Average finding of 7 individuals,	8.01%
Minimum " " 7 "	6.39%
Maximum " " 7 "	11.2%
Extreme variation in all cases,	4.81%

The variation found in these normal findings for carbohydrates is, if we take the minimum and maximum records, very considerable in proportion to the quantity of carbohydrates present. A further study of the records, however, reveals the fact that a discrepancy from the common finding exists only in the cases of the two young children examined, the findings of the older children and adults showing a fairly uniform character. The findings in the two children are both much higher than in the other cases, but are very similar to each other. The suggestion of this showing of our experiment is that the utilization of carbohydrates upon this diet is less good in younger children than in older persons. In using this method of examination for the study of function in the general run of clinical cases, therefore, we must use two separate sets of normal records for comparison,—one for young children and one for adults. If this course is followed, it would appear from the results of our experiment that the method provides fairly accurate means of determining the existence of any considerable disturbance of the function of utilization of carbohydrates, since the records obtained in normal individuals of the same general class as to age are fairly uniform. The number of observations made in regard to this point is, of course, too small to justify a decided statement to this effect. But as far as these records go this is the evidence: the extreme variation of the 5 cases of older children and adults being only 0.71%, the minimum finding 6.39%, and the maximum 7.1%, the average 6.78%, while the two cases of young children show records of 11% and 11.2%, respectively.

The finding in regard to starch remains as revealed by the microscopic examination of the feces, which serves as the index of starch digestion in our experiment, showed marked uniformity in all the normal individuals examined. The result of our experiment upon this point convinced us that under the Schmidt and Strasburger test diet the findings are so definite that any trained observer can determine in any case the existence of a normality or abnormality of this finding.

BLOOD CULTURES IN TYPHOID FEVER WITH COMMENTS UPON THE HOSPITAL TREATMENT.

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CONRADI¹ has recently found typhoid bacilli in the blood of a child four days before the first symptoms of the disease appeared, and he further

records the discovery of typhoid bacilli in the feces of two individuals eight and eleven days, respectively, before they developed typhoid fever. These facts indicate that typhoid fever can be contagious in the prodromal and early stages of the disease, and in confirmation of this point Conradi has also been able to furnish statistical evidence. Of some six hundred cases of typhoid fever, eighty-five were shown to have acquired the disease by contact, and of this number forty-nine contracted the infection during the first week of illness of the primary case. It, therefore, follows that an early diagnosis of typhoid fever is absolutely essential if its spread is to be prevented.

The Widal reaction is rarely positive in the first week, but it is present in about seventy-five per cent of the cases in the second week, and eighty-five per cent of the cases in the third week, thus becoming a more valuable test diagnostically the longer the disease lasts. Although the Widal reaction is present at some time or other in practically all cases of typhoid fever, it may persist for so short a time as to be overlooked. Furthermore it is not absolutely reliable, because it occasionally persists after a previous typhoid infection, and may even develop in the course of some other acute illness. The test represents an incalculable advance over previous methods of diagnosis, but Conradi's work on the early contagiousness of typhoid fever shows that earlier methods of diagnosis must be sought.

The cultivation of typhoid bacilli from the circulating blood appears to answer this requirement, for it has been convincingly shown² that it is possible to obtain a positive blood culture from over ninety per cent of typhoid patients during the first week of illness. The per cent of positive cultures falls very rapidly as the disease progresses, varying according to different observers from fifty-seven to seventy-three per cent in the second week, forty-three to sixty per cent in the third week, and from twenty-six to thirty-eight per cent in the fourth and fifth weeks. The blood culture method is, therefore, pre-eminently advantageous for the early, and the Widal method for the late diagnosis of typhoid fever.

The technic was at first a bar to the general adoption of this method, but the introduction of various bile media³ by Conradi, Kayser, Meyerstein and others has greatly simplified the process. It was supposed that the blood used for the test must be removed from a vein to avoid contaminating organisms, but Conradi found that the blood taken from the ear⁴ would do as well, and his observations have been confirmed by Peabody⁵ working at the Massachusetts General Hospital. The Kayser-Conradi Typhus Galleröhre for the use of the general practitioner have been employed for some time in Germany, and similar outfits are now furnished by our own boards of health.

The difficulty of an early clinical diagnosis in typhoid fever was well illustrated this last summer by the admission and discharge diagnoses at the Boston City Hospital. During the last seven months of 1907, two hundred and fifty-one patients entered with the diagnosis of typhoid fever,

but only one hundred and sixty-five of this number were given the same diagnosis on discharge. Errors in diagnoses were undoubtedly made by the physicians who sent the patients to the hospital, but any one who has followed a medical service for some months is aware of the mild fever cases of doubtful etiology which occur upon it, and will be ready to concede that if these had been seen throughout their whole course many new diagnoses of typhoid fever would probably be made.

It was with the purpose of testing the new cultural method, particularly in the early and doubtful cases of typhoid fever, that our work was undertaken.

Technic. — Normal ox gall was collected in a sterile flask immediately after the death of the animal and then transferred to test tubes in quantities of 5 ccm. each. These were then sterilized for ten minutes at 100° C. on three successive days, but as contaminations with motile organisms occasionally appeared, the autoclave was later employed subjecting the media to a pressure of 10 lb. for ten minutes, the pressure reaching as a rule 18 lb.

The arm was prepared by a nurse or orderly who first scrubbed a broad area including and surrounding the elbow with soap and water, and then with 70% alcohol and finally applied a corrosive poultice for thirty minutes. The blood was invariably taken from the median cephalic vein, which, after the first few attempts, proved to be a simple procedure. We were surprised to find that it was often easier to puncture a vein which was not plainly seen, but was palpable, than a vein visible to the naked eye, but freely movable beneath the skin. The operation caused as a rule less pain than the removal of several drops of blood from the ear. It is far cleaner and allows one to obtain an abundance of blood which is entirely free from contamination. Its disadvantages are the time consumed in the disinfection of the arm with the consequent apprehension on the part of the patient, the risk of infection and the need of an assistant.

Five to ten cubic centimeters of blood were usually removed, and of this quantity 2½ ccm. were placed in each of the test tubes containing 5 ccm. of ox gall; a portion was also saved for Widal reactions and histological study. We found it of advantage to use two bile tubes. Thus, of twenty-one positive cultures eight times the bacilli were obtained from only one of the tubes after the first transfer, and in four of these eight cases one tube never showed a growth. The blood, after its transfer to the bile-enriching medium, was incubated for about eight to ten hours, and then four loops from each tube were transplanted respectively to two plain bouillon tubes. These were examined twelve hours later and of those thus examined five — 62% — were positive at this time. The growth in bouillon should be sufficient for the performance of a Widal test in less than twelve hours. In another series of cases we should use a greater number of loops of bile in the transfer. The bacilli were easily detected in the bouil-

lon, which medium has this advantage over the other media that from it a Widal test can be made at once. Typhoid bacilli were obtained in twelve out of twenty-one instances on transfer to bouillon after twenty-four hours' incubation in the bile medium, not until after forty-eight hours' incubation in one instance, and only after seventy-two hours' incubation in three instances. Motility did not prove to be a safe guide in diagnosis and we preferred to first test the bacilli with a typhoid serum of known agglutinative power. The organisms were invariably found in pure culture and their reactions easily tested. Transfers were always made to plain agar (not sugar free) and often to blood serum and glucose agar, but we soon found that if the bacilli grew upon one medium they grew upon all.

We did not have much success with the transference of the bile to dextrose agar, making at the same time a stab in order to determine its ability to form gas. This method should enable a positive diagnosis of the paratyphoid group to be made in twelve hours.

The total number of cases studied was forty-five. Fifteen of these patients were later shown by the absence of the Widal reaction and course of the disease not to have had typhoid fever. The blood of one of these patients showed a positive culture of staphylococcus pyogenes aureus, and this occurred at a time when a positive diagnosis of osteomyelitis had not been made from the physical signs, and while typhoid fever was considered the probable diagnosis. This was the only instance in which we encountered an organism other than those of the typhoid group. It shows that the bile medium may be useful for the detection of other organisms than Eberth's bacillus.

Cultures from the circulating blood showed the presence of typhoid bacilli in twenty-one out of thirty cases of typhoid fever. The number of cases is so small that conclusions are only justified when these cases are considered in connection with those of other authors. For convenience we have classified them according to the week of the disease in which the culture was taken:

Week of disease.	Number of cases.	Culture: negative.	positive.
1	5	0	5
2	19	8	11
3	2	0	2
4	0	0	0
5	1	1	0
?	1	0	1
relapse,	2	0	2
Total,	30	9	21

In three instances in which we examined the blood in a relapse typhoid bacilli were found. It would thus appear probable that blood cultures would be a useful point in the differential diagnosis between relapses and complications.

Positive blood cultures are somewhat more frequently obtained in the severe than in the mild cases of typhoid fever. Kayser (*loc. cit.*) gives the following data:

Nature of typhoid cases.	Total cases.	Positive cultures obtained.
Very severe,	27	21 or 78%
Severe,	21	16 or 76%
Medium,	41	25 or 61%
Mild,	36	15 or 42%

The difficulty of classifying cases of typhoid fever in terms of severity is obvious. We have attempted to do it more from the general impression the individual made upon us than from any one arbitrary criterion. It would not be justifiable to draw far-reaching conclusions from such a small number of cases as we present in the following table:

Nature of Typhoid cases.	Total cases examined.	Positive cultures obtained.
Severe,	9	8 or 88%
Medium,	15	12 or 80%
Mild,	6	1 or 16%

We repeatedly attempted to prove that mild cases of fever entering the wards were of typhoidal origin, but almost invariably failed to do so. In only one such case, in fact, were we successful. There is no doubt but that better results would have been obtained if the mild cases had been examined earlier. The severe cases were examined on an average by the eleventh day, the cases of medium severity on the twelfth day, but the mild ones, on an average, not until the sixteenth day.

It is certainly only fair to state that as time went on our experience improved, and it is quite possible that an occasional positive case may have been overlooked in the first part of our work. Improvement in technic, of course, was bound to occur. The time saved in investigating a single case was easily reduced two thirds, so that we feel the blood culture method of diagnosing typhoid fever can be introduced as a routine measure.

The organisms from nineteen of the twenty-one positive cases gave all the typical reactions for typhoid bacilli. The organism isolated from one of the patients, who clinically did not differ in type from the others, produced gas in dextrose agar, to a slight extent in plain agar and had a more diffuse growth on plain agar than was the case with the other organisms, but the initial acidity in litmus milk persisted. This organism was uncommonly motile, shorter and of smaller diameter than the typical typhoid bacilli. It resisted clumping with the sera of many other typhoid patients except in a dilution of one to ten, and was not agglutinated even by the patient's own serum until thirty-three days from the onset of the disease, and only then in a similar dilution. This patient's serum also failed to clump the laboratory stock cultures of typhoid bacilli except in a dilution of one to ten. It also completely failed to clump the laboratory stock cultures of alpha- or beta-paratyphoid bacilli except in the same dilution. v. Hösslin⁶ has recently reported cases of this character. This case illustrates the advantage which the cultural method of diagnosis has over the agglutinative reaction.

The organisms of another case gave all the positive reactions for typhoid bacilli except that

after the initial acidity was produced the latter changed back to a deeper blue than before. The changes in the acidity of the milk produced by this case (Gay) as well as by the previous case (Roan) are merely qualitative reactions and do not determine the classification of the organism.

The following tables show the variations of these two organisms in acidity and gas formation with the different sugar media in comparison with typhoid and alpha- and beta-paratyphoid bacilli. Plain bouillon was used from which the sugar was removed by the colon bacillus. To portions of this were added one per cent of lactose, saccharose, mannite, dextrin, maltose, galactose and dextrose. The fermentation tubes used were those devised by Theobald Smith to whom we are indebted for many suggestions.

TABLE OF ACIDITY AFTER INCUBATION FOR FORTY-EIGHT HOURS.

Bouillon.	Control.	Typhoid.	Gay.	Roan.	Alpha-paratyphoid.	Beta-paratyphoid.
					No. of ccm. of $\frac{N}{100}$ NaOH used.	
Plain,	0.6	0.8	0.8	0.8	0.7	0.4
Lactose,	0.7	0.9	0.7	0.9	1.0	0.8
Saccharose,	0.8	0.7	1.0?	0.6	0.7	0.6
Mannite,	0.5	3.4	3.4	3.6	3.5	4.1
Dextrin,	0.6	0.8	1.3	1.2	1.3	1.0
Maltose,	0.6	3.3	3.3	2.8	3.0	3.6
Galactose,	0.7	3.4	3.6	2.6	3.1	3.8
Dextrose,	0.6	3.6	3.6	3.9	3.8	4.5

TABLE SHOWING GAS FORMATION AFTER FORTY-EIGHT HOURS' INCUBATION.

Bouillon.	Control.	Typhoid.	Gay.	Roan.	Alpha-paratyphoid.	Beta-paratyphoid.
Plain,	0	0	0	0	0	0
Lactose,	0	0	0	0	0	0
Saccharose,	0	0	0	0	0	0
Mannite,	0	0	0	+	+	+
Dextrin,	0	0	0	0	0	0
Maltose,	0	0	0	+	+	+
Galactose,	0	0	0	+	+	+
Dextrose,	0	0	0	+	+	+

From the quantitative results shown in the above tables, it is evident that Gay's organism agrees well with the typhoid organism, except that it produces a higher acidity in dextrin bouillon. In the table showing gas formation it corresponds throughout with the typhoid.

Likewise, it will be seen that the organism obtained from Roan agrees with the paratyphoids in acidity, especially alpha-paratyphoid, with which the greatest difference is but 0.5 ccm. in galactose bouillon. In gas formation this organism is identical with the paratyphoids.

Control tests were invariably made in the gas formation and acidity tests and were repeated until constant results were obtained.

HOSPITAL TREATMENT OF PATIENTS WITH TYPHOID FEVER.

Typhoid fever caused nearly six times as many deaths in Boston during 1907 as it did in Munich during 1906, yet the two cities have about the same population. Other cities in Germany and England also show much less typhoid fever than does our city. The record is still more unfavorable if we go farther back, because the year 1907

showed the smallest typhoid death-rate which Boston has so far attained.

The recent lowering of the typhoid death-rate has been brought about in this vicinity chiefly by hygienic measures of a general nature — such as closer inspection of water, milk and shellfish, both by the city and state authorities. Little has been done to prevent contact infection which Conradi and others have demonstrated to be the source of about one-fourth of all cases. It would therefore appear that the prevention of contact infection was the factor which demanded especial attention here at this time.

Two opportunities are open by which contact infection can be avoided: first, the early diagnosis of typhoid fever, and second, the detection of the bacillus carrier.

We have already alluded to Conradi's work which has shown that typhoid is especially contagious in the first week, and have demonstrated that by blood cultures an early diagnosis is possible. We are glad to again call attention to the fact that the Boston Board of Health is prepared to furnish blood culture outfits to those desiring them. Yet by this means only a portion of the contact infections can be avoided. The other source, the bacillus carriers, is entirely overlooked. With commendable energy, however, the State Board of Health has undertaken work along this line also and we undoubtedly shall hear much of it soon.

Fifty-five per cent of all diphtheria cases occurring in Boston during 1907 were treated in the South Department of the Boston City Hospital, and similarly fifty-four per cent of all fatal cases of typhoid fever which occurred in the city during the last five years were treated at one or the other of the three large hospitals. This is as it should be, because immediate contact infection is thereby reduced. That the practitioners in the city thoroughly approve of this course is shown by the large number of doubtful cases which they send to the Boston City Hospital, one third of the cases admitted with the diagnosis of typhoid fever in the course of seven months last year proving not to have the disease.

It is probable that the per cent of cases of typhoid fever which will be treated in the large public hospitals will increase, and for several reasons. Typhoid fever is a very expensive disease in private life. The duration of the illness, the necessity for at least one and usually two nurses, the two daily visits of the physician, or even the need of a doctor in constant attendance, and the frequent calls for specialists of one description or another contribute to this end. The cost is not lowered by sending typhoid patients to a private hospital. These hospitals consider such patients so undesirable that they demand rigid isolation with absolutely no contact between them and the nurses of other patients. Indeed, several of the private hospitals absolutely refuse to admit typhoid patients at all, because the surgeons, who chiefly patronize such institutions, will not tolerate the chance of infection of their own surgical cases with typhoid fever. Only wealthy patients can enjoy

the privilege of being treated for typhoid fever in a modern manner in their own homes.

The large institutions on the other hand are well adapted to the care of typhoid fever. They contain many wards, and it is a simple matter to so group the typhoid patients that infection of other patients and attendants can be reduced to a minimum. The isolation of typhoid fever patients in hospitals was provided for in Germany in 1905.⁶

Nurses should be protected during the care of typhoid fever patients in hospitals. In a former paper⁷ we showed that nurses working in six hospitals in Massachusetts were eight times as liable to contract typhoid fever as the ordinary citizen, and that hospital ward tenders under the same circumstances were thirteen times as apt to acquire the disease.

This last year (1907) forty-seven nurses in the State of Massachusetts have been thus attacked, while the total number of reported cases of typhoid fever in the state was two thousand three hundred and eighty-nine. Another year might not show that for every group of fifty typhoid patients a nurse developed the disease, but we think this not at all unlikely. Only ten of these nurses apparently contracted typhoid fever in private nursing, but thirteen of the hospital nurses, it is only fair to say, were infected by an early unrecognized typhoid case in a nurses' dining-room. It does not seem justifiable to expose twenty-three female nurses, fifteen male nurses and thirteen physicians on one day in the same institution to the risk of contracting typhoid fever from twenty-eight typhoid patients when a hospital possesses many wards and rooms into which these patients could be gathered and cared for by a third of the above number of attendants.

Isolation in separate wards is not by any means the whole story. Early diagnoses to determine when to isolate are essential. Fortunately, by the use of blood cultures, the early diagnoses are the ones most easily made. The possibility of making an early diagnosis probably decreases about five per cent a day after the first few days until well along in the second week when the Widal test becomes rapidly more and more positive. On comparing the dates upon which we made blood cultures with the dates of admission of these same patients to the hospital, we find that we lost on an average two days of time. This shows the need of such work being performed by those living in the hospital rather than by voluntary workers from outside. An early diagnosis demands much time, and allowance must be made for this in the organization of a medical clinic.

If it is really intended to stamp out typhoid from the community, patients should not be discharged from the hospital without a knowledge on the part of the health authorities as to whether they are typhoid carriers. The time at which the typhoid bacilli disappear from the stools and urine is a variable factor, and as far as the stools are concerned an uncontrollable one. It is perfectly feasible, however, to determine whether patients are free from bacilli. German regulations require isolation, when bacilli persist in the

stools, until ten weeks after the beginning of the disease; after this period special rules are provided for those who may still be bacillus carriers. As yet no such regulation exists in Boston or Massachusetts, but a knowledge of the presence or absence of typhoid bacilli in the stools would exert much influence upon the date recommended for the discharge of a patient. Such work would demand much time, but it would represent a high standard of preventive medicine.

CONCLUSIONS.

1. Our data agree with those of investigators having much larger series of cases, namely, that typhoid fever generally can be diagnosed in the first week by use of blood cultures, but that this method yields positive results in only about sixty per cent of the cases in the second week.

2. The typhoid bacilli are most easily obtained by blood cultures from the severest cases.

3. The typhoid bacilli were found in the relapse of typhoid fever in three individuals.

4. Typhoid fever is becoming more and more a disease to be treated in the larger public hospitals.

5. Isolation of typhoid fever patients in hospitals for the sake of other patients and particularly for the nursing staff is demanded.

6. Early diagnoses on entrance to the hospital and the detection of bacillus carriers before discharge are requisites in the present campaign against typhoid fever.

We wish to express our appreciation of the courtesy extended to us in our work by Dr. George B. Shattuck, Dr. John L. Ames and Dr. John Bartol who placed all their typhoid patients at our disposal, and to Dr. Francis H. Williams and Dr. Horace D. Arnold from whom we obtained special cases. The work would have been impossible without the co-operation of Drs. Rhea, Mabee and Bosworth of the Pathological Laboratory to whom we feel much indebted as well as to Dr. Adler for helpful suggestions.

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THE USE OF TUBERCULIN IN THE TREATMENT OF LOCALIZED TUBERCULOSIS EXCLUDING PULMONARY TUBERCULOSIS.*

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THE treatment of tuberculosis with the various products of the tubercle bacillus is nearly as old as the discovery of the specific cause of tuberculosis. A considerable mass of evidence has been collected concerning the therapeutic use of tuberculin in various ways. More recently, Trudeau and his associates at Saranac Lake have argued that the end to be attained was immunity against the tubercle bacillus. Some facts of animal experimentation also seem to favor this view. Those observers have reported a considerable series of cases of pulmonary tuberculosis showing the value of increasing doses of tuberculin. Sir A. E. Wright, of England, has utilized the theory of phagocytosis. He believes that in cases favorable for treatment, which are essentially localized tuberculosis, there is a deficient amount of opsonins, those substances in the blood which prepare the bacteria for ingestion by the leucocytes. According to his theory tuberculin acts by increasing the amount of opsonins, and the treatment should be controlled by the determination of the opsonic index.

It is not the purpose of this paper to discuss the theories of the action of tuberculin but to give the results obtained in a series of cases of localized tuberculosis. There were 25 cases, divided as follows: 9 cases of tuberculous adenitis, 4 cases of lupus vulgaris, 4 cases of tuberculosis of the genito-urinary tract, 3 cases of tuberculosis of the wrist, and 1 case each of tuberculosis of the knee, tuberculosis of the spine and pelvis, tuberculous sinus, tuberculous fistula in ano, and erythema induratum. As far as known no cases of pulmonary tuberculosis are included. In the early cases the opsonic index was determined as a routine, as a rule, twice a week. Of the cases included in this list, the opsonic indices were followed in 9 for varying lengths of time during the treatment. Seven were followed for over four months. Four cases (I, II, XI and XIII) showed an opsonic index of 1 or above, at two or more observations at the beginning of treatment. According to the rules laid down by Wright they were not satisfactory cases for treatment. However, they were not doing well at the time. Nevertheless, under treatment by tuberculin, 3 of the 4 showed a most satisfactory result. In 5 cases (X, XIV, XVIII, XIX and XXIII) the initial observations were distinctly below normal. All these 5 are classed as distinctly benefited. In none of the 9 cases was a marked tendency for the opsonic indices to follow any particular curves noticed. As a rule, it should be said, however, that if a case was doing badly the index was often low, but not invariably so. The clinical manifestations were markedly more accurate. At first, attempt was made to re-

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