

TYPHOID FEVER.

SYNONYMS.—*Enteric Fever; Abdominal Typhus; Nervous Fever; Autumnal Fever.*

Definition.—Typhoid fever, a disease characterized by the penetration into the intestinal lymph follicles, and often into the fluids of the body at large, of the bacillus typhi or of the bacillus coli (when the latter has assumed virulence) and their toxins or endotoxins, is the expression of a reaction of the adrenal system, having for its purpose to rid the body of these pathogenic germs and their poisons.*

Symptoms.—The incubation period lasts generally two or three weeks, occasionally less. The symptoms appear gradually, beginning with a feeling of weariness, slight nausea, loss of appetite, sometimes diarrhoea. The tongue becomes coated, the expression dull. Pain is often present as headache, and in the back and legs; in the head and neck it is sometimes so severe and persistent as to resemble that of meningitis. The rise of temperature is usually gradual, sometimes sudden, to reach 102° F. (38.9° C.) or even 103° F. (39.5° C.) by the time the disease is well started. Chills of varying severity, followed by sweats, are not unusual. At the onset, delirium and bronchitis may also be seen, the latter especially in children. In the pneumonic and renal types of typhoid, the nature of the disease is likely to be marked for some days by evidences of pneumonia or acute nephritis; at the end of this period the diagnosis is warranted if fever is observed to continue.

The disease is generally considered to have begun when the patient is obliged to take to bed. From this time on it is found convenient to summarize the symptoms as they occur in successive weekly periods.

First Week.—The pains already mentioned persist. The intellect is generally blunted, but this is not an infallible sign. Wakefulness is sometimes met with, but there is usually no delirium in the first week. Fever continues, and the skin is hot and dry; a diffuse erythematous rash may appear. The daily temperature shows a slight rise from morning to evening; it also rises gradually throughout the week. The pulse

* Author's definition.

shows greater frequency, less marked, however, than the temperature rise; it is easily compressed and often dicrotic.

Near the end of this period, spots of a rose color appear on the skin, usually on the abdomen. They number usually not more than twenty or thirty, except in those cases where the distribution is widespread. Other symptoms include nausea, disinclination to take solid food, white furred tongue, diarrhoea (occasionally constipation) and slight cough. At the end of the week the spleen is found to be enlarged, but it is rarely the seat of pain. The urine is usually lessened.

Second Week.—The symptoms become more severe. There is rapid loss of strength. Dullness of countenance and apathy increase, until the face shows little or no expression; deafness is an additional factor. The headache slowly disappears, and is replaced by delirium of variable severity, more apt to be of a quiet, muttering character than otherwise. The rose-colored spots appear on the abdomen and chest in successive crops, each lasting three or four days, and leaving a slight discoloration of the skin. The temperature remains high and may rise above that attained in the first week; diurnal variations continue. The height which it reaches affords commonly, but not invariably, an indication of the severity of the case. The pulse-beat shows a rise in frequency, but usually does not exceed 100 until the latter part of the second week. The first sound of the heart is perceptibly lowered in volume, and congestion in the lungs may appear as an evidence of cardiac weakness. Moist and dry râles may be heard. The tongue again has a white, furry coat; later this disappears, leaving the tongue bare and red, with a tendency to become dry and cracked. The lips are similarly affected. Commonly the mouth contains mucus, which renders it sticky and hinders mastication, and provokes thirst, while the gums and tongue are apt to bleed. The stomach is less irritable than during the first week, but in general nausea and anorexia persist. The abdomen is now found to be tympanitic, owing to the accumulated gases resulting from fermentation and the inability of the weakened muscular layer to drive it out. Constipation may occur, but more commonly there are numerous diarrhoeal evacuations, ochre-yellow in color, copious, liquid, with shreddy matter and offensive odor.

In these stools the bacillus of typhoid can be detected in the course of the second week. Death occasionally occurs toward the end of this period, owing to perforation of the intestine.

Third Week.—Muscular weakness and emaciation have become marked. Delirium is continued, depending in severity on the individual. In the severe type it may be replaced by coma vigil and subsultus tendinum. Staring eyes and flushed skin give the face a peculiar expression; the patient is no longer conscious. The rose-colored spots continue to appear. Repeated sweats occur at this stage, in a few cases earlier in the course of the disease. They are followed by eruption of small, temporary vesicles or sudamina. The temperature continues high, but with more considerable remissions, the morning and evening determinations differing sometimes by three or four degrees. The pulse is now found to be more frequent and small in volume. The cardiac first sound is markedly weakened. In bad cases breathing may be shallow and hastened.

Diarrhoea is continued and may be severe; large numbers of bacilli are present in the stools. Sometimes the stomach remains irritable, and the resulting insufficient nutrition causes the patient to become exhausted. Jaundice is occasionally seen; with it is often associated epistaxis of corresponding severity. In such cases the stools are dark colored and the urine contains albumin. Thrombosis of the veins is not uncommon and usually occurs in the legs. Dilation of the heart from degeneration and weakening of the musculature should be watched for; the first sound is decreased and the second pulmonic accentuated. The quantity of urine is now greater, and its toxicity remains high, particularly when treatment with cold baths has been used. Typhoid bacilli are found in the urine in twenty-five per cent. of all cases.

At this stage perforation and hæmorrhage are commonest. These are favored by the accumulation of gas in the bowel. Hæmorrhage occurs in about 5 per cent. of the cases and is fatal in one-third of this number. It may be gradual and slight in amount, or sudden and voluminous. The symptoms, which sometimes appear before hæmorrhage has occurred, include lowered temperature, cold skin, weak and frequent pulse. The

likelihood of fatal result is indicated by the degree of prostration of the patient. In general, the loss of blood is followed by cessation of delirium and return of consciousness. Pain is present in some cases of hæmorrhage.

Perforation of the intestine is accompanied by a fall in temperature, also by a cold skin and increased pulse-rate, as in the case of hæmorrhage. There is sudden pain in the belly, in most cases; the abdomen is at first tense, but soon shows swelling from the escape of gas from the gut. The face has a pinched expression, and the rate of respiration is increased. Vomiting is not uncommon. The urine may be lessened in amount. Death almost invariably follows perforation, either at once from collapse, or in the course of a few days from peritonitis. Perforation and peritonitis sometimes follow hæmorrhage, but it may occur without perforation. Death can result from complicating inflammations in various portions of the body, commonly in the lungs. This may occur in cases otherwise apparently mild.

Fourth Week.—In this period the symptoms usually diminish in severity, and convalescence begins. Sweats are likely to persist. The temperature gradually falls and becomes intermittent, being normal in the morning and rising again in the evening. Additional elevations may be noted as the result of excitement, exertion, or mistakes in diet. The pulse-rate usually subsides to normal, but may remain high for some time. Evidence of continued cardiac weakness is sometimes seen in œdema of the lower extremities, and thrombosis of the veins is common in this stage. Boils and bed-sores may occur, and the hair has a marked tendency to fall out. Inflammation of the bones is not unusual in the young during convalescence.

In more serious cases of typhoid, the symptoms may continue through the fourth and fifth weeks. Sometimes the temperature may show irregular and rapid rises and falls of wide range. Emaciation and weakness are marked in these prolonged cases. The pulse becomes very weak, and the sphincter muscles lose their tonicity. Death may occur from perforation, exhaustion, or cardiac failure.

Pathogenesis and Pathology.—The bacilli of the typhoid group include the colon bacillus and, whether as a result of

rapid multiplication of the latter or of the assumption by it of greater activity, it can assume the virulence of the typhoid bacillus irrespective of any infection, when the environment is suitable. In the intestinal canal, which contains constantly the bacillus coli communis, the condition which renders possible such an assumption of virulence by this germ is the presence in the intestinal juice of an insufficient proportion of auto-antitoxin.*

Typhoid fever may be caused, therefore, without infection of external origin when, either through hypoactivity of the adrenal system, or through excessive utilization of the blood's adrenoxidase (as during exhaustion and prolonged exertion or labor), the proportion of auto-antitoxin in the body at large is inadequate.* This accounts for the development of typhoid fever in the so-called "spontaneous origin" group: in troops, after long and exhausting marches, in the overworked and debilitated, etc., where there is no evidence of infection by typhoid bacilli of exogenous origin.*

In the great majority of cases, however, the disease is caused by typhoid bacilli ingested with food or beverages, especially water derived from a contaminated source. While debilitated individuals, *i.e.*, individuals in whom the adrenal system is hypoactive (and whose intestinal juice is therefore poor in auto-antitoxin) are more readily infected,* subjects in apparently normal health do not seem to be exempt.

The close kinship between the colon bacillus and the typhoid bacillus is now generally recognized. Ohlmacher¹¹² writes in this connection: "One of the most significant arguments for the close relationship of these bacterial groups seems to be afforded by the now generally adopted practice of 'rejuvenating' bacilli of the colon group secured from saprophytic surroundings, as from *water*, by growing them for several generations under the artificial laboratory environment before making physiologic differential tests." . . . "Many of the acquired characteristics make a suspiciously typhoid-like behavior in a so-called colon bacillus."

The development of typhoid fever among troops during hard campaigns involving much fatigue, is well known. Houston¹¹³ states that "the efficiency of the army medical service, although high, has failed to prevent the British troops in South Africa from suffering from enteric fever to a deplorable extent." Constans of Montpellier¹¹⁴ showed twelve years ago, that fatigue was a very important factor in the pathogenesis of typhoid fever; while T. Legry¹¹⁵ concludes, with other observers, that

* Author's conclusion.

¹¹² Ohlmacher: "Amer. T. B. of Pathology," p. 234, 1901.

¹¹³ Houston: Brit. Med. Jour., Aug. 17, 1901.

¹¹⁴ Constans: Brit. Med. Jour., Feb. 16, 1895.

¹¹⁵ T. Legry: Gaillard's Med. Jour., Jan., 1896.

"overwork, fatigue, loss of sleep, poverty, immoderate exercise, play a very important part" in the development of sporadic cases and epidemics.

That the colon bacillus may become pathogenic under the circumstances mentioned is suggested by the marked influence of general adynamia upon the virulence of the pneumococcus, although in the case of the latter germ, the pathogenicity is due to its rapid multiplication.

Some of the morbid phenomena enumerated are but manifestations of a violent reaction of the body's protective resources.* The fact that animals may be immunized by gradually increased doses of living or dead typhoid bacilli and that they are now known to cause the appearance of a bacteriolytic and antitoxic substance in their blood, points clearly to the identity of the organs stimulated by the typhoid toxin or endotoxin: those of the adrenal system, through the test-organ.* Hence the marked febrile process, which continues until the pathogenic organisms—living and dead—and their toxins or endotoxins are destroyed.*

The energy with which the protective functions are stimulated by the typhoid toxins or endotoxins is well shown by the marked localized leucocytosis evoked in favorable cases.* The swelling of the intestinal lymphoid follicles is in fact greatly due to the presence therein of an enormous number of phagocytic endothelioid cells. This is an important feature of the prognosis of these cases, since the efficiency of the defensive process depends greatly upon the power of the small and large phagocytes—microphages and macrophages—to offset the multiplication of the typhoid germs. The importance of this fact is also emphasized by the identity of these follicles as barriers to general infection.*

The protective vaccinations used during the war in South Africa by Sir A. E. Wright elucidated many of the above features; they showed clearly the reaction of the body under their influence and an increase of what he terms the "bacteriotropic substances"—which, as I have shown, is composed of the aggregate of bodies which make up auto-antitoxin.

As to the localized leucocytosis, Ohlmacher¹¹⁶ writes: "From the more recent and precise histological studies, especially those by Mallory, it appears that the tumefaction of the intestinal, mesenteric and splenic lymph-apparatus is due to the excessive proliferation of the phagocytic endothelioid cells arising from the lymph-spaces, lymph-vessels and endothelial layers of the blood-vessels. These cells are diffusely scattered throughout the swollen follicles and glands in immense numbers, or accumulated in large groups, and they manifest pronounced phagocytic activity, as well as multiplication or retrogressive changes."

* Author's conclusion.

¹¹⁶ Ohlmacher: *Loc. cit.*, p. 236.

If the phagocytes—both small and large, the latter (the macrophages) ingesting the former when bacteria-laden—succeed in ridding the lymphoid follicles of the pathogenic germs, a feature of the average case which occurs about the eighth or *tenth day*, *resolution* occurs. The amœboid cells collect the local detritus and remove it and the lymphoid elements resume their normal functions.

When, however, such is not the case, both the small and large phagocytes, either because of excessively rapid multiplication of the bacilli, or inability of the phagocytic cells to digest them* (through deficiency of the digestive agent—the auto-antitoxin—they contain), and also the epithelial elements, become necrotic, and *sloughing* occurs; a grayish mass of cellular detritus is then formed which becomes detached. This usually carries the case to the end of the *third week*. The detached slough leaves a dangerous feature of the lesions, however, viz., a round or elliptical ulcer occupying a solitary follicle or a portion of a Peyer's patch which may reach down to the muscular layer and even through to the serous coat. It may also give rise to *intestinal hæmorrhage*, owing to erosion of an artery or vein; or perforation of the intestinal wall may be followed by peritonitis, a condition which may also be brought about by extension of the inflammatory process in the lymphoid tissues.

Resolution of the ulcerated areas begins—provided the reparative functions be adequate—as soon as the slough has fallen off, new epithelium growing into the area from its periphery. Fortunately, the cicatricial tissue formed is longitudinally disposed, and does not, therefore, tend to cause constriction of the corresponding portion of the intestinal canal. The healing process terminates the fever.

This differs only from the usual version in that the all-importance of the phagocytes is emphasized. It is not deemed necessary, therefore, to adduce evidence.

Treatment.—The cardinal indication suggests itself in the light of the foregoing facts, viz., to enhance not only the bacteriolytic powers of the blood as soon as possible, but to charge it simultaneously with thyroïdase (opsonin) in order to sensi-

* *Author's conclusion.*

tize the bacteria and activate their ingestion and digestion by the phagocytes.*

The first step in this direction is accomplished by administering—when the patient is first seen, and even where the diagnosis is not certain—*calomel* in 5-grain (0.3 gm.) doses every three hours until green liquid stools occur. Biliverdin, which gives the passages this color, being mainly composed of reduced adrenoxidase,* these stools indicate that an active bacteriolytic and antitoxic process has been provoked both in the liver and intestine. It does not show, however, that the latter has been rid of the pathogenic germs it contains,* and inasmuch as dead typhoid bacilli are pathogenic, the intestinal canal should be cleared of them by provoking a flow of intestinal fluid (which contains auto-antitoxin) through it, by means of a saline purgative—either a bottle of *citrate of magnesia* or a dose of *Epsom salts*. Violent saline purgation should be avoided, however, since it depletes too freely the blood of serum and of adrenoxidase, and reduces, therefore, its defensive properties.*

Calomel has an excellent record in the treatment of typhoid fever. Liebermeister, Bouhard and other equally prominent authorities have placed it first in the list of our resources. It has also formed the foundation of various methods which have shown a low mortality, even though its effects were hampered by the addition of intestinal "antiseptics" and other injudicious combinations. The value of Kalb's method to abort typhoid fever by mercurial inunctions in cases seen before the ninth day, was confirmed by Bartlett¹¹⁷ and others. In Bartlett's cases the temperature fell to normal on the third day of treatment, and all symptoms had disappeared by the sixth. J. C. Wilson¹¹⁸ treated systematically five cases by means of hypodermic injections of calomel. The cases were all severe, and all recovered. Three of them ran an exceptionally favorable course. The author concluded that calomel thus introduced into the organism exerts a decided therapeutic influence in ameliorating the symptoms and in modifying the temperature range in enteric fever. Andrievsky¹¹⁹ conducted a series of experiments to determine the value of calomel. In 71 cases calomel was given in a dose of 30 grams (4 gr.) thrice daily, while for the purpose of comparison quinine was given in the same doses in 40 other cases. The patients in the first group continued to take the calomel till their evening temperature became normal; this result was obtained after a total amount of the drug, varying from 8 to 20 grams (2 to 5 drachms), had been taken. Stomatitis never occurred, nor was diarrhœa aggravated. The disease in all these patients was mild in type and often aborted. The fever abated more quickly, and the mortality (2.82 per cent.) was less than in the cases treated with quinine. No patient who was put on the calomel treatment within

* *Author's conclusion.*

¹¹⁷ Bartlett: Australasian Med. Gaz., Nov., 1888.

¹¹⁸ J. C. Wilson: Trans. Assoc. of Amer. Phys., vol. iii, p. 109, 1888.

¹¹⁹ Andrievsky: La semaine méd., Dec. 28, 1898.

the first week of the illness, died. After using it in 90 cases, C. H. Lewis¹²⁰ concluded that calomel was the most useful agent at our disposal. Bettman,¹²¹ who concludes in the same vein, gave calomel hourly in $\frac{1}{12}$ -grain (0.0055 gm.) doses as much as twelve days before salivation appeared, a sign that these cases show considerable toleration. Hackett,¹²² who regards mercury as a specific in typhoid fever (blue mass to point of toleration and an alkaline every morning), reached a similar conclusion. A large number of authors recommended calomel.

The larger preliminary doses and the saline purgative should be followed by *small doses*, $\frac{1}{10}$ grain (0.0065 gm.), of *calomel* every three hours to sustain and enhance the functional activity of the adrenal system.* This may be continued until salivation appears, when the intervals between the doses may be increased sufficiently to keep its action just within this symptom, which shows that the limit of safety has been reached.

The second indication, namely, to sensitize (opsonize) the bacilli and facilitate their ingestion by phagocytes, is not satisfactorily met by mercury;* it must, therefore, be brought about through another agent such as *thyroid gland*, which contributes thyroidase (opsonin) to the blood.* Its use with mercury would offer some danger, however, since it might coincide with the presence of an amount of thyroidase almost sufficient to sensitize the depressor nerve and thus inhibit the functional activity of the adrenal system*—an undesirable result. Iodine and the iodides are preferable. Given with mercury, $\frac{1}{2}$ grain (0.033 gm.) of *iodine* and 5 grains (0.3 gm.) of *potassium iodide* night and morning, are sufficient to insure adequate sensitization of all pathogenic elements.* In cases in which the mercurials cannot be used, iodine and the iodides can be used alone, as shown below. In that case, however, *thyroid gland* will prove more active, 3 grains (0.2 gm.) three times daily being sufficient to increase markedly the blood's defensive properties.

Iodine, recommended by Sauer in 1840, has likewise been considered a "specific" in typhoid fever. Klietsch,¹²³ for example, after using a combination of potassium iodide and iodine in 81 cases, had but two deaths, one caused by perforation due to a dietetic error, the other from meningitis. These results were obtained during an epidemic, and were considerably better than those obtained by him during the same epidemic in 40 cases treated by the standard method—cold baths. Cavaz-

* *Author's conclusion.*

¹²⁰ C. H. Lewis: Med. Record, Aug. 2, 1902.

¹²¹ Bettman: Cincinnati Lancet-Clinic, June 25, 1898.

¹²² Hackett: Medical Record, Oct. 15, 1904.

¹²³ Klietsch: Münch. med. Woch., Bd. xxxix, S. 535, 1892.

zani¹²⁴ reported 62 cases. He began with a calomel purge, followed it up with sulphate of sodium and then the iodine, giving twenty drops (adults) of a solution containing $7\frac{1}{2}$ grains (0.5 gm.) of iodine, 70 grains (4.6 gm.) of potassium iodide, in divided doses daily. He found that this treatment not only gave better results than any other, but that the complications were less frequent, that the temperature was rapidly reduced and finally that the convalescence period was considerably shorter than is usually the case. Ceriolo,¹²⁵ who practices in a region in which the disease is endemic and always severe, states that since he has been using iodine systematically, all his cases remained mild—even those which had shown a stormy onset.

A method of the utmost importance in typhoid fever, as in all febrile diseases, is the use of *saline solution from the outset* to preserve the osmotic properties of the body fluids, and, therefore, the efficiency of the defensive functions.* Even though the blood be rich in auto-antitoxin, abnormal viscosity of the blood itself, and especially of the lymph, prevents its action on germs and the poisons derived from them. The reader is referred to the general article on page 1367 for the necessary details.

The *diet* should be that generally advocated, viz., one having in view the fact that the intestine is the seat of lesions which render the use of foods that impose physical irritation or undue peristaltic action upon the organ dangerous, in that they tend to promote local complications.

The prevailing custom is to await hæmorrhage or the practical collapse of the patient before using the saline solution. As shown in the article referred to, this is based upon the prevailing lack of appreciation of the importance of the inorganic salts upon all functions, and particularly upon the defensive functions. Acting upon my conclusions to this effect, published in 1903, Todd¹²⁶ used saline solution from the outset and found that it kept the tongue moist—the dry, parched tongue indicating deficiency of fluids and alkaline salts—and that the course of the disease was generally improved. The important feature of his observation, however, is that he found that saline beverages proved as effective, used in the following way: Ten grains (0.6 gm.) of sodium chloride and 5 grains (0.3 gm.) of potassium bicarbonate added to 8 ounces (236 gm.) of water; a teaspoonful of lemon juice is added, which produces a mild effervescence and renders the drink very palatable. J. Madison Taylor found that the ordinary decinormal gave equally satisfactory results used as a beverage. The cardinal indication is to insure an adequate intake of this fluid to replace as much as needed of the half-ounce (15 gm.) of sodium chloride voided every day with the urine and other excretions, and which is not replaced when the diet is low.

* *Author's conclusion.*

¹²⁴ Cavazzani: Riforma medica, June 5 and 6, 1900.

¹²⁵ Ceriolo: Gazzeta degli Ospedali, vol. xxvi, p. 74, 1905.

¹²⁶ Todd: Medical Record, Apr. 14, 1906.

As to the use of *cold baths*, they are not necessary if the foregoing measures are carried out. *Sponging* is useful, however, when the temperature—a manifestation of the curative process—exceeds 103° F. (39.5° C.), to enhance the dissipation of heat from the skin.

If *hæmorrhage* occur, the aim should be to cause constriction of the intestinal arterioles;* we have seen that *morphine* produces this effect. Its value is shown by the fact that it is generally employed in this identical condition. *Constipation* is best met by means of large enemas of saline solution at 110° F. (43.3° C.).

Prophylaxis.—The influence of excessive fatigue, a predisposing cause in the epidemics observed in troops during arduous campaigns,* should be borne in mind, in view of the likelihood that the bacillus coli can assume the virulence of the typhoid bacillus.* Proper periods of rest and increased transportation facilities will obviate this danger. An important feature of this question is that “excessive fatigue” means in this connection, abnormal consumption of adrenoxidase, nucleoproteid and of the zymogens which jointly sustain metabolism—the identical substances of which auto-antitoxin is composed.* The use of agents such as *quinine* or *coffee*, which stimulate the adrenal and vasomotor centers, is therefore indicated.* A very pernicious agent in this connection is *alcohol*, which, by reducing the blood’s adrenoxidase, produces effects similar to fatigue.*

While a militia officer, during my younger days, I frequently noted the pallor which overcame the men of my command after a prolonged parade, regimental drills, etc., a clear indication of two facts, viz.: that their adrenoxidase had become deficient, and that, as a result, the blood-pressure was abnormally low. The pernicious influence of alcohol in this connection was referred to when that agent was studied.

In civil life, infection occurring often irrespective of any appreciable subjective cause, we have a powerful prophylactic combination in *thyroid gland*, 1 grain (0.06 gm.) and *quinine*, 2 grains (0.13 gm.) taken after meals, when there is a likelihood of infection or even when the premonitory symptoms of the disease have occurred. Thyroid gland, by increasing powerfully the bacteriolytic power of the blood, and quinine,

* Author's conclusion.

by driving the blood towards the capillaries, cause the intestinal mucosa and its lymphoid follicles to become congested with blood rich in protective properties, while the digestive activity of the phagocytes is also increased. Both the blood and its cells being likewise fully supplied with thyroidase, pathogenic germs are readily sensitized, thus augmenting greatly their vulnerability to destruction by the phagocytes.

Iodine and the *iodides* can also be combined with quinine, preferably the *quinine hydrochlorate*. None of the other agents of our pharmacopœia are sufficiently active to afford adequate protection.*

* Author's conclusion.