It is conceivable that complications and mortality would have been greater but for the sulphonamides, but I do not think so.

The 17 patients considered in this paper were aged 12 to 60. Pneumonia in infants did not differ essentially from the cases I saw in the previous year. Many chronic bronchitis over the age of 60 who would almost certainly have died during the winter from bronchopneumonia and congestive heart failure had death precipitated by influenza. Of the 17 cases, 12 recovered. Recurrent epistaxes were prominent in one boy, another patient had haemorrhagic vesicles of the inner cheeks, and one had a small pleural effusion. Pneumonia was bilateral in 4 patients. Before the epidemic proper began, 2 cases of influenzal pneumonia were seen—a fatal case in August on which a necropsy was done, and one in mid-October which recovered.

It is of interest to compare this experience of influenzal pneumonia with 5 deaths and 5 cases of lung abscess (and *Staph. aureus* the chief organism concerned) with recent experience of lobar pneumonia. From Oct. 1, 1942, to Dec. 31, 1943, I saw 107 consecutive cases of primary lobar pneumonia, the ages ranging from 5 to 65. There were 2 deaths, and 2 cases of lung abscess with recovery. From Jan. to Oct., 1943, I saw 13 cases of primary atypical pneumonia (one with rising titre of psittacosis antibody—Prof. Bedson), but none since. It is tempting to inquire if there is any relation between the recent frequency of primary atypical pneumonia and the influenza epidemic.

Concurrently with the influenza epidemic, primary lobar pneumonia became much more frequent here; 26 patients aged 5 to 65 were seen in 40 days, with one death. It may be that a number of these cases were really influenzal pneumonias, but there was not enough clinical evidence for so regarding them.

Summary

In the recent influenza epidemic, among 17 cases of influenzal pneumonia—ages 12 to 60—there were 5 deaths. There were 5 cases of lung abscess (3 fatal), and one patient who recovered had a metastatic panophthalmitis. *Staph. aureus* was an important invader. Sulphonamides were not beneficial. In 107 cases of primary lobar pneumonia—aged 5 to 65—there were 2 deaths, and 2 cases of lung abscess with recovery.

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PROGNOSTIC VALUE OF LABORATORY INVESTIGATIONS IN TYPHOID FEVER

BY

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Laboratory investigations in typhoid fever are usually employed for the confirmation of clinical diagnosis, either directly by the isolation of the infecting organism from blood, urine, or faeces, or indirectly by the estimation of antibody production, chiefly Vi and O agglutinins, as proof presumptive of the presence of *Bact. typhosum* in the human body. In military hospitals in India blood cultures in the early stages, agglutinations throughout the course of infection, and collection of evidence for the excretion of micro-organisms, even during convalescence, comprise the routine procedure for such cases. The analysis of collective results so obtained, in conjunction with clinical observations, indicated that the various combinations of signs and symptoms met with in this disease were associated with distinct variations in laboratory findings, the study of which was of considerable prognostic significance. Not only was it thus possible to gain an insight into the ups and downs of the struggle between host and parasite, but specific antityphoid serum therapy, practised in a large number of cases (to be presented in a subsequent communication), could also be placed on a more satisfactory basis.

The object of this paper is to describe and discuss the prognostic inferences drawn from a study of 280 cases of typhoid fever in which laboratory investigations were carried out at short intervals throughout the course of infection. Reference is made to certain aspects of the diagnosis and prophylaxis of typhoid that are directly related to the observations recorded here. For reasons of space tables and charts are not included.

The whole group of cases has been subdivided into six different clinical and bacteriological identities. Although some overlapping of symptoms, rather than of signs, was noticeable between the various subgroups, it was not extensive enough to confuse the main issues.

Clinical and Bacteriological Types of Typhoid Cases

1. *Simple Type*.—These cases presented the textbook description of the disease, with temperature which followed the course of three well-known stadia—*incrementi*, *acmes*, and *decrementi*. The total duration of pyrexia varied from 10 to 25 days, depending upon the inoculated state of the individual. In a person who had had multiple injections of T.A.B. vaccine—prepared in a reliable institution with appropriate strains of *Bact. typhosum*—all the stages were completed quickly, and the patient looked so well towards the end of the second week that, in the absence of laboratory diagnosis, doubts could be expressed as to the nature of the infection. Such cases were usually met with among military personnel with more than six years of colour service. In the uninoculated pyrexia was prolonged until the fourth week. In both types of individuals, however, the entire course of the disease was free from complications. Bacteriologically, blood culture was usually negative, since bacteraemia in such cases was of short duration. Agglutination tests, on the other hand, were most satisfactory, and of the type commonly designated as “Widal-positive”; the O titre was about 200 and the Vi agglutinins were as described in a previous communication (Bhatnagar, 1938). It was easy to isolate the infecting organism from urine or faeces, or both, during the second, third, or fourth week. The strain isolated was agglutinable by both O and Vi sera, and its average lethal dose (a.l.d.), for white mice weighing from 20 to 22 g., was more than 100 millions—the V-W type of organism described by Kauffmann (1935).

2. *Ambulatory Type*.—These cases represented the other extreme of the prognostic picture in that they were invariably fatal. Before the patient was obliged to seek admission to a hospital or take to bed properly, he had been definitely ill for over a week. The case below illustrates the various points:

A robust, healthy man, 28 years of age and 14 stone in weight, was feeling seedy for about 10 days before admission to hospital. During this period he took aspirin and quinine regularly to enable him to carry out his duties. He was ultimately obliged to stay in bed. On admission enteric was suspected, and in spite of careful nursing and efficient palliative treatment his condition deteriorated. On the fifth day he complained of pain in the lower abdomen. Clinical examination revealed perforative peritonitis. His general condition was, however, so bad that any surgical intervention was ruled out; he died a few hours later with a rectal temperature of 110° F. Necropsy revealed typical typhoid ulcers in the small intestine.

Laboratory investigations in such cases were most disappointing: they presented a completely negative picture—so much so that the reliability of clinical diagnosis was questioned on more than one occasion. No Vi agglutinins were detected at any stage of the disease, although in some cases the O antibody titre could be considered to be suggestive of typhoid infection. Diagnosis could be confirmed post mortem only by direct culture from inflamed Peyer's patches, spleen, gall-bladder, and bone marrow. In the few cases in which this facility was available it was particularly observed that the growth of *Bact. typhosum* on first isolation was scanty and the strain of only average virulence—a.l.d. more than 100 millions, and the organism agglutinable by both O and Vi sera.

3. *Toxic Type*.—These cases were usually seen either among the civilian population or among military personnel—such as drafts arriving from over-seas—who had not had the benefit of multiple T.A.B. inoculations. The patient was clinically toxic before the end of the first week of illness; the skin

was dry and the tongue dry and deeply furred. There was general clouding of intellect, and the mental processes varied from simple slow cerebration to general apathy or, conversely, marked delirium. Usually there was no localized involvement of any particular organ, but haemorrhage from the bowels occurred in a number of cases. The most characteristic bacteriological feature was an abnormal rise in the titre of O agglutinins with no evidence of Vi antibody formation. In this series the O titre varied from 2,000 to as much as 20,000. Blood culture was usually positive during the first week, but no excretion of organisms could be detected in later stages. In cases which ended fatally this held true and the high titre of O agglutinins was maintained. On the other hand, in those who recovered, either naturally but more often through serological intervention, some remarkable changes took place in the bacteriological picture within as short a period as 24 hours. There was a sudden drop in O titre to normal proportions (200–500), with simultaneous appearance of Vi antibody accompanied by what may be termed a flooding of both urine and faeces with typhoid bacilli. The strains isolated were fully virulent, inagglutinable by an O serum, but easily clumped by a Vi serum with an a.l.d. of less than 100 millions—the V type of organism described by Kauffmann (1935).

4. Prolonged Pyrexia (P.P.) Type.—The duration of pyrexia in such cases varied from 6 to 12 weeks. During this prolonged course the temperature showed a tendency to drop to normal on more than one occasion; but these oscillations could be easily distinguished from true relapses in that the temperature did not stay at normal longer than from 24 to 48 hours. Such cases were usually free from complications, the only complaint being "fever" for which causes other than typhoid infection—especially *B. coli*, pyelitis, and pulmonary tuberculosis—were looked for with negative results. The diagnosis was easily established by a positive blood, urine, or faeces culture. The characteristic feature was either a complete absence or a very low titre of Vi antibody. So long as Vi titre did not improve, the fever continued. It was only when this antibody developed, either naturally or by artificial introduction into the system through serum therapy, that the host got the better of the parasite and infection terminated. The micro-organism isolated was easily agglutinable by both O and Vi sera with an a.l.d. of more than 100 millions.

5. Embolic Type.—The predominant feature of these cases was the abnormal localization of the infecting organism in one of the organs—chiefly lungs, meninges, or intestine—resulting in bronchopneumonia, specific meningitis, or a severe form of melaena respectively. The clinical picture is commonly referred to as complicated typhoid fever. The course of infection was unduly severe and the mortality heavy. There was no evidence that the condition was metastatic in origin, the term "embolic" being applied only for descriptive purposes. The infecting organism was isolated from the peripheral blood with ease not only in the early stage but also during the second and third weeks if the patient lived. There was considerable excretion of bacteria via both the kidneys and the intestine; and in certain cases the unusual picture of blood, urine, and faeces all being positive at the same time was encountered. Serological tests, on the other hand, were disappointing, there being complete absence of Vi antibody with little rise in O agglutinins. The strain of *Bact. typhosum* isolated was highly virulent, with an a.l.d. in the region of 60 to 80 millions, inagglutinable by an O serum but reacting to Vi antibody.

6. Relapse Type.—During the course of typhoid infection relapses occur in a certain percentage of cases. Clinically there are no means by which we can assess the possibility of such an event taking place. Laboratory investigations, however, suggested that certain unusual occurrences should arouse suspicion about the possibility of a relapse—namely: (a) a positive blood culture during the third week where previous cultures had proved sterile; (b) a positive blood culture with the temperature on the down grade; (c) a fall in the titre of Vi agglutinins in the third week without a similar simultaneous effect on temperature; and (d), conversely, the maintenance of a high Vi titre with temperature showing a normal tendency.

Discussion

To appreciate the prognostic significance of the variations in laboratory findings in different types of clinical manifestations of typhoid fever it is necessary to take into account the part played by Vi antibody in typhoid immunity as described by Felix and his co-workers—for references see Topley and Wilson (1936). In our experience the presence of this antibody in a sufficiently high titre (50–250) always connoted a satisfactory outlook. If this antibody was present early in the disease and the high titre was maintained over a number of days it could be predicted with confidence that the course of infection was going to be short and the patient on the road to convalescence by the third week. Such cases are included in the *simple type* of infection described. They formed a large component of a previous communication on the value of Vi agglutination in typhoid fever, to which reference has already been made.

We have no record of a case in this series in which a high Vi agglutinin titre was associated with such fulminating symptoms as are included under the *embolic type* of infection, although 73 cases of this nature were studied. The Vi antibody was either completely absent or, if detected, the reading was seldom higher than 10–20; even this low titre was not maintained, and it appeared only spasmodically. If the case was to end fatally there was no rise in Vi agglutinins. On the other hand, in the few cases that recovered naturally—only 4 out of 73 in this group—the improvement in the clinical condition was preceded by an elevation of Vi titre. In two of these, with lung involvement, Vi antibody developed suddenly and a high titre (80–160) was kept up for 11 days. The lung condition cleared and the patient recovered after prolonged convalescence. In the other two, with bowel haemorrhages, the Vi titre dropped from 160 to 20 within 3 days, with a concurrent fall of temperature to subnormal. Both these cases relapsed—on the fifth and the sixth day respectively, with one and two similar relapses subsequently—before a sustained Vi antibody titre was elaborated naturally and the infection was eventually overcome on the 79th and the 88th day of disease.

Study of the *prolonged pyrexia (P.P.) type* of infection lent further support to the role of Vi antibody in the pathogenesis of typhoid fever. Nineteen such cases were observed. Clinically, everything was in the patient's favour, especially his general condition and the freedom from complications. The fever, however, continued for weeks. It came to an end only when a sustained Vi titre was recorded, either produced naturally or provided by specific serum therapy.

An abnormal rise in O agglutinins was seen to be associated with the *toxic type* of case, the titre of this antibody in different cases varying from 2,000 to as much as 20,000. In none of the other types of typhoid fever cases was this high reading encountered, nor was it experienced in their treatment with either Felix or convalescent serum. In view of the high mortality in this group—15 out of 27 cases studied having proved fatal—and the fact that recovery was always preceded by a considerable drop in the O titre of serum, the high rise in O agglutinins must be considered to be pathological, since its prognostic interpretation is directly opposed both to the generally accepted clinical concept associating O antibody production with favourable prognosis and the immunological observation that the O titre of a serum expressed its protective value in relation to endotoxins. As all the cases were highly toxic the possibility of *abnormal* O-antibody production becoming associated in some unknown manner with toxin liberation, rather than being responsible for its neutralization, cannot be ruled out, although there is no experimental evidence to support this view. It will also be seen from the observations recorded that O antibody is not concerned in the excretion of typhoid bacilli from the human body, since none was found to take place while the high titre lasted.

Of the *ambulatory type* 32 cases were under review. All of them were characterized by: (1) absence of complete rest during the first week after the signs and symptoms associated with the early stage of typhoid fever had appeared; and (2) the employment of antipyretic drugs. Both these factors produced catastrophic results, our records showing 100%

mortality. It can therefore be assumed that complete rest and free play for the rise in temperature are of paramount importance in the second stage of typhoid infection—the first being the incubation period—and that interference by such drugs as aspirin, quinine, and those of the sulphapyridine group, etc., for any length of time, is likely to affect the prognosis adversely if *Bact. typhosum* happens to be the responsible organism.

True relapses were recorded in 18 cases—over 6% of the total series. In 10 of these there was one relapse, in 7 others it was repeated, and one case relapsed three times. While a high percentage of positive blood cultures was obtained during the relapse period (in 14 out of 18 cases), on six occasions cultures were positive before the relapse had taken place. In four of these the temperature was on the down grade and two previous blood cultures had proved sterile; in the remaining two, cultures were sterile after the temperature had stayed subnormal for 4 and 5 days respectively. In all but two cases Vi agglutinins had practically disappeared during the subnormal stage of temperature. In these two exceptions, however, the curious combination of subnormal temperature, positive blood culture, and a Vi titre of 40–80 was encountered. The case with three relapses started well in that Vi agglutinins appeared early—on the ninth day—and continued until the 22nd day. Then there was a sudden drop, with temperature still at 100.2° F. Although the subnormal stage was reached on the 25th day, it remained so for only 5 days, the temperature then rising, with two similar subsequent events. These observations would justify the assertion already made as to the possibility of a relapse in the presence of unusual laboratory findings. The practice of a blood culture and an agglutination test when the temperature shows a downward tendency should therefore be considered worth a trial during the later stages of typhoid infection.

Some Practical Points

Reference may now be made briefly to the application of observations discussed here from the prognostic and prophylactic points of view. In a case suspected clinically to be suffering from typhoid fever there is a tendency to assess the result of an agglutination test in terms of a positive or a negative Widal reaction, depending upon the titre of antibodies so detected. And, what is more important, a so-called negative Widal is taken to mean the exclusion of typhoid infection. From the present observations, and the experience of typhoid serology over a number of years, it cannot be too strongly emphasized that, in a case of remittent pyrexia, absence of Vi antibody or a lack of an appropriate rise in the titre of O agglutinins does not in any way exclude the possibility of the infection being typhoid in origin. It would therefore be better if the term "negative Widal" were entirely eliminated from typhoid terminology, since the meaning commonly attached to it leads to a sense of false security and indulgence in medication of a type likely to worsen the ultimate prognosis in the manner already pointed out.

The utility of Vi agglutination as a diagnostic measure has given rise to considerable differences of opinion. The present communication should throw some light on this problem. It will now be clear that an early rise in Vi agglutinins should be expected only in cases with mild symptomatology. Where complications have set in, a reasonably high Vi titre will be encountered only if and when the clinical tide turns in favour of the patient, and this Vi reading will persist at least for the next few days. In spite of observations to the contrary we have failed to discover this antibody as a natural agglutinin. Its presence had always been found to be associated with the existence of *Bact. typhosum* in the human body. Results to the contrary were mainly due to non-specific reactions likely to arise when suspensions of Vi I strain (Bhatnagar *et al.*, 1938), now employed almost universally for the purpose of Vi agglutination, had been preserved too long and the organism, either before or after the preparation of agglutinating suspensions, allowed to undergo S→R variation.

From the prophylactic point of view attention has already been drawn to favourable prognosis in an individual who has

had the benefit of multiple antityphoid inoculations over a number of years. Credit in such cases is usually given to the quality or type of vaccine employed. From a series of experiments on antibody production after T.A.B. inoculation in human beings it was pointed out a few years ago (Bhatnagar *et al.*, 1937) that protection against infection was best afforded by repetition at suitable intervals of stimuli given to the antibody-forming apparatus rather than by the quality or type of a single stimulus. The correctness of this view has now been confirmed by a change towards severity in the type of an average case of typhoid fever in military hospitals, due to a large influx of comparatively unprotected civilian personnel for military service and the drafts of non-tropical residents from over-seas, the majority of whom have had only one course of T.A.B. vaccine. It is the considered opinion that the practice of this prophylactic measure at shorter intervals during the first two years of military service in the Tropics—(a) on being called up, (b) on disembarking in a tropical country, and (c) subsequently at the end of 6 and 15 months—would result in a great improvement in the prognostic outlook in the event of actual typhoid infection.

Summary

A close association between prognostic outlook and the results of laboratory investigations has been found to exist from the analysis of 280 cases of typhoid fever.

The cases have been classified into 6 groups, each with varying clinical and bacteriological characteristics.

Observations showed that if Vi antibody was present early in typhoid fever in a sufficiently high titre (50–250), and this titre was maintained over a number of days, the course of the infection would most likely be short (*simple type*).

In the *embolic type*—in which the Vi antibody was either absent or seldom above 10 to 20—improvement was preceded by a rise in Vi titre.

The *prolonged pyrexia (P.P) type* resolved only when a sustained Vi titre was recorded. It must be stressed that, in the case of remittent fever, absence of Vi antibody or the lack of an appropriate rise in O agglutinins does not exclude the possibility of the affection being typhoid.

An abnormal rise in O agglutinins was observed in the *toxic type*, the titre varying from 2,000 to 20,000. Since a considerable fall in the O titre of serum always preceded recovery, the high rise of O agglutinins must be regarded as pathological.

In the *ambulatory type* complete rest and non-interference with the rise in temperature appear to be of the greatest importance in the second stage of the disease.

Relapses occurred in 6% of the whole series. Unusual laboratory findings appeared to be associated with the possibility of relapse.

An early rise in Vi agglutinins should be expected only in mild cases.

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R. Torpin (*Amer. J. Obstet. Gynec.*, 1943, **46**, 557), who records a personal case and has collected 27 others from the literature, states that spontaneous haematoma of the rectus abdominis muscle occurs in both white and negro women. Primary aetiological causes were trauma, cough, labour, strain, or, rarely, external injury. Other primary factors were, rarely, muscle degeneration from typhoid fever or influenza. Secondary aetiological influences were age, multiparity, and terminal stages of pregnancy. Conservative treatment consisted in early diagnosis, complete rest, and blood transfusion. The maternal mortality was 15% and the foetal much higher. Torpin's case was a negress aged 34, a 12-gravida; operation was performed without evacuation of the clot, and both mother and child lived.