority of carriers, however, are naturally "open" because their lesions are upon the surfaces of cavities connected with the outside world. In these cases, there is a great tendency to variation in the number of germs excreted from the body, but whether the foci really "intermit" in the excretion of bacilli is open to question. In the case of urinary carriers, where the excretion of bacilli from the foci is practically equivalent to excretion from the body, since there is not the long period of destructive competition with other organisms which occurs in the intestine, the constancy with which the organisms can be isolated day after day is remarkable. The nearest approach to a negative result in our experience was that on four occasions there were no bacilli in 0.05 c.c. of urine—the amount plated—which is by no means equivalent to saying that there were no bacilli in the urine. It is, of course, possible that "pouching" of the infective foci may lead to an occasional intermission in excretion, but the point we wish to make is that urinary carriers appear to "intermit" much less frequently than fecal carriers.

In the latter, the question whether the typhoid bacilli are to be excreted from the body will depend largely on the time of exposure to, and the bacterial nature of, the competition with other organisms in the large intestine. Of course, the initial number of germs reaching the bowel with the bile will be a very important factor in their survival also, as numerical superiority has a great bearing on success or failure in the "competition" that we have mentioned. Let us turn first to the numbers of bacilli contributed by the infective foci. This appears to vary with conditions of bodily resistance. The number of germs excreted by Carrier F. I. (urinary) was much less when this man was quiet in hospital than when he was at large and engaged in hard work. In the same patient a most
interesting “reaction” increase of germs was also seen after each considerable injection of typhoid vaccine (vide vol. xx, p. 647, Part I), a phenomenon also noted by Irwin and Houston who suggested that, in this manner, the fact of “carrying” might be brought to light during an intermission. Carrier F. I. on one occasion absented himself without leave while under treatment, and went on a long search for work (he was, at the time, a pensioner, under treatment as a “special case”) ending up with a social evening and beer. On returning next morning, a sample of urine was taken which gave a count that was enormous compared to those made under hospital conditions, though very much below the counts obtained when the patient was engaged in work.

<table>
<thead>
<tr>
<th>Date of observation</th>
<th>Fiscal Carriers</th>
<th>Urinary Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W. S. 20.8.08</td>
<td>F. C. 10.3.08</td>
</tr>
<tr>
<td>1909—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>+</td>
<td>..</td>
</tr>
<tr>
<td>+</td>
<td>:</td>
<td>:</td>
</tr>
<tr>
<td>July</td>
<td>+</td>
<td>..</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>August</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>September</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

TABLE II.—PERSISTENCE IN EXCRETION BY CARRIERS.


### TABLE II.—Persistence in Excretion by Carriers.—Continued.

<table>
<thead>
<tr>
<th>Date of observation</th>
<th>Fecal Carriers</th>
<th>Urinary Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>October</td>
<td>+ + + - +</td>
<td>+ + - - + + +</td>
</tr>
<tr>
<td></td>
<td>+ + + + + + +</td>
<td>+ + + + + + +</td>
</tr>
<tr>
<td>November</td>
<td>+ + + + +</td>
<td>+ + + + + +</td>
</tr>
<tr>
<td></td>
<td>+ + + + + +</td>
<td>+ + + + + +</td>
</tr>
<tr>
<td>December</td>
<td>+ + + + + +</td>
<td>+ + + + + +</td>
</tr>
<tr>
<td>1911</td>
<td>+ + + + + +</td>
<td>+ + + + + +</td>
</tr>
<tr>
<td>1912</td>
<td>+ + + + + +</td>
<td>+ + + + + +</td>
</tr>
</tbody>
</table>

In a case recorded by Cummins it there were two long intermissions in excretion by a fecal carrier with distinct gall-bladder symptoms, each apparently initiated by a course of X-ray treatment, though on both occasions the excretion recommenced at a later date after the treatment had been suspended. These intermissions were in all probability due to an amelioration of the local conditions at the focus, which was not maintained.

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The Causation and Prevention of Enteric Fever

In a urinary carrier, then, a true cessation to excrete bacilli, especially if maintained for long, may be regarded as very hopeful as it almost certainly points to an amelioration of the local condition at the infective foci. In a faecal carrier, a prolonged intermission is probably due to the same cause, but in view of the small chance of survival in the bowel where the number excreted from the foci is small, a negative result of examination of the faeces must be regarded as of but little significance unless it is repeated on many occasions over a long period. In this connexion the limitations of technique must be borne in mind. It does not follow that because *B. typhosus* cannot be recovered from a mixed culture it is therefore absent. It may be that a dilution only just sufficient to give a "countable" plate of *B. coli* will be so high as to quite dilute out the small number of typhoid bacilli present.

We regard it as more than likely that many persons who have ceased to excrete bacilli even during long periods may still be carriers, though with few and not extensive lesions. Such persons may again become excretors if the local condition changes for the worse under circumstances involving fatigue or privation.

"DETECTION OF CARRIERS."

The final proof of "carrying" still rests with the detection of the *B. typhosus* in the excreta. In other words, we can only say that a man is a carrier when we have proved him to be an excretor. We are thus, at once, face to face with a limitation, since there is reason to believe that many carriers do not excrete under normal conditions.

Assuming that we are dealing with a carrier who is also excreting germs and that the only problem is to find them, our success will depend upon our skill in applying the technique at our disposal. The relative merits of different media have been discussed *ad nauseam*, and this essay, all too long as it is, shall not be further burdened with a reiteration of what has been so often and so well said before. We may, however, deal briefly with a few of the principles which underlie the attempts to separate the *B. typhosus* from other organisms.

(1) In dealing with solid media, it is established that the addition of 0.5 per cent of sodium taurocholate will inhibit for a time the growth of organisms other than those of the typhoid colon group.
The inclusion of one (or several) substances not acidified by the organism sought for but rapidly acidified by other organisms expected to be present with it will, in the presence of an indicator, lead to the organism sought remaining colourless, while the others produce a colour reaction with the indicator employed.

These two cardinal principles are applied in most of the media used for the isolation of *B. typhosus* from faeces. Where *B. coli* is present in much larger numbers than *B. typhosus*, attempts are made to retard the growth of the former while not interfering with the latter organism. The most successful achievement in this direction has been the introduction of "brilliant green" by Conradi. The point here is that *B. coli* is only retarded, not entirely inhibited, and this involves a very early examination of the plates. Unfortunately, in our experience, *B. typhosus* is also retarded to some extent. The modification of Fawcus,1 while clearly differentiating the two organisms, owing to the lactose which it contains, should perhaps, be classed with the differential media properly so called, rather than with the inhibitory.

There remains the method of "enrichment" of *B. typhosus* in a mixed culture, either by increasing its growth as compared to other organisms present, or inhibiting the growth of other organisms while not retarding *B. typhosus* to the same extent.

This line of research involves a preliminary growth in a fluid medium with subsequent plating on a differential solid medium. In the case of the *B. typhosus*, the usual enrichment method of growing the faeces in a fluid medium containing a substance fermented by the organism which it is sought to increase, but not fermented by those that it is desired to retard, is inapplicable, as the substances acidified by *B. typhosus* are also strongly fermented by *B. coli*. It is necessary, therefore, to work on the line of retarding the growth of *B. coli* while not retarding *B. typhosus*. This object is obtained to some extent by malachite green broth, and we have tried a "brilliant green" bile-salt broth with results that were at the time regarded as promising. Our experience in this line of work is not yet sufficient to justify definite conclusions, but we think that, on theoretical grounds, it certainly offers a prospect of success. It is necessary to subculture on to plates after a short period of incubation and to take the upper layers of the fluid only.

All the methods mentioned will be successful if properly used. The points to be borne in mind in direct "plating" of faeces are:

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1 *Journal of the Royal Army Medical Corps*, vol. xii, p. 147.
The Causation and Prevention of Enteric Fever

(1) That the emulsion should be thin—about 1 per cent of faeces in the diluent answers well, but the worker soon learns to judge the proper consistency with the eye; (2) That the emulsion should stand for some little time, say half an hour, before it is plated; (3) and that the plates should be thoroughly dry before use. In examining colonies, it is well to subculture each suspected colony in broth and glucose peptone water with a fermentation tube, and also on an agar slope. The glucose tube, if acidified without formation of gas, gives valuable evidence in favour of the colony being *B. typhosus*, while the addition of 0·1 c.c. of a known anti-typhoid serum to the broth tube (which contains approximately 10 c.c.) will give a serum dilution of 1 in 100, which rapidly agglutinates the culture if it is the specific germ. The agar slope is still available for a complete examination of all suspected strains.

The procedure is thus quite simple where the *B. typhosus* is present in fair numbers. Where, however, it is greatly outnumbered by *B. coli*, it may be diluted out before discrete colonies of the latter organism are obtained, and the difficulty of finding it may be very great.

The observer should then aim at increasing the relative number of *B. typhosus* in the stools. This may be done by decreasing the time of transit through the large intestine by a smart purge, the second or third stool after the dose being most likely to give successful results. We strongly recommend that where a person is suspected, on epidemiological grounds, of being a "carrier," and the preliminary examination has proved negative, a dose of 1,000 million dead bacilli be injected as a test. This will, we believe, often give rise to a diagnostic focal reaction in the form of pain referred to the gall-bladder or kidneys, while an examination of the excreta carried out within the subsequent twenty-four hours will frequently give a positive result. If the direct search for *B. typhosus* fail, it is unlikely that the patient is causing infection at the moment, but the question of intermission again comes in and it is highly desirable that other methods should be invoked to supplement the examination of the excreta in doubtful cases.

There is also the need for some rapid and rough test, less complicated than the direct examination of the dejecta, where the problem is to find the carrier amongst a number of suspected persons.

It is usual in this case to apply the "Widal" reaction, and to select those who give a positive result for further examination. This test should always be applied in such cases, but its results are
### TABLE III.—TYPHOID AGGLUTININS.

_S. L. Cummins_ 59

**September 8, 1909.**

| Serum of five typhoid carriers tested against a laboratory and autogenous strains | Serum dilutions |
|---|---|---|---|---|---|---|---|---|
| **Date of attack** | **Carrier** | **F.I.** | **Urinary** | **F.S.** | **Urinary** | **F.C.** | **Fecal** | **W.S.** | **Fecal** | **F.L.** | **Fecal** |
| | | Lab. strain | F.L. strain | F.S. strain | F.S. strain | Lab. strain | F.C. strain | Lab. strain | F.C. strain | Lab. strain | E. strain |
| 12.5.04 | Lab. strain | ++ | ++ | ++ | + | ± | - | - | - | - | - |
| 20.5.08 | Lab. strain | ++ | ++ | ++ | + | ± | - | - | - | - | - |
| 10.3.08 | Lab. strain | + | ± | - | - | - | - | - | - | - | - |
| 20.8.08 | Lab. strain | + | ± | - | - | - | - | - | - | - | - |
| 11.4.07 | Lab. strain | + | ± | - | - | - | - | - | - | - | - |
| 10.3.08 | F.C. strain | + | ± | - | - | - | - | - | - | - | - |
| 20.8.08 | W.S. strain | + | ± | - | - | - | - | - | - | - | - |
| 11.4.07 | E. strain | Not carried out. | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; |

In the above table the agglutinins of both the urinary carriers are seen to be higher than those of the faecal carriers, the agglutinins of the latter being negligible in quantity.

### TABLE IV.—TYPHOID AGGLUTININS, DECEMBER 2, 1909.

| Serum of three faecal carriers, against laboratory and autogenous strains | Serum dilutions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Carrier** | **F. C.** | **W. S.** | **F. L.** |
| **Date of attack** | 10.3.08 | 20.8.08 | 11.4.07 |
| **Lab. strain** | + | + | + |
| **F. C. strain** | + | + | + |
| **W. S. strain** | + | + | + |
| **F. L. strain** | + | + | + |

This table again brings out the fact that these three faecal carriers had little or no power of agglutination for *B. typhosus*. The laboratory strain used was notoriously easy to agglutinate, and therefore constituted a delicate test.

### TABLE V.—“IMMUNE BODIES” IN SERUM OF TWO CARRIERS (PARATYPHOSUS A.) AGGLUTININS.

<table>
<thead>
<tr>
<th>Serum dilutions</th>
<th>1/10</th>
<th>1/20</th>
<th>1/50</th>
<th>1/100</th>
<th>1/200</th>
<th>1/500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal (Para. A) Carrier C---r</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urinary (Para. A) Carrier C---t</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>±</td>
</tr>
</tbody>
</table>
The Causation and Prevention of Enteric Fever

by no means conclusive. It will furnish valuable information, where a positive reaction is obtained, but a negative result may be, and often is, given by a chronic carrier. Tables III and IV demonstrate conclusively that chronic faecal carriers may be excreting large numbers of typhoid bacilli and yet give a practically negative reaction. The urinary carriers examined by us gave positive "Widals" in every case, and always in higher dilutions than the faecal carriers. Of special interest is Table V, showing the agglutinins of two B. paratyphosus A carriers, the one faecal and the other urinary. Although the latter was not excreting the germ on the day of observation, his serum was positive to a dilution of 1 in 80 for the specific organism, an unusually high titre for B. paratyphosus A, a germ notoriously unable to evoke the formation of "high" agglutinins even in acute cases. The serum of the faecal carrier, though he was excreting the germ, failed to agglutinate it above a dilution of 1 in 4. To sum up, we recommend that in the search for carriers by means of the Widal reaction, even very "low" positive results should be regarded as suspicious, and the possibility of a negative Widal in a chronic carrier be borne in mind. In such an investigation, where the "Widal" has failed to give a satisfactory indication, we think that the injection of typhoid vaccine should be carried out in all suspected persons as a diagnostic measure, just as tuberculin injections are used to detect animals suffering from latent foci of the disease. The elicitation of focal pain may give a valuable indication for further examination of some of the persons while the others will benefit by the acquisition of immunity conferred on them by the diagnostic inoculation. Although too elaborate to be applied on a large scale, the calculation of the opsonic index is likely to give more information than any other serological method. It should always be applied where it is a question of deciding whether a man is still a carrier and where the direct search for the organism has proved negative. Great difficulties and many fallacies surround the application of Wright's method in the case of the typhoid bacillus, but the method of Klien is likely to give satisfactory results. This method, however, is laborious and requires some practice. For the mere question whether specific opsonins for B. typhosus are present in a serum or not, a much less lengthy procedure is sufficient. It is well to inactivate the non-specific opsonins either by heating the

S. L. Cummins

Serum to 58° C. for twenty-five minutes or by leaving it standing for a week, the normal control serum being treated in the same way. A comparison of the two sera, diluted to 1 in 3 with saline, a fairly thick emulsion of the bacillus being used, will almost invariably show the presence of specific opsonins in the sera of typhoid carriers. We show the results of some observations in Tables VI and VII, and would especially refer the reader to the series of observations, by Klien's technique, on the serum of Carrier

### TABLE VI.—Typhoid Opsonins. Fecal Carrier F.C.

<table>
<thead>
<tr>
<th>Description of carrier</th>
<th>Serum—how treated</th>
<th>Date of observation</th>
<th>Typhoid strain used</th>
<th>Phagocytosis</th>
<th>Cells counted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier F.C.</td>
<td>Unheated. Diluted 1-5</td>
<td>5.10.10</td>
<td>&quot;F.C.&quot;</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Ditto</td>
<td>Ditto</td>
<td>5.10.10</td>
<td>Laboratory strain</td>
<td>45</td>
<td>27</td>
</tr>
<tr>
<td>Ditto</td>
<td>Unheated. Six days old. Diluted 1-3</td>
<td>12.10.10</td>
<td>Freshly isolated strain &quot;M.E.&quot;</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td>Ditto</td>
<td>Unheated. Diluted 1-3</td>
<td>7.2.11</td>
<td>&quot;F.C.&quot;</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>Ditto</td>
<td>Heated. Diluted 1-5</td>
<td>8.3.12</td>
<td>&quot;F.C.&quot;</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Ditto</td>
<td>Unheated. Diluted 1-3</td>
<td>13.1.11</td>
<td>Virulent strain E.</td>
<td>86</td>
<td>35</td>
</tr>
<tr>
<td>Ditto</td>
<td>Heated. Undiluted 13.1.11</td>
<td>13.1.11</td>
<td>Virulent strain E.</td>
<td>37</td>
<td>17</td>
</tr>
</tbody>
</table>

### TABLE VII.—Typhoid Opsonins.

<table>
<thead>
<tr>
<th>Description of carrier</th>
<th>Serum—how treated</th>
<th>Date of observation</th>
<th>Typhoid strains used</th>
<th>Phagocytosis</th>
<th>Cells counted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier M. F.</td>
<td>Heated. Undiluted 1909</td>
<td>M. F.</td>
<td>258</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Ditto</td>
<td>Heated</td>
<td>10.6.10</td>
<td>&quot;F.&quot;</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Ditto</td>
<td>Unheated. Undiluted 10.6.10</td>
<td>&quot;F.&quot;</td>
<td>609</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>Carrier X.</td>
<td>Serum six days old. Diluted 1-3. Unheated 12.10.10</td>
<td>Freshly isolated strain M.E.</td>
<td>78</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>Carrier Capt. S.</td>
<td>Unheated. Diluted 1-3</td>
<td>8.1.11</td>
<td>Virulent strain E.</td>
<td>269</td>
<td>196</td>
</tr>
<tr>
<td>Carrier H.</td>
<td>Serum four days old. Unheated. Diluted 1-3 5.1.11</td>
<td>Freshly isolated strain &quot;B.E.&quot;</td>
<td>48</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Carrier P.</td>
<td>Unheated. Diluted 1-3</td>
<td>30.1.11</td>
<td>Virulent strain E.</td>
<td>160</td>
<td>133</td>
</tr>
</tbody>
</table>
F.I., "charted" after the method of Cummins and Cumming to show graphically the opsonic content of the serum on each day of observation (Chart II). If due regard be given to the period that has elapsed since the acute attack the presence of considerable specific opsonin in the serum of a suspected person is, in our opinion, almost diagnostic of the "carrier state." A negative result, though uncommon, is still possible, as is shown in one of the observations on the faecal carrier, F.C.

The Possibility of Cure.

Although a limited number of cases have been claimed as "cured" by direct interference, there is as yet no evidence to show that any known therapeutic measure is a cure for the typhoid carrier state. Having made this admission, we do not propose to discuss the relative demerits of the methods so far devised for the treatment of this condition. Suffice it to say that while lactic acid bacilli, urotropin, salol, Röntgen rays, and even chloroform injections per rectum (the last, so far as we know, in experimental animals only) have all given encouraging results, they have not proved of any real value in curing the chronic carrier. Antityphoid vaccine, too, though several cures are attributed to its use (Irwin and Houston, Clemens and Dawson, &c.), has signally failed in a large number of cases. We propose, however, to discuss the last method, as there is reason to believe that it is the only line of treatment that at present offers any prospect of success. There is one encouraging fact to be remembered. It is that, while there is no distinction to be drawn between the protracted "temporary carrier" and the "chronic carrier" except the arbitrary time-limit of "three months," the former cease spontaneously to excrete bacilli in a large majority of cases. There is again the fact that an accession of health such as may result from a sea-voyage sometimes leads to a cessation of excretion of germs. We are aware of several cases where men, invalided from India as "chronic carriers," have been found no longer excreting on their arrival in England, though very carefully examined on a series of occasions. These facts point to a tendency to a natural cure of the typhoid carrier state where this has not become absolutely established.

We are, therefore, inclined to think that continued use of vaccine, combined with attempts to alkalinize the urine as recommended

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1 Journal of the Royal Army Medical Corps, October, 1912.
CHART II.—Chart (after Cummins and Cumming) showing Opsonic Indices (Klien), given by the Serum of Urinary Carrier F.F. (during course of vaccine therapy).

Horizontal measurements represent number of bacteria per phagocyte. Vertical measurements represent the dilutions of serum used.
by Irwin and Houston, where the patient is of the urinary type, may possibly succeed if applied fairly early in the case. To give this treatment a fair chance, the carrier should be detected during convalescence and steadily treated from that time onwards. Once the lesions become shut off from the access of bacteriotropic substances by chronic inflammatory processes, the chances of successful vaccine therapy are greatly reduced, and may be regarded as non-existent where some deposit such as a calculus helps to perpetuate the mischief by mechanical irritation. The researches of J. A. Johnston, already quoted, on the typhoid carrier state in rabbits, are distinctly hopeful for the success of vaccine therapy if undertaken early in the case. Of eleven untreated rabbits killed at varying intervals after intravenous inoculation of *B. typhosus*, ten were found to harbour the germ in the bile or gall-bladder wall or both. Of seven animals inoculated at the same time with a similar dose of *B. typhosus*, but subsequently treated by the injection of vaccine, two only were found to harbour the bacillus, one of these being examined only two days after vaccination. Five out of seven were clear of the typhoid bacillus.

Our own results in the case of Carrier F.I. (*vide* Chart II) were discouraging. The injections were not followed by any rise in the titre of opsonins. The result, as to the excretion of germs, was merely to lead to a reactionary increase where large doses were given.

Operative treatment holds out a distinct promise of success where one kidney only is involved, but in the case of infection of the biliary tract, removal of the gall-bladder or of gall-stones will often be disappointing, as there is nearly always coincident infection in the liver and parts of the bile area out of the reach of operative interference.

Where vaccine therapy and operative procedures fail or are contra-indicated, it must be admitted that no known remedy exists. We can only wait for the discovery of some drug which, as salvarsan for syphilis, will be parasitotropic but not organotropic.

**Prevention of Enteric Fever with Special Reference to "Carriers."**

Deducting the number of men invalided and dying as the result of enteric fever, the British Regular Army may be taken to produce, each year, from 300 to 500 men who, having recovered from the disease, are again serving with their units. Multiplying the
lesser figure by the average colour-service of the soldier, subsequent to the attack, say, seven years, we infer that about 2,100 men are to be found in the ranks, at any given time, who have had enteric fever. How many of these may we expect to be chronic carriers? Observers differ markedly as to the percentage of acute cases that pass on into the chronic carrier state, some putting it as high as 5 per cent, others as low as 1 per cent. Allowing for the fact that people of advanced age and females—the classes most prone to become carriers—do not come into consideration in military service, we may place the actual number of "chronic excretors" at about 1 per cent, giving about twenty-one such persons as constantly present in the regular army in peace. We have already expressed the opinion that the mere fact of "excretion," the basis on which all figures as to the percentage of chronic carriers are founded, does not necessarily or probably give a true index of the number of persons actually carrying the germ. It is likely that, under conditions of active service, a number of men who have suffered from enteric fever would become active excretors. There is also the question of the reservists who join the colours on mobilization, and who, being older men, are likely to include a higher percentage of carriers than that just given. In addition to the chronic carriers, there are certain to be a fair number of temporary carriers as well as a proportion of men actually in the incubation stage of the disease and who will develop it later on. It is obvious, then, that while the "carriers" are not a very serious matter in times of peace, they will assume great importance in time of war. We have already devoted considerable space to this question and need not return to it in detail, but it is necessary to bear the extent of the problem in mind in considering methods of prevention. Let it be but remembered that "contact infection" has been proved to be the main source of the prevalence of enteric fever in war and that enteric fever has always been "the scourge of armies in the field," and the importance of the "carrier question" will be evident.

Leaving out of consideration the routine methods of general hygiene, the prevention of "contact" or "carrier" infection must be considered under three headings:—

(1) The discovery and disposal of "chronic carriers" who are likely to initiate epidemics.

(2) The detection of early, atypical and abortive cases, and the disposal of convalescents, who are certain, if undetected, to maintain epidemics.
66 The Causation and Prevention of Enteric Fever

(3) The rendering of healthy persons immune to the disease.

We make no attempt, in this essay, to deal with the disposal of excreta, the sterilization of water supplies, or the measures to be taken to protect food from infected dust and flies. All these questions are of vital importance in rendering harmless the undiscovered carriers that must always be present, but our concern here is with the carriers themselves.

(1) The Discovery and Disposal of Chronic Carriers.

This should be carried out in peace in order that the army may take the field with as few “carriers” as possible within its ranks.

The procedure that should be followed throughout the army has been already initiated in India. It seems illogical that the splendid work of the Enteric Convalescent Depot at Naini Tal should not have already led to the formation of similar institutions outside India. We should recommend that in all foreign stations where the garrison exceeds a certain strength—say 2,000 troops—there should be a depot for enteric convalescents under the charge of a “specialist” officer, trained in the bacteriological study of enteric fever. This officer should be regarded as the pathologist of the command also, where the work of the depot is not so heavy as to justify a whole-time worker. To deal with convalescents from foreign stations with garrisons below this strength there should be a “Home Depot” at some such place as Netley, to which all enteric convalescents should be sent. This station would also dispose of “carriers” sent home from the other depots, and receive convalescents from military hospitals in England. The duties of this central Home Depot would be arduous, and would require the whole time of one officer, under whom the clinical pathologist at Netley might serve as an assistant when available. We would further recommend that all “temporary” and “chronic” carriers regarded as cured and returned to the ranks should be “followed” during at least a year after return to duty, samples not only of faeces, but of blood being sent either to the depot at Netley or the Royal Army Medical College for examination. Where “immune bodies” were found to persist for many months in the blood, the soldier should be invalided. A negative result in a sample of faeces sent by post means very little where twenty-four hours or more have elapsed since it was passed, on this account a blood sample is advisable. No enteric convalescent
should return to the ranks without having passed a period at a convalescent depot and being certified as no longer excreting germs.

(2) The Detection of Early, Atypical and Abortive Cases.

In peace this should be, and is, fairly successfully carried out. It is another matter on active service. We believe that there is too great a tendency to regard bacteriological work as “out of place” on actual active service. There is no sanitary measure more important to a commander than the early diagnosis of enteric fever cases. If this is successfully carried out, and the methods of observation and isolation of “contacts” laid down in “R.A.M.C. Training” are honestly and thoroughly observed, we see no reason why enteric fever should prevail in the future to anything like the extent that it has done in the past on active service.

The early diagnosis of typhoid fever is a matter of blood-culture. This requires skill, care, and deliberation, but not an elaborate outfit of bacteriological appliances. Our idea is that a mobile “laboratory,” consisting of a closed motor vehicle, containing the apparatus for preparing media, incubating “cultures,” and for the necessary microscopic and other work of isolating bacteria, should be attached to each division and accompany this formation as part of the Divisional Headquarters. A specially trained officer with two trained orderlies (one as batman) and a driver (A.S.C.) should constitute the staff. Regimental medical officers and officers commanding field ambulances should be directed to co-operate with this officer by sending to him all suspicious cases for blood-culture and such other work as may be necessary. At present this work is allocated to the Laboratory at the advanced Base or Rail Head. [Vide R.A.M.C. Training Para. 147 (iii)]. Our plea is for a Mobile Laboratory marching and working with the divisions.

During active operations, convalescent enteric cases should invariably be invalided to home territory, and should not rejoin the colours until certified “safe” by the Central Home Depot. The numbers so invalided would be comparatively few if the measures already mentioned had been thoroughly carried out.

(3) The Rendering of Healthy Persons Immune to the Disease.

This is a matter of inoculation with anti-typhoid vaccine. We realize that it is impossible to carry out this procedure effectually on mobilization. Medical officers would then be too busy for the enormous mechanical operation of inoculating 168,000
men, and the men themselves could not be made available at such a time.

There is only one possible solution of the difficulty—*the inoculation of all troops of the expeditionary force in peace*, and a thorough organization for the inoculation of all "drafts" proceeding to the scene of operations during war. The necessity for inoculation of the Territorial Force on mobilization will be apparent when it is recalled that this force will be accommodated in billets in the home territory. The results of anti-typhoid inoculation speak for themselves. The consequences of sending out large numbers of young soldiers at the most susceptible age, to be exposed to the intensive infection that has, so far, always existed on active service, can be studied in the Medical History of the South African War and other campaigns. If the remedy—general immunization—is at all possible, it should be applied.