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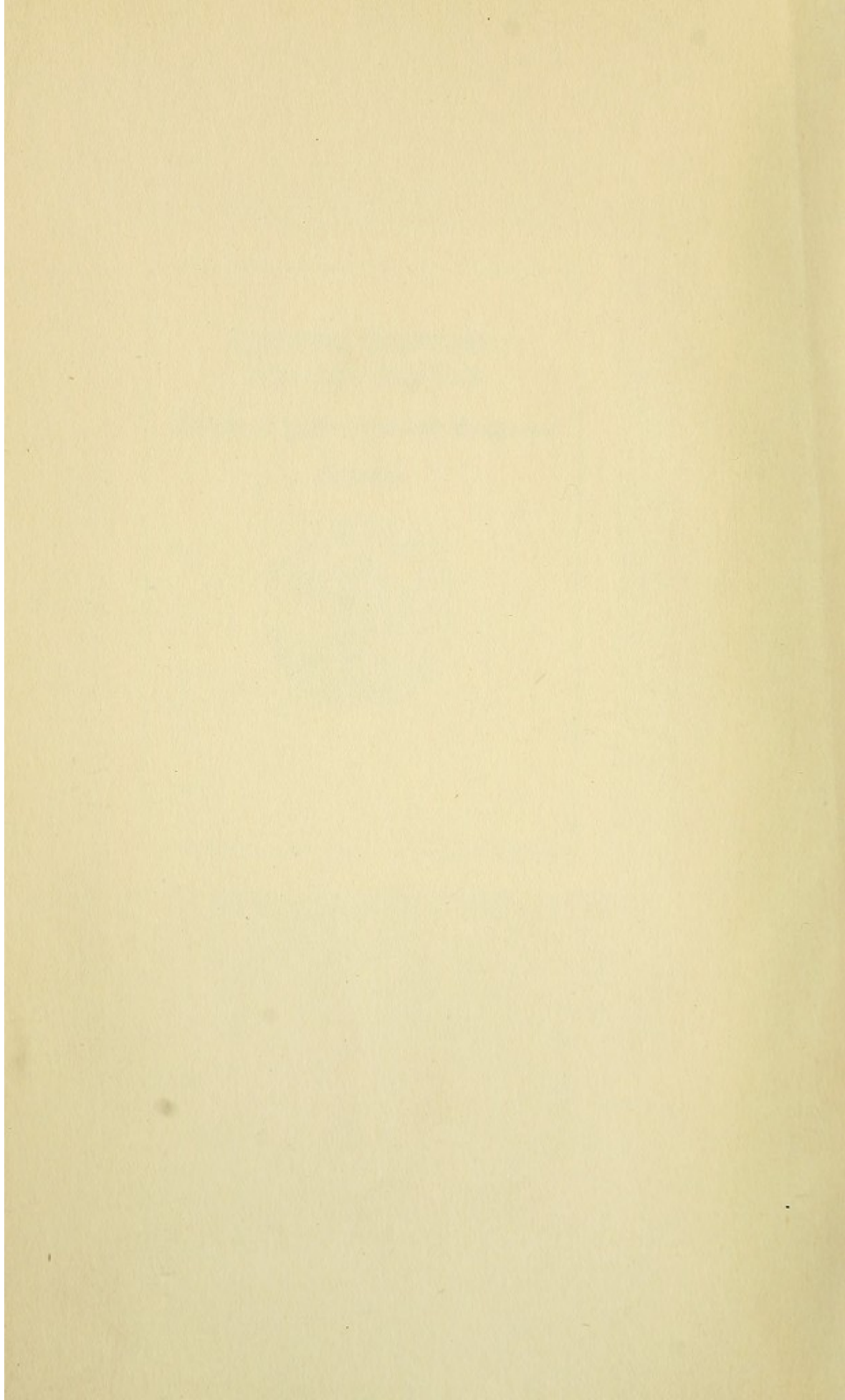
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RECENT PROGRESS
IN THE
BACTERIOLOGY OF TYPHOID FEVER.

By MARK W. RICHARDSON, M.D.
OF BOSTON.

Read at the Annual Meeting of the Massachusetts Medical Society,
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RECENT PROGRESS IN THE BACTERIOLOGY OF TYPHOID FEVER.

It is nearly twenty years since Eberth, after a most elaborate series of pathological and bacteriological observations, first claimed to have established an etiological relationship between the so-called typhoid bacillus and the disease-condition known as typhoid or enteric fever. To-day we know that the claim of Eberth was justified. There are few of us, I think, however, who realize the immense amount of scientific labor which has been necessary to solve this great medical problem. To be sure, the fact that typhoid fever is, in practically all cases, associated with the presence in the body of the typhoid bacillus, has been confirmed by many observers since Eberth. Moreover, the biological characters of the new organism have been very thoroughly studied, but these observations, while extremely important and interesting in themselves, failed by far to establish incontrovertibly a specific relation between the bacillus and the disease.

The difficulties to be overcome have been many. In the first place, no animal has been found capable of developing a typhoid infection similar to that seen in human beings. To be sure, guinea-pigs, rabbits, and other animals succumbed rapidly as the result of inoculation with cultures of the typhoid organism, but at the post-mortem examination the pathological findings were those simply of a toxæmia, a septicæmia, or a combination of these two conditions,

and the production of anything resembling intestinal ulceration was of the rarest occurrence. Moreover, exactly similar results could be obtained by inoculation with cultures of the *bacillus coli communis*, the ordinary inhabitant of the intestine, so that the evidence of any action characteristic for the typhoid bacillus was entirely lacking. Furthermore, the resemblance of the typhoid bacillus in many of its characters to the *bacillus coli communis* led many to maintain that the new organism had no distinct entity, but was merely the colon bacillus altered as to its characters and virulence by external conditions.

Direct animal experimentation, therefore, failed to furnish convincing proof that the new bacillus was the specific cause of typhoid fever, and the solution of the problem devolved upon the more indirect methods pursued in studies upon typhoid immunity.

In these studies upon typhoid immunity the name of R. Pfeiffer of Berlin stands out pre-eminent, and the results obtained have been of the greatest possible interest and value.

As has already been said, the typhoid bacillus, in sufficient doses, is pathogenic for a number of the experimental animals. If, however, the animal is inoculated with small and gradually increasing doses, death does not follow, but the animal finally reaches a point where it can bear without detriment doses which would be certainly fatal to animals unaccustomed to the typhoid poison. In other words, the animal has become immune as far as the typhoid bacillus is concerned, and its condition resembles exactly that of a human being convalescent from typhoid fever or any other disease which carries, with a single infection, freedom from a future attack.

The next point of interest to be brought out was the fact that the blood of an animal made thus artificially immune to typhoid infection, when injected into a second animal,

protected the latter from the otherwise fatal consequences of subsequent typhoid inoculation.

There are, therefore, in the blood serum of typhoid immunes very powerful protective agents. They are styled by Pfeiffer "antikörper," or antagonistic bodies. They are not in the nature of antitoxines, however, but produce their curative effect by actual destruction of the bacteria themselves.

This bactericidal action was demonstrated by Pfeiffer in the following manner :

He first injected into the peritoneal cavity of guinea-pigs a certain amount of typhoid culture, and found that the organisms multiplied rapidly, finally producing the death of the animal.

If, however, he introduced together with his culture a certain amount of blood serum from an animal made immune to typhoid, the organisms, instead of multiplying rapidly, lost their motility, became clumped together, swelled up, and finally, breaking up into small granules, disappeared. Furthermore, under these circumstances the life of the animal was preserved.

Moreover, Pfeiffer demonstrated the fact that this reaction was specific ; that it took place only when a special organism was treated with its own corresponding serum ; that a similar relation existed between cholera vibrios and cholera serum ; that typhoid serum had no effect upon cholera vibrios, and *vice versa*, cholera serum had no effect upon typhoid bacilli.

It remained only to see whether the serum of a human being convalescent from typhoid fever would not, when brought in relation with the typhoid bacillus, have protective and bactericidal properties similar to those exhibited by the serum of animals artificially immunized to the typhoid organism, and such has been found to be the case, the bacilli becoming clumped together and finally destroyed.

This specific immunity reaction of Pfeiffer has, therefore,

not only differentiated absolutely the typhoid bacillus from the colon bacillus, but also has fastened the responsibility for the disease typhoid fever upon its true cause, the typhoid bacillus.

Indeed this specific reaction has been of great use in other directions. It is the very foundation of the Widal serum test, which is now so extensively used in the diagnosis of typhoid fever.

As is now well known, this new procedure enables us in most cases to make an absolute diagnosis of typhoid fever as early as the tenth or twelfth day of the disease. In a few cases, however, the blood changes necessary for the reaction do not occur till the later stages of the malady, until convalescence, or perhaps until the occurrence of a relapse. A negative result with the serum test, therefore, carries with it little if any diagnostic value. In such cases we may have recourse to the examination of the stools for the specific bacillus, and with very fair prospect of success.

The most recent work in this line has been done by Hiss, of the New York Department of Health. Hiss has devised a special medium for the work, and has been able to isolate the typhoid bacillus in fifty per cent. of cases where a single examination of the stools was made, and in about ninety per cent. of the cases where repeated examinations were possible. The New York Board of Health now uses this method of diagnosis to supplement the serum test, and considers it of great value.

From what has been said, it is easy to see the very important part which bacteriology has played in fixing the etiology and in furthering the early diagnosis of typhoid fever; but the radiation of our knowledge of the disease has by no means been confined to these two directions. Indeed, as a result of modern investigation, we must modify very largely our conception of the typhoid process. For instance, we now know that a typhoid infection may take

place with no involvement whatever of the intestinal tract. In all these cases there had been a positive serum reaction. Such cases have been published by Guarnieri, Kühnau, Flexner and others, in which, at autopsy, the intestine was found intact, and which were, nevertheless, undoubted typhoid infections, as proved by the clinical course and serum reaction during life, and the isolation of the typhoid bacillus from the organs after death.

Furthermore, the discovery of the specific typhoid germ suggested immediately a possible etiological relation between it and the various conditions complicating or following typhoid fever, and it has been definitely shown that a considerable proportion of these associated affections are due to secondary invasion by the typhoid bacillus.

We must, therefore, in the light of our present knowledge, recognize peritonitis, pleurisy, cholecystitis, meningitis, parotitis, prostatitis, epididymitis, orchitis, periostitis, and osteomyelitis, as being in many cases essentially typhoidal in character.

In other cases, to be sure, we do *not* find the typhoid bacillus, but other organisms, notably staphylococci and streptococci, and this fact has led some observers to the belief that pus cocci are always present in these conditions at some period of the process, and that the typhoid bacilli are simply secondary invaders. The extremely elaborate experiments of Dmochowski and Janowski, however, have proved, as it seems to me, almost absolutely that the typhoid bacillus can become a pus producer, and this fact, coupled with the utter failure to find in inflammatory exudates any organism other than the typhoid bacillus, must be taken as conclusive proof that the typhoid organism is the cause of the pathological condition.

These sequelæ and complications of typhoid fever offer many points of bacteriological interest. For instance, the bile is very commonly invaded by the typhoid bacillus, and

while in most cases it causes no disturbance, in others the organism may persist for great length of time and inaugurate serious conditions and consequences. Of these conditions suppurative cholecystitis is the most common and important. Again, it has been claimed that typhoid fever is a very common precursor of gall stones, and, to explain this sequence, it has been supposed that the bacilli acted as nuclei upon which the biliary salts were deposited. This theory has gained in plausibility by the demonstration by Cushing and myself in two cases of typhoidal cholecystitis of large clumps of typhoid bacilli, such as one sees in carrying out the serum test. That these clumps of bacteria should serve as nuclei for stones certainly offers less objection than that single organisms should act in that capacity. Further, the theory receives additional confirmation from the fact that Welch has demonstrated micro-organisms in the centre of a gall stone.

As has been said already, the invasion of the bile is nearly always secondary; but that this is not necessarily so is shown by cases such as those of Guarnieri and Cushing, where the infection began in and was limited to the bile passages.

The tendency of the typhoid bacillus to persist in the body long after the original infection is ended, is well shown in the gall bladder. In a case recently reported from Johns Hopkins Hospital the typhoid bacillus was cultivated from the gall bladder in a case of gall stones seven years after an attack of typhoid fever.

Furthermore, a similar tendency to persist is shown when the urine has been invaded by the typhoid bacillus. In an article recently published I have shown that about twenty-five per cent. of the cases show bacilli in the urine; that when present the bacilli are in very large numbers, and that they may persist indefinitely into convalescence. Out of nine positive cases, two died; of the remaining

seven, the bacilli disappeared spontaneously in one,—in one the bacilli were made to disappear by irrigation of the bladder with corrosive sublimate, 1: 7000,—and in five cases the bacilli were still present in the urines in undiminished numbers when the patients were discharged. Ten days after leaving the hospital the bacilli were no longer to be found in the urines of two patients. The three remaining cases could not be followed after discharge from the hospital. It is therefore impossible to say exactly how long the bacilli may persist in the urine. Petruschky, in a recent article, records a case where the bacilli were still present two months after beginning of convalescence.

The importance of this urinary invasion is very great in several ways. In the first place, we see that whereas in the past we have disinfected almost exclusively the stools in typhoid fever, we must now bestow at least equal, if not greater attention on the disinfection of the urine. This necessity cannot perhaps be impressed more strongly upon your mind than by telling you that in one case Petruschky calculated that each cubic centimetre of urine contained 170,000,000 typhoid organisms.

An infected typhoid urine may, however, cause trouble in another way. As I have said, we get in typhoid fever a certain number of cases of prostatitis, epididymitis, and orchitis, and bacteriological examination has often showed the typhoid bacillus in pure cultures. The probability that such inflammation is due to an ascending infection from urine containing typhoid bacilli seems to me very great. Certain it is that the only case of epididymitis occurring in typhoid fever during the past year at the Massachusetts General Hospital appeared in one of the cases with bacilli in the urine.

It is very important, therefore, if possible, to remove the organism from the urine, not only because of the danger to public health, but also to prevent secondary complications

in the prostate, epididymus and the testicle. As has already been stated, in one case irrigation with corrosive sublimate, 1-7000, caused the bacilli to disappear permanently from the urine. Recently I have been trying the efficiency of internal medication, and the results, though far from conclusive, are encouraging. Three cases have been under observation. Two were given salol alone; in one of these cases the bacilli disappeared; in the other there was no appreciable effect. The third case received at first salol, with negative result. Urotropine was then given, and the bacilli rapidly disappeared. I am thus encouraged to hope that in urotropine we have a remedy capable of coping successfully with the condition; but further trial will of course be necessary to establish absolutely its curative power.

In diagnosis the bacteriological examination of the urine could have no value except in those cases in which the serum reaction was considerably delayed, for the bacilli rarely appear in the urine until the third week, whereas, as I have said, the serum test can be applied as early as the tenth day in most cases.

Another interesting point to consider is the possibility of the existence of a true typhoid pneumonia. Several cases have been reported where puncture of the lung during a pneumonia has revealed the presence of the typhoid bacillus. Furthermore, in a single case I have been able to cultivate the typhoid organism from the sputum. Of course the mere presence of the typhoid bacillus in a pneumonic lung does not necessarily establish a causal relation between the organism and the disease process, but the coincidence is certainly suggestive.

The presence of the typhoid bacillus in the sputum offers, moreover, another possible danger to those in the environment of a typhoid patient; but the danger of infection from this source in comparison with that from the stools, and especially the urine, must be very small indeed.

As to typhoidal meningitis, we now know that such a condition is entirely possible. Especially interesting is the fact that in one case the diagnosis was made by finding the typhoid bacillus in fluid removed by lumbar puncture from the spinal canal.

A rare but interesting sequela of typhoid fever has been reported by Swiezinski in the form of a periarticular abscess under the right deltoid muscle. This abscess developed in the sixth week of the disease, and the pus revealed the typhoid bacillus in pure culture. Another rarity which may be mentioned in this connection is a case in which seven and one-half months after typhoid fever, a dermoid cyst of the ovary suppurated, and typhoid bacilli were found in the pus.

The presence of the typhoid bacillus in portions of the body, so various and remote from each other, is due undoubtedly to the transfer, in most cases, of the specific bacilli by the blood current, and, in a number of instances, the diagnosis of typhoid fever has been made from the bacteriological examination of the blood. The organisms, when found, however, are very few in number, and several cubic centimeters of blood at least are required for the test. The procedure is, therefore, quite formidable, and not likely to come into general use for diagnosis.

Finally, in diagnosis it is important to bear in mind that typhoid fever is not necessarily the only pathological condition, but may be associated with other pathological processes, notably tuberculosis. A number of cases have been recorded in which a general tuberculosis, a pulmonary tuberculosis, or a tubercular meningitis, has been complicated by an intercurrent affection, which, by the serum test and the post-mortem examination, has been proved to be typhoid.

As to a specific treatment in typhoid fever, a large number of attempts have been made to devise such a treatment, but with little success as yet.

These attempts have been along three lines. I.—The employment of dead cultures, either of the typhoid bacillus alone or combined with the bacillus pyocyaneus. II.—The employment of the serum of animals made artificially immune to the typhoid bacillus. III.—The employment of the serum of patients convalescent from typhoid fever.

As to the first method—the injection of dead cultures—it seems to me utterly and completely irrational: for, inasmuch as the typhoid poison is contained almost entirely in the bodies of the bacilli, by this proceeding we simply add fuel to the flame and do not, in the least, assist in quenching the conflagration.

As to the second and third methods—the use of immune sera—I think they give us reason for encouragement, although the results obtained thus far are not entirely satisfactory. In animal experimentation the immune sera certainly exercise great curative powers, but, as unfortunately often happens, the results of animal experimentation cannot be applied always to conditions obtaining in the human body. A number of observers have thought that they have seen favorable results from the serum treatment, but the series of cases have not been sufficiently large, nor the evidence sufficiently convincing to inspire any considerable confidence.

A number of attempts have been made to vaccinate persons against typhoid fever, and the results have been quite interesting and suggestive. In vaccination dead cultures of the typhoid organism are used, and, in this instance, as it seems to me, with some show of reason; for here we are dealing with healthy individuals, and not with those nearly overwhelmed with typhoid poison. In this process the individual is accustomed to larger and larger doses of the typhoid culture, and his blood acquires greater and greater protective power. Pfeiffer and Kolle assert that, after a single inoculation made in this way, the blood exceeds in

protective power that of a typhoid convalescent. These observers think such vaccination could be of great value in time of war, or during epidemics. As supplementing this work the experience of Tew at the Barming Asylum during the recent typhoid epidemic at Maidstone, England, is interesting. Of 84 individuals who were vaccinated all escaped; whereas, of 120 nurses and attendants unvaccinated 16 contracted the fever. The possible value of typhoid vaccination in military campaigns and during epidemics may be, therefore, great. As an every-day procedure, however, it is not likely to become popular.

To summarize: We have seen—

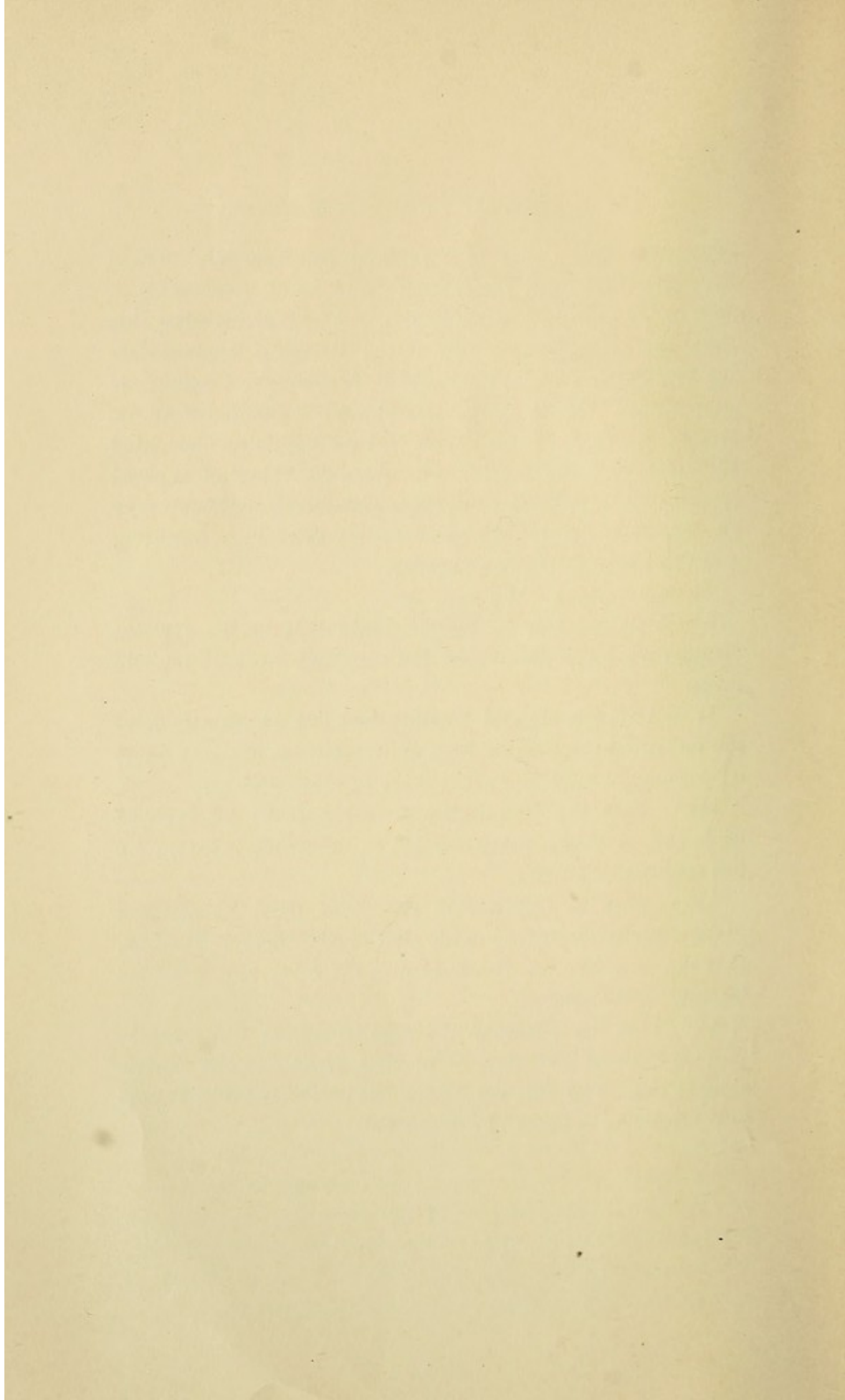
I.—That we can no longer doubt that in the typhoid bacillus we have discovered the essential cause of typhoid fever.

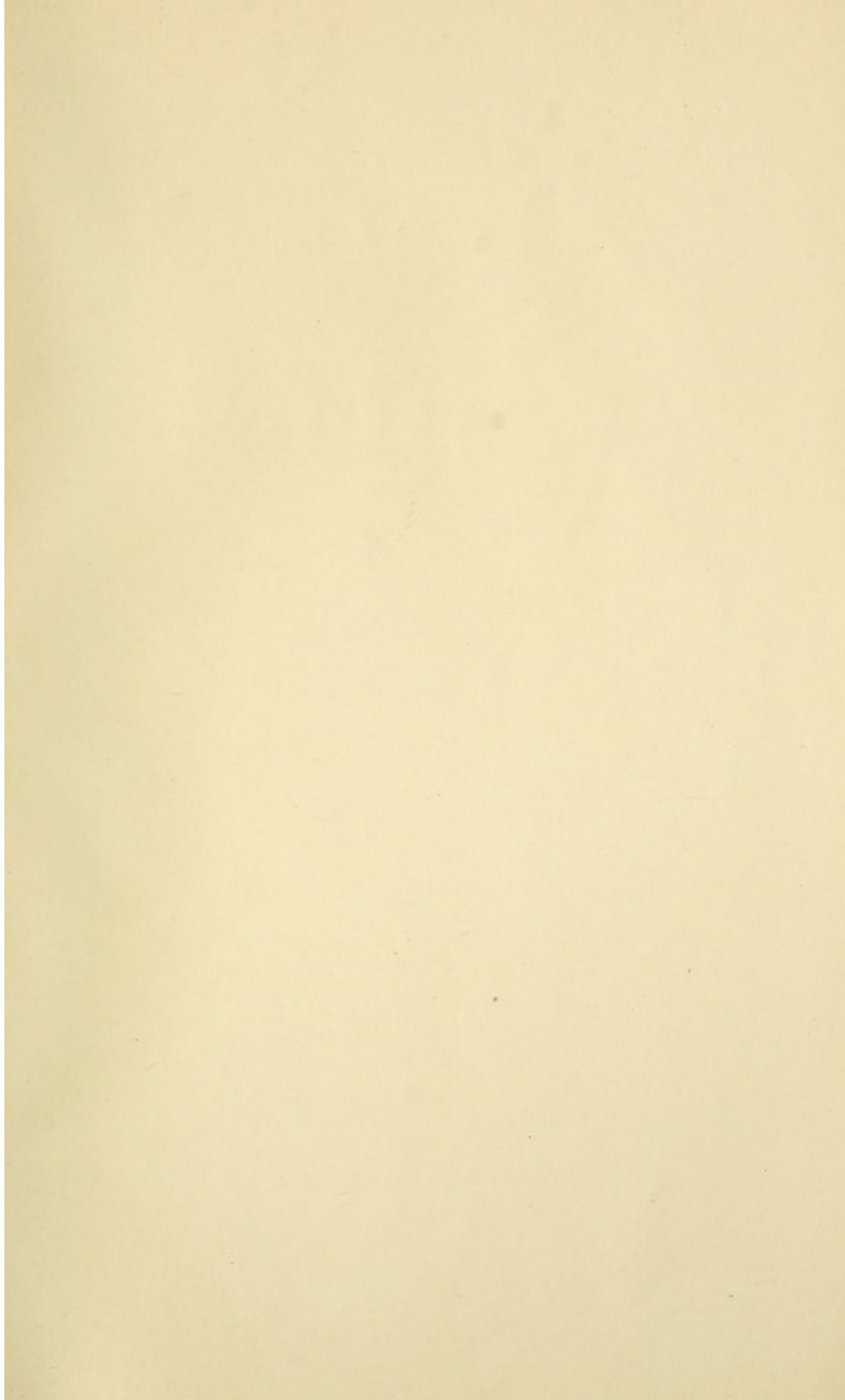
II.—That the typhoid bacillus does not necessarily elect the intestinal tract as its base of operations, but may exert its pathologic influence exclusively in other organs.

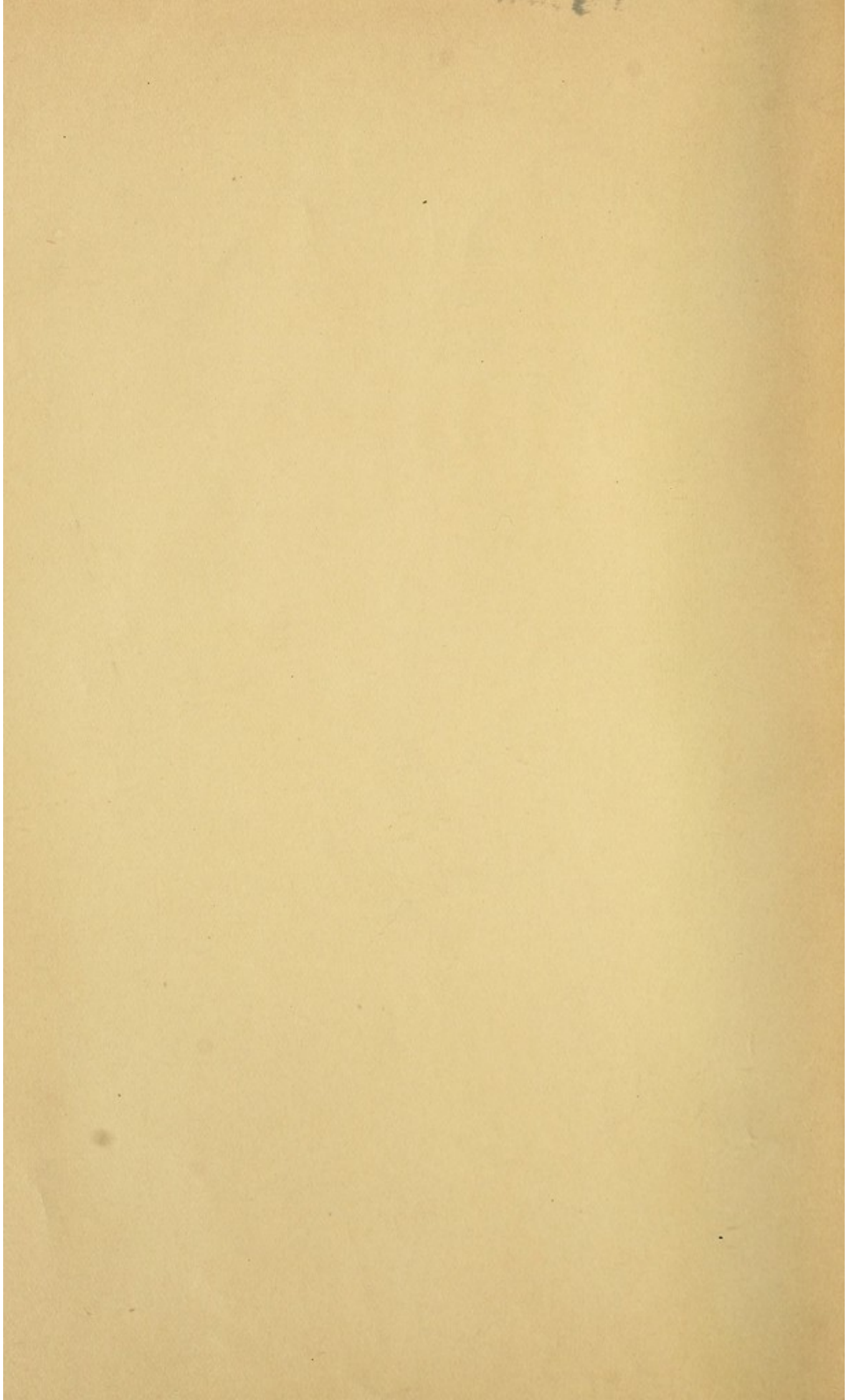
III.—That the complications and sequelæ of typhoid fever are, in many instances, due to secondary invasion by the typhoid organism.

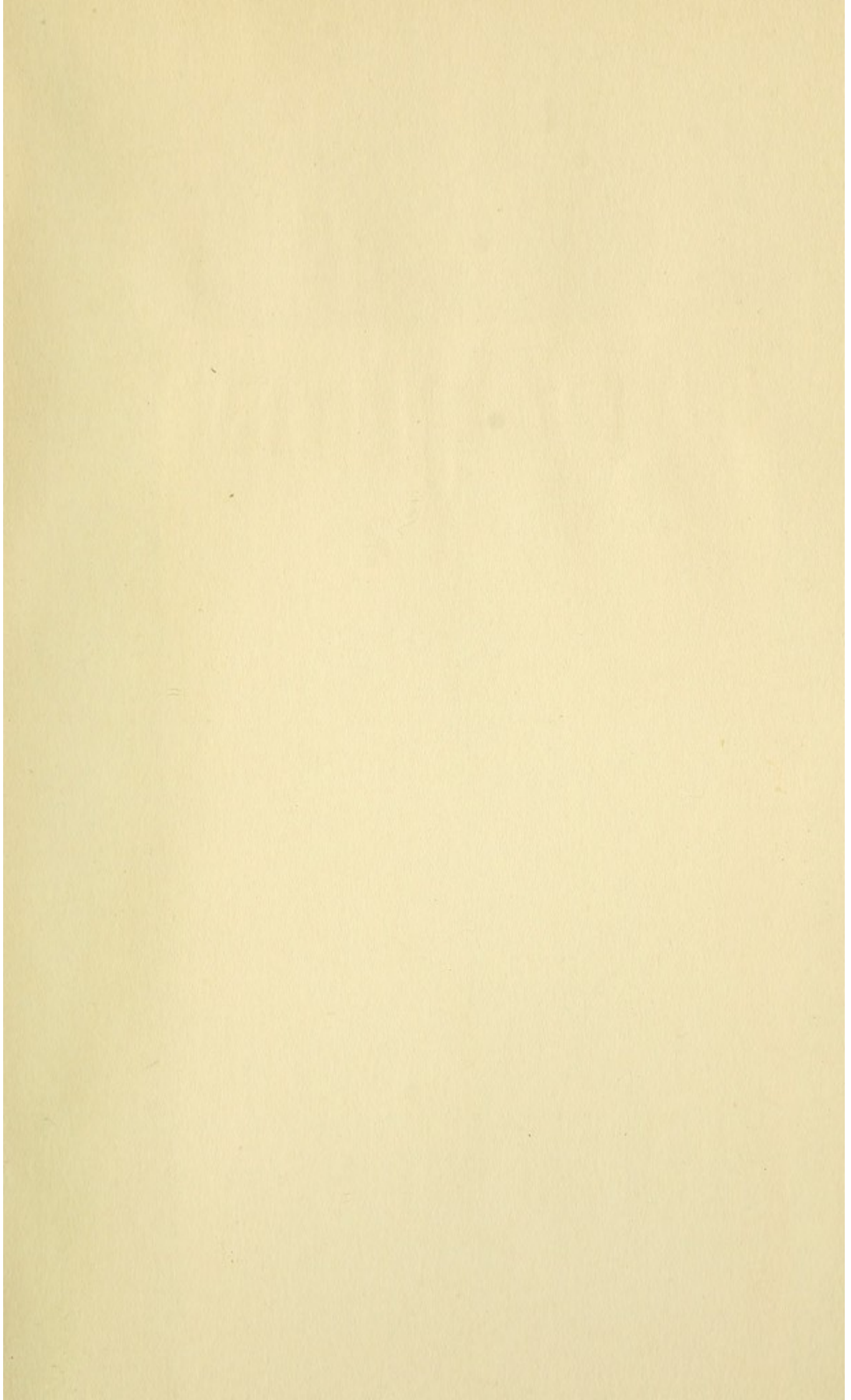
IV.—That in disinfection the urine must be given a place equally important with that of the feces. Further, that the necessity for disinfection of the urine may continue far into convalescence.

V.—That the questions of serum treatment and vaccination in typhoid fever are, at present, largely in the experimental stage, but that the future will probably bring important advances in these two directions.









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