A consideration of the various kinds of food suitable for the different conditions that lead to dilatation I have not touched on, and I have contented myself with calling attention to the more obvious methods of treatment I have usually found efficacious.

WIDAL'S SERO-DIAGNOSIS OF TYPHOID FEVER.*

BY E. T. FISON, M.B., B.C.CANTAB,

(From the Bacteriological Laboratory of St. George's Hospital.)

INTRODUCTORY.

IN the practice of medicine certain and early diagnosis is the most important factor. To Widal belongs the honour of having shown that it is possible with some certainty to diagnose enteric fever by a method he terms "sero-diagnosis." I propose to give a cursory history of the evolution of this method. As long as eight years ago work directly bearing upon this subject was published, since then much more has been learned; but it was not until last year that these observations were turned to practical use.

In 1889 Charrin and Roger, while working at the cause of immunity, found that sera from animals, which had been injected with living or dead cultures of bacillus pyocyaneus, exerted an effect on the living bacillus pyocyaneus; they proved this by growing bacillus pyocyaneus in a test tube in serum from an animal immunised against it; the bacilli formed flakes and fell to the bottom of the tube, whereas the supernatant fluid became clear. If the bacillus pyocyaneus were grown in serum from a non-immunised animal uniform turbidity resulted.

In 1894 Issaeff and Ivanoff made a like observation on a vibrio described by Ivanoff.

In 1894 R. Pfeiffer injected into the peritoneal cavity of a guinea-pig, previously immunised against spirillum choleræ, a culture of living cholera microbes. He found on examining the peritoneal exudation that the spirilla had lost their motility and had come to rest in clumps, and also that after a time they underwent a granular degeneration and ultimately disappeared.

He also found the same phenomena happened with bacillus typhosus. If bacilli not of the same species as the one which had been used to immunise the animal were injected, clumping did not take place.

He also showed that the phenomena of degeneration and ultimate absorption of the microbes occurred when a living typhoid culture was mixed with serum of an animal immunised against typhoid and injected into the peritoneal cavity of a non-immunised animal. This came to be used as a test for doubtful cultures of bacillus typhosus.

The clumping, granular degeneration, and ultimate absorption of the microbes observed when specific living organisms were injected into the peritoneal cavity of an animal immunised against that organism, as a whole, came to be known as "Pfeiffer's Reaction."

Metchnikoff and Bordet next showed that the phenomena, which Pfeiffer observed in the living animal, could be seen in the hanging drop preparation under the microscope. To apply this test one drop of serum of an animal immunised against the specific microbe is added to two drops of an emulsion of the doubtful culture; if the microbe be the specific one the organisms come to rest in clumps, and if more serum be added granular degeneration takes place. Vibrios or bacilli other than the one against which the animal is immunised do not react in this way. Gruber and Durham mixed in a test tube the microbe to be tested with a more or less diluted serum from an animal immunised against the microbe to be found. If the microbe were the specific one, the organisms in half to one hour fell to the bottom of the test tube and the supernatant fluid became clear; if the microbe belonged to a species different from the one against which the animal has been immunised, the contents of the tube remained uniform.

The above experiments showed that the serum from an animal in a state of immunity exhibited definite qualities when mixed with the specific organism only. The changes which resulted were also used as a test for doubtful microbes. Hitherto these changes in the organisms had only been shown with sera from animals in the stage of immunity.

Widal, however, believed that the blood of patients suffering from typhoid fever acquired qualities which gave the changes mentioned above at a period long before immunity could have been reached, indeed during the period of infection. On this hypothesis, he thought it would be more practical to mix typhoid bacilli with serum from typhoid patients, and see whether the same changes observed by Pfeiffer *in vivo* or *in vitro* by Metchnikoff, Bordet, and Durham took place, and if so to make use of these phenomena for the diagnosis of typhoid fever rather than of typhoid bacilli.

This he did, and last June brought before the Medical Society of Paris a new method for the diagnosis of typhoid fever which he termed "sero-diagnosis." He described several processes. One consisted in adding a few drops of serum from a suspected typhoid case to a bouillon culture of Eberth's bacillus, already cloudy, and observing a few hours later whether it became clear at the top with a precipitate at the bottom of the tube. Another consisted in adding a few drops of serum from a supposed typhoid patient to a bouillon tube, then inoculating with Eberth's bacillus and observing whether the same phenomena took place as mentioned above. A third method was the mingling of one drop of serum from the supposed typhoid patient with ten drops of a young bouillon culture of bacillus typhosus on a cover glass, and then examining under the microscope to see whether the microbes formed heaps or agglomerations. He also showed that the reaction could be obtained with dried serum or blood emulsified and then added to bacillus typhosus.

In fairness to Grünbaum, it must be stated that he had been working at the same subject simultaneously with Widal: but his theses were not published till two months after Widal's announcement; he cannot, therefore, have the same claim as Widal to this most important discovery.

Chantemesse added typhoid organisms to sera from cases of pneumonia, influenza, erysipelas, and peritonitis, and found that no agglutination of the organisms took place.

Professor Wright, acting on an observation of Widal that serum from patients suffering from typhoid fever showed the agglutinative action when added to dead typhoid organisms in the same way as when mixed with living ones, published a paper on this point in the BRITISH MEDICAL JOURNAL of May 15th, 1897.

He has experimented with the bacillus typhosus and the micrococcus melitensis of Bruce. Emulsions of the living organisms were taken up, placed in capsules, and then subjected to a temperature of 60° C. for five to ten minutes; serum was then taken from a subject who had been vaccinated against typhoid fever six months previously, and from a patient suffering from Malta fever; these sera were added to the respective specific dead organisms in a sedimentation tube. He found that the reaction was quite as definite as when these sera were added to living organisms, and that there was no difference in the method of agglomeration.

If this new method be found reliable, it will greatly facilitate the performance of the test, and any practitioner who cares to provide himself with sterilised cultures of bacillus typhosus will be able to conduct it.

The serum of typhoid patients shows this agglutinative reaction early in the disease. Johnston and McTaggart state that they observed an incomplete reaction within forty-eight hours of the attack of the fever. Most observers are agreed that the serum obtains this agglutinating power by the end of the first week.

The serum from patients who have had typhoid fever seems to retain these qualities for a remarkable length of time, and may as a rule be reckoned by years. This fact bears strongly on immunity to second attacks of typhoid fever, for it is well known that two attacks of the disease in the same individual is a rare coincidence. Besides the serum of typhoid patients reacting in this way with typhoid bacilli, it is claimed that the milk of nursing women suffering from typhoid fever, the tears, the exudations from blisters, and the urine give the same reaction.

Achard states that the blood of a fœtus from a mother in the acute stage of typhoid fever gave no reaction; so it

* This is part of a Thesis written for the M.D. degree of Cambridge University.

appears that this quality of the serum does not pass to the offspring.

Devoto states that the product in the serum which causes this action is a globulin; he finds that this globulin, which he separated, is chemically indistinguishable from globulin obtained from the blood of other people. If dried at 55° C. he found that it lost its bacillus-precipitating properties, but if dried at ordinary temperature it preserves them for eight to ten days.

Jemma has found that a temperature of 70° C. for ten minutes completely destroyed the agglutinative properties of the serum.

TECHNIQUE.

It is now apparent from the above introductory note that there are many ways in which the reaction may be obtained. For a method to be of practical usefulness it must be free from complications and easy of performance, and therefore in the conduct of my own experiments I have chosen Widal's microscopic method, which has given very satisfactory results. "All that is necessary," Widal says, "is to have at one's disposal pure cultures of Eberth's bacillus, a microscope, and a few drops of serum, or even only one drop of the blood of of the patient." I will indicate the way in which I have carried out this method. With a sterile needle a prick is made on the dorsum of the finger near to the base of the nail, into a sterilised capillary pipette about three drops of blood are taken, and the end of the tube is then sealed in the flame, taking care that the blood does not get heated. The finger is cleaned, but not sterilised, a precaution which does not seem to be necessary.

In twenty-four hours the serum is completely separated from the blood clot, and can be blown out almost free of corpuscles, or the blood may be centrifugalised. A culture on agar of the bacillus typhosus was used which reacted to all the tests. An emulsion of the cultures with a few drops of water was made, and this was used to add to the serum. The agar tubes were inoculated about every fortnight; this method, however, led to serious error, and had to be abandoned. After the agar tubes had been inoculated at intervals of a fortnight for about three months, I suddenly found that on the addition of serum from patients suffering from other diseases and from healthy individuals, a clumping resulted at once which exactly resembled that obtained with typhoid serum. It appeared, therefore, that the cultures inoculated in this way became attenuated, and so some other method of keeping culture going had to be tried. Professor Delépine has experienced the same thing, and emphasises the fact that fresh and virulent cultures of the bacillus typhosus must be used.

In order to obtain such cultures he recommends that the bacillus should be grown on a solid medium, and that fluid cultures should be made from day to day as required. In my later experiments I have followed this plan, and have had no recurrence of the trouble. I have inoculated agar tubes weekly, and from these tubes made bouillon cultures, and used them after growing at 37° C. for twenty-four hours. If the culture becomes attenuated, inoculation on agar daily for four days seems to restore its virulence.

A clean coverglass is now taken, and nine loopfuls of the emulsion, in my early experiment, but later of the twenty-four hour old bouillon culture, are placed on the coverglass; to this is added one loopful of the serum; the serum and the culture are now mingled, the preparation is placed on a slide and examined with the oil immersion lens, a positive reaction is denoted by the organisms running together in clumps becoming motionless and by the clearance of the field between the clumps. It is well to examine the emulsion or the bouillon culture from time to time to see if clumps are present, or if they form after a short time.

In most of my experiments I have used two proportions of serum to culture, this one to nine mentioned above and one serum to two of culture as well. Grünbaum lays great stress on adequate dilution of the serum. Thus he finds that in a case of carcinoma with icterus serum undiluted and in the proportion of one to four gives a "good reaction" with bacillus typhosus, but not in a one to sixteen solution, and so he meets the difficulty of diagnosing a doubtful reaction. He, however, does not mention the most important points, to my mind, about the reaction as regards the clumps themselves, the loss of motility in field and clumps, and whether the field cleared or not. I have found the one to nine dilution work very well for all cases, and although I have frequently seen small clumps within half an hour, yet by studying the reaction as a whole, I have rarely found any difficulty in estimating its value. The stronger proportion, although it increases the reaction in somewhat weak sera from typhoid patients, has never given rise to definite clumping, with clearance of the field, in cases that were not typhoid within the time limit I have fixed for the reaction, namely, half an hour.

In the majority of the experiments observation was made of the preparation at once, and in my earlier ones at the end of twenty-four hours; in my later experiments I only examined the preparation once if clumping had occurred, and again at the end of half an hour if the reaction at first was only partial or negative.

I am quite sure that it is unsafe to make a diagnosis of enteric fever from clumping that occurs after the lapse of twenty-four hours; for in my experiments I found that many diseases other than typhoid gave rise to this, though as a rule the reaction does not show the loss of motility observed in a typhoid reaction. I therefore came to the conclusion that it is necessary to affix a definite time limit for the appearance of this reaction; I have fixed this at half an hour from the time of making the preparation. Grünbaum, Durham, and Gruber have all laid stress on this point, and fixed the same time limit.

In one case a typical positive reaction was obtained after the lapse of an hour and a-half; the patient died, and at the necropsy no lesion of enteric fever was found. In some cases I used the hanging-drop method, but this method appeared to have no advantages over that which I have generally followed.

In carrying out this series of experiments I have nearly always tested on the same day sera from patients suffering from diseases other than typhoid, so that my results have been controlled.

I have not used the dried blood method, concerning which Wyatt Johnston and McTaggart, of Montreal, published a paper in December last, recording results of 290 examinations. In their hands this appears to have yielded satisfactory results; they report, however, that it is necessary to use a somewhat attenuated culture of typhoid bacilli. This seems the weak point in the method, for many observers, including myself, have noted the great readiness with which attenuated cultures clump by themselves and when mixed with sera from diseases other than typhoid.

Neither have I used to any extent the reaction in the test tube for diagnosis. This appears a very reliable method, but requires abstraction of more blood from the patient, and is altogether rather more complicated. Professor Wright has lately invented some very ingenious capillary pipettes for taking blood from the finger, and also what he terms "sero-sedimentation tubes" for carrying out the test tube reaction.

THE REACTION.

As soon as the preparation is made it is put under the microscope, and, if the reaction be positive, the following phenomena are seen:

1. Formation of clumps of non-motile organisms. These clumps are composed of organisms at times closely packed together, at others more loosely so; they are made up of organisms in a heap and not all in focus at the same time, and so differing very much from pseudo-clumping, which often comes on after a varying period in sera from patients suffering from other diseases. In pseudo-clumping the organisms lie very much in the same plane, and are not, as a rule, densely packed together.

2. Almost immediate clearance of the field between the clumps; this is the most characteristic part of the reaction. The few organisms that remain in the field move sluggishly about, and often can be seen running up to the clumps to increase their size.

3. If the preparation be watched, the reaction not being complete, the field soon becomes quite clear, and the clumps increase in size. At times, however, with serum from a typhoid patient the reaction is not always so definite at once. In fact, at first nothing can be noted beyond a loss of

the usual motility of the organisms; in a short time, however, very small clumps or clusters of organisms form, and these increase in size till at the end of half an hour the reaction is quite positive. Reactions intermediate between this, and the above typical phenomena occur.

In cases where the 1 to 9 proportion has failed to give clumps at once the 1 to 2 proportion has at times given them, and has indicated what almost invariably follows in the weaker dilution. It is extremely rare for any serious difficulty to arise in determining a positive reaction. In the false reaction obtained with other sera there is rarely loss of motility of organisms in the field, and the clumps that form are generally very small, being composed of a few organisms only, and these very often actively motile. There is never within the time limit I have fixed clearance of the field. At a later period I have often observed definite clumping, with clearance of the field and some loss of motility. Many of these reactions, indeed, would have been called positive had they occurred within half an hour.

Discussion of Results of Experiments.

The results I have obtained are based on 161 cases; 81 of these were cases of typhoid fever during disease or early convalescence; 21 were cases of typhoid fever at a period remote from the original attack; 21 were cases simulating typhoid fever; and 38 were cases of various diseases and of persons in health.

In a large number of the 81 cases of typhoid fever the diagnosis was at the time of examination undoubted. In these cases the purpose of testing the serum was to see whether in all cases of typhoid fever the serum gave the agglutinative reaction, and thus to prove the value of the test.

As to the results obtained I think they may be said to be satisfactory. Taking the 81 cases of typhoid during disease or early convalescence, 73, or 90.1 per cent. of these cases, the reaction was considered positive in 8, or 9.8 per cent. negative. This shows clearly that a negative result does not absolutely disprove the case to be one of enteric fever. It is difficult to understand why this 9.8 per cent. of typhoid sera did not give the reaction exhibited by far the larger number. How is it that the agglutinative power does not belong to all cases? Three explanations may be given.

1. There may have been some mistake in the performance of the experiment, such as heating the serum; however, in cases where it was possible I have tested the serum twice, in one case four times, after sterilisation of the patient's finger, and the result was always the same.

2. These cases may not have been enteric, but out of these 8 cases on only 1 can any reasonable doubt be thrown, and the clinical symptoms were definitely those of enteric fever.

3. The agglutinative properties might have been present at an earlier date. The latest day from date of attack was the 76th. The objection to this explanation is that the power of the serum lasts for many months as a rule.

Durham found that out of 10 patients suffering from typhoid fever, 4 failed to give the reaction. Delépine, on the other hand, obtained a positive reaction in 25 consecutive cases of typhoid fever. Johnson and McTaggart in their paper only had 6 failures to record out of 129 cases of enteric fever.

As regards the earliest day of disease on which this reaction appears, I have not many apposite cases. I have found it very difficult to get sera from patients early in the disease, as in hospital practice patients do not, as a rule, present themselves till they are definitely ill.

The earliest case taken was one in which the serum was examined on the fourth day, and the reaction was entirely negative; on the eighth day it was decidedly positive, so it would appear that in this case the serum might have shown its qualities on the sixth day. Seven other cases gave a decided positive reaction from the sixth to the ninth day. Judging from these cases, it may be stated that the reaction always appears in the first week of the disease, but that, if it is not present in the first few days, a re-examination should be made.

The reaction appears to reach its greatest intensity very rapidly. I have not found that it bears any relation to the severity of the attack; in fact, a mild case often gives a more decided reaction than a very severe one. I had a case which illustrated this; the disease was most severe, yet the reaction was not positive with a 1 to 9 dilution, but only with a 1 to 2. Possibly the weak action of the serum may have been the cause of the severe type of the disease.

Nor does there seem to be any decided relation between the degree of reaction and tendency to relapse. Three cases had relapses, and in all of them the reaction was feeble; but, on the other hand, four other cases of relapse all gave very positive reactions. The reaction in convalescence is generally quite as intense as during the height of the fever.

The Diagnostic Value of the Test.

Many of these 81 cases showed the great value of the test for diagnostic purposes. Enteric fever is practically never absolutely ascertained by clinical means of diagnosis before the tenth day; so that a positive reaction in a case before the tenth day has much diagnostic value.

Besides this, there are many cases which clinically remain in some doubt for two weeks or longer, and some which are doubtful throughout. I have mentioned most of the cases which gave the reaction before the tenth day. I will now speak shortly of a few cases which were doubtful at some later period of the disease, and in which a positive reaction being obtained were, I maintain, diagnosed correctly and the doubt removed at once.

CASE I.—Here there were definite signs of phthisis complicated with some other illness of a doubtful nature. The serum gave a positive reaction, and therefore in my opinion the patient had enteric fever concurrently with phthisis.

CASE II.—This patient had a very doubtful attack of enteric clinically; besides this he had syphilitic ulceration of the rectum, so that there was much doubt as to whether the latter lesion might not have been the cause of the whole illness. I think the test cleared up the diagnosis in favour of a concurrent attack of enteric fever. Diagnosis of cases such as these would be very important in tracing the epidemiology of an outbreak of enteric fever.

CASE III was entirely uncertain as to diagnosis on the sixteenth day. I diagnosed enteric fever by Widal's method, and the ultimate course of the case showed that I was correct.

CASE IV was very doubtful even at the twentieth day. Enteric was diagnosed by the serum test.

CASE V is of extreme interest. Originally it was thought to be influenza, and on arrival at hospital a universal rather punctate erythema suggested scarlet fever. The disease ran the course of enteric fever, and to it the patient succumbed. The test gave a correct diagnosis on the ninth day.

CASE VI on the sixteenth day was extremely doubtful clinically, but was diagnosed correctly by the serum test.

CASE VII was one of doubt throughout; clinically it seemed to be a combination of enteric fever and malaria. The surgeon considered the disease to be appendicitis, yet the serum gave a most positive reaction in favour of enteric fever.

CASE VIII was impossible to diagnose clinically at the eleventh day, yet the serum test gave a most positive reaction.

CASE IX on the fourteenth day was doubtful, but the course of the case showed that the diagnosis of enteric fever, by a positive reaction from the serum, was correct.

CASE X at the fourteenth day was very doubtful, but the reaction, which was positive, cleared up the diagnosis.

I think these cases are sufficient in number to show that this sero-diagnosis method is a great aid to the clinician. The 21 cases at periods subsequent to the attack, varying from three months to eight years and a half, show the long period that the reaction lasts; of these 18 gave a positive reaction, 1 a doubtful positive, and 2 were negative. The longest period after attack at which a positive reaction was obtained was seven years and a half. Of the two negative reactions, one was fifteen months from the onset of the disease, the other eight and a half years. Thus the time this quality of the serum lasts is not definite. In many cases the reaction was as marked as I have seen it in the height of the disease. Whether all subjects, if exposed severely to the poison of enteric fever, would remain immune so long as the serum retains these active qualities, is a doubtful point, and one not yet worked out.

As this action goes on for such a long time it is always well to ask about any previous attack of enteric fever before applying the test. In fact it may be stated that a positive reaction obtained with serum from a patient who previously suffered from enteric fever is absolutely valueless. The diagnosis must be made by the clinician.

As to the 21 cases which simulated enteric fever, in all of these at the time of testing the blood the disease was indistinguishable from enteric fever. Yet all of these patients proved to be suffering from some other disease, and not from enteric fever. Every serum in this class gave a complete

negative reaction. These cases show that for diagnosis a negative reaction is fairly strong evidence that the disease is not enteric fever. This, I have said above, is not absolute, for 9.8 per cent. of my cases of enteric fever gave a negative reaction.

The last class is made up from 35 patients who were suffering from various diseases, and 3 cases who were in perfect health. Not one positive reaction was obtained. Many pseudo-agglomerations were observed, but these occurred only after the preparation had been made some time; and, as explained above, the false reaction as a whole differs greatly from the true. In fact it seemed very unusual to find diseases, especially if attended with fever, whose sera did not give rise to clumps after a certain period. The motility always seems to become lessened after twenty-four hours, and as a rule a few clumps appeared; and often, indeed, a few clusters of organisms could be seen at once. In one case a typical reaction showed itself in an hour and a-half with a 1 to 2 dilution. This impressed upon me the necessity of fixing a time limit, namely half an hour, for the reaction to take place in. This patient died, and at the necropsy no lesion of enteric fever was found.

I have tried the action of typhoid sera, which react with typhoid microbes, on bacillus coli communis; clumping never took place in a 1 to 9 or 1 to 2 dilution; in twenty-four hours in some cases there were a few clusters, but active motility was retained. I have also tried the action of the urine from typhoid patients upon typhoid organisms. In a few cases this certainly gave rise to clumping, but the result was not so rapid or so clear as the serum reaction. The saliva from healthy people gave clumps as well as that from typhoid patients. Other typhoid saliva gave no sign of clumping. This, therefore, is obviously untrustworthy, and there is no doubt that it is the blood serum which gives the best results.

CONCLUSIONS.

1. Absolutely certain and virulent cultures of bacillus typhosus are needed. If the culture becomes attenuated it will clump to any serum in a typical manner. It is well to examine the culture first to see that there are no clumps before the addition of the serum.
2. It is well to make two dilutions, in the proportions of 1 to 9 and in 1 to 2.
3. It is necessary to have a time limit for the reaction to take place in, from experience half an hour is a sufficient interval.
4. A positive reaction is, I believe, absolute proof of enteric fever (provided there is no history of a former attack), and is found in a very large percentage of cases.
5. A negative reaction is strong evidence against typhoid fever.
6. The reaction nearly always appears in the first week of the disease, therefore the diagnosis can be made earlier by this means than by clinical.
7. The agglutinative power of the serum lasts for an indefinite but as a rule lengthy period, so it is necessary to have evidence as to former attacks.
8. There appears to be no relation between the intensity of the agglutination, the severity of the case, or the degree of the fever.
9. It is undoubtedly the best method we have of certain diagnosis of enteric fever.

[Since writing this Dr. Kanthack has informed me that he obtained a typical positive reaction with serum from a patient suffering from an obscure disease; death followed, and at the necropsy no lesion of enteric was found, and cultures made from the spleen were entirely negative.]

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GASTRO-INTESTINAL TOXINS: THEIR CLINICAL SIGNIFICANCE AND THERAPEUTIC INDICATIONS.

BY WM. ARMSTRONG, M.R.C.S.,
Buxton.

THE fact that processes are always going on in our bodies, the products of which, by reason either of excess in formation or of deficiency in elimination, may become harmful to comfort, health, or even life itself, should arrest immediate attention.

The morbid manifestations of this condition are spoken of as "auto-intoxication," or "self-poisoning of the individual." Careful study of these processes throws much new light upon the causation of many chronic and intractable ailments, and encourages the hope that an increasing measure of success may attend our efforts to combat them.

Ptomaines, formed from decomposed food substances, had long been recognised as the cause of certain occasional cases of severe and deadly illness. It was not, however, until 1885, when Gautier demonstrated that poisonous bodies, to which he gave the name of leucomaines, were formed from sound food during normal digestion (and in larger quantities and more virulent form if those digestive processes were interfered with), that consideration was given to the possibility of these obscure bodies being responsible for the genesis of many forms of confirmed ill-health.

Gautier's researches showed that the animal economy was frequently poisoned by its own products. He pointed out that poisonous matters were being continuously formed by the decomposition of albumen in the intestinal canal during the process of digestion; and also in the blood and tissues by the metabolism which occurs during the functional activities of life. The normal products of digestion are poisons of considerable power; and if, through inadequacy of the organic functions, they reach the circulation in any considerable quantity, alarming or even dangerous symptoms occur.

Autointoxication may be either slight and transient, or severe and lasting. The most common form of all is, I consider, a daily storage of small quantities of noxious material which gradually deteriorates the nervous system, and disturbs the nutrition of the various organs of the body. Vital action is much more quickly interfered with through the accumulation of waste products within the organs than by any want of nutriment of those organs themselves.

The toxins developed in the human body are many and varied:

1. Alkaloids, divided into two groups:
   (*a*) Ptomaines, formed from the action of bacteria, or of ferments, on the albuminoid substance of the dead tissues.
   (*b*) Lencomaines, which are elaborated by the vital energy of the cells themselves.
2. The primary products of the albuminous decomposition of digestive ferments, such as peptones.
3. Acids—acetic, butyric, valeric, and sulphuric.
4. Ammonia and the ammonia compounds.
5. Leucin, tyrosin, indol, skatol, cresol, and phenol.
6. The salts of potash.
7. Bile acids.
8. Biliary colouring matters, especially bilirubin.
9. Various gases, of which sulphuretted hydrogen is probably the most toxic.

All these are capable, under conditions of excessive formation or deficient elimination, of setting up a train of morbid symptoms without any organic disease being present.

The fact that self-poisoning more or less acute is not constantly present is probably due to two factors:

1. The action of the liver, which seems to have the power, when in good working order, of destroying or modifying certain poisons and of eliminating others.
2. The antagonistic action of the poisons themselves.

The chief causes of excessive formation of these poisons seem to be:

(*a*) Defective action of the nervous system, leading to a failure of the processes of digestion, such as deficient or abnormal secretion of the various gastric and intestinal juices; or to torpidity of the muscular structures of the stomach and bowels, and a consequent loss of power to make the necessary movements. Then follows retention of food products, and consequent fermentation and putrefaction.
(*b*) The taking of food in too large a quantity, in wrong form, or, as is most common, in improper combination.
(*c*) Gastric dilatation.
(*d*) Duodenal dyspepsia and atony.
(*e*) Atony of the small and large intestines.