TYPHOID AND THE PARATYPHOIDS: A REVIEW

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Preliminary reports of the efficacy of chloromycetin in the treatment of typhoid fever are sufficiently encouraging to suggest that a new measure of control may readily be applied to this disease which is endemic throughout practically the whole world, and which has carried a mortality rate such as to have played no small part in history. It is worthwhile, therefore, to review at this time some of the immense literature which has accumulated, and in particular to note the various approaches that have been made towards the treatment and control of typhoid and its related fevers.

Historical

Typhoid fever was prevalent during the Parliamentary Wars (1642-48), and one of the earliest descriptions was that left by Thomas Willis (1684). Huxham (1739) described the Plymouth epidemic of 1737. There was little distinction drawn, however, during the 18th century between typhus and typhoid fevers. Petit and Serres described typhoid fever in 1813, and Trouseau (1826) described the intestinal lesions ‘both for the glory of my Master and for science,’ on behalf of his chief, Pierre Bretonneau, who seems not to have committed himself to print although he did make known his findings to the Academy. Louis (1829), at La Pitié Hospital also described the disease and the intestinal lesions, and was the first to use the term ‘fièvre typhoïde.’ To Gerhard of Philadelphia (1837), who had been a pupil of Louis, must be credited the first clear clinical and anatomical descriptions of the two diseases. Gerhard’s work was substantiated by that of Schönlein (1839) in Germany and of Ritchie (1847) and of Jenner (1849) in Britain. Ritchie introduced the term ‘enteric fever.’

An interesting contribution made before the bacteriological era was that by Budd (1873) who had also studied at La Pitié Hospital. He insisted that typhoid fever was spread by contaminated water and milk, the likely contaminant being the faeces of the convalescent patient. Eberth (1880) discovered the typhoid bacillus although it is likely that Klebs had recognized it earlier, and in 1884 Gaffky obtained the first pure culture of the bacillus which he showed to be the true activator of the disease.

By 1896 Widal and Sicard had demonstrated specific agglutinins in the serum of typhoid patients, making possible an agglutination reaction in the diagnosis of the disease, and the experimental work of Chantemesse and Widal (1898) led to the employment of anti-typhoid inoculation by Wright and Leishman (1900).

Clinical

The most comprehensive analysis of the clinical course and complications of typhoid fever is to be found in the writings of Osler, Thayer, Flexner, Cushing and others in the Johns Hopkins Reports of the years 1894-95, 1895 and 1900. These papers present a detailed account of typhoid fever as it occurred in Baltimore over a period of some eight years, and are well worthy of study. At the same time, however, it is to be remembered that typhoid fever is a disease of great variability in its virulence, its manner of onset and in the severity and duration of its course, varying greatly from one outbreak to the next. Hence no great benefit is derived from a study of the incidence of symptoms, the duration of the fever, the incidence of complications or even of the mortality rate as these apply in any one epidemic. Moreover, this peculiar variability of typhoid fever makes it extremely difficult to assess the value of therapeutic procedures.

For descriptive purposes it is usual to consider an invasive phase or period of onset, then to describe the features as they present themselves from week to week; the febrile period may last one week only or six weeks or even longer.

Period of Onset

The incubation period may be from one to three weeks but usually is about ten days. Willis (1684) wrote that ‘... the first assault is for the most part accompanied with a shivering or horror ...’. This is not so, for chills are not a pronounced feature of the early stage. Headache, often intense, loss of appetite and malaise are most common. Diarrhoea or constipation, usually the former, may be the earliest complaint. Epistaxis, which may be copious, is frequent, and occurs more often
in typhoid fever than in any other infectious disease. Bronchitis is usual and dry cough a very common feature. More unusual but no less important are the onset with abdominal pain which so easily simulates acute appendicitis, and that with meningism and photophobia, neck retraction and vomiting, even progressing to a purulent meningitis (Stuart, 1948).

**First Week**

During the first week the fever which is now the leading feature of the illness, gradually rises in a 'staircase' manner, the evening temperature being a degree or so higher than that of the previous evening, to reach its fastigium at 104° or 105°F. This is not necessarily so, however, in the case which begins with a chill as the fever may reach its fastigium in a matter of hours and often has done so by the time the patient takes to bed. The pulse is increased in rate but not in proportion to the degree of fever and is of characteristic dicrotic type. The eyes are bright and the face flushed; often there is at this early stage a flush over the chest—typhoid erythema. The tongue becomes coated and the abdomen is slightly distended and vaguely tender. Constipation may now be the rule rather than diarrhoea.

The fever becomes steady with only a small morning remission and is remarkably resistant to attempts to lower it by means of tepid sponging. It persists towards the second week at which stage a few crops of 'rose spots' appear on the chest and abdomen. Each crop lasts a day or two and is usually seen in approximately 80 per cent. of those with fair skins but in not more than a quarter of the dark-skinned. At the same time the antibodies of the infecting organism become demonstrable in the serum of the majority of cases.

**Second Week**

The fever is maintained or may fall to a lower level though usually still of a remittent character; the pulse is still slow but tends to lose its dicrotic character, and the clinical picture depends very much upon the severity of the illness. In a mild case the fever will gradually subside, the tongue clean and the appetite return, and one may well imagine that resolution is taking place in the turgid and infiltrated lymphatic tissue of the intestine. But in the severe cases toxæmia is the dominant feature and a clouding of consciousness, which is so typical of typhoid fever as to be implicit in the name itself (Greek Ἐφος, a cloud) and makes the victim of the disease so uncomplaining, deepens to the much more gross disturbance of consciousness of the 'typhoid state.' The eyes sunken but bright and roving, staring but unseeing, delirium only rarely noisy, restless movements of the arms and picking at the bed-clothes are all features of the typhoid state, and reminiscent of encephalitis. The skin is hot and dry and often loose from loss of weight and dehydration. The tongue is dry and dirty and sordes collect on the teeth and at the angles of the mouth. The toxic state may be so great as to cause death at this stage, not uncommonly in the first half of the second week.

Between the tenth and fourteenth days the enlarged Peyer's patches and lymphoid follicles of the intestine undergo necrosis and slough to form ulcers. The mesenteric nodes are enlarged, sometimes palpable and tender, and may also undergo necrosis. The spleen is enlarged and the liver may be palpable and vaguely tender. Haemorrhage may occur with the sloughing and formation of ulcers and is sometimes accompanied by a sharp drop in temperature to a subnormal level. Necrosis and sloughing may be extensive so that the whole of the mucosa of the terminal ileum and caecum appears gangrenous and in such cases there is marked abdominal tenderness; it is often a very difficult matter to decide whether or not perforation into the peritoneal cavity has occurred.

**Third Week**

Towards the end of the second week the fever has become intermittent in character and now gradually settles by lysis; the pulse, no longer dicrotic, is more in keeping with the temperature; loss of weight is by now very apparent and the patient is weak and exhausted. Though the disease process will often subside, other complications are wont to appear at this stage. The sorely-tried gut seems paralysed and meteorism may be troublesome and persistent. In a severely cachetic subject femoral and iliac vein thrombosis and parotitis are not unlikely. Neuritis is common and the 'tender toes of typhoid' seem to be a localized form of neuritis. Mental depression may last long into convalescence.

In subsequent weeks the temperature may remain well below normal, the hypothermia of convalescence common to both typhoid fever and malaria. Sometimes, however, the fever may relapse with a fresh invasion of the blood stream by typhoid bacilli, but often there are rises of temperature not accountable in this way, possibly related to too early physical effort or even to constipation.

A persistent irregular fever in the fifth and sixth weeks may be related to localization of the infection as in mastoiditis, periostitis, pyelitis, arthritis and liver abscess, to a necrotic mesenteric lymph node, to secondary pneumonia or to venous thrombosis.
Ambulant Cases

It must be mentioned that occasionally the sufferer from typhoid fever may never complain or take to bed despite high fever and occasionally patients may be admitted to hospital because of intestinal haemorrhage or perforation or sometimes because of ruptured recti muscles. The explanation may be that the clouding of consciousness, already referred to, is enough to prevent the patient realizing how ill he is and enables him to make light of his symptoms.

Paratyphoid Fevers

Achard and Bensaude (1896) isolated an organism which was not the typhoid bacillus from an osteomyelitic lesion of the sternoclavicular joint in a case of 'typhoid fever,' and introduced the term paratyphoid fever. Two years later in a similar way Gwyn isolated an organism which he called a paracolon bacillus. Gwyn's organism was subsequently isolated by Schottmüller (1900, 1901) and by Brion and Kayser (1902), and was designated *Bacillus paratyphosus A*. Schottmüller also isolated the organism of Achard and Bensaude, and it was termed the *B. paratyphosum B*. In 1916 Hirschfeld isolated an organism from the blood of a Serbian soldier who died of paratyphoid fever, an organism for which he suggested the name *B. paratyphosum C*.

These organisms and the typhoid bacillus differ in their pathogenicity and in the type of disease which they cause in man. The typhoid bacillus and the paratyphoid A and C bacilli are not natural pathogens of animals though the paratyphoid A bacillus has been isolated from the pig (Broudin, 1927); they commonly cause enteric fever but not acute gastro-enteritis in man. The paratyphoid B bacillus, on the other hand, although mainly a human pathogen has been more often recovered from animals and birds (Hor-maeche and Salsamendi, 1936, 1939; Bartel, 1938; Edwards and Bruner, 1943). In man the organism causes enteric fever but may also cause acute gastro-enteritis. Topley and Wilson (1946), however, point out that there are differences between the strains causing enteric fever and gastro-enteritis.

In general the dose of paratyphoid organisms required to produce infection is greater than the corresponding dose of typhoid organisms. Hence epidemics of paratyphoid fever are less commonly water-borne than are epidemics of typhoid fever. Infected food and flies are the means whereby paratyphoid fevers are spread. Paratyphoid A fever is the commoner in the Middle and Far East and paratyphoid B in Western Europe. Paratyphoid C fever is practically confined to the Middle and Far East.

Clinical

The paratyphoid fevers may produce a picture similar in all respects to typhoid fever but the tendency to produce necrosis and ulceration of the lymphoid aggregations in the bowel is much less, and is extremely rare in paratyphoid C fever. Catarrhal inflammation of the small bowel and ulceration of the large bowel, especially the caecum and ascending colon, are common in paratyphoid B fever and diarrhoea is in consequence a leading feature. The lesser tendency to necrosis and ulceration means also a much diminished incidence of the complications of perforation and haemorrhage.

The fever pattern is less clear-cut as a rule than that of typhoid fever and is frequently of an irregular and intermittent character. Bradycardia is not typical as in typhoid fever. On the whole the overwhelming toxæmia of the 'typhoid state' is absent except in paratyphoid C fever and in some cases of paratyphoid A fever; rose spots are not so frequent and the illness is generally less severe. There is, however, a greater tendency in the paratyphoid fevers, and especially so in paratyphoid C fever, to the development of fixation abscesses from which a pure growth of the paratyphoid bacillus may often be obtained. The development of such an abscess causes a recrudescence of the fever and may by reason of its site determine a fatal outcome.

Less Common Varieties of Enteric Fever

Several of the salmonella organisms which commonly cause gastro-enteritis in man have, on occasion, been recovered from the blood stream in cases of continued fever.

*S. cholerae-suis* and its Kunzendorf variant may give rise to a septicaemia and typhoid-like fever. Boycott and McNee (1936) record a case of continued fever with a fatal purulent meningitis. *S. cholerae-suis* was isolated both from the blood stream and from post-mortem material. Harvey (1937) published 21 cases admitted to the Johns Hopkins Hospital over a period of four years and found 50 other cases in the literature. Schwabacher, Taylor and White (1943) mentioned a further 17 cases in the literature following Harvey's paper and added two fatal cases of their own. They suggest that the comparative rarity of the disease in man is related to the relative inability of the organisms to establish themselves in the small numbers usually ingested. *S. bareilly* was isolated from cases of enteric fever in India by Bridges and Scott (1931). *S. enteritidis* was isolated from cases of enteric fever during the Chaco War by Savino and Menendez (1934) and was a relatively common cause of enteric fever during the Japanese Campaign (1942-45). Smith
and Scott (1930) described three cases of continued fever in Aberdeen, the infecting organism being *S. dublin*. This organism also caused enteric fever as did *S. typhimurium* amongst troops engaged in the recent campaign in Assam and Burma. Kerrin, et al., in 1935, and more recently Partington and Cooper (1948) have each reported a case of septicæmia due to *S. orien-amburg*.

These organisms can give rise to enteric fever of varying degree of severity and in some there may be intestinal ulceration comparable to typhoid fever. In addition there is a marked tendency to such complications as abscess formation, arthritis and purulent meningitis.

**Diagnosis**

The first essential towards early diagnosis of typhoid fever is awareness that the disease is endemic in most countries of the world and hence cases are liable to be met at any time. Further, enteric fever should be suspected in any case of sustained fever, otherwise inadequately explained after three days' duration, and blood culture carried out. For primary culture a fairly heavy inoculum of blood into a broth medium containing 'liquide' to eliminate the effect of complement is probably the best method. Blood culture will generally be positive in the first week of the disease and with decreasing frequency thereafter. At the same time, but with an increasing frequency of positive results in the subsequent weeks, urine and faeces should be cultured, ideally using several enrichment media for the latter. Sometimes in the later stages of the paratyphoid fevers the organism can be isolated from the pus aspirated from an abscess, and very often in fatal cases of enteric fever of all types, from the contents of the gall bladder.

Isolation of the causative organism thus remains the method of choice not only in establishing an early diagnosis but also as the certain method of differentiation between the varieties of enteric fever. In convalescence, culture of the faeces and urine, and possibly of the duodenal contents after aspiration through a Miller-Abbott tube, serves to discover which cases become transient or chronic carriers (about 2 to 3 per cent. cases).

The Widal agglutination reaction generally becomes positive at the end of the first week, but can only be a contributory diagnostic procedure. In a patient with no history of inoculation or of previous infection a titre of 1/50 for 'H' agglutinins or of 1/100 for 'O' agglutinins in the first ten days affords strong presumptive evidence of infection. In the previously inoculated, 'H' agglutinins may remain in the blood and even a rise in titre is of no diagnostic significance. On the other hand the presence of 'O' agglutinins to a titre of 1/100 six months after inoculation is suggestive particularly when the titre continues to rise. In the rare cases in which both 'H' and 'O' agglutinins are absent from the blood throughout the course of the disease, the Vi agglutination reaction may prove helpful (Monthly Bull. Emerg. Publ. Hlth. Lab. Service, 1943).

Leucopenia is usual in typhoid fever and may be of additional assistance in the early stages of the disease, but is by no means the rule in the para- typhoid fevers where even a polymorphonuclear leucocytosis may be found.

**Treatment**

There is considerable controversy in the past literature on how the victim of typhoid fever ought to be fed; severely restricted diets and ample diets have both had their proponents. However, since the disease lasts for two to three weeks or even longer and there is no means of foretelling how long it may last in the individual case, and since exhaustion becomes so marked a feature of the later stages there is now some measure of agreement that it is necessary to persuade the patient to take a diet of at least 2,500 calories per day. The diet should be easily digestible with roughage reduced to a minimum. Glucose, milk, fruit juice, bread and butter, mashed potatoes, minced meat and milk puddings may all be given. Dehydration tends readily to occur but is obviated if the fluid intake exceeds the urinary output by a litre and a half per day. Relief of symptoms, especially cough, headache and hyperpyrexia, good nursing and the efficient disposal of excreta are implicit in good management.

Of the complications, meteorism is often most troublesome, but is often relieved by the application of heat to the abdominal wall (Jenner's turpentine stupe is surprisingly effective in many cases). In more resistant cases, pituitrin, eserine and duodenal suction through a Miller-Abbott tube may be tried. Where haemorrhage occurs the patient should be kept quiet and comfortable with as little sedation as is necessary. Transfusion should not be resorted to unless the haemorrhage is gross and continuing. Where perforation is suspected laparotomy should be carried out although it is not often a life saving procedure.

During the past ten years efforts have been made on a world-wide scale to discover some more specific means of treatment and there has been considerable encouragement in the development of serum and bacteriophage therapy, of chemotherpay and of the use of antibiotics.
Serum Therapy

Grasset and Gory immunized guinea-pigs, rabbits and horses and studied the immune sera at the Pasteur Institute in Paris (Grasset and Gory, 1927a, 1927b; Gory and Grasset, 1928). Grasset (1930) then used the immune serum prepared from the horse in a therapeutic trial at Johannesburg, where he found it of advantage to use local strains of the typhoid bacillus in preparing the serum and to concentrate the immune serum. Using this serum he found that in a series of 35 cases treated during the first 12 days of the disease, 32 showed considerable remission of fever and decrease of toxemia symptoms, and that 19 of 24 cases in which the serum treatment was commenced after the twelfth day showed similar though less marked improvement. By 1931 (Grasset, 1931) he was using a polyvalent (TABC) serum and had treated over 600 cases, and by 1938 (Grasset, 1938) was able to report that he had reduced the mortality rate from 20 per cent. to 10 per cent., having treated about 3,500 cases. Furthermore, where serum had been administered in the first three days of the disease, the mortality rate fell to 3 per cent.

Felix and Pitt (1934) conducted experiments on mice and concluded that a serum having a high titre of 'O' and 'Vi' antibodies was the most effective therapeutic agent. Felix (1935) extended his investigation to human cases of typhoid fever in Palestine and found a very striking amelioration of the toxemic symptoms following serum injection. He attributed this to the 'O' antibodies, but was unable to demonstrate that the 'Vi' antibodies effectively suppressed bacterial invasion as he had hoped. A therapeutic serum containing both antibodies prepared according to the method of Felix and Petrie (1938) and standardized by Felix' (1938) technique was adopted by a League of Nations Commission in 1938 as a standard serum.

With Felix' serum Robertson and Yu (1936) treated 52 patients in Shanghai. Twenty showed a decrease in toxemia symptoms and decrease of pyrexia, and seven a decrease in toxemia symptoms only. Cookson and Facey (1937) treated 73 cases at Poole, McSweeney (1937) 61 cases at Dublin, Hodgson (1944) 57 cases of whom 25 cases had serum, at Liverpool, Pijper and Crocker (1939) 36 cases at Pretoria and Landor (1941) used serum at Singapore in a number of cases, though he was unable to supervise personally all the cases being treated. All of these observers confirmed Felix's view as to the value of serum therapy and Pijper and Crocker considered that there is a definite relation between the course of the disease and the titre of 'Vi' antibodies in the patient's serum. The serum was prepared by the Lister Institute and dispensed in 33 cc. and 66 cc. quantities. Administration was by intramuscular injection or intravenously in the more toxic cases.

Bacteriophage Therapy

In 1926 D'Herelle suggested the use of bacteriophage in the treatment of typhoid fever, but though some excellent results were obtained they were, on the whole, variable (Bower, 1938). Craigie and Brandon (1936a, 1936b) then demonstrated not only specific Vi-anti-typhoid bacteriophage but that there were several such bacteriophages, and later Craigie and Yen (1938) showed that serologically identical strains of S. typhi could be differentiated by the use of specific phages. Fisk (1938) and Ward (1943) showed that mice experimentally infected with S. typhi could be treated successfully by means of parenteral injection of type-specific phage. Knouf and his colleagues (1946) continued Bower's work at Los Angeles using type-specific bacteriophage in the treatment of 96 patients; 1 ml. of the Craigie and Yen type II phage diluted to 500 ml. with 5 per cent. glucose was given by slow intravenous drip. Since not all strains are sensitive to this phage and several days are occupied in testing them, Desranleau (1948) used a polyphage (types I to IV) in 20 cases.

The results were very promising, particularly where treatment was given in the early stages. There is a rigor with a fall in blood pressure and rise in temperature for a few hours after injection. The temperature falls to normal within 24 to 48 hours and the 'typhoid state' disappears. Blood cultures became negative but three of Desranleau's cases given phage late in the disease became carriers.

Chemotherapy and Antibiotics

Buttle, et al. (1937) demonstrated that sulphanilamide inhibited the growth of S. typhi in normal blood in vitro though not in broth, and that mice could be protected from multiple lethal doses of S. typhi and S. paratyphi B by its use. However the sulphonamide drugs alone have not proved to be of value in the treatment of typhoid and paratyphoid fevers in man (Medical Research Council Report, 1943).

Bigger (1946) found that the combination of penicillin and sulphathiazole had a pronounced bactericidal effect on S. typhi and suggested making use of this synergistic action in treatment. McSweeney (1946) tried this method in six cases of typhoid fever in Dublin and reported dramatic improvement. He gave ten million units of penicillin and about 34 gm. sulphathiazole in four days and a second similar course after an interval of two days. Pyrexia subsided, toxic symptoms dis-
appeared and the organisms were cleared from the blood, faeces and urine. Parsons (1948) reported on a trial of this method on cases of typhoid fever in British Military Hospitals in the Middle East, but was unable to confirm McSweeney’s results.

Reimann and his colleagues (1945) reported the trial of streptomycin in five cases of typhoid fever and considered that it had exerted some bactericidal effect. They recommended its administration by both parenteral and oral routes.

Chloromycetin, originally isolated from *Streptomycyes venezuelae* by Erhlich et al. (1947), was found to be active against rickettsiae, and used therapeutically in typhus fever due to *R. prowazeki* by Smadel and his colleagues (1948). Smadel’s group then proceeded to try its effect on scrub typhus fever in Malaya and in so doing accidentally treated and observed its effect on typhoid fever. Woodward, Smadel and others (1948) reported the first ten cases of typhoid fever treated with chloromycetin. There is an immediate improvement in the patient’s general condition, a lessening of toxicity and a rapid fall of temperature. Given orally there is a rapid disappearance of bacilli from the faeces. Murgatroyd (1949) reports a case of typhoid fever in which the favourable outcome may well have been due to chloromycetin therapy, and Bradley (1949) in a preliminary communication on the use of chloromycetin in a recent outbreak of typhoid fever comments on the dramatic relief of symptoms and pyrexia. Chloromycetin has recently been synthesized and named chloramphenicol (Brit. Med. J. 1949). The synthetic product is effective in typhus, in lymphogranuloma venereum and in psittacosis, and reports of its use in typhoid fever are awaited.

**Treatment of Carriers**

The control of the chronic carrier is a troublesome problem and where the occupation of the individual has involved the handling of food, subsidies and even threats have been amongst the many measures to which resort has been made. It is of small wonder that numerous medical and surgical procedures have been advocated in order to rid the unfortunate carrier of his organism. Laxatives, biliary disinfectants, vaccines and phages have generally proved unsatisfactory.

Cholecystectomy, originally suggested by Dehler (1907), is in some cases effective (Bigelow and Anderson, 1933; Coller and Forsbeck, 1937). Appendicectomy and nephrectomy have also been carried out.

Iodophthalein, a biliary antiseptic, was suggested by Onodera et al. (1931), and several successes have been reported (Saphir and Howell, 1940; Enright, 1941; Saphir et al., 1942).

Levi and Willen (1941) reported the cure of a chronic typhoid carrier with sulphaguanidine, and Loewenthal and Corfield (1943) found this drug effective in a chronic carrier of *B. paratyphosum*. Cutting and Robson (1942), however, failed to produce any effect in six chronic carriers after treatment with iodophthalein, sulphonamides and phenothiazine.

Bigger’s method of employing the synergistic action of penicillin and sulphathiazole was applied to two carriers by Comerford, Richmond and Kay (1946, 1947) with success. Fry and his colleagues (1948) tried the method on a larger series of cases but did not have encouraging results though they considered that penicillin was excreted in the bile in adequate amount. Rumball and Moore (1949a) cleared a chronic carrier using a combination of penicillin and sulphaerazine and suggest that it is necessary to maintain the blood sulpha level at over 10 mgm. per 100 ml. in order to obtain the full synergistic effect of penicillin.

Rustein et al. (1945) studied the effect of streptomycin. Parenterally administered streptomycin had little or no bacteriostatic effect on typhoid bacilli in the faeces, and given orally in capsules the effect was only transitory.

Chloromycetin has been used recently in a chronic typhoid carrier by Rumball and Moore (1949b), but although the organism was sensitive to chloromycetin in vitro, it was not cleared from the faeces after chloromycetin had been given in doses of 30 mgm./Kg. body weight for seven days. The authors state that this dose was about three times greater than the calculated therapeutic dose for the acute disease and suggest that even heavier dosage may be required for the chronic carrier.

**Prevention**

**Hygiene.** The decline in the incidence of enteric fever in this country dates from the passage of the Public Health Act of 1875, together with the abatement of the grosser nuisances. At about the same time Max von Pettenkofer had all but rid the city of Munich from typhoid by the provision of a proper drainage system. Pure water supplies, efficient sewage and garbage disposal, and the maintenance of standards of cleanliness for food production and distribution still provide the best means of limiting the disease. Notification of the disease when it occurs and the search for and control and treatment of carriers are other indispensable measures.

**Immunization.** The practicability of inoculation was demonstrated by Wright (Wright and Semple, 1897; Wright, 1902), and he inoculated over 3,000 troops in India and the British Forces in the South African War. Russell (1913) continued and
extended this work in America. Greenwood and Yule (1915) demonstrated the markedly lower incidence of typhoid fever in a statistical analysis of the data of the Antityphoid Committee (1913). Boyd (1943a), in an account of the experiences gained in P.O.W. Camps near Benghazi where sanitary conditions were of a very low order, provides strong evidence of the effectiveness of the TAB vaccine used by the British Army and demonstrates its superiority to that used by the Italians. In one camp where there were about 24,000 British troops there was an absence of enteric fever although it was present among their Italian captors. In the other camp with Italian prisoners, enteric fever was not controlled by their own vaccine but diminished strikingly after the prisoners had been inoculated with the British Army vaccine.

An efficient vaccine must be prepared from virulent strains under standard and controlled conditions. The British Army TAB was a heat-killed, phenol-preserved vaccine. Grasset (1935) in South Africa prepared an endotoxoid vaccine which was used in South African troops in the North African Campaign with a protective effect equal to that used by the British Army (Boyd, 1943b). Felix (1941) prepared an alcoholized vaccine in which the Vi antigen is destroyed to a lesser extent than in a heat-killed vaccine. Although this vaccine has not been used in a field trial on a wide scale, there is no reason to doubt that it will be at least as effective as the others.

Despite the apparent success of inoculation, however, there are those who argue that the real factor to which the lowering of the incidence of typhoid fever is due rests in improved sanitation. The experience of Anderson and Richards (1948) might lead to such a conclusion. They encountered an outbreak of typhoid fever in a closed community of inoculated persons and concluded that the immunity conferred by TAB inoculation cannot be of a high order; that once there is a breakdown of hygiene and the typhoid bacillus is liable to gain access to the body, the magnitude of the infecting dose and the virulence of the strain play a part in addition to the resistance of the individual. Immunization, therefore, cannot replace hygienic measures and however effective it may be in producing immunity, it ought not to be allowed to induce a false sense of security.

Anderson and Richards also noted that the clinical course of the disease was not significantly influenced by previous immunization. Such, too, was the conclusion of Bulmer (1943) in a report based on the cases admitted to a military hospital in the Middle East over a period of 18 months.
A SURVEY OF RECENT DEVELOPMENTS IN BLOOD TRANSFUSION
PART I

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At the outbreak of the recent world war, the study of blood transfusion passed from the clinician to the laboratory worker. Since that time bacteriologists, pathologists, serologists, geneticists, physicists, biochemists, statisticians and engineers have all played a part in covering a vast field of study. The developments resulting from their work have been such that it is no easy matter for even the full-time laboratory worker to keep abreast of the times. These two articles can therefore survey only some of the advances, as seen by the author, which are of common interest to the laboratory worker and to the clinician.

Developments will be considered under the following headings:—

1. Collection, storage, preservation and handling of blood. The in vivo survival of transfused red cells.
4. The diagnosis and treatment of haemolytic transfusion reactions, including incompatible transfusion.
5. The study of disease with the aid of transfusion.


Selection of Donors

The past ten years has seen greatly improved standards with regard to blood donation. The National Transfusion Service permits only healthy persons who have not suffered from certain diseases to be bled. This is essential since the assurance must be given that blood donation is harmless. Such an assurance, presumably, has always been given, but cannot always have been justifiable since persons suffering from certain diseases, for instance high blood pressure, were often used as donors, and such persons may suffer serious harm when bled, especially repeatedly, the standard amount (420 cc). Rigid precautions must be taken to see that donors are in fact...