Soured milk and pure cultures of lactic acid bacilli in the treatment of disease / by George Herschell.

SOURED MILK AND PURE CULTURES OF LACTIC ACID BACILLI IN THE TREATMENT OF DISEASE

HERSCHELL

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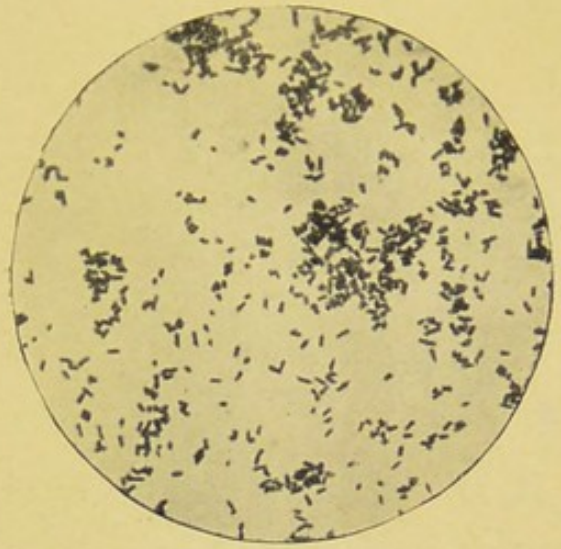

Fig. 1

Fig. 1. Lactic acid bacillus in milk curdled by contamination from the air.

× 1000

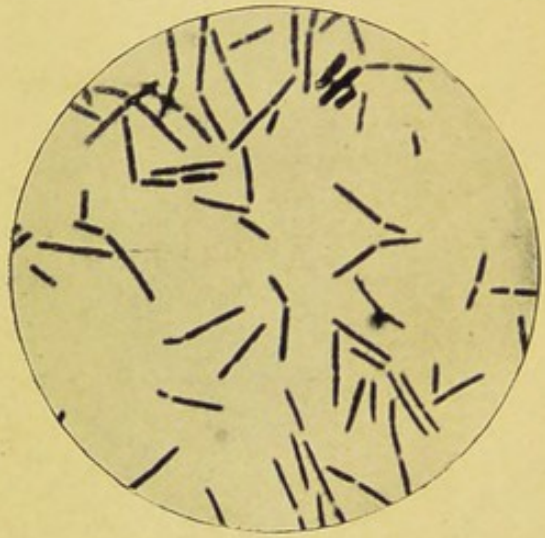

Fig. 2

Fig. 2. Pure culture of the bacillus of Boucard as present in tablets for internal use.

× 1000

Fig. 3

Fig 3. Bacillus of Boucard and strepto-bacillus contained in the powder for souring milk.

× 1000

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Soured Milk and Pure Cultures of Lactic Acid Bacilli in the Treatment of Disease

By

GEORGE HERSCHELL, M.D., Lond.

Fellow of the Royal Society of Medicine. Late Senior Physician to the National Hospital for Diseases of the Heart. Physician to the West End Hospital for Diseases of the Nervous System, and Physician to the Farringdon General Dispensary

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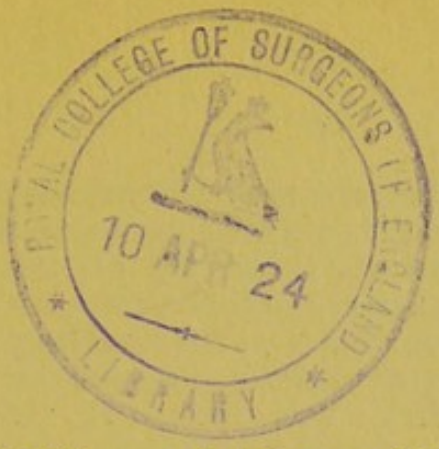
Preface

THIS little work is an amplification of a paper with the same title which appeared in *The Lancet* of August 8, 1908. In it no attempt has been made to deal with the subject exhaustively, and it is offered to the Practitioner of Medicine merely as a brief résumé of just so much of our present knowledge of Lactic Acid Ferments as may be likely to be of assistance to him in prescribing them in a scientific manner.

GEORGE HERSCHELL.

36, HARLEY STREET, W.

Contents



Soured Milk and Pure Cultures of Lactic Acid Bacilli in the Treatment of Disease.

CHAPTER I

AUTO-INTOXICATION, AND INTESTINAL PUTREFACTION

THE term auto-intoxication is used to denote poisoning of the body by substances resulting from the processes incidental to its life. This may occur in four ways :—

1. The poisons may be produced in the tissues themselves.—From faulty processes we may have an excess of the decomposition products of nuclein, as in the gouty diathesis ; and we may have acidosis from the conversion of albumin and fat into fatty acids, acetone, and allied bodies.

2. Normal secretions which are poisonous if retained may fail to be eliminated owing to partial failure of the organs of excretion, whose office is to remove them from the body.—In this group we find jaundice and uraemia.

3. The internal secretion of the ductless glands may be in excess of the needs of the organism.—As examples we have myxoedema, acromegaly, and Addison's disease.

4. From absorption into the system of poisonous substances generated during the process of digestion.—The auto-intoxication may be due to actual excess of the poisonous material, or to relative excess if the tissues and organs, which should normally protect the system from their effects, are not functionally competent for their task.

Until comparatively recently the theory of auto-intoxication, although admitted to be a fascinating method of accounting for certain derangements of function, could not be taken as absolutely proved, and many authorities, especially in Germany, absolutely denied its existence, explaining the clinical symptoms in question as being the result of reflex irritation. One of the chief difficulties in accepting the auto-intoxication hypothesis was that the actual poisons could not be isolated and their effects demonstrated experimentally. But since 1904 the

progress of physiological chemistry has been very great, and not only have the presence of poisonous substances been demonstrated in the stools and urine, but the parallel progress in experimental pathology has enabled Charrin [1] and others, by means of injections with material from the intestines, to reproduce in animals many of the phenomena observed in man as the result of auto-intoxication. The theory is, therefore, now upon a firm foundation and may be taken as settled.

The poisonous substances produced in the intestines are the result in the greater number of cases of the action of the digestive fluids and of microbes upon proteids. The most important of them are ammonia and the aromatic bodies such as phenol, indol, scatol, and their derivatives, which have all been proved not to be formed in the intestine to any great extent except as the result of microbian putrefaction. For clinical purposes we can roughly ascertain whether these bodies are produced in excess by measuring the daily amount excreted in the urine. The amount of phenol excreted in the twenty-four hours should not exceed from 0·010 to 0·015 grammes, and indol and scatol from 0·005 to 0·015 in each case. All these substances are largely increased in suppurations and in abnormal putrefaction of proteids in the intestine. Phenol is increased when there is stasis in the large intestine, whilst indol and scatol are found in excess when there is delay in the passage of food through the small intestines.

It has now been definitely proved that the abnormal putrefactions in the intestine are mainly effected through the agency of anaerobic bacteria. The researches of Herter,[2] Grigoroff,[3] Combe,[4] and Cohendy [5] have demonstrated that whilst in the normal intestine the microbes met with are either aerobic or facultative anaerobes, and the quantity of strict anaerobes extremely small, the contrary condition is present in cases in which there is abnormal intestinal putrefaction. In these cases we shall find a remarkable diminution in the aerobic bacteria which inhibit abnormal putrefaction, and a great increase in the anaerobic proteolytes which favour and produce it.

The causes met with in practice which will favour the growth of these anaerobic bacteria and allow abnormal putrefaction to take place are many, and may be briefly classified as follows :—

[1] Charrin, "*Le rôle pathologique des poisons de l' intestin.*" *Semaine médicale*, 23 Novembre, 1904.

[2] Herter. *Bacterial infections of the Digestive Tract.* London and New York, 1907.

[3] Grigoroff. *Thèse de Genève*, 1905, p. 87.

[4] Combe. *Traitment de l'Entèrite*, Paris, 1906.

[5] Cohendy. "*Apperçus sur la morphologie de la flore intestinale de l'homme. Nombre respectif des anaerobies et des facultatifs dans les selles.*" *Comptes rendus de la Societe de Biologie.* 1906, i., p. 415.

(A) *Alimentary.*—The most important dietetic error which results in intestinal putrefaction will naturally be an excess of animal food. I am personally convinced that one of the chief causes for the prevalence of auto-intoxication at the present day is the large excess of animal food over the real requirements of the body habitually indulged in by the majority of mankind.

This supposition rests also upon an experimental basis, since it has been demonstrated that the number of anaerobes is relatively large, and the colon bacilli (aerobes) small, in animals fed largely upon meat. In these experiments it was found that a large proportion of the abnormal organisms consisted of the bacillus capsulatus. In herbivora the contrary condition of things is present, the dominant organisms being aerobic.

The consumption of food which is not perfectly fresh is also a fertile cause of intestinal auto-intoxication. Not only may such food contain toxines already, but they are at the same time, in many cases, in an early stage of putrefaction, and only need the favourable conditions which they will find in the intestines for the process to continue.

(B) *Gastric.*—There are several conditions under which food may pass from the stomach into the duodenum in a state which predisposes it to putrefactive changes. It may contain an excessive number of bacteria which have been swallowed. This happens in cases of pyorrhoea alveolaris when every mouthful of food is necessarily mixed with pus from the diseased gums teeming with micro-organisms. We also meet the same condition in post-nasal catarrh, as during the night when the stomach contains no hydrochloric acid with which to defend itself, the patient continually and automatically swallows a larger or smaller amount of mucus containing virulent microbes, the most common being the bacillus of Friedlander. In other cases the food may pass from the stomach in an imperfectly digested condition. This is invariably the case when the gastric juice is deficient in pepsin and hydrochloric acid, as we find it in many cases of chronic gastritis, and achylia gastrica. Again, whenever there is either a mechanical impediment to the stomach emptying itself at the proper time, or when from muscular weakness it is unable to do so efficiently, food residues will remain in the stomach even until putrefactible changes have begun, and in that condition be passed into the duodenum.

(C) *Intestinal.*—Any condition which will produce retardation in the rate of passage of the digested food along the intestinal tract will favour the occurrence of putrefaction. We thus encounter it, especially in cases of enteroptosis (*Glénard's Disease*), motor insufficiency of the intestine, dilatation of the colon and sigmoid, and in chronic intestinal obstruction. We shall

also find it in various forms of enteritis, especially mucomembranous colitis, and when intestinal parasites are present.

Cases of intestinal putrefaction according to Herter may be conveniently divided into three groups :—

(1) *The indolic type.*—This is characterized by indicanuria dependent chiefly upon excessive decomposition induced through members of the bacillus coli type, and possibly the bacillus putrificus Bienstock. As the colon bacilli are known to have only a feeble action upon the native proteids used as food, it is only fair to assume that not only that there must have been some previous digestion of them, but also that such digestion must have been imperfect and quite possibly associated with some functional pancreatic affection. In this group we may provisionally include certain cases of chronic intestinal indigestion in children marked by retardation of growth, distension of the abdomen with gas, intolerance of carbohydrates, voluminous light coloured stools containing much gas, and sweating about the head. A remarkable feature of these cases is the large amount of indican and phenol contained in the urine, the latter sometimes amounting to as much as 100 milligramms in twenty-four hours in a child of three years. In these cases there is an actual and not merely relative increase in the ethereal sulphates. An important feature is the readiness with which fatigue is induced. In adults the symptoms are very similar, consisting of flatulence, abdominal distension and intestinal indigestion, following slight divergence from strict diet. Fatigue symptoms are also well marked.

(2) *The saccharo-butyric type.*—This is due to the action of strict anaerobes capable of multiplying by spore formation, and is common among adults, accounting for many cases of so-called dyspepsia. Patients who are otherwise healthy have attacks of " indigestion," associated with a temporary multiplication of these bacilli, the effect upon the system being a constant decline in the capacity of the organism to perform work. Eventually they often drift into a condition of chronic invalidism. A frequent symptom is the occurrence of diarrhoea or flatulence after a relatively slight excess of starchy food, the explanation being that the intestinal mucous membrane is kept in such a constant condition of irritation that stimuli which in normal people would meet with no response, give rise to excessive peristalsis. It is also possible that a slight acidosis from the excessive formation of fatty acids may be a factor in the case. The end of many of these cases is a progressive anaemia, possibly due to the formation of haemolytic substances in the intestines.

(3) *Combined indolic and saccharo-butyric type of chronic intestinal putrefaction.*—This group is probably the commonest to be met with among adults in practice, and is marked by the

combination of indicanuria of a high grade with an excess of putrefactive anaerobes. The symptoms most commonly met with are those forming the well known clinical picture of neurasthenia. Irritable weakness of the nervous system, mental depression, morbid introspection, with fatigue symptoms both bodily and mental. In some of these cases I have met with well marked morbid fears, especially claustrophobia. Later on blood signs show themselves, and the patients, if neglected, may drift into chronic invalidism.

The exact symptoms produced by any of the types of intestinal putrefaction will evidently depend upon three factors: the particular poison produced in the intestines, the integrity of the line of defence of the organism, and the relative vulnerability of the different tissues of the body.

It is obvious that the human body must possess some means of protecting itself against the poisons which are continually being produced in the gastro-intestinal tract, and with this object Nature has provided on the one hand the triple line of defence so well described by Combe,[1] consisting of the intestinal mucosa, the liver and the antitoxic glands, and on the other the antagonism of the obligate inhabitants of the intestines. The importance of the intestinal mucosa as a means of protecting the body from the effects of intestinal toxines was, in the first instance, deduced by Cassin and Charin from the observation that the action of these is far greater when injected directly into the portal vein or absorbed through a portion of intestine denuded of its epithelium, than when absorbed through normal mucous membrane. As a corolary it was evident that the liver alone is insufficient to entirely protect the body from intestinal toxines. The protective action of the liver is the second line of defence. This organ intercepts such of the intestinal toxines as have escaped the action of the intestinal mucosa and changes them into harmless substances which can safely be allowed to enter the general circulation. Ammonia and amines are transformed into urea, and the aromatic bodies into ethereal sulphates. In addition the liver cells have the power of fixing and appropriating aromatic bodies, especially indol and scatol. The third line consists of the thyroid gland, the suprarenals, and probably the hypophysis cerebri, and in babies the thymus, and there is now abundant evidence available to suggest that the toxines which have escaped the intestinal mucosa and the liver are dealt with to some extent by these bodies.

In the methods of defence which we have enumerated the poisons are destroyed and prevented from entering into the general circulation as such. But there is another expedient

[1] Combe. *L'auto-intoxication intestinale.* Paris, 1907, p. 92.

which Nature employs to protect the organism from injury, and that is the limitation of the amount of toxines actually produced in the intestine. This limitation of toxines produced, is effected mainly through the agency of the normal obligate flora of the large intestine, which consist principally of the bacillus coli. "The evidence now available suggests that the colon bacillus exerts an important function in combating the injurious saprophytes with which even in ordinary health the human intestine abounds. A long largely anaerobic intestinal tract, permitting gradual resorbtion of its contents, is a physiological necessity in order that a loss of water and its injurious consequences may be spared the organism. We have thus the most rational explanation of the meaning of the myriads of colon bacilli which inhabit the large intestine. These bacilli are essential as a defence against bacterial foes, which it is impractical to wholly exclude. This view is not inconsistent with the conception that, under some conditions, the colon bacilli multiply to such an extent as to prove harmful" (Herter).[1]

It had been previously supposed that the main function of the bacteria inhabiting the intestines was the decomposition of cellulose, but this has been disproved by Bergman,[2] who has shown that most of the cellulose-containing plants produce intracellular enzymes capable of digesting it.

As regards the precise manner in which the bacillus coli inhibits the growth of other bacteria, considerable light has been thrown upon the subject by the researches of Conradi and Kurjuweit,[3] who have proved that members of this group manufacture thermolabile and thermostabile substances which not only inhibit the growth of other organisms, but also their own, if given long enough time in which to act. This fact will account for the diminished number of bacillus coli in some cases of chronic constipation.

Diagnosis of intestinal auto-intoxication.—This is made from the examination of the urine by calculating the coefficient of Amann, and that of Combe, or in lieu of the latter finding the capillary constant.

The coefficient of Amann is the ratio which the ethereal sulphates bear to the total nitrogen.

Normally, the ratio of the ethereal sulphates to the total nitrogen is from 1·4 to 1·5. per cent. In auto-intoxication the amount is largely increased.

[1] Herter, *op. cit.*, p. 5.

[2] *Studien uber die Digestion der Pflanzenfresser." Skandinavische Archiv f Physiologie*, xviii., p. 119. 1906.

[3] *"Ueber die Bedeutang der bacteriellen Hemmungstoffe fur die Physiologie und Pathologie des Darms." Munch. med. Sochenschrift.*, lii., pp. 2164, 2228. 1905.

The following is a simple method of finding the ethereal sulphates. Place in a flask 50 c.c. urine + 5 c.c. HCl. + 10 c.c. solution of barium (30·5 gm. chloride of barium to the litre). Heat 15 minutes over naked flame. Filter, wash, dry, calcine and weigh precipitate. Result (*A*) = total sulphuric acid. Into a flask put 50 c.c. urine + 5 c.c. acid acetic + 10 c.c. of aforesaid barium solution. Heat gently. Wash, filter, dry, calcine and weigh precipitate. Result (*B*) = the sulphuric acid of the sulphates. A — B × 6·8692 = the quantity of milligrammes of ethereal sulphates contained in a litre of urine. The coefficient of Combe is the number of milligrammes of aromatic substances which the urine contains for each 100 grammes of total nitrogen. The result is obtained by dividing the total nitrogen of the urine in grammes by the total number of milligrammes of aromatic substances.

In obtaining both this ratio and that of Amann, for clinical work the total urea nitrogen, as estimated by Liebig's mercuric test, may be used instead of the actual total nitrogen obtained by Kjeldahls method. The amount of aromatic substances can also be estimated colorimetrically with sufficient accuracy for clinical purposes by means of Amann's chromometer.

The capillary constant gives us a rough measure of the amount of aromatic substances in the urine. It has been discovered experimentally that the superficial tension of the urine is lowered by the presence of uric acid, hippuric acid, and the aromatic bodies. We may, therefore, within certain limits and with some reservations, take the amount of lowering of the superficial tension as a measure of the amount present of the bodies which produce auto-intoxication. We may measure the superficial tension in the following manner. Take an ordinary burette with a stop cock, and attach to its tip half an inch of capillary tube by means of a little piece of rubber tube. Fill the burette up to the zero mark with distilled water, turn on the tap, and commence to count the drops which fall from the capillary orifice. When exactly 100 drops have fallen, note the amount of water which has been used. Mark this spot on the burette with a diamond. You have now an apparratus with which you can estimate the superficial tension of urine. You simply fill the burette with urine up to the zero mark and count the number of drops which will fall until the level of the urine reaches the mark. The number of drops of urine, minus 100, divided by the difference between the specific gravity of the urine under examination and 1,000, will give a quotent which is termed the capillary constant, and which bears a fixed relation to the superficial tension.

An example will make this plain. Suppose we take urine of a specific gravity of 1,020, and 110 drops fall before the level of

the urine in the burette reaches the mark, then the capillary constant will be obtained by the following formula :—

Capillary constant $= \frac{110-100}{1020-1000} = \frac{10}{20} = 0{\cdot}5$. This is the capillary constant of normal urine.

Having established the fact that there is intestinal auto-intoxication, the next point to ascertain is whether this is due to diminution in the protective power of the liver, to increase in the intestinal fermentation, or to both.

We are not able to directly test the antitoxic power of the liver, but we can deduce it by observing the efficiency of its other work. It has been demonstrated by Roger that the glycogenic function of the liver and the power of the hepatic parenchyma in arresting intestinal poisons increased and diminished *pari passu*. It has been proposed to give a dose of 150 grammes of glucose and afterwards to test the urine for sugar. Its appearance would be a proof of hepatic non-efficiency. This and the intermittent elimination of methylene blue are yet in the experimental stage, and we must at present rely upon the two following tests :—

Ratio of urea to the total nitrogen.—A deficiency of urea in the urine is not of necessity a sign of hepatic inefficiency, unless we know at the same time that the intake of nitrogen is normal. This is impossible in daily practice, and we overcome the difficulty by taking the ratio of total urea nitrogen to the total urinary nitrogen. When the urea nitrogen is less than 83 per cent. of the total urinary nitrogen, we may assume hepatic insufficiency.

Ratio of ammonia to total urinary nitrogen.—With the exception of about 5 per cent., the ammonia formed during digestion in the intestines is converted by the liver into urea. A ratio over 5 : 100 will denote hepatic inefficiency.

Presence of leucine in the urine.—Leucine is changed by the hepatic cells into urea. Anything beyond a mere trace in the urine will denote hepatic inefficiency.

Diagnosis of Intestinal Putrefaction and Fermentation.—For use in daily practice we must content ourselves with methods which do not require the use of a laboratory or a profound knowledge of bacteriology, and moreover do not occupy much time. For all practical purposes the following will serve :—

The character of the microscopic fields in stained preparations of the stools.—In preparations stained with Gram and counter-stained with fuchsin, the red stained organisms will normally preponderate (the colon bacillus being Gram negative). In abnormal putrefaction, in proportion as the aerobic bacilli are replaced by strict anaerobes (most of which are Gram positive), the blue stained organisms will be in excess. It is therefore

possible to tell at a glance with a little practice whether there is abnormal putrefaction in the intestine, and to form an idea as to the presence of B. bifidus, Gram positive diplococci and Gram negative organisms of the type of the B. liquefaciens ilei.

The growth of the mixed faecal flora in sterile milk.—A little piece of faeces about the size of half a pea is introduced into a tube of sterile milk and placed in an incubator. A rapid breaking up of the curd formed by the gas evolved will point to the presence of abnormal organisms such as the B. aerogenes Capsulatus.

Gas production in fermentation tubes containing sugar bouillon.—The amount of gas produced by the mixed flora of healthy faeces is, roughly speaking, from 15 to 39 per cent. of the height of the anaerobic limb.[1]

In cases in which the gas production is increased, one should suspect the presence of yeasts. In the saccharo-butyric fermentation the amount of gas is usually diminished owing to elimination of the colon bacilli. As a matter of fact the gas formation is diminished in most putrefactive conditions in the intestine, and points to a profound alteration in the flora.

We may consider that there is no abnormal putrefaction in the intestines if we find indol and phenol present only in small quantities in the faeces, perhaps only a few milligrammes to each 100 grammes of moist faeces, the ethereal sulphates low in proportion to the total nitrogen, the urinary reaction with dimethoamidoazobenzaldehyde very slight, and the capillary constant somewhere about 0·5.

Therapeutic Inhibition of Intestinal Putrefaction by the Acclimatization of Lactic Acid Bacilli.

Curdled milk has from time immemorial formed an important part of the diet of many peoples, notably those inhabiting Turkey, Roumania, Bulgaria, Servia, and some parts of Africa, the milk being in all cases soured with a special ferment. The best known of these ferments is the Bulgarian maya, with which is produced the article of food called yoghourt or yohourth. This ferment was first studied bacteriologically by Grigoroff[2] in the laboratory of Professor Massol of Geneva, who found that it contained three lactic acid-forming microbes—(*a*) a long bacillus which on cultivation proved to be the most energetic lactic acid producer known (the Bulgarian bacillus); (*b*) a diplococcus; and (*c*) a streptococcus. All three coagulated milk, produced lactic acid in different proportions, and were Gram

[1] Herter, *op. cit.*, p. 126.
[2] Massol: *Revue Médicale de la Suisse Romande*, 1905, p. 716.

*

positive. The first of these is the most important and is known as the Bulgarian bacillus or the bacillus of Massol.

We are undoubtedly indebted to Metchnikoff for the brilliant conception that the daily use of yohourt or its equivalent could be utilized in the treatment of disease, and that by means of it, or preferably by the use of a pure culture of the principal bacillus, we might assist the colon bacilli to inhibit abnormal putrefaction in the intestines. We owe the elaboration of a practical working method to Dr. Michel Cohendy,[1] who, working in the Pasteur Institute with the Bulgarian bacillus, as the result of a prolonged series of investigations, ascertained the following important points : That with a normal diet the bacillus appeared in the stools in from three to four days after it had begun to be taken regularly with the food ; that it took about eight days to become properly acclimatized in the intestine, and that when this had taken place would continue to live and thrive for twelve more days without another dose being swallowed, after that gradually disappearing ; that it caused absolutely no harm to the organism ; that the presence of the bacillus in the intestine caused an increase in the number of bacilli and coccobacilli taking the Gram stain ; and that its regular administration caused an increase in the weight and bulk of the faeces.

Characteristics of the Bulgarian Bacillus.—*Microscopical.*—The bacillus is a large one, somewhat resembling the B. Anthracis, and is from 2 to 20 microms in length. It stains well with all the usual stains and is Gram positive.

Cultivation.—It does not spore in any medium in which it has yet been grown. It grows badly upon the ordinary laboratory mediums and is best cultivated upon the following :—

1. Serum of milk—(Cohendy). 2. Serum of milk peptonized. —The above with the addition of 1·5 per cent. of Wittes' peptone. 3. Agar milk peptone.—Peptonized serum of milk as above with the addition of 17 per cent. of agar. 4. Lactic litmus milk.—This medium is especially useful for testing the stools to establish the fact of acclimatization of the bacillus during treatment, and is prepared as follows :—3·5 grammes of lactic acid are added to a litre of litmus milk. This forms a semi-solid mass and is tubed and sterilized. The bacillus is nearly the only organism which will grow freely upon this medium. The presence of the litmus will indicate putrefactive organisms by its change of colour.

[1] Cohendy : *Comptes Rendus de la Société de Biologie.* 1906, vol. i. *' Essais d'Acclimatation Microbienne Persistante dans la Cavité Intestinale,"* p. 364. *" Description d'un Ferment Lactique Puissant capable de s'acclimater dans l'Intestin de l'Homme,"* p. 558. *" De la Désinfection Intestinale obtenue, sans Régime Spéciale, par l'Acclimatation d'un Ferment Lactique dans le Gros Intestin,"* p. 602.

The bacillus does not grow upon potato nor sugared gelatine. On the solid agar milk peptone it forms chains of from 2 to 19 individuals. Below 35° C. and above 44° C. its growth is feeble. It resists a temperature of 0° C. for twenty-four hours, but is killed in a few minutes at 63° C.

Fermentation.—It actively ferments sugars such as lactose, maltose, saccharose, levulose and glucose, the presence of these hydrocarbons being necessary for its life. Its action upon starch and hard boiled white of egg is negative.

The effect of acclimatizing the bacillus in the intestine is to inhibit the growth of the proteolytic microbes which are the most common cause of abnormal putrefaction and consequent auto-intoxication. This has been proved by the great diminution in the daily excretion of the ethereal sulphates which has been observed, and the alteration in the character of the faeces during the process. The main agent in effecting the inhibition of other bacteria is probably the lactic acid produced, according to the general rule established by Tissier in conjunction with Martelly [1] and with Gasching,[2] that an acid-producing bacillus is able in a saccharine medium to arrest the growth of a putrefactive (alkaline) organism.

But it is extremely likely that in the same manner as the bacillus coli the lactic acid bacillus in question also produces some toxine which is inimical to the growth of anaerobes.

As regards the harmlessness of the lactic acid which is produced in the intestine as the result of the growth of the Bulgarian bacillus it has been calculated by Cohendy that whilst the average Bulgarian peasant consumes more than 10 grammes of lactic acid daily in the yohourt which forms so large a part of his diet, the amount in the 250 cubic centimetres of sour milk, the average daily medicinal dose, does not exceed 60 centigrammes. Moreover, the lactic acid which is liberated in the intestine does not remain long as such, as it will be quickly neutralized by the alkaline reaction obtaining there. This theoretical consideration is confirmed by the observed fact that the stools of patients taking curdled milk are never strongly acid.

CHAPTER II

THE SELECTION AND PREPARATION OF LACTIC ACID FERMENTS FOR USE IN PRACTICE

THE first problem which will present itself to the medical man who wishes to make use of these agents in his practice is the

[1] *Annales de l'Institut Pasteur*, December, 1902. [2] *Ibid*, August, 1903.

selection of the best preparation for his purpose from the number with which the market is now flooded. One or two of these are good, some are useless, and the remainder probably injurious. At present we are able to obtain commercially: (1) Yoghourt prepared with the Maya ferment; (2) ready soured milks; (3) several varieties of liquid cultures supplied in bottles for internal administration; (4) liquid ferment in tubes for souring milk; (5) seven or eight brands of dry ferments in the form of powder or tablets. We will discuss these seriatim as regards their suitability for clinical use:—

(1) *Commercial Yoghourt prepared with the Maya ferment.*—When we take into consideration the fact that this, the original method of employing the lactic acid ferments, was almost from the beginning abandoned by Metchnikoff himself in favour of milk curdled with pure cultures, we must see that from a scientific point of view we are taking a retrograde step if we make use of it. Besides, Maya, in addition to the active bacillus which we want, contains alcohol-producing bacilli, yeasts and other micro-organisms which can be of no utility and may even prove injurious.

(2) *Commercial soured milks.*—I think that we shall be wise in rejecting these, except as articles of food pure and simple, and in not making use of them for therapeutic purposes. We, as physicians, should know exactly what we are giving to our patients, and not leave the selection of the milk souring ferments to the discretion of a dairy company. If a proper ferment has not been employed, we shall have a curdled milk, possibly delicious to the palate and apparently much better than we can produce ourselves, which is nevertheless quite useless for the acclimatization of the lactic bacillus in the intestine. Again, as some considerable time must elapse between the preparation and consumption of commercial soured milk, there is risk of the process being carried too far and of the product becoming irritating to the stomach. In any case it will be quite impossible to insure that the patient always gets it in the same stage. I feel sure that we shall be acting in the best interest of the patient if we avoid milk soured in large quantities for sale to the public and persuade the patient to take the very small amount of trouble involved in preparing it himself, from milk of known quality with a reliable ferment.

(3) *Liquid cultures for internal use.*—After the Bulgarian bacillus had been isolated and successfully acclimatized in the intestines the first therapeutic attempts were made with liquid cultures. Cohendy at first used his serum of milk. Later he used a culture of the bacillus in a solution of extract of malt. Following this we have had several liquid cultures produced commercially at different laboratories, the medium being in

most cases extract of malt, with or without peptones. The use of these is more or less impractical because they rapidly deteriorate, and the continual growth of the bacillus causes a progressive increase in the acidity which renders them after a short time very irritating to the stomach. I have also found that they are invariably repulsive to the patients. Fortunately we can do very well without them, as all the effect of a liquid culture can be obtained by administering a dry preparation suspended in water.

(4) *Liquid cultures in tubes for souring milk.*—What has been already said in the last paragraph will also apply. These cultures do not keep well, and whilst they undoubtedly produce results better than the earlier dry preparations, they are now far inferior to the dry preparations produced by more modern methods.

(5) *Dried cultures.*—We find these in commerce in the form of powder or tablets, and for practical clinical work they are to be preferred either for direct administration or for the preparation of soured milk. In these preparations the bacilli are in a condition of suspended animation (*vie ralentie*), in which they remain indefinitely, to be revived and to again become active under the influence of warmth and moisture. But even in this form an indiscriminate choice cannot safely be made from the dozen or so brands upon the market. Several of the powders and tablets which are advertised appear to have been made by simply drying milk containing a culture of the bacillus. The prolonged process of drying the caseous mass exposes the product to endless risk of contamination and putrefactive changes, the bacilli are not evenly distributed through the mass and the base of condensed milk does not readily allow the tablet to disintegrate in water. This last point is of great importance, as they should always be given suspended in water.

Some manufacturers, in order to mask the insolubility of the base of which their tablets are composed, mix an effervescing powder with it. This certainly causes it to disintegrate, but it does so in flakes and the solubility is apparent not real, its miscibility with water not being actually increased. Besides, the products of the effervescing material will remain in solution and communicate an acid reaction to the water in which the tablet is suspended, possibly interfering with the development of the ferment.

That these points are not imaginary is shown by the following results of comparative tests of several of the brands of tablets of lactic acid bacilli now being advertised.

Seven different kind of commercial lactic acid tablets were taken and examined as to solubility, colour, smell, and reaction of suspension, with the following results:—

Tablet (1). White, odourless, disintegrates in two minutes without shaking into a heap of white powder, which suspends well on shaking; reaction neutral.

Tablet (2). Greyish white, odourless, in five minute disintegrates into coarse white floccules, which do not suspend at all well in water; reaction neutral.

Tablet (3). Whitish brown, slight odour of cheese, in ten minutes has only partly disintegrated; reaction faintly acid.

Tablet (4). Greyish white, distinct sharp odour, at the end of ten minutes has not commenced to disintegrate. When crushed with water reaction is distinctly acid.

Tablet (5). Whitish brown, odourless, after four minutes has disintegrated into coarse brownish flakes which do not suspend well in water; reaction acid.

Tablet (6). White, odour of cheese, after ten minutes the surface is eroded but otherwise unaltered; reaction acid.

Tablet (7). Brownish, odourless, floats on water, absolutely unchanged after 24 hours in water; reaction acid.

From a consideration of the foregoing the practical conclusions at which one arrives is that not only are the dry preparations the best, but that we must exercise the greatest care in the selection of these. We see that a bouillon prepared by suspending a disintegrated tablet in water is to be preferred to any of the commercial liquid preparations, or even to fresh cultures. It is easier prepared, not so repulsive to the patient, and, to say the least, equally efficacious. If we wish to employ curdled milk for its food value we shall use a dry culture in powder form for its preparation. If our aim is to acclimatize the bacillus in the intestine we shall best do so by administering one or more of the tablets suspended in water three times a day, it being understood that we have made a wise selection of the brand.

As a practical guide in the selection of the tablet or powder we may lay down the following rules:—

In the case of a tablet—

1. It should be pure white in colour.

2. It should be odourless, both when in the dry state and when moistened with water.

3. It should disintegrate when immersed in within three minutes into a fine powder without the aid of crushing or stirring, and this disintegration must not be accompanied with effervescence.

4. The suspension should be neutral to litmus paper.

5. When cultivated upon Cohendy's serum or other suitable medium it should give an abundant growth of the Bulgarian bacillus and no other micro-organism should be present.

In the case of the powder for souring milk—

1. It should produce a good firm clot upon pure milk in eight hours at a temperature of 100° Fahr.

2. The clot should be nearly white, spongy, with a faint acid smell and taste and the entire absence of acridity.

3. No brown sediment should form during the incubation.

4. The only organisms present in the soured milk should be the Bulgarian bacillus and one other organism added to prevent the saponification of the milk fat.

As regards these requirements some preparations answer one and some another. The only one which fills them in their entirety is the first on the list of tablets and the corresponding powder. These are preparations produced by Dr. Boucard, of Paris, who has much increased the resisting power and activity of the bacillus by successive cultivations in certain special media.[1] The tablet consists of nothing else than a pure culture of what we must now call the bacillus of Boucard, all other kinds of lactic acid ferments having been eliminated both because their activity is much less and for the reason that their faculty of becoming acclimatized in the intestine is practically nil. The basis is sugar of milk, thus avoiding the long drying process and consequent risk of contamination incidental to the manufacture of tablets from condensed milk.

The powder for souring milk consist of the bacillus of Boucard, with the addition of a streptobacillus added to render the taste more agreeable by preventing the saponification of the fat of the milk.

The bacterial contents of Dr. Boucard's tablets and powder are well shown in the frontispiece. Fig. 1 represents the ordinary lactic acid bacillus as found in milk which has curdled naturally by contamination from the atmosphere. Fig. 2 shows the pure culture of the bacillus of Boucard present in the tablets. Fig. 3 shows the bacilli and the streptobacilli in the powder for curdling milk.

The bacillus as modified by Boucard exhibits a well marked granulose reaction when treated with Lugol's solution, a characteristic which it possesses in common with the Oppler-Boas bacillus. It is thus easily recognized in fresh preparations.[2]

Directions for Use by Patients.

Patients should always be provided with precise directions, as success depends largely upon the observance of details.

(A) Directions for Taking the Tablets.—One or more tablets as directed by the medical attendant are to be put into a tumbler

[1] Lacteol tablets and powder, manufactured by the Laboratoire de Biologie, 6, Rue Guillaume Tell, Paris. These can be obtained in London from Roberts, 76, New Bond Street.

[2] For particulars of this reaction see "*Ueber das Vorkommen der sog. 'langen Bazillen" im Verdauungstractus*, Von Dr. E. Fricker. *Archiv für Verdauungs-Krankheiten.* Band xiv. Heft 5.

half full of cold (preferably filtered) water and allowed to stand. As soon as they have broken up into a heap of white powder, which should take place at the end of two or three minutes, stir well, and drink, taking all the sediment. Should any remain at the bottom, add a little fresh water, stir and drink. If sugar is not being taken at meals a lump should be dissolved in the water before dropping in the tablets. In other cases the water may be sweetened with a teaspoonful of extract of malt.

(B) The Preparation of Soured Milk.—This is quite simple, but a strict ritual must be observed if the best results are to be obtained. Given a proper ferment there are four other points essential for success. These are: the selection of a good quality of milk, its sterilization, the proper sterilization of the jars used to contain it, and the maintenance of the proper temperature during the process of curdling.

The jars mentioned in the following directions are the glass or earthenware vessels provided with a cover, supplied with the commercial apparatus for curdling the milk, and each contain about 120 c.c., or 8 oz.

When using an extemporized apparatus we may make use of three ordinary tumblers if we provide them with covers. The screw tops of French plum jars do very well for this if we select the size which will fit loosely over the top of the tumbler.

Step 1. The sterilization of the jars and covers.—This is the first thing to do, as they can be cooling whilst we are preparing the milk. Place the jars in a saucepan of cold water large enough to allow them to be quite covered, heat gradually and allow them to boil for five minutes. At the same time we should boil the spoon with which we are afterwards going to mix the ferment. Take them all out and stand upon a clean plate, the jars and covers being mouth downwards. Wipe the outsides with a clean cloth as they stand on the plate. Do not wipe the spoon.

Step 2. The sterilization of the milk.—Whilst the jars are cooling, you proceed with the sterilization of the milk. Raw milk when curdled possesses by far the most pleasant taste, but is unsafe. As delivered at the house it probably contains faecal dust from the cow, loaded with microbes, and quite possibly pathogenic germs such as those of tubercle or typhoid. There will also be milk curdling germs which, if allowed to develop, will take part in the souring of the milk and prevent it being a pure culture of the ferment which we are using. Pasteurization at 60° C. whilst preserving the taste of the milk does not destroy the spores of the butyric acid bacillus, nor the tubercle bacillus. Sterilization at 120° C. is efficacious, but communicates such a disagreeable taste to the milk that patients cannot take it for any length of time. We have in simple boiling the happy mean. By this we destroy everything except the butyric acid spores

and those of the bacillus subtilis, and this is practically sufficient for our purpose as they will not germinate in eight hours.

Method (*a*).—We place 24 oz. of milk (sufficient for the three jars) in a saucepan and bring to the boil, and allow it to boil for five minutes. In this case we have not concentrated the milk.

Method (*b*).—We may imitate the preparation of the original Yoghourt (which was made with milk reduced to one half its bulk) and boil the milk for a longer period with the object of getting a stiffer curd. This is an advantage when the curd is to be eaten with cream and sugar as dessert at the close of a meal. It is also useful in cases such as sprue and Bright's disease, in which we are feeding the patient entirely upon milk and have reached the limit beyond which we apparently cannot increase the amount taken. The most practical reduction is to two-thirds, and for this purpose we shall take 36 oz. for the three jars.

Method (*c*).—It is often noticed by nurses preparing soured milk that some samples curdle easily and some not at all or very imperfectly. Excluding those cases in which an improper ferment is being used the explanation is to be found in the pernicious practice adopted by far too many dairymen of adding preservatives to the milk before sale. It stands to reason that agents added to milk to prevent it from turning sour through the agency of the wild microbes of the air will be equally efficacious against the pure cultures which we are using. When any difficulty of this kind is experienced we may make use of milk which can now be obtained put up in hermetically sealed bottles, which is guaranteed to have been cleaned mechanically, and preserved by Pasteurization, without the aid of antiseptics. Such milk, although nominally sterile, should, as a matter of precaution, be well boiled before use.

Method (*d*).—Under similar circumstances we may make use of one of the brands of unsweetened sterilized condensed milk which are now procurable. A tin of Ideal milk [1] contains 12 oz., and we may dilute it with 30 oz. of water to produce an unconcentrated milk, or with 18 oz. for a concentration to about two-thirds.

Having prepared our milk by one of the above methods we turn the jars the right way up, pour a third of the milk into each jar put on the lids and wait for it to cool sufficiently for us to introduce the ferment. It is needless to say that if we put the ferment into boiling milk we shall destroy its vitality. We can ascertain the temperature of the milk in the jars with sufficient accuracy by feeling the outside with the back of the hand. We must never use a thermometer to the milk in the jars, nor try the temperature as is often done by dipping in the finger, as neither the thermometer nor the finger will be sterile under

[1] Manufactured by Nestlé, 6, Eastcheap, E.C.

ordinary circumstances. As soon as the outside of the jars is comfortably warm to the hand the milk will be ready for the introduction of the ferment.

Step 4. The introduction of the ferment.—Pour one-third of a tube of powder into each jar, stir well with the boiled spoon and replace the lids.

Step 5. The incubation. The jars now require to be kept at a temperature of about 38° C. (100° Fahr.) for about eight hours. To accomplish this we may either extemporize an apparatus or we may purchase one especially designed for the purpose.

(*a*) *Extemporized incubator.*—When only a small quantity of curdled milk is required we may make use of a Clark's or Price's food warmer. When we require to make the usual quantity of 24 oz. we shall require a saucepan, three tumblers with covers as described (see p. 16), and an eight hour nightlight. Support the saucepan upon two bricks, or better still upon one of the iron tripods used in laboratories, costing a few pence,[1] and half fill with water at 100° Fahr. The tumblers, having been sterilized, filled with milk, and inseminated with ferment in the manner described in paragraphs 1, 2, 3 and 4, are covered and placed in the saucepan. The nightlight is adjusted so that the flame is about two inches from the bottom of the saucepan. When using this arrangement for the first time the temperature of the water should be taken at the end of the first hour and the nightlight if necessary raised or lowered to secure the proper heat.

(*b*) *Commercial incubators.*—It saves a great deal of trouble to use one of these. There are now two varieties to be obtained. The first, which was the original pattern, consists of a felt-lined box to contain the jars which stand alongside a tin box of hot water. The disadvantage of this apparatus is that the hot water must be renewed once or more during the incubation. The second form,[2] which has practically superceded the former, consists of a wooden box supported upon legs in such a manner as to leave room underneath for a nightlight, the distance being so adjusted as to secure the required temperature the heat entering through a hole below. Within is a box of tin to contain the jars. It is quite safe and efficient.

The jars containing the inseminated milk having been placed in the box and the lid closed, one of Price's six or eight hour nightlights should be placed in its glass in the hole provided for it in the middle of the shelf under the box. If an ordinary nightlight be used it should be placed in the same position in a saucer

[1] Can be procured at Baird & Tatlock, Cross Street, Hatton Garden, or rom Griffin & Son, Kingsway.

[2] Made by the Laboratoire de Biologie, 6, Rue Guillaume Tell, Paris. London agents, Roberts & Co., 76, New Bond Street.

containing a little water. The nightlight will raise the interior of the box to a temperature of 104° Fahr. (40° C.), which will ensure the fluid in the interior of the jars being subjected to one of about 100° Fahr. (38° C.). Which nightlight we select (six or eight hours) will depend upon the degree to which we wish to carry the souring process. As soon as the nightlight has burnt out we should remove the jars and cool them as rapidly as possible, either by standing in cold water or by placing in a refrigerator. This is advisable in order to arrest the growth of the bacillus and prevent the souring process from being carried too far. It is as well to note that some samples of milk will not curdle properly unless allowed to remain in the apparatus for one or two hours after the nightlight has burnt out. The acidity of the product should never exceed a pleasant sourness, in fact, if with any particular sample of ferment we get an excessively acid curd we should suspect that this is the result of rennet ferment which has been added to the tablet by the manufacturer to increase its power of curdling milk.

The curd will be found separated from the whey which will occupy the lower part of the jar. This should, as a rule, be consumed as well as the curd, and if the latter is not too thick a convenient method of taking it will be to empty the whole contents of the jar into a tumbler and break up the curd with a fork, or better still an egg whisk. The whole can then be taken as a beverage. If we have produced a thick curd by reducing the milk, we can eat it with sugar and cream, or with preserve as a dessert at the close of a meal. In some cases the patient may make a meal off the thick curd by eating it with bread. Soured milk will keep good for a couple of days if kept in a cool place, but is far the best to consume it the same day that it is made, in case the process should continue and the milk become too sour to be agreeable.

CHAPTER III

THE ADMINISTRATION OF LACTIC ACID FERMENTS IN DISEASE

(*A*) As an Article of Diet

Milk curdled by means of the bacillus of Boucard is a most wholesome food as we have already seen, and may be used as such quite apart from any question of acclimatizing the bacterium in the

intestine, provided that there is no contraindication. In practice we may utilize it in the following conditions :—

(1) Loss of Appetite.—This symptom is, as we all know by painful experience, a very troublesome one in many conditions met with in daily practice, and we shall often find soured milk of great assistance. When properly made and served it is most appetising, and patients will often fancy it when other articles of food are refused. Among the cases in which it may be of service are anorexia nervosa, phthisis, cancer of the stomach, and neurasthenia, in all of which loss of appetite is one of the many difficulties to be met.

(2) Cases in which it is necessary to keep the patient upon a purely milk diet.—It here finds its sphere in the feeding of acute specific diseases, and offers the important advantage that in addition to presenting the milk in a highly digestible form it effectually combats excessive and abnormal intestinal fermentation, and in the case of typhoid may be reasonably expected to exercise some influence upon the bacillus typhosus. In a case of sprue, in which I gave it, the result was extremely satisfactory and it appeared to produce far better results than the plain milk upon which the patient had previously been fed.

(3) Cases in which the amount of hydrochloric acid in the gastric juice is diminished.—Thus we may order it in cases of hypochlorhydria, achylia gastrica, chronic mucous gastritis, and cancer of the stomach, with good results. In these cases the deficient hydrochloric acid in the stomach and consequent lessened acidity of the chyme usually leads to associated deficiency of the pancreatic secretion, and the free lactic acid present in the milk will be of distinct advantage as it can certainly replace to a considerable extent the absent hydrochloric acid as an activator of the pancreatic secretion.

It should also supply the hypothetical deficiency of hydrogen ions, as shown by the small amount or absence of HCl in the gastric juice.

(4) When it is advisable to avoid throwing more work upon the liver and kidneys than can be avoided.—As we have already seen, the liver and kidneys assist in defending the organism against the toxines produced in the gastro-intestinal tract, during the digestive process. In cases in which there is any weakness or defect, or chronic disease, or functional disability in these organs, common sense will prompt us to lighten their work as much as possible both for their own benefit and to avoid auto-intoxication. We may, therefore, with obvious advantage, include a generous amount of soured milk in the diet of those suffering from hepatic cirrhosis, hepatic congestion from cardiac disease, and granular contracted kidney.

(5) Irritability and hyperaesthesia of the stomach.—Soured

milk will often be retained when all other articles of food are rejected. This is especially the case in those unfortunate patients suffering from malignant disease of the stomach in which no operation is possible. In these cases one of the chief problems is the feeding of the patient, and in soured milk we often find a very useful auxiliary. It is important in these cases not to carry the souring of the milk too far, and to break up the curd thoroughly before serving it to the patient.

In the vomiting of pregnancy also soured milk will often be found of considerable utility. In a case which I saw some little while ago the vomiting promptly ceased from the moment when this treatment was commenced.

A word of caution may here be given not to prescribe soured milk in any case in which there is hyperchlorhydria. Cases of hypersthenic gastritis are invariably made worse by soured milk, and unless we would lose reputation we should always by a test meal assure ourselves of the absence of excess of hydrochloric acid in all gastric cases before ordering it.

(*B*) Cases which may Depend upon Auto-Intoxication from the Intestineal Tract

Affections occurring in practice in which we are justified in suspecting chronic poisoning from the intestines may be classified as follows :—

(1) Skin diseases which are not obviously of a parasitic or specific nature.—Until recently the great difference in the standpoint of the family physician and the dermatologist as regards the pathology of skin affections was that whilst the former had observed in his daily practice the evident dependence of many of them upon disorders of the gastro-intestinal tract, especially among children, and was confirmed in his belief by the well-marked effect of remedies given on that hypothesis, the latter was inclined to be sceptical and ascribed them almost universally to local causes.

Events have proved that the family physician was in the right, and skin specialists are now, with few exceptions, ready to admit that a considerable number of cutaneous affections owe their origin to auto-intoxication from the alimentary tract. They may be induced in one of three methods at least.

(*a*) The toxines are eliminated by the sweat glands and in their passage set up sufficient irritation to cause the lesion.

(*b*) The terminations of the cutaneous nerve may be directly irritated.

(*c*) The irritation of the nerve may be central.

The chief skin affections which may be caused by auto-intoxication are apparently strophulus, pruritus, urticaria, acne, furunculosis, and some forms of seborrheic eczema. In a case

of chronic urticaria reported by Combe the number of milligrammes of aromatic substances per 100 grammes of total urinary nitrogen was 629 (normal, 200),and in a case of acute urticaria, 755.

(2) Neurasthenia not obviously due to excessive strain or work.—Our conception of neurasthenia has vastly changed during the last few years. Introduced in the first instance by Beard as a distinct disease entity, we know now that it is merely a convenient method of designating a symptom group or syndrome which may be present in several widely-differing conditions. The syndrome itself is familiar to all of us, the fatigue symptoms both of mind and body, the panics, the indecision, loss of memory and concentration, the headaches, sleeplessness and dyspepsia. The mistake made by writers and clinicians was in trying to find a single cause for the condition. As a matter of fact the whole subject becomes quite clear if we can once grasp the fact that we have at least the following different neurasthenias :—

1. A neurasthenia due to the effect of excessive expenditure of nerve force in an individual inheriting a weak nervous system.

2. A neurasthenia due to chronic poisioning by tobacco, alcohol, tea, or other neurotic.

3. A neurasthenia which is the first stage of melancholia or general paralysis of the insane.

4. A neurasthenia due to imperfect metabolism, i.e., lithaemia or gout.

5. A neurasthenia due to auto-intoxication from the intestines.

Auto-intoxication, we thus see, is not the first cause to be thought of, but really the last, having eliminated the other possible ones. In groups 1 and 3 we may find soured milk a useful food. In groups 4 and 5 only may we expect benefit to follow the acclimatization of the Bulgarian bacillus in the intestines.

(3) Gout. (4) Arteriosclerosis.—Whether gout and arteriosclerosis are caused by auto-intoxication from the intestine is at present undecided. In such cases it is quite certain that we very frequently find increased arterial tension, associated with increase of the ratio of etherial sulphates to total nitrogen, and also that these patients often experience a marked amelioration under the lactic acid treatment, the following being a case in point :—

General de C. consulted me in September, 1907, complaining of chronic gouty symptoms from which he had been a sufferer for some years. On examination the maximum systolic pressure, as shown by the Riva Rocci sphygmometer, was 220, the radial arteries were hard and tortuous, urine showed an excess of indican, capillary constant was 1·7, ratio of etherial sulphates to total urinary nitrogen = 4 (normal = 1·5). After six week's treatment with soured milk, systolic pressure = 190, ratio of

etherial sulphates = 2·1, and capillary constant = 0·8 (normal = ·5).

(5) Chronic arthritis.—Overgrowth of the natural tubercles of the distal digital phalangeal bones and of the big toe joints without the ordinary classical manifestations of chronic gouty arthritis have been familiar to us since the time of Heberden,[1] who denied their gouty origin. Bouchard ascribed them to auto-intoxication from a dilated stomach. I have seen several cases in which all the signs pointed to chronic auto-intoxication from the intestine.

A medical man at the age of thirty suffered with persistent dyspepsia for which he dieted himself for nearly two years, taking a diet consisting almost entirely of meat with bread and very little green vegetables. Since that time he has suffered from progressive enlargement of the big toe joints, usually quite painless, commencing in the right foot. Occasional attacks of pain on movement after excess in red wine or champagne. At the age of forty the left toe joint commenced to be involved. He consulted me last year and I found the ratio of etherial sulphates to total nitrogen = 6·1. After four month's use of sour milk this had sunk to 2·2 (normal, 1·5).

(6) Neuritis and polyneuritis. (7) Progressive muscular atrophy. (8) Acute ascending paralysis.—We do not know for certain yet whether any of the aforesaid three groups of affections are due to auto-intoxication. We know that polyneuritis is certainly of toxic origin in many cases, being due to alcohol or arsenic, and we know that the multiple neuritis met with in syphilis, tuberculosis and diabetes is probably due to the absorption of toxic materials into the blood. Acute ascending paralysis is certainly due to some toxic agent from the rapidity with which it evolves. Cases have been known in which it was apparently produced by the typhoid bacillus and Combe and Kouche have described cases due to the ingestion of mussels. We shall be justified, therefore, in acclimatizing the bacillus of Boucard in the intestine as a mode of treatment which cannot possibly do any harm and possibly may produce good results.

(9) Chronic ill-health without any obvious cause.—We find a number of patients in middle life in fair health, but who are conscious of progressive deterioration and failing of their powers. They are able to do less work than formerly. Any excessive effort, both mental or physical, is followed by much more fatigue than they have been accustomed to notice. Any excess in diet or even an ordinary good dinner is followed by unpleasant results and they have the annoyance of having to live very carefully in order to preserve their fitness to do their daily work. If such cases are examined it will be found that most likely there

[1] *Commentarii*, cap. xxviii., 1802.

is a little indican in the urine, and the ratio of ethereal sulphates to total urinary nitrogen is raised. The number of colon bacilli is often not markedly diminished, as seen in stained fields, but by plating in blood agar the number of colonies of the B. capsulatus will often be found to exceed the normal.

Such cases are certainly suffering from a slight degree of intestinal auto-intoxication and should be placed on appropriate treatment. After the acclimatization of a lactic bacillus in the intestine, they will be found to regain their forces in a remarkable manner and often express themselves as feeling much younger and more vigorous.

It has been pointed out by Herter that in old people who are exceptionally vigorous, there is evidence that there are no abnormal putrefactions in the intestinal tract. On the contrary, in the remainder, which he says amounts to about 70 per cent., there is proof of distinct putrefactive processes. This is shown by diminution in the number of typical colon bacilli in the microscopical fields, and by the diminution of gas production in fermentation tubes. He is inclined to consider the B. aerogines capsulatus as the most important factor in these putrefactive decompositions of old age.[1]

(*C*) Affections Resulting from the Local Irritation of Abnormal Fermentation and Putrefaction in the Intestine

(1) Acute enteritis.—For the treatment of these cases Cohendy recommends the use of a pure culture made by cultivating the bacillus in a solution of malt extract marking 2·5 to 3 with the densimetre at the temperature of 15° C. The reaction of this solution should be neutral, and after twenty-four to forty-eight hours in an incubator at 37° C., one should get a culture slightly acid, forming a pleasant drink. Of a culture prepared in this manner from 100 to 200 grammes should be given per diem either in one dose fasting, or in two doses, one fasting and the other at 5 p.m.[2]

In order to supply the bacilli with a suitable medium in the intestine it is a good plan in these cases to suppress all food at first except sugar of milk in water, solution of malt extract in water, and of course the culture which we are giving. Personally, I do not use the malt extract solution now, as I find that a suspension of Boucard's tablets in sweetened water produces just as good effects. By thus limiting the diet to a saccharine solution we secure as rapid an acclimatization of the bacillus in the intestine as possible. After two or three days of this diet we can proceed to a menu of milk, gruel, and Evian water.

[1] *Op. cit.*, 78. [2] Cohendy. *Comptes rendus de Biologie.* 1906, i. p. 872.

(2) Chronic Colitis, Diarrhoea, and Mucous Colitis.—In these cases the diet requires careful attention in order that we may get the best results from the ferment.

Diet of subacute cases.—For the first week we must eliminate meat from the diet, which should consist of yolks of eggs, butter, bread, potatoes, milk puddings, fruit, and vegetables. Later we can allow meat at one meal in quantity nor to exceed 6 ounces.

Diet of ordinary chronic cases.—The following rules are taken from Combe. 1. Avoid all substances which can act as culture media for proteolytic bacilli. Thus stock, gravy, meat jelly, extract of meat, white of egg, and milk unmixed with farinaceous material. 2. Avoid all meat fat. Limit the patient to fresh butter and yolks of egg. 3. Avoid all high meat and game. In addition to these rules it is best that meat should be taken only once a day, that alcohol except in the form of light wines in strict moderation must be cut off, and that tobacco in excess must be avoided.

As it is impossible for the bacilli properly to acclimatize themselves in the intestine unless they are provided with abundance of saccharine food, it is essential to include a certain amount of sugar in the diet scheme. One of the most convenient methods of doing this is to put 50 grammes of sugar of milk into a bottle of filtered water and consume it during the day at meals. If preferred one or two spoonfuls of malt extract may be used instead of the sugar of milk.

Although in any of the preceding conditions auto-intoxication may be a possible explanation of the illness of the patient, we must be ever upon our guard not to allow ourselves to be biassed and not to adopt the fascinating theory of auto-intoxication without in the first place having eliminated every other cause, and in the second place having distinct proof from the examination of the urine that such is really the case.

Especially in cases of chronic ill-health without any very definite symptoms we must not rush into a diagnosis of auto-intoxication. In a young person gradual loss of energy and strength is much more likely to point to commencing phthisis, and in an individual of more mature years chronic Bright's disease of the kidney and cancer of the stomach in an early stage must be put out of court. As I have pointed out elsewhere [1] malignant disease of the stomach often sets in without any very definite symptoms. The patient may begin to lose his appetite and feel uneasy after meals, or simply to feel run down, and as if he wanted a tonic. In a case which consulted me last year the first sign was the inability to play as many holes at golf as formerly.

[1] *The Diagnosis of Cancer of the Stomach.* London, 1907.

Having eliminated other things we should examine the urine in the manner set forth on p. 7, and when we have shown that there is a real relative increase in the etherial sulphates or ammonia, and in the capillary constant, then and then only shall we be justified in making a diagnosis of auto-intoxication.

(*D*) Intestinal Dyspepsia in Children

We find remarkable effects from the use of soured milk in the chronic intestinal dyspepsia of children.

This affection, although in the first instance undoubtedly induced in most cases by improper food and the neglect of hygienic laws, very soon evidently becomes of a bacterial nature, as is shown by the character of the stools. These vary from two to six or seven a day, dirty green or muddy yellow in colour, pasty, pale, and stinking. In these cases a rapid improvement will usually follow the plan of treatment suggested on p. 24. for acute enteritis in adults.

In the more chronic cases, in which the chief effects are shown in the malnutrition of the child, progressive loss of weight, harshness and dryness of the skin, eruptions of an eczematous nature, loss of appetite, and excessive thirst, we shall get the best results from the use of soured milk given in a dose of from one to three oz. twice a day, according to the age of the child.

(*E*) Some Forms of Constipation

On the first introduction of all new modes of treatment there is a tendency to prescribe them indiscriminately under circumstances in which a little thought would show that good results could hardly be expected. Statistics compiled from such source are quite misleading and often go far to retard the real appreciation of valuable methods. The treatment of constipation by soured milk and cultures of lactic acid bacilli is a case in point. Having read in the descriptive matter, which the manufacturer takes care should accompany the article, that it is useful in constipation, the patient either takes it himself or recommends it to friends whom he may know to be troubled with that symptom. As the mathemetical chances are against the fact that the individual who takes it has the precise kind of constipation which will be benefited, the probability of cure are correspondingly remote.

To avoid disappointment this method of treatment should only be given in cases in which it is theoretically indicated.

For practical purposes we may divide cases of constipation into the following groups :—

(*A*) *The act of defaecation is defective.*

(1) From loss of the rectal reflex.—This is commonly the

result of habitual disregard of the calls of nature, or the use of glycerine injection, or suppositories.

(2) Dilatation of sigmoid.

(3) Loss of power in the abdominal or pelvic muscles or diaphragm.

(*B*) *Slow passage of the alimentary debris through the intestines above the sigmoid.*

(4) From imperfect response of the bowel to normal food stimuli.

(*a*) From primary or secondary weakness of the muscularis.

(*b*) Mechanical hindering by local causes such as adhesions.

(*c*) Defective innervation of the intestine (Atonic constipation).

(5) From excessive response of the bowel to normal food stimuli, the result being spasm (Spastic constipation).

(6) Alteration in the faeces making them more difficult to propel.

(7) Defect in the normal stimulating properties of the faeces.

These last two groups may with advantage be studied in conjunction, as they have much in common, are frequently met with together, and are the only ones which should theoretically be benefited by the use of lactic acid ferments.

It may now be taken as a settled point that many of the cases of chronic constipation which we were accustomed to term "atonic" and regard as due to defective peristalsis depending upon muscular weakness or upon deficient innervation are really of another nature. Strasburger [1] and Lohrisch [2] have shown us that in the faeces in these cases there is a considerable diminution in the solid material as compared with normal stools, and Schmidt [3] has confirmed their observations. In fact, the latter has pointed out that if patients with this form of constipation are put on a test diet in a large proportion of cases the amount of faeces (marked off for three days) is excessively small. For instance, whilst we find that a healthy person will pass in this time a quantity which will weigh about 60 grammes when dried, that of the constipated patient will average 30 grammes. That weakened peristalsis alone will not give these characteristic stools is proved by the fact that when constipation is induced by opium the stools, although small from the extraction of water, weigh the same when dry as they normally should. In these cases there is found on a microscopical examination to be a much smaller amount of undigested residues than normal, digestion being apparently too completely carried out. The result of this

[1] *Münchener Medicinische Wochenschrift*, December 29, 1903, and *Zeitschrift für Klinische Medicin*, 1902, vol. lxxvi., p. 413.

[2] *Deutsches Archiv für Klinische Medicin*, vol. xlxix., parts 5, 6, p. 383.

[3] *Examination of the Functions of the Intestines by means of a Test Diet*, Philadelphia, 1906.

deficient pabulum provided for the bacteria of the intestine results in their starvation, diminution in number, and consequently a diminution in the fatty acids and gases, the products of their growth, which form the normal stimuli to the peristals is of the intestine. Hence the constipation. In such cases it must be obviously futile to attempt to restore tone to the intestines by strychnine, massage, and electricity, there being no want of tone to restore. The attempt also to supply the absent stimulus to the intestine by a diet containing a superabundance of cellulose, such as brown bread, is commonly unsuccessful, as the digestion in these patients is so good that this is readily disposed of. But in the use of curdled milk we have an ideal method of combating the condition as we can introduce into the intestine an organism which produces large quantities of the normal stimulus to the peristalsis, and at the same time are able to keep it supplied with the food necessary to its growth by the simple expedient of adding a certain amount of sugar to the patient's food.

The diagnosis of this form of constipation is easy. All we have to do is to place the patient upon Schmidt's test diet for a few days, mark off the stools of three days by doses of carmine or charcoal, collect, dry, and weigh the total stools passed in this time. If below 40 grammes we may confidently assume that this condition is present. This investigation should be carried out in every case of chronic constipation which it is proposed to treat seriously with the idea of making a cure. Nothing can be more irrational than the, I am sorry to say, very common practice of putting these patients through a course of massage or electricity without having the least idea as to whether their constipation depends upon true atony of the bowel or upon the condition which has been described.

We can obviously not increase the power of the abdominal muscles nor supply an absent rectal reflex by increasing the stimulating properties of the material in the ilium and upper colon, and we cannot empty a dilated sigmoid by the *vis a tergo* of increased peristaltic movements higher up. It is true that in cases of muscular atony or defective innervation of the intestines, if not too advanced, we can produce a temporary effect by increasing the natural stimulus, but as in the case of abuse of purgatives, the overstimulation of weak or exhausted muscle or nerve cell will tend to further exhaust it and perpetuate and aggravate the evil instead of curing it. In spastic constipation too, increase in the stimulus which acts upon the intestines must do positive harm, as we well know that these cases are best treated by sedatives such as opium and belladonna.

If, therefore, we would do the best for our patients, and incidentally for our own reputation, we must in every case of con-

stipation make a proper diagnosis as to the cause of the trouble before prescribing, and never prescribe the lactic ferment treatment except in the group of cases characterized by deficiency in the acids and gases which form the normal stimulus to the action of the bowels or by real deficiency in the solid material excreted.

But in these cases we shall often obtain brilliant results.

(*F*) Some Forms of Anaemia

It is difficult to imagine that we can influence the production of new blood in any way by the administration of lactic acid ferments. It is on the other hand quite rational to suppose that we may be able to prevent its abnormal destruction if such destruction were due to poisons produced in the intestine as the result of bacterial action.

That such is actually the case has now been abundantly proved. It is a matter of common knowledge that anaemia frequently complicates the later stages of intestinal putrefactive diseases, and it has been experimentally demonstrated that haemolytic changes can be produced in the red blood cells of rabbits and monkeys by injecting into them faecal extracts from patients suffering from saccharbutyric fermentation.[1]

The actual agent in producing the haemolytic substance is probably the bacillus aerogenes capsulatus. It is important to bear in mind the important fact that in its early stages excessive haemolysis cannot be diagnosed by an examination of the blood. Blood production is probably always sufficiently in excess of blood destruction as to allow some considerable loss to take place before any marked anaemia occurs. We can fortunately tell if haemolysis is taking place by the presence of pathological urobilin in the urine. The test for this substance should never be omitted in all cases of anaemia as we can thus arrive at some idea as to whether the case in point is likely to be benefited by the lactic acid ferments.

(*G*) To Render the Gastro-Intestinal Tract Aseptic previously to Operating upon it

This is a subject which has always appeared to me to be much neglected. We find surgeons taking the greatest pains to feed the patients upon boiled water and sterilized food for days before an operation, whilst taking no active steps to diminish the number of putrefactive microbes in the intestine. The matter is especially of importance if there should be any pyorrhoea alveolaris present. In such cases it is true that a few surgeons order an antiseptic mouth wash, but this will not go very far in reducing

[1] Herter, *op. cit.*, p. 302.

the number of microbes swallowed with the food. The proper procedure is first of all to have the teeth properly scaled, after this the pus pockets must be treated with peroxide, nitrate of silver, argyrol, iodine or other suitable agent. When the mouth is clean the patient should have two or three tablets of the lactic acid ferment suspended in water three times a day before his food, and the operation should not be performed until the bacillus has had time to become acclimatized in the intestine, and we have ascertained by means of acid litmus milk (see p. 10) that such has taken place, or inferentially by the diminution in the ethereal sulphates in the urine.

The Dose of Lactic Acid Ferments.

The dose of the dry culture in tablets is one to three tablets three times a day before meals in suspension in water which should in most cases be sweetened with sugar, sugar of milk, or malt extract. When a considerable amount of sugar is consumed with the food this will be unnecessary.

The dose of soured milk may be anything up to three pints a day. An average dose would be three jars, each containing 8 oz., during the day. In some cases one or two jars will be enough. The soured milk being given in most cases chiefly for its food value the daily amount will be determined by the dietary scheme which is being adopted. Soured milk may be taken in one, two or three doses before, during or after meals, according to the inclination of the patient. When forming an important part of the diet the feeds of curdled milk may be given at regular intervals during the day, alternating with other articles of diet. It may be eaten with sugar and cream, preserve, salt, or may be taken as a distinct meal with bread. It may also be flavoured with cinnamon, ginger, vanilla, or other suitable agent, or thickened with glutin flour.

Before ordering a lactic acid ferment to a patient we must have a distinct idea of what our aim is in so doing.

(*a*) If our object is to give it mainly as a food we shall order soured milk.

(*b*) If we wish to acclimatize the bacillus in the intestine we should prefer the tablets in suspension, unless the feeding also comes in question, in which case we shall give the milk alone or the milk and the tablets both at the same time.

Reaction of the Patient during the Treatment.

It is important to warn the patient that he may expect some disagreeable sensations and perhaps some apparent increase in his trouble during the first couple of weeks of treatment. During the first week I have seen slight diarrhoea

attended with flatulence and colicy pains. In another case there was severe headache. In yet another there was typical migraine with teichopsia and scintillating scotomata. Cohendy [1] describes three stages. First stage.—The acclimatization in the intestines is not accomplished without sensible discomforts. The patient may suffer from some colic, intestinal flatulence, and discomfort. Perhaps there is some alkaline and offensive diarrhoea. Second stage.—Constipation more or less marked usually comes on whatever the general disease may be. The intestinal sensibility disappears. At the same time there is a notable deodoration of the stool and the ratio of sulphoconjugates to total urinary nitrogen is reduced by two-thirds approximately without any special alteration in the diet. Third stage.—The stools commence to become regular and give one the impression of lubrication of the bowels. Their colour form and reaction become normal. The symptoms due to auto-intoxication disappear and the patient progresses towards recovery.

Proof of the Acclimatization of the Bacillus in the Intestine.—This should never be omitted. Admitted that we have correctly diagnosed our case and have decided that this method of treatment is indicated, it will not be scientific medicine just to order a preparation of lactic acid ferment and trust to luck that all will be well. We should make periodical examinations of the stools to see whether acclimatization is taking place in a proper manner. This is easily done by cultivating a little of the stools in the lactic litmus milk, the formula of which is given on p. 10. If at the end of three weeks we do not find the bacillus in our stools, one of three conditions must be present.—1. Our ferment is inactive and we must change it. 2. We are giving the ferment in insufficient dose. 3. The diet of the patient requires modification. Probably we are not giving him enough sugar.

In conclusion I would, at the risk of reiteration, impress upon my readers the following aphorisms which make for success :—

First of all be sure that you have a case in which there is really some condition present likely to be benefited by this method of treatment.

Do not assume the presence of auto-intoxication because the patient is in a condition of chronic ill-health for which there appears to be no obvious cause. Test the urine for the ratio of ethereal sulphates to total nitrogen before you hazard an opinion. In like manner do not infer from mere looseness of the stools that there is abnormal putrefaction in the intestine. First be sure that the intestinal affection is not gastrogenic, and then carry out the appropriate fermentation tests.

[1] "*Therapeutique microbienne des affections intestinales chez l'adult.*" *Archives de maladies de l'appareil digestiv et de la nutrition.* September 1907.

Make sure that you have a ferment preparation which really contains the true Bulgarian bacillus, and that it is not a bogus one made up with rennin and one of the smaller and weaker bacilli just to curdle milk, but of no further therapeutic value. Also be sure that the preparation is aseptic, is not made with a basis of curdled milk, and has not become contaminated during the manufacture.

Lastly, continue the treatment for a sufficient time to allow the bacillus to become acclimatized in the intestine. Do not give it up in the second week because the patient suffers from flatulence or because his constipation is increased.

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