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A CONTRIBUTION TO THE STUDY OF THE DIAGNOSIS OF TYPHOID FEVER BY MEANS OF THE BLOOD.

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BY A. HIRST APPEL, A.B., M.D.

CAPTAIN MEDICAL DEPARTMENT U. S. ARMY, AND

FRANK J. THORNBURY, M.D.

LECTURER ON BACTERIOLOGY, UNIVERSITY OF BUFFALO.

In a recent article upon the subject of continued fevers,¹ its distinguished author commenting upon anomalous typhoid, writes "it will lurk and hide its features completely, where it is unsuspected the difficulties attending its clear discernment from certain continued fevers of considerable duration not typhoid, may baffle even the most sagacious physician."

Among the febrile conditions the diagnosis of which may offer at times extreme difficulties of differentiation, he enumerates remittent and relapsing fevers; influenza; the the "ardent fever" of the tropics; "thermic" fever (Guitéras); "asthenic" simple fever (Murchison); "starvation" fever (DaCosta); "Malta" or "rock" fever (Milner); atypical continued fever" (Cain), from a supposed septic agency in the soil; "cypress" fever (probably relapsing fever); the "simple continued fever" described by Baumgarten (doubtful as to its being anomalous typhoid); the prolonged fevers arising in connection with local conditions, as from miliary tubercle, the fever of fecal accumulations, at times closely resembling typhoid; anemic fever; the fever of purpura, especially hemorrhagica; "hysterical" fever, in which the disturbance of heat function may last weeks, months, or even years; the "innominate" fever, described by Goddheart; fevers arising from organic changes—as rapidly advancing arterio-sclerosis; the fever of lithemics; of organic disease, as the endocardium, lung, pleura, duodenum, in which the lesion is slight, masking the etiology; of catarrhal pneumonia; of local plastic pleuritis; and the cases of "inexplicable pyrexia" described by Hale White.

Outlining the distinguishing clinical features of these various conditions, and the bacteriologic, microscopic, and chemic examinations of the blood upon which reliance is placed for making the differential diagnosis, no mention is made of the reaction obtained, in cases of true typhoid, with the blood when applied to active cultures of the Eberth bacillus; a test which since 1894, when Pfeiffer first called attention to the subject, has been confirmed in value, and bids fair to become pathognomonic, if this expression can be applied to a test, in the differentiation of these obscure febrile conditions from true typhoid.

The antagonism existing between the typhoid bacillus and blood in which an antitoxin has been devel-

oped by the presence of its products, has been known since 1888, when Chantemesse and Widai demonstrated that certain animals could be rendered immune against the typhoid bacillus, by the subcutaneous injection of sterilized cultures of this organism.

In 1892, Bitter concluded that immunity, which he induced in rabbits in the same manner, was due to the presence in the animal of "antitoxin."

Bruschettini in the same year, following the same line of research, noted that the blood serum of animals immunized by cultures sterilized at 60 degrees C., possessed antitoxic properties, and had far greater germicidal potency over the typhoid bacillus than the blood of the normal rabbit. Stern (1892) observed that the blood of a man who had suffered an attack of typhoid fever 17½ years previously, showed unusual bactericidal power over the bacillus of Eberth; and Chantemesse and Widai arrived at the conclusion that "in general the guinea pig is immunized against the action of virulent typhoid cultures by the subcutaneous injection of a small quantity of the serum of persons who have suffered an attack of typhoid fever, no matter how remote." The fact of the existence of antitoxin in the blood of patients who are or have been victims of typhoid, and of its presence also in the blood of immunized animals has been utilized successfully, experimentally, in animal therapy and more recently to some extent in man.² The serum of the blood from a fatal case of typhoid was found by Stern to be still more potent in animal as a therapeutic agent, than that of recent convalescents.

In 1894 the discovery was made by Richard Pfeiffer of Berlin that the specific poison of the bacillus of Eberth is not present in the filtered culture but is closely associated and remains with the bacterial cells. The bacilli may be killed by a temperature of 56 C. without injury to this toxic substance. By the latter, then, animals may be immunized and their blood be found to contain an antitoxin *which has a specific bactericidal action upon the typhoid bacillus*. Pfeiffer also clearly established the presence of this antitoxin

² Pfeiffer and Kolle, (Deutsche Medicinische Wochenschrift, Nov. 16 p. 6), publish results obtained upon the human subject by injection, into the subcutaneous tissue of the back, of bouillon cultures of typhoid bacilli, sterilized at 56 degrees C.

Healthy persons having no previous history of typhoid fever, experienced malaise, chills, giddiness and pain at sight of puncture, usually two or three hours after injection, with evening temperature upon the first day of about 101.3 F. which soon fell to the normal. They find that one injection of culture brings about the specific change in the blood which causes agglutination and immobility of the typhoid bacilli in pure cultures, recognizable in about six days, and exercised in as great a degree as they have ever been able to observe in convalescents from typhoid.

By mixing serum thus obtained with unsterilized bouillon cultures and injecting the mixture intraperitoneally, they find that guinea-pigs, although succumbing to the unsterilized cultures alone, will survive inoculation with the mixture, and tabulated the quantities of dead culture thus required to secure immunity.

Injection of dead cultures in man resulting in the production of substances in the blood serum inhibiting the specific bacteria, they hope thus to secure immunity by prophylactic inoculations, analogous to the results of Haffkine's protective inoculations against cholera, now substantiated by many thousands of cases. Should further observations confirm that they can confer the same immunity as exists in persons having had the disease, the procedure will become one of the greatest practical value, especially "in the face of epidemics or in war, since whole armies having been at times decimated by this scourge."

¹ DaCosta: Am. Journal Medical Sciences, June, 1896.

in the blood of patients who had recently suffered an attack of typhoid, and in the same year demonstrated its peculiar action upon the Eberth bacillus. Undoubtedly however, to Widal of Paris is due the credit of first utilizing this knowledge in every-day practical clinical work. Instead of obtaining the serum from the vein of a patient's arm, by means of a sterilized syringe, decanting after separation, the technique originally employed, he found that the dried blood or serum would give the result as published by him in the *Bulletin Médical* of August 12, 1896.

On Sept. 17, 1896, Wyatt Johnston of Montreal, observing the same fact, read a paper before the American Public Health Association, advocating the use of dried blood, as better adapted for bringing this test within the range of ordinary public-health laboratory work, and "enabling it to be dealt with in a wholesale manner." The latter method makes the discovery easy of application, and gives it the practical importance it now possesses. A drop or two of blood dried upon a slip of paper or cover glass (absolute sterilization is not essential), can be transmitted long distances with ease and safety, and is sufficient, in most cases, to determine the presence or absence of the disease.

To obtain the reaction it is simply necessary to dissolve the drop in sterile water and transferring it to a cover slip, inoculate with the pure culture and examine. If the case is one of typhoid fever, the reaction becomes manifest within a few minutes.

The following scale, formulated by Widal, enables the stating in terms of more or less exactness the measure of agglutinating power of any given specimen, indicating the strength of the antitoxin in the serum examined, and may be useful in doubtful cases.

Taking a series of sterile tubes containing respectively 1, 2, 3, 4, and 5 c.c. of bouillon, he added to each a drop of the serum to be examined; inoculates with a trace of culture, and examines in from twelve to twenty-four hours. If, for example, the tube containing 3 c.c. of bouillon, gives a typical reaction, while that which contains 4 c.c. does not, the agglutinating power of the fluid studied is exercised between 1 to 60 and 1* to 80; in a typhoid case the agglutinating power of the serum varies generally between 1 to 60 and 1 to 80; it could reach 1 to 100, rarely passing this limit; where it reaches 1 to 80 or 1 to 100 we find the reaction always takes place immediately. Let the specimen be prepared ever so quickly and examined as soon as it can be placed under the microscope, beginning of the clumping process of the bacilli will have already taken place. In the very early stages of the disease we found the reaction less pronounced at first, but gradually increasing in intensity, although even late a few bacilli may still retain some motion. These evidently were not acted upon by the agglutinating substance, which apparently had exhausted its energy upon the organisms already aggregated into clumps. Its action here presents some similarity to the chemic process of disinfection, which results in the production of a third substance through *contact* of the bactericidal agent with the cells. But that the process of agglutination is probably not a chemic change in the composition of the bacteria, but rather a sort of catalytic action, is proven by inoculating suitable media with the bacteria which had been agglutinated and rendered immotile by typhoid serum. Strangely enough, they grew with apparently the same vigor as the original cultures, their progeny

recover their independence and active motion and the new growths again respond to the typhoid reaction.³

The blood retains its agglutinating power with great tenacity. In dried specimens reexamined after two or three months we found it undiminished, although no particular care was taken to guard against contamination. A number of specimens sent us for examination from a distance, were collected without aseptic precaution upon ordinary writing paper and transmitted by mail. The method employed did not appear to affect the result, typhoid cases promptly giving the reaction, thus indicating that unusual precaution in the collection of specimens to be examined may be quite unnecessary. Dried blood is slow to undergo putrefactive changes, the saphrophytes responsible for such changes needing moisture for their proliferation.

That the agglutinating property be exhibited it is not necessary that the culture be living and active; dead bacilli are likewise massed into clumps by the serum. After exposing a pure culture of Eberth's bacillus to 60 C. for half an hour (the thermal death point being 56 degrees) they were still found to agglutinate. Further illustrating the tenacity with which the antitoxic power is retained in Stern's case, cited above, showing unusual bactericidal power in the blood of a man who had suffered an attack of typhoid fever seventeen and a half years previously, and Widal's reported case, which gave the reaction after seven years, we were successful in obtaining a decided reaction in a case thirty-one years after recovery,⁴ and other cases examined after one, two, eight and ten years, gave the reaction with virulent cultures. We have also found, as stated by Dieulafoy, that the agglutinative power is by no means confined to blood serum, but is found in other fluids of the economy. The reaction appears, exceptionally, in the *urine* of typhoid cases. It is constantly found in the serum of *vesication*. Widal and Sicard found it in the pericardial, peritoneal and pleural serum in three cases, post-mortem. A marked reaction can be obtained from the *milk* of nursing women affected with typhoid; likewise from the milk or the colostrum of rabbits and the milk of goats inoculated with Eberth's bacillus.⁵

The serum of *edematous infiltration* in typhoid cases agglutinates powerfully. In a case of grave typhoid recently reported (Étienne), which provoked abortion in a pregnant woman, the blood of the patient agglutinated typically, but that of the fetus was negative. In rabbits, however, inoculated by Widal and Sicard six hours before, the fetal blood agglutinated from birth, although less powerfully than in the mother, proving that the agglutinating substance passed into the fetal circulation. The reaction can be obtained from the human biliary secretion. Negative results were obtained from the cerebro-spinal fluid and that of the vesiculæ seminales. Negative results were obtained from the saliva, but Achard and Bensaude have demonstrated the reaction where the submaxillary or parotid secretions were collected within the gland ducts. The *aqueous humor* and the secretion from the *lachrymal gland* will also in typhoid

³ It may be possible, however, that these cultures result from a few cells which, enclosed in the mass, escaped the action of the agglutinating agent. [We found also that the bacilli, after agglutination, stain readily with the anilin colors. Where doubt exists, fibrin particles may thus be easily differentiated from masses of bacilli.]

⁴ In a physician who happened into the laboratory while we were examining blood specimens.

⁵ Journal Académie de Médecine, Sept. 26, 1896.

cases give the reaction of agglutination. The tears constitute a secretion always easy to obtain. The fact that they give the reaction is important. From the internal angle of the eye, with a fine pipette, a drop sufficient for an extemporaneous examination can always be aspirated. A distinction is made by the French observers between the secretion naturally present and that provoked artificially, as by ammonia or menthol. They find in the latter case the reaction often fails. Examining in both ways cases giving the blood reaction typically, our results confirm the observations of Widal and Sicard, who found the reaction in the tears of ten out of fourteen cases examined with the natural secretion, but when provoked artificially it persisted to a slight degree in but three. In two immunized rabbits the reaction appeared typically in a mixture of two drops of secretion to ten of culture. The lachrymal secretion of persons never having had typhoid, and of normal rabbits, was negative. In immunized rabbits the aqueous humor gave the reaction in seven out of nine cases. In normal rabbits the aqueous was negative.⁶

From these results, showing the agglutinating property in the tears, the aqueous and the serum of edema the conclusion is reached that the leucocytes play no part in the secretion of the agglutinating substance. Duclaux has shown that the greater part of the casein of milk is separated from the filtrate, after passing through a Chamberland filter. Achard and Bensaude demonstrated that milk thus filtered, in parting with this albuminoid, loses its power of agglutination previously possessed. In blood serum thus filtered the power is also greatly diminished. In fluids poor in albuminoids (as the cerebro-spinal and saliva) the reaction fails. The inference is therefore logical that for the production of the agglutinating reaction the albuminoids are essential.

The albuminoids existing in the blood include serum-albumin, serum-globulin and fibrinogen, the latter existing in the circulating serum, but in the act of coagulation under the influence of the fibrin-ferment, separating into fibrin (which forms the clot), a globulin and probably other substances. To separate the serum-albumin from the serum-globulin, they add magnesium sulphate to saturation to a tube of typhoid serum. The globulin is precipitated and separated by filtration. Mixing now two or three drops of the filtrate deprived of globulin to ten drops of culture, it is found that the bacilli retain their independence and motility. The serum deprived of its globulin seems to have lost its agglutinating property. The globulin remaining upon the filter, from which possible remaining traces of serum-albumin is removed by again washing the precipitate with a concentrated solution of magnesium sulphate until the filtrate will no longer coagulate by heat, mixed with an equal part of distilled water is found to possess the agglutinating property in a high degree. The phenomenon is still further intensified if less water is added, showing thus that the agglutinating property is definitely associated with the globulin.

Arthus and Pagès, in order to study the fibrinogen as it exists in the blood, prevented coagulation by adding potassium oxalate, about 1.5 to 1,000, to the blood as it issued from the vessels. In the plasma thus obtained the fibrinogen is retained. To precipitate this they add 15 parts to 100 by weight of sodium

chlorid, dissolving the precipitate in distilled water. The solution of fibrinogen thus derived from typhoid blood agglutinated the bacilli. Treating now the plasma, deprived of its fibrinogen, with a saturated solution of magnesium sulphate and filtering they obtained the same result as in the serum of coagulated blood; the filtrate containing the albumin had lost its agglutinating power which was retained by the globulin remaining upon the filter.

The other body fluids experimented upon, the serum of blisters, of the peritoneum, of the pericardium and of edema in typhoid cases, react in the same manner as the blood plasma. Fibrinogen and globulin apparently possess the agglutinating property.

Dieulafoy, Widal and Sicard have made an analysis also of the milk, which contains an albuminoid not found in solution in the blood. A goat inoculated with typhoid furnished, seven days afterward, milk possessed of a high degree of agglutinating power. By adding an excess of magnesia sulphate, the casein and lacto-globulin are precipitated together with the fat globules. The filtrate containing but the albuminoid lactalbumin, shows but slight agglutinating capacity. Adding a solution of sodium chlorid to saturation, the casein is precipitated with the fat globules, while the lacto-globulin remains in solution in the liquid with the lactalbumin. The filtrate gives the reaction typically, even though the whole milk is but feebly agglutinative. The phenomenon could not be due but to the presence of the lacto-globulin, for, on now adding magnesium sulphate to saturation the power of agglutination in the filtrate disappeared entirely. By coagulating the milk with rennet, the lacto-serum obtained was powerfully agglutinative, which property again disappeared upon precipitation with magnesium sulphate to saturation. To determine the presence of this property in the casein they now add to the milk acetic acid in the proportion of 1 to 2 parts per 1,000, to precipitate the casein, washing with water to get rid of the acid and of traces of lacto-globulin. Dissolving the precipitate, after filtration, in sodium hydrate, 1 to 100, they found that the solution, containing no other albuminoid but the casein, strongly agglutinated the bacilli. It is thus shown that the albuminoids contained in the blood of typhoids do not alone possess the power of agglutination, but that casein and without doubt other albuminoids can also acquire it, imparting this power to their solutions and regaining it upon precipitation.

The practical bearing of these experiments lies in the fact that the whole blood, containing *all* the albuminoid elements, instead of being less sensitive to the typhoid reactions, as Widal and others first supposed, is in fact *more* so than the serum alone; we therefore obtain incomplete or pseudo-reactions from typhoids years after recovery and perhaps other conditions from solutions of the whole blood, fluid or dried, which are not observed when the serum alone is used, and which may be misleading; the agglutination observed being at times equal to that of true typhoid fever in the active stage of the disease. In these cases, however, there is not observed the same progressive loss of motion that is found in true typhoid, and herein lies the differentiation; more stress must be laid upon the *loss of motility* of the bacilli than upon their clumping. In fact, in pseudo cases the latter is sometimes more complete and often more quickly exhibited than in true typhoid. Where doubt still exists, the differentiation is more readily accomplished after

⁶ Ibid. The chemie analyses and experiments upon the fluids of the body are translated from Widal and Sicard's paper quoted.

twenty-four hours, the specimen being meanwhile kept at blood temperature.

While the clumping for the most part persists there are at the same time numbers of individual bacilli in the clear spaces that retain their active motion, this activity being much greater than we find in true typhoid cases. Their number also increases upon longer exposure, thus definitely making the distinction from typhoid blood. Clumps once formed we have never seen break up again in true typhoid; the reverse often happens in pseudo-reactions. There still remains, however, a number of cases, especially where the history shows previous typhoid, in which the agglutination and loss of motion is so marked and so closely resembles the reaction of typhoid in its active febrile stage, that errors in diagnosis might still readily be made when dried blood is tested with virulent cultures of the bacilli.

As already stated, pseudo-reactions are rare with the serum alone separated from the clot. But when *all* the albuminoids are present, as in the dried blood, the agglutinative property, intensified, is readily excited when brought in contact with a very virulent culture, even where there are no present symptoms of the disease.

The "quantitative" test, under such circumstances, affords a valuable means of guarding against error. By diluting, with sterile water, the specimen to be examined, a point is reached where the reaction becomes negative; but where a control specimen from an undoubted typhoid case, with equal dilution, still gives a typical reaction.⁷

Still more reliable conclusions may be obtained by discarding entirely the very virulent culture, using instead one the virulence of which has not been increased by successive seedings, but instead is transplanted from a month-old growth upon agar into bouillon and incubated twelve to twenty-four hours before use.⁸ Thus grown, the bacilli are still measurably active, but their rapid, darting motion is absent; they exhibit but gliding, serpentine movements across the field.

Reexamining with the culture thus obtained blood specimens in which agglutination occurred with virulent cultures, we were able to completely eliminate the troublesome pseudo-reactions, and by this technic therefore obviate much of the confusion and error resulting from the examination by the dried blood method. The conclusion seems indicated, that given a case of acute pyrexia of some duration, in which the blood gives the reaction of agglutination with a culture thus prepared, *and where there is corresponding loss of motility in addition to the clumping*, we may safely decide that we are dealing with a case of typhoid fever.

Where active motion persists with clumping, the specimen must be kept at blood temperature for twenty-four hours. In typhoid cases the reaction is *progressive*, clumps once formed do not again separate; immotility becomes more complete and the clear spaces between the clumps of bacilli more defined. The reverse obtains in pseudo-reactions, when, after twenty-four or forty-eight hours, the hanging drop may perhaps be swarming with active bacilli.

In dried blood specimens from fifty cases examined, in nearly all of which the clinical symptoms were more or less typical and sufficient to make the diag-

nosis of typhoid fever, we were able to obtain the reaction upon cultures thus attenuated, even when the blood was diluted until the color was scarcely discernible; while in cases, as above noted, in which we had obtained the reaction with *virulent* cultures from blood in health a number of years after recovery, the reaction, under the same conditions, was constantly negative.

Another point of distinction may often be found in the *time* required for agglutination to take place, it often occurring in pseudo-reactions *more quickly* than in typhoid. The rapidly formed, oscillating, swaying masses of bacilli are not, as a rule, the effect of typhoid blood. With the latter, more often, especially with largely diluted blood, the *motion* is first arrested, clumps not forming until later.

To determine the differential *character* of the reaction we made a large number of comparative examinations of the action of typhoid blood upon other motile organisms, especially of those closely allied to Eberth's bacillus in morphologic and biologic characteristics. Of these the "colon" bacillus is the most important, closely resembling Eberth's bacillus, always associated with the latter in typhoid discharges, and believed by many observers to be one and the same organism, an evolution from saprophytic existence to pathogenic potency taking place in cases of typhoid fever. In the operative procedures recently successfully undertaken for suture of perforations of ulcerated intestine in this disease, it is remarkable that the "colon" and not Eberth's bacillus was found upon bacteriologic examinations of the scrapings of the ulcerated surfaces.

Both the typhoid and the colon bacillus vary considerably as a result of conditions relating to their environment, and it is difficult to determine whether certain bacilli of this group, sometimes found in river water, etc., are to be regarded as varieties of one or the other species mentioned, or as distinct species. Cesaris-Demel and Orlandi concluded (1894) that animals immunized against the "colon" bacillus furnish a serum which has protective and therapeutic value against infection by the typhoid bacillus, and the reverse.⁹

But in regard to their response, in artificial cultures at least, to typhoid serum, they differ widely. No matter how powerfully and quickly the serum used agglutinated the bacillus of Eberth, we were never able to observe the least effect upon the "colon."

Among other motile organisms tested in pure culture, the behavior of the *B. pyocyaneus* with typhoid serum is also of interest. It is but recently that the use of sterilized cultures of this bacillus was tested in the treatment of typhoid fever—it having been shown by experiments upon animals that sterilized cultures of *pyocyaneus* exercised an immunizing influence against typhoid infection, similar to its known antagonism to the bacillus of anthrax. The results we obtained in a measure confirmed these observations, although Kraus and Buswell concluded from their observations in twelve cases treated with sterilized *pyocyaneus* cultures, that this method of treatment "has no specific curative value." By inoculating guinea-pigs with *pyocyaneus* we secured a serum from the abdominal cavity containing the bacilli in large numbers. Active typhoid serum had a slight agglutinating effect upon these bacilli, rather more in the serum thus obtained than in artificial culture. When,

⁷ Widal; Greenbaum.

⁸ Report Board of Health Province of Quebec, Johnston and McTaggart, Jan., 7, 1897.

⁹ Sternberg: Immunity and Serum Therapy, 1895.

however, the blood serum from the same guinea-pig (a control containing no bacilli), or the diluted dried blood, was inoculated with a virulent bouillon culture of Eberth's bacillus, the latter were quickly agglutinated and immobilized as by typhoid blood serum; showing, as well as by their immunizing influence, that an undoubted antagonism exists between these organisms. The normal blood serum of the guinea-pig gave negative results.

The effect of the typhoid serum upon a number of other motile bacteria found in water, the *B. fluorescens*, *Indicus*, *subtilis*, *violaceus*, etc., in each case was negative. They continued their motion as freely and independently in the serum as in their normal habitat.

Little or no antitoxic effect could be observed upon the pathogenic organisms causing, like typhoid, notable intestinal lesions, as the spirilla of Asiatic cholera (which are agglutinated promptly by cholera serum), or of Metchnikoff or of Finkler-Prior, or upon the bacillus of hog cholera, closely resembling the "colon" bacillus morphologically.

The essential etiologic organisms of malignant edema and tetanus also retained their separate existence and motility in the serum.

Excepting, then, the reaction with virulent culture of the *B. pyocyaneus*, we were unable to find that other motile organisms, saprophytic or pathogenic, were at all affected by typhoid blood.

Regarding the action of blood from pathologic conditions other than typhoid upon the Eberth bacillus, it has not been possible for us to compare the result of blood examination in many of the obscure forms of continued fevers above described, which often offer such great difficulty in diagnosis. From such affections, however, as we have been able to examine, fairly definite conclusions were obtained.

In addition to the fifty cases of more or less typical typhoid, our conclusions are based upon the study of about twenty-five cases in which the clinical symptoms were more or less doubtful and suggestive of typhoid, of miscellaneous affections, and of many specimens of normal blood of man and the lower animals.

The examinations made included blood from acute and chronic rheumatism, gout, aseptic (surgical) fever, mumps, malarial fevers (intermittent and remittent), influenza, cystitis, acute bronchitis, acute enteritis, catarrhal pneumonia, appendicitis, acute pericarditis, syphilis, etc.

At times we obtained from apparently normal blood, and from that of miscellaneous affections in which there was no suspicion of typhoid fever, an unmistakable reaction, resembling that of typhoid blood; confirming the experience of Stern (1894), who concluded therefrom that a protective influence was exercised, in some cases, upon animals, with blood from individuals who had never suffered from typhoid fever, although larger doses were required. He suggested that this antitoxic power is possibly due to mild or unrecognized previous infection.

The agglutinating effect has been found in diabetes. The normal placental serum is said to possess marked destructive power for the *B. typhosus*.¹⁰

The presence of the reaction in such cases may occasion errors in the diagnosis, which must be guarded against. In a case of influenza, with nervous symptoms, headache, prostration, fever, bronchitis, we found

a decided reaction with a virulent culture. It was learned that the patient had had an attack of "typhomalarial" fever some eight years before. We established the diagnosis of influenza in this case by culture test, isolating the influenza bacillus from the blood, cultivating it in nutrient agar and examining in stained preparation.

Such difficulty is not confined to the blood of the human subject. In testing the blood of an apparently normal rabbit, not immunized, we were astonished to find that it possessed a high degree of agglutinating power upon the bacilli of virulent cultures, resembling in every respect that of typhoid serum. To determine whether this property was a normal attribute of rabbit's blood generally, we tested in ten other rabbits, but with negative results.

The blood of the horse, as stated by Bordet, often produces a clumping and granular appearance in typhoid culture, not distinguishable from typhoid blood except that it produces a similar agglutinative effect upon the "colon" bacilli, which typhoid does not.¹¹

We observed also, in testing hen's blood, that one specimen (of a number examined) produced marked effect upon the typhoid bacilli, agglutinating them in the same manner as typhoid serum.

We could not find it in the blood of other animals, that of the ox, sheep, calf, deer, dog, cat, pig, guinea-pig, mouse, pigeon, all acting in the manner of normal blood. Rabbit No. 1 was repeatedly examined, a number of specimens taken upon several different days, with a like result.

What causes the phenomenon in these particular animals? Although the numerous attempts to communicate typhoid fever to the lower animals have given a negative result in every instance, so far as producing the characteristic lesions as found in man, the fact is well established that Eberth's bacillus will multiply abundantly in many of them, and can be obtained from the spleen exactly as in the human subject, and that although infection is often fatal, a large proportion survive artificial inoculation.

A reasonable hypothesis might thus be drawn to account for the occurrence of typhoid fever in previously uninhabited districts, upon the prairies or in the depths of the woods, where the source of the infection can not be traced to human importation.

Descazals¹² reports an epidemic of "psittacose," a disease which Peter characterized as "typhus of parrots," recording the cases of forty-seven persons affected, with fifteen deaths. The disease is traced to the importation of parrots. An infected individual seems capable of transmitting the infection to others. The infection closely resembles typhoid, but the onset is often marked by local manifestations about the mouth.

But from whatever other cause this agglutinating substance may be present in the albuminoids of the blood, whether in lower animals or in man, the effect upon the typhoid bacilli may be distinguished from that obtained from typhoid fever blood. Upon dilution of the specimen examined, discarding the virulent for attenuated cultures, the bacilli in the latter will still become typically agglutinated with typhoid fever blood when diluted to a degree in which the pseudo-reactions entirely disappear.

Regarding the possibility of obtaining the diagnos-

¹⁰ Flexnor: Jour. Exp. Med., July, 1896.

¹¹ W. H. Jamieson: Brit. Med. Journal.

¹² Gazette des Hôpitaux, No. 111.

tic reaction in the early stages of typhoid, Case No. 16 of our series warrants especial attention from the fact that it was elicited upon the third day of the fever. A copy of the temperature chart, in this case received by mail from the neighboring city of Rochester, with the specimen of blood, we pass around for your inspection. The subsequent clinical history of this case confirmed the diagnosis. If further experience proves the practicability of recognizing the disease thus early, the value of the test, especially in justifying prompt adoption of precautions for the prevention of future infection, will be very great.

Five of the specimens of blood examined elicited from us a report contradictory to the clinical diagnosis. To these cases great interest also attaches—as their subsequent histories all tended to confirm the bacteriologic rather than the clinical diagnosis.

In Case No. 22 of our series the blood examination was made upon the fifth day after admission to the hospital.

The temperature record in this case; the significant clinical symptoms: Enlarged spleen (common, however, in many conditions in children), diarrhea, semi-stupor for several days; some doubtful rose-colored spots upon the abdomen, and finally, the fact that the child was taken from a typhoid-fever infected house (a sister occupying the adjoining bed in the hospital with a typical attack); certainly strongly suggested the clinical diagnosis of typhoid fever, which in fact had been made.

But note the result of the blood examination: The reaction was entirely negative, while that of the sister was prompt and decided. An opinion in accordance with this examination was therefore given. Naturally, the further progress of these two cases was watched with the greatest interest, and the hospital records, which we here also present, can be fairly assumed to be confirmatory evidence of the reliability of the test; the temperature of the boy falling to 99 degrees two days afterward, and not going above this again during the remainder of his stay in the hospital—some ten days.

In Case No. 34 of our series, the “typhoid state,” was especially marked; dry fissured tongue covered with a brownish-black fur, sordes-covered lips and teeth; temperature ranging between 102 and 104; diarrhea; no rose spots; hebetude; early epistaxis. Repeated examinations failed to reveal any agglutinating property of the blood. The subsequent history of this case was not that of typhoid, the grave fever symptoms disappearing two or three days after the examination. This patient, it may be interesting to note, developed instead a mild form of insanity, which persisting, he has since been committed to the State Asylum in this city.

In case No. 41, in which the typhoid condition and symptoms were also very suggestive; examined on the fifth day of the disease, the reaction was negative and our opinion, rendered in accordance, elicited the counter-opinion from the attending physician, a gentleman of wide experience, that he *knew* his patient had typhoid fever, notwithstanding. The subsequent clinical history of the case, however, did not justify his diagnosis, the joint lesions of rheumatic fever developing a few days later, typically. While many, especially of the etiologically obscure continued fevers, remain still to be submitted to the test, such work as has thus far been done seems in a remarkable degree to confirm its great value in diagnosis.

Widal concludes, as the result of his admirable work upon this subject, that: “A negative result obtained with the serum of a case of suspected typhoid, affords a presumption against the diagnosis of typhoid fever; but it is only a probability, especially if the examination has been made in the first few days of the disease. The examination should then be repeated in the next few days. The presumption that a case in which a negative result has been obtained is not typhoid becomes correspondingly stronger as the disease becomes more advanced.”

As supplementing investigations regarding the diagnosis of typhoid fever by means of the typhoid organism in the blood, we have made experimental observation upon the reverse problem, to wit: The detection, by means of the serum, of the typhoid bacillus in water, an important problem usually attended with much practical difficulty and often of doubtful result. The bacteriologic examination of drinking water resolves itself, ordinarily, into a search for the bacillus of Eberth and its differentiation when presumably found from the bacilli coli communis and other allied motile water organisms.

Miquel's scale for the classification of the purity of water, ascending from the “exceptionally pure,” containing from 0 to 10 bacteria per c.c., to the “very impure,” containing 100,000 and upward per c.c. while affording an excellent standard limit of comparison, is practically valueless from the standpoint of pathogenesis; water classed as “very pure,” containing but 100 bacteria per c.c., may be more dangerous than the very highest of this scale.

We demonstrate under the microscopes upon the table, the results obtained from an analyses of a specimen of ordinary hydrant water, infected with the bacilli of Eberth from a pure culture, and at the same time with “colon” bacilli and a number of other motile water bacteria.

Mixing in sterile tubes each containing 10 c.c. of beef tea, a few drops of this water, adding Parrietti's solution (ac. carboli., 5 grams; ac. hydrochlor., aq. dest., grams 100) and incubating at 40 degrees C. to eliminate most of the ordinary water bacteria. The tubes were plated (using agar) and these were maintained at 40 degrees C. for twenty-four hours, when we could distinguish with dry lenses, colonies suggestive of the typhoid bacillus by their landscape appearance.

With the sterilized needle these colonies were fished and after proper dilution active typhoid serum inoculated with the organisms. The specimens upon the table are hanging drops of the serum thus prepared. The colon and other motile organisms in the same serum are seen independently and moving in the field. The typhoid bacilli, proved to be such by animal inoculations and other tests, in striking contrast are agglutinated and motionless.

These results indicate that typhoid serum affords a simple and apparently certain means of differentiating the typhoid from similar organisms found in water, or at least, of corroborating results obtained from other methods of analysis.

Tincture of Moringa as Remedy for Icterus.—Dhargalker of Bombay, has secured remarkable results with the bark of the root of the *Moringa pterygosperma* in eight cases of catarrhal icterus, administered in a tincture prepared from the bark of the root, 2 to 4 grams, three times a day for adults, and 15 drops for children.—*Semaine Médicale*, December 23.