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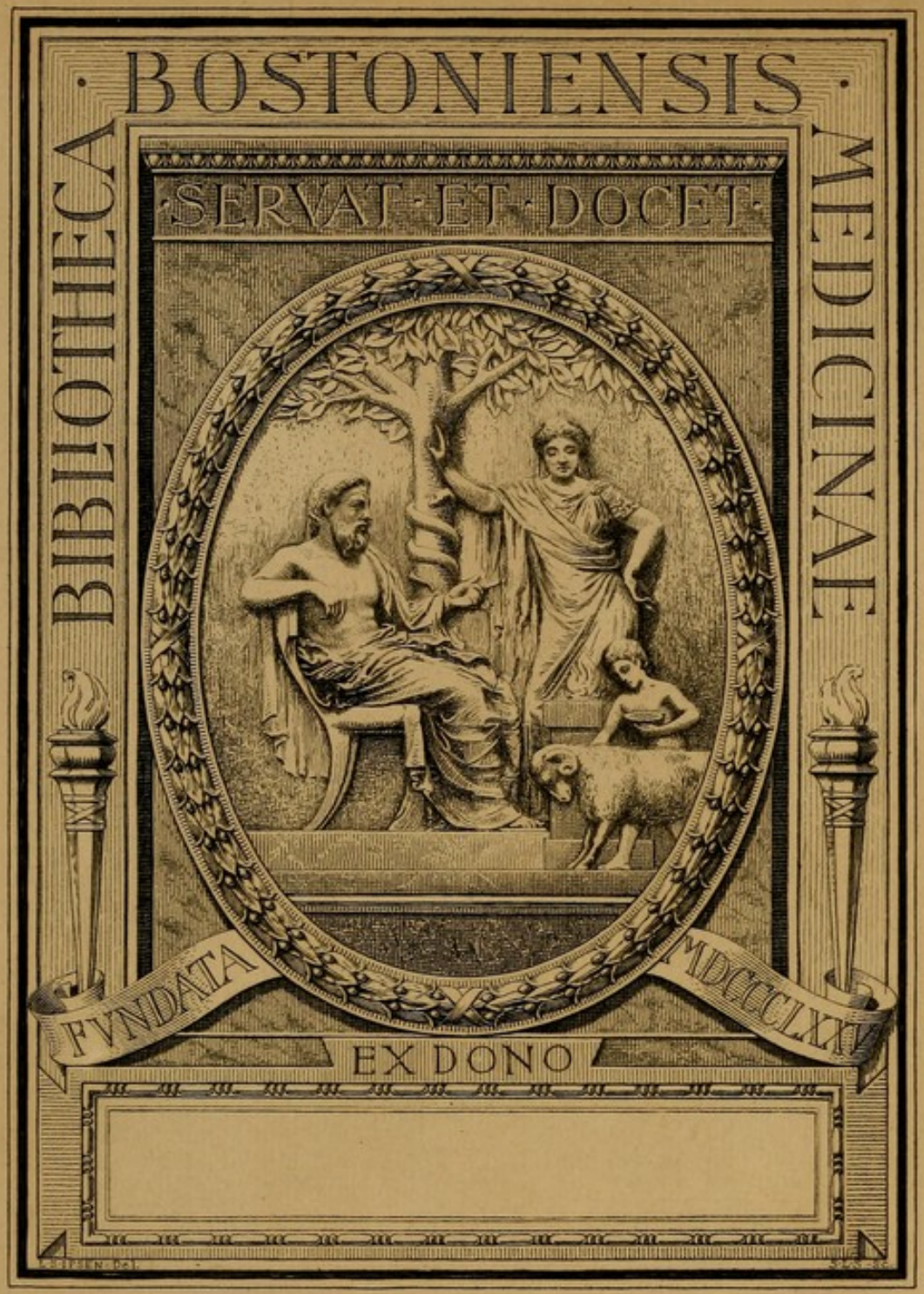
NEW METHODS OF TREATMENT



NEW
METHODS OF TREATMENT.

NEW METHODS OF TREATMENT.

BY

DR. LAUMONIER.

TRANSLATED AND EDITED FROM THE SECOND REVISED AND ENLARGED FRENCH EDITION BY

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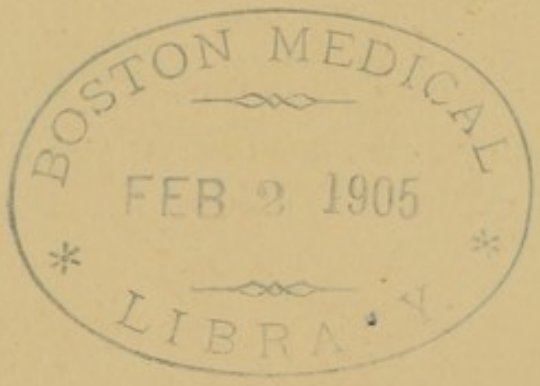

TRANSLATOR'S PREFACE.

The purpose of this book is so clearly stated by the author in his Preface that it is scarcely necessary for the translator to make further reference to the subject.

That vast difference of opinion should exist regarding new methods of treatment is perhaps not to be wondered at, when we consider how short-lived many of the most vaunted methods prove to be in the light of practical experience. Although, obviously, a book of this kind must contain an account of a considerable number of methods which in the near future will be more or less apt to be replaced and superseded by others, yet the author has rendered accessible to the reader of this work a large number of modes of treatment which will prove of permanent value. The success with which Dr. Laumonier's book has met since its first publication in 1903 has made a second edition necessary, which has been the basis of the present English edition.

In presenting this excellent work on modern therapeutics to English readers, the translator has endeavoured, while closely following the original plan and subject-matter of the French edition, to bring the text into line with the English style and method.

H. W. Syers.

75, Wimpole Street, W.
August, 1904.

AUTHOR'S PREFACE.

The number of new remedies which are almost daily being introduced renders it extremely difficult for the practitioner to make a selection amongst them. Wrapped up in his daily routine work, he has no leisure to read the criticisms published in the technical and medical journals concerning experimental observations and results. Sometimes, in response to the request of his patient, who is often better acquainted with the latest fashion in therapeutics than is frequently supposed, he finds himself constrained to employ such and such a drug or such and such a method without always satisfactorily realising the special suitability of or the exact indication for the treatment of which he is urged to make trial. Hence it happens that remedies which may be very valuable when appropriately employed give but unsatisfactory results, and hence the unmerited disfavour with which these remedies are afterwards regarded.

As a matter of fact, in order to render more easy the work of the practitioner, it has been of late the custom

to publish formularies of the newer remedies, and of these some are excellent. But these formularies, although they particularly aim at being comprehensive, as a matter of fact, except as regards that of Dr. Bardet, do not generally distinguish between those remedies which are more or less worthless and those which have a real value. Further, as they aim at being short and succinct, they reduce to mere incomplete notes everything which relates to physiological action and to the therapeutic indications which arise therefrom ; yet these points are of paramount importance for the serious determination of the choice of medical treatment. Lastly, the greater number of these formularies of necessity systematically pass by those methods of treatment which are not purely pharmacodynamic, and hence it is necessary to refer to large works or to special treatises.

My publisher, M. Alcan, considering that as regards this matter a gap existed in medical literature, has courteously invited me to fill it. Although I have used my best endeavours I am unable to flatter myself, when I take into consideration the difficulty of the task, that I have completely succeeded. Be this as it may, in writing this book I have endeavoured to furnish medical men, and those who are interested in the subject of therapeutics, with definite and complete, and at the same time short and clear, information concerning the new drugs and methods of treatment whose worth has been established and which are sufficiently well known

to be described in a definite and practical manner. Thus I have not noticed methods which are well recognised or classical, or those which are known to be imperfect or which have been too recently introduced to have given sufficiently convincing proofs of their value. But that which chiefly distinguishes this book from the formularies of which I have spoken above is the summary account of pathological physiology and pathogeny which I have placed at the beginning of each chapter, so that the mechanism of therapeutic action may be deduced from the knowledge of the functional alterations which give rise to the disease. I trust that this innovation will be appreciated by my readers.

Several articles already published in the medical transactions and journals, more especially in the *Bulletin général de thérapeutique*, and the *Nouveaux Remèdes*, in the *Gazette des hôpitaux*, the *Gazette hebdomadaire de médécine et de chirurgie*, the *Progrès medical*, &c., will be found in this volume, but without those technical details, references, and observations which would have needlessly increased the size of this small work.

J. L.

October, 1902.

FROM THE AUTHOR'S PREFACE TO THE SECOND EDITION, OCTOBER, 1903.

The time which has elapsed between the appearance of this book and its second edition has not been sufficient to permit of numerous modifications. Not that the output of new remedies has become less large, but that, owing to the shortness of the interval, no striking discovery has been effected, and sanctioned by experience, in the domain of therapeutics. Hence, here will merely be found in addition some articles devoted to *adrenalin*, to *salicylate of methyl*, to *ulmarene*, to *quinoformine*, to *collargol* and to the *colloid metals* which have lately been much discussed. The study of these colloid metals, if it be followed up and the results prove to be such as are hoped for, will allow of the development of a new subject relative to the therapeutic action of certain ferments recently experimented on, namely, *oxydases*, *réductases*, and *kinases*. The remarkable properties of these ferments may perhaps be attributed to the traces of radio-active substances which they contain. Here will probably be found a new and fruitful therapeutic field, but as yet it would be premature to undertake action therein, as definite and harmonious results are so far lacking.

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COMPARATIVE TABLE OF WEIGHTS AND MEASURES.

Grm. = gramme.

C.c. = cubic centimètre.

1 grm. = 15·432 grains.

0 grm. ·1 = 1 decigramme = 1·5432 grains (about $1\frac{1}{2}$ grains).

0 grm. ·01 = 1 centigramme = 0·15432 grain (about $\frac{1}{6}$ grain).

0 grm. ·001 = 1 milligramme = 0·015432 grain (about $\frac{1}{60}$ grain).

1 c.c. = 16·9 minims.

3·54 c.c. = 1 fluid drachm.

28·35 c.c. =1 fluid ounce.

NEW METHODS OF TREATMENT.

I.

NUTRITIVE ALTERANTS.

1. Disorders of Nutrition.

Assimilation, or the sum of those intra-cellular phenomena by which certain materials derived from the external world are transformed into plastic substances identical with those which the cell previously contained, is the essential and fundamental factor of nutrition.

All other factors are merely preliminary and preparatory operations, being intended to bring into contact with each other the plastic materials and the substances which are capable of reacting directly upon them, or of furnishing by oxidation the amount of energy which is necessary for the performance of organic synthesis.

In unicellular beings these preparatory operations are reduced to a minimum; this is by no means the case in the higher vertebrata and in man, in whom the physiological division of labour has led to a specialisation of apparatus whose duty it is to perform each of them. These special functions, although altogether preparatory, are not on this account the less necessary for assimilation, since, if one of them is disordered or abolished, the synthesis of assimilation becomes difficult or impossible

of performance, or else is only effected at the expense of materials already elaborated, in which case wasting must obviously occur, as also organic decay and consequent diminution of physical resistance. It is this, apart from the fact of their accessibility to observation, which explains the great importance always attached to the healthy performance of these preparatory functions by physiologists and physicians.

These preparatory functions may be classified as follows:—

1. Digestion, which converts by resolution and hydrolysis colloid alimentary materials into dialysable substances. These changes are effected under the influence of soluble ferments which are secreted by the glands of the alimentary canal; they are thus subordinated to the healthy functional activity of these glands.

2. Absorption, by which the assimilable matters thus produced pass through the intestinal wall, not merely as the result of physical forces, but also in consequence of the vital activity of the mucous membrane and, at all events so far as concerns fatty emulsions, of the activity of leucocytes and phagocytes. Hence this function must depend upon the integrity of the digestive mucous membrane.

3. Unless the dialysable substances to be absorbed undergo a partial (or incomplete) dehydration, they would be liable once again to diffusion in the intestinal cavity according to their degree of concentration in the internal medium. This dehydration takes place under the influence of certain little understood ferments, or of vital activity itself; in the first instance in the structures included in the mucous membrane, and finally in the lymphatic glands and the liver. This process results in the formation of the chyle, lymph and blood plasma; and

without the necessity of any specialised apparatus for its performance, this function yet implies a healthy condition of the numerous cells which must take part in its discharge.

4. Circulation, which carries all the transformed and partially elaborated materials, as also the liberated nutritive reserves, to the different organs. Circulation is subordinated not only to the condition of the motor organ and of the conducting structures, but also to the nervous influences which regulate and apportion, through vaso-constriction or vaso-dilatation, the supply of blood.

5. Finally respiration, which does not take part in assimilation itself, but which presides over the conditions which allow of its performance, by supplying oxygen and consequently the force which is necessary for the due execution of the organic syntheses. Respiration is dependent upon the state of the lungs, the richness of the blood in hæmoglobin and the integrity of the respiratory centre.

Such are the functions by which assimilation is effected, by means of a liquid, lymph, which escapes from the blood through the walls of the blood vessels, which bathes all the anatomical elements and from which each one of these draws those materials which are necessary for its maintenance and growth. This synthetic process is thus really subordinated, on the one hand to the composition of the nutritive fluid, and on the other to the physiological and anatomical integrity of the cell; that is to say, its successful performance depends upon the presence of all those plastic materials and formed elements which the study of merotomy has proved to be indispensable in order that the phenomena of assimilation may be allowed free play.

Other conditions, however, are necessary for the

effective exercise of the assimilative functions, so that a series of derived and secondary functions has been established, whose importance, as will be seen immediately, is by no means less marked.

As a matter of fact, assimilation does not imply the indiscriminate absorption of all the materials which are accessible; only certain definite chemical combinations of the molecular structure of nutritive matters are made use of, the remainder being rejected. These accessory products of assimilation are partly soluble, partly insoluble. The latter are deposited in the locality in which they take their origin, and are represented by keratin, chondrin, ossein, cartilaginin, elastin, &c., all of which are employed in building up that tissue which unites the anatomical elements of structures and forms the supporting material of the tissues and organs generally —the skeleton, in fact. These materials may ultimately become infiltrated with mineral matters (ossification of cartilage, for instance), and the accumulation of such substances, consecutive to prolonged or intense functional activity, gives rise to the phenomena of old age.[1]

The accessory soluble matters, conjointly with the results of fermentative decomposition, of complete or incomplete oxidations, of the destruction and degeneration of tissues which are in a state of functional repose, represent the waste products of functional activity. These waste materials, when too abundant in the intracellular connective tissue, cause in the first instance a failure, and finally a complete cessation, of vital activity; hence when the accumulation of these matters is confined

[1] Cf. Le Dantec, "Théorie nouvelle de la vie" (Paris: F. Alcan, 1896). J. Laumonier, "Physiologie générale," Chap. ix., pp. 412 *et seq.*

to a single organ, local fatigue results; when this collection of products of retrogade metamorphosis loads and occupies the interior tissues, general debility, followed by sleepiness, ensues. For this reason these waste products are sometimes described as *ponogenes*, following the terminology of W. Preyer.

Hence it follows that these *ponogenes* must be eliminated. This elimination is normally effected by the emunctory organs (lungs, kidneys, skin, &c.), because, thanks to their power of dialysis, the *ponogenes* pass from the intercellular tissue where their quantity is unduly elevated into the blood where it is considerably less, and thence, partly owing to the difference of tension of the external medium (CO^2,H^2O), partly also through the activity of certain anatomical elements (those of the kidney, for example), into the external medium. But first of all certain organs, the liver especially, deal with the waste matters in order to modify them and thus to render their elimination more easy by increasing their solubility. Thus it follows that if the function of the liver is altered, if the kidneys are no longer permeable and the lungs cease to exercise depuratory functions, the waste materials must accumulate, and in doing so must give rise to general intoxication, to auto-intoxication, which may lead to fatal results. Hence it follows that the healthy discharge of their duties, on the part of the emunctories, is as essential for the normal performance of the functions of assimilation as is the proper discharge of their duties by the organs which perform these preparatory assimilative functions.

This short account of the complex mechanism which subserves nutrition will render it clear that, leaving out of account the alterations which may occur in the

functions of the emunctories, to which it will be necessary to return later, the causes of nutritive disturbance may be grouped in two main divisions—(1) the deficiency, the absence, the excess and the unsuitability of alimentary materials; (2) the disturbance which may affect the earlier and preparatory nutritive functions.

1. Want of food causes inanition, which is in reality a consumption of the bodily tissues of more or less prolonged duration, according to the quantity of the nutritive reserves and according to the supply or withholding of water, which dilutes and eliminates waste products and retards the toxic effects of autoconsumption of the bodily tissues. When there is merely an insufficiency of food, physiological wasting ensues, and this, by diminishing the vital resistance and the protective or antitoxic powers of the bodily juices, renders the organism more susceptible to infections, such as those of typhoid fever, tuberculosis, &c. But it must not be forgotten that inanition may also be due, not to want or scarcity of food, but to organic disease, such as stenosis of the pylorus, of the œsophagus, &c. Then, together with anæmia, anasarca, heart and brain disease, pulmonary gangrene, blood infections, tuberculosis, &c., may be present.

When food is accidentally given in excess, purely mechanical or toxic troubles (indigestion) ensue, but these are of quite temporary duration. When this overrepletion is persistent, then these disturbances become chronic, and ultimately cause such alterations in the mode in which the assimilative organs discharge their functions that the alimentary materials ingested can no longer be properly transformed and elaborated. Then will ensue such maladies as glycosuria of alimentary

origin, due to the excessive consumption of hydrocarbons; uricæmia, gout and arthritis in all their protean manifestations, the latter maladies being specially liable to supervene when an excess of nitrogenous food is taken in the form of meat, game, &c.

But an unsuitable diet may lead to still graver troubles, to more rapidly developed and acute maladies, for in these cases the aliments are incapable of being assimilated; they are unsuited both to the condition of the digestive organs and for the nutrition of the body; hence the results of insufficiency of diet are added to those due to intoxication. For example, the wasting of young babies is due not merely to the blood poisoning which results from the ingestion of materials which the infant is wholly incapable of absorbing, but also to the fact that the supply of assimilable materials is insufficient.

The condition is the same in sausage poisoning, scorbutus, in intoxication, the result of the prolonged use of preserved foods, and when damaged or infected aliments are made use of. Nutritive disorders may also be induced by non-edible matters—for example, by alcohol and phosphorus, which give rise to obesity and to fatty degeneration, or by lead, which induces attacks of gout by modifying the metabolism of the nitrogenous principles. Loss of flesh, again, may be caused by the employment of morphia or of the iodides, as also by microbic toxins, as occurs in severe infections.

All these fundamental derangements of nutrition take their origin and are conditioned by one and the same mechanism. The ultimate element of the tissues, the cell, ceases to assimilate, it may be because the surrounding medium is wanting as regards the elements which are indispensable for the performance of its

assimilative function, or perhaps because noxious principles are present in this medium. The cell having ceased to assimilate, and consequently having lost its functional activity, it passes into a condition of repose and is destroyed with greater or lesser rapidity according as it does or does not form with the toxic matters of the surrounding medium stable combinations. If this condition continues it is possible that a morbid temperament or diathesis may be established, which varies with age, heredity and sex, leading sometimes to rickets, sometimes to osteomalacia, or to fatty osteoporosis; or again, scrofula, gout, or lymphatic disease may result.

Further, the assimilative functions may undergo important physiological modifications. These functions, which are very active during the period of growth and continue in a state of functional vigour in adult life, begin to decay with the onset of old age—that is to say, at the period in which the tissues tend to become sclerosed under the influence of the accumulation of insoluble waste products, the result of organic synthesis. On the other hand, the same functions are, or may be, upset by the appearance of adolescence, in the course of evolution of which new organs take an active function. These are the reproductive organs whose secretion exerts a marked influence on the general co-ordination of function and initiates a new balance of power, the changes being manifested by the striking bodily alteration which occurs at this period of life. Pregnancy and lactation, too, exert an influence on the functions of assimilation, for both involve a disturbance of nutrition similar to that excited by the presence of parasites or of new growths. And the influence of the menopause in causing similar disturbances must not be left out of account. The period at which

menstruation ceases is generally marked by symptoms pointing to a disorder of co-ordination, and by efforts on the part of the organism to establish a new state of equilibrium.

2. These different defects of nutrition due to want, insufficiency, or excess of food, inappropriate nature of aliments, intoxication, heredity, tendency to assimilative troubles, or physiological abnormalities are certainly the most common causes—apart from the action of direct pathogenic influences, traumatism, caustics, &c.—of secondary disorders, that is to say, of those which affect the functions which are preparatory to the assimilative process and the organs by which these functions are discharged. Gastric and intestinal dyspepsia, gastro-enteritis, renal and hepatic lithiasis, alimentary albuminuria, diabetes, chlorosis, dermatoses, cirrhosis, nephritis, peptonuria &c., all take their origin from one of the primitive derangements of assimilation just enumerated which affect certain definite organs, a derangement which may finally induce a lesion and which, by disorganising an essential preparatory function, may lead to a general disorder of nutrition.

Yet another factor which frequently takes part in the morbid process is the action of the nervous system. Formerly it was thought that the nutrition of certain organs was under the control of trophic nerves. As a matter of fact, there are no trophic nerves, but every neuron, by the nervous force which it transmits, acts on functional activity, and hence upon the assimilation of the anatomical elements with which it is connected. According to the nature and intensity of the excitation thus transmitted, the functional and assimilative reaction naturally varies.

The effect of emotion, such as grief or joy, and of prolonged anxiety, of cerebral overstrain, on assimilation is well known; on the other hand, the beneficial influence of an equable temper and a quiet easy life is very obvious.

In the neuroses this action is again manifest; thus in paralysis agitans, in certain forms of neurasthenia and in acute mania the assimilative functions are often overactive, while in hysteria they may be almost in abeyance, as in the case of hysterical women, who refuse every kind of nutriment and yet do not markedly waste. The great diminution in the quantity of urea eliminated—it may fall to 4, 2, or even 1 grm. per diem—and the inversion in the elimination of phosphates which occurs after the hysterical attack both tend to indicate, and the elimination renders manifest, that nutrition is profoundly modified.[1]

In connection with these several functional alterations, and leaving on one side those which relate more especially to the mineralisation of the plasma, to oxidations, to the elimination of waste products, &c., all of which will be considered later, there are two sorts of modifying agents. The one relates more particularly to the cell, and supplies it under a directly utilisable form with the elements necessary for its organic synthesis, in this way economising the work of those organs which are adapted to the discharge of the preparatory functions, and thus permitting their assistance to be dispensed with without the nutrition suffering in any way; the other modifying factor is concerned with the accessory functions, which by it are either stimulated or depressed, and in this way

[1] Cf. Bouchard, "Traité de pathologie générale," t. iii., "Réactions nerveuses."

assimilation is kept within its normal bounds. We proceed to briefly consider the physiological and therapeutic properties of these new modifying elements of metabolism which are comprised in these two categories.

2. Soluble Albumins.

Long before Berthelot had humorously spoken of the tablets of nitrogen which human beings would in the future assimilate instead of the cutlets and beefsteaks which are at present in use, the possibility had been considered of preparing products richer than natural aliments in nutritive principles, and which would be suitable for the needs of invalids and convalescents, as well as for soldiers and sailors. The first and most popular of these preparations were concentrated soups and extracts of meat, which are, indeed, very far from being useless, and which have maintained their position as valuable resources in practical cookery—if not in practical therapeutics—on account of their agreeable flavour and their eupeptic power. But inasmuch as the different alimentary products of this kind cannot be regarded as true and genuine foods, and thus are wanting in essential factors, the attempt has been made to produce condensed preparations of albumin, in the form either of powdered meat or of blood, which are certainly rich and nutritious, but which are unpleasant as regards taste, and are often intolerable except to very strong stomachs. These productions are often original—they are the result of scientific combinations which the Germans and Americans are particularly clever in elaborating, being as they are strong believers in artificial alimentation. The same end is also attained to some

extent by the use of preparations of natural materials which have been artificially digested. It is these latter alone that we shall here consider.

Under the influence of the soluble ferments of the stomach and pancreas (pepsin, trypsin) the albuminous matters contained in the food, being colloid, coaguable, and directly unassimilable, are transformed into soluble substances which are incoaguable, dialysable, and assimilable, namely, into *peptones*, which appear to be, chemically considered, neither more nor less than the polymerised molecule of albumin isolated by hydration. These peptones give the ordinary colour tests of albumins, but they are not precipitated by the mineral acids, or more particularly by nitric acid; further, when injected into veins, they manifest certain toxic properties, not escaping by the urine, but rendering the blood incoaguable and lowering the blood pressure.

However, in the fermentative disintegration of albuminoids, several transitory products are developed which fill up the gaps, as it were, between albumin at one end of the scale and peptone at the other. These unstable products are: (1) *Syntonin* or *acid albumin* precipitated by alkalies; (2) *proteoses* or *albumoses* which include propeptone of Schmidt-Mulheim, and which are divided into proto-albumose, deutero-albumose, hetero-albumose, and dys-albumose—these products are generally soluble in water, but are precipitated by sulphate of ammonium; and (3) the true *peptones*, the result of disintegration of albumoses. At the same time leucin, tyrosin, and toxalbumins, whose properties are but little understood, also appear.

To each type of albuminoid a special peptone naturally corresponds; thus it follows that there are *albumin*

peptone, myosin peptone, fibrin peptone, casein peptone, &c., all of which substances are possessed of very similar properties, and which differ only in the extent of their rotatory power. These peptones are white, amorphous, odourless, but possessing a sour and bitter taste, especially when they are impure; they are distinctly hygrometric and easily dialysable, but less so than saline matters, so that they may be purified by dialysis. They are insoluble in ether and chloroform, and very slightly soluble in cold absolute alcohol; they dissolve freely in water, furnishing a feebly acid liquid which is omewhat sticky, and which, when warm, filters readily, tending to froth freely.

The successive disintegrations which albuminous matters undergo in the course of natural or artificial digestion furnish a general method for determining the quantity of the transitional forms of each (syntonin, albumose, peptone) in a given digestive solution, whether natural or artificial. The following method is at once simple and practical:—(1) The liquid obtained by treating, for example, meat from which the bone and fat have been removed with acid pepsin at + 40° C. for four to five hours is boiled, in order that the undissolved albumin may be coagulated; it is then filtered. (2) The filtrate is neutralised, the syntonin being precipitated, and once again the liquid is filtered. (3) The clear liquid is now treated with sulphate of ammonium, by which the albumoses are precipitated. (4) Finally, after again filtering, pure peptone alone remains in solution.

Physiologically and chemically, albumoses and peptones may be obtained: by the action of pepsin in acid solution and of trypsin in alkaline solution; by the action of vegetable peptonising ferments, and more

especially by that of papain obtained from the *Carica Papaya* and of the agave juice; by the action of peptonising ferments secreted by some bacteria and other micro-organisms; by the action of certain mineral matters, chloride of sodium, fluoride of sodium, and certain dilute acids; finally, by the action of steam under pressure at +100° C., and particularly at +120° C., this latter transformation being encouraged by the presence of traces of hydrochloric acid.

These different processes have all (with the exception of that involving the use of saline mineral matters) been employed on the commercial scale for the preparation of peptones and albumoses.

Albumoses and peptones are made use of for feeding the sick, more especially in cases in which the secreting action of the digestive viscera is disturbed, unduly slow in the performance of its functions, or altogether absent. The same method of alimentation is employed in convalescence and for children who are growing rapidly, as also for old people. The nutritious matters may be given either by the rectum or by the mouth. Further, peptones and albumoses are consumed in constantly increasing quantity, as their manufacture becomes more perfect and is effected on a larger scale; obviously this manufacture is greatest in those cattle-breeding countries where the price of beef is very low. This increased use of artificially digestive alimentary materials is due to the ease with which they are absorbed and assimilated, and also to the fact, confirmed by the researches of Plosz, de Maly, Adamkiewicz, Munk, Deiters, Pollitzer, A. Gautier, &c., that these materials perform the same nutritive office as does the albumin of ordinary aliments. But although formerly peptones were chiefly made use of, at

the present time the preference is given to albumoses, and this for several reasons.

In the first place the peptones formerly employed were bitter and offensive to the taste, rendering it necessary to disguise them by means of a pleasant vehicle. Secondly, certain varieties which, having a less disagreeable taste, are on that account preferred, yet contain gelatine chiefly, together with extractive matters and a little albumose, being, in fact, merely extracts of meat. Finally, those varieties whose action is most trustworthy in the therapeutic sense, such as good French commercial peptones, contain a proportion of albumose which is equal, if not superior, to that of the peptone. Ordinary peptones are almost always impure, and contain the toxic products which make their appearance at the end of the process by which fermentative disintegration of the albumins takes place.

The albumoses are free from these serious defects. On account of the fact that they are not liable to undergo the process of total disintegration, they do not contain toxic products, they have no disagreeable odour or taste; they are absorbed more easily than the commercial peptone, and they usually contain sulphur, a necessary aliment, while the pure peptones are free from this admixture. Further, comparative observations made by means of artificial alimentation with peptones and albumoses have shown the incontestable superiority of the latter. The only drawback to the use of these matters is that they occasionally cause, but to a lesser extent than the commercial peptones, some gastro-intestinal disturbance, especially diarrhœa. It should be added that powdered meat, and above all the

powder of broiled meat, is ten times more easily absorbed, as is proved by the experiments of Ellinger, than the albumoses and similar products.

It is, however, right to add that the larger number of preparations known as *peptones* contain, especially at the present time, albumoses; so that the albumoses of commerce possess no real superiority as regards these products. Somatose is a yellow, slightly granular powder, soluble in water, without appreciable smell or taste, and contains, according to Goldman, 78 per cent. of true albumose and only 2 to 4 per cent. of peptone.

This preparation is of value in cases of dyspepsia due to functional weakness, in anæmia with anorexia, in fevers, especially typhoid fever, in tuberculosis and in hysteria and syphilis during the stage of wasting. In chlorosis the administration of somatose causes the disappearance of menstrual irregularities, of headache, of giddiness, &c. Finally, it acts as an efficient galactogogue. When given to wet nurses whose milk supply is scanty or in whom lactation is not normally performed, it increases or renews the flow of milk, whether this action be due, as Drews believes, to its exciting the secretion of the glandular structure, or whether it is the result, as Joachim maintains, of an improvement of the general nutrition brought about by the remedy. Further, it has been proved that somatose increases the number of the red blood corpuscles, and hence also the percentage of hæmoglobin. In the case of infants at the period of weaning, and in wasted children, this albumose gives good results, and is also always well tolerated on account of its tastelessness.

Somatose is given in quantities of 15 to 30 grammes *per diem* in adults, children taking from 3 to 10 grammes.

It may be administered in milk, soup, cocoa, &c., and it can be combined with other albuminoids which are easy of digestion, especially with milk, eggs, &c.

Similar to somatose are a certain number of new products also containing albumoses. Such are *alcarnose*, of a brownish colour and viscous consistence, which is inodourless, of sweet taste, soluble in ten times its volume of warm water, soup, or coffee, and which contains 23 per cent. of albumose. It is well borne by invalids and appears to be easily assimilable. *Globone* is prepared, according to the method of Lilienfeld, by decomposition of the paranucleines, both animal and vegetable; it is a yellowish powder, without smell or taste, insoluble in water, but soluble in alcohol, especially when in the presence of a small quantity of organic acid; it seems to contain a considerable quantity of albumose. According to Tittel, it dissolves completely and rapidly in artificial gastric juice, and is useful as a dietetic adjunct in severe general disease, and also for children. It is given in doses of 1 to 3 teaspoonfuls in soup, milk, coffee, wine, &c. (Merck).

3. Organic Matters Containing Phosphorus.

Among the matters which participate in the synthesis of assimilation and in the general metabolism, phosphorus would appear to occupy the first place. This idea is not of old standing, and the agriculturists were the first to bring it forward. Boussingart especially has arrived at the interesting conclusion that it is possible to determine the statistics of nutrition by estimating the value of the nitrogen and phosphorus eliminated. On the other hand, the researches of Miescher, Kossel, and of Altmann, and

later those of Danilewski, have demonstrated that the most active tissues are those which are the richest in phosphorus, and that in the cell itself the chromatins and the nucleins regulate, so to say, the mitosis and all the phenomena of functional activity. Some authors[1] have endeavoured to explain the organic synthesis carried out by the cell nucleus through the properties possessed by phosphoric acid, in the manner suggested by Haacke, and they have regarded the phosphorised albumins as the only absolutely essential ingredient of the ration which is required for the effective performance of the functions of growth and regeneration (for example, casein of milk in the case of young children), and as the centre around which are carried out the several metabolic changes of the organism. The reflex of this conception is obvious in the constantly growing importance attached in urine examination to the phosphoric acidity, and to the relation of the phosphates to the nitrogen of the discarded living materials.

The phosphated and phosphorised preparations have been long made use of in medicine, but the discoveries and ideas to which we have just briefly referred have naturally led to a marked extension of the compass of this medication, and have modified its nature and increased the number of means at its command. When Brown-Séquard propounded the method of special injections (testicular juice), the tonic and the restorative effects of this treatment appeared, in spite of the differences of opinion which it aroused, to be attributable to histo-chemical combinations of phosphorus which are so numerous in the nucleus of the spermatozoa, and hence Crocq, junior,

[1] Cf. J. Laumonier, "Physiologie générale," pp. 312 *et seq.*

of Brussels, thought it feasible to replace these injections by those of standardised solutions (2 per cent.) of phosphate of soda in cherry laurel water, assuming that the phosphates are the only essential constituent in this form of medication.

But at this period it was well known that lecithin, a phosphorised and nitrogenous fat, is abundant in yolk of egg and in the nervous structures, and from April, 1894, Professor A. Robin has strongly recommended the glycerophosphates for the purpose of improving general nutrition by the intermediation of the nervous system, inasmuch as these salts contain glycerophosphoric acid, which also enters into the composition of lecithin.

In spite of the very satisfactory results yielded by the use of the glycerophosphates, and more especially of the acid glycerophosphates, certain authorities give the preference to those natural physiological products which are rich in phosphorus, in order to strengthen the assimilative functions and to give tone to the nervous system. The utilisation of these products by the organism should obviously be more easily effected and more perfect than that of the artificial preparations, since the tendency is to definitely admit that the cells of the tissues are far more ready to make use, for their syntheses, of materials offered to them when these latter, by their constitution and origin, resemble those of the living protoplasm and nucleus. This is one of the considerations which explain and justify zomotherapy. Hence it is that lecithin, praised by Danilewski, has been employed either in the pure state or in the form of *huile d'œuf*, or, on the other hand, the nucleins, both animal and vegetable, whose fixative value has been proved, in the

first instance by Bunge, and afterwards by Horbaczewski. We pass on to the examination of these different substances, treating both of their physiological value and of their therapeutic uses.

A. *Lecithins.*

The lecithins are, as just stated, phosphorised and nitrogenous fats formed by the union of glycerophosphoric acid, of fatty acid, and of an ammoniated base, choline. Strecker looks upon lecithin as being an oleomargaroglycerophosphate of choline, but the researches of Hundeshagen and Gilson have not confirmed this view, and the theory of Diakonow seems to be preferable that lecithin is an ethereal combination in which choline plays the part of alcohol. There are several other lecithins whose formulæ are as follows:

Diastearic lecithin = $C^{44}\ H^{90}\ N\ PO^{9}$
Dipalmitic ,, = $C^{40}\ H^{82}\ N\ PO^{9}$
Dioleic ,, = $C^{44}\ H^{86}\ N\ PO^{9}$

Lecithin is soluble in alcohol, ether and chloroform, but insoluble in dilute acids and alkalies; according to Strecker, it forms combinations with bases; finally, if it is not acted upon by pepsin, the pancreatic juice breaks it up rapidily (Lambling). When treated with ether and afterwards taken up by warm alcohol, it forms when mixed with glycerine small pellets and fibrils which resemble myelin tubes; the pellets give a black cross with a polarising microscope.

Lecithin is widely diffused in the animal organism; it represents 10 per cent. of the white substance, and 19 per cent. of the grey matter of the brain, and 5 per cent. of the yolk of fowl's egg, &c. It has been found to be present

in all the tissues which are in process of development; it forms a portion of many cells, not indeed as living matter, of matter endowed with the power of assimilative synthesis, but as a reserve substance, or, more exactly, as an accessory product of synthetic phenomena, which is capable of being used later in special conditions.

Regarded as a product of regression, as the first stage, so to speak, of the decay of cellular nuclei, and, in general terms, of the phosphorised albumins—a degeneration the mechanism of whose progress A. Gautier[1] has endeavoured to explain—lecithin is probably only made use of by certain anatomical elements, and above all by the cellular body of the neuron and the egg; at all events this view of its function is supported by the accumulation of lecithin in the nervous structures and in the lecithin reserves.

In truth we are in almost total ignorance as to how this utilisation of lecithin is effected and what is the nature of the waste product which results from this utilisation. Nevertheless, the observations of Robin and Bardet, that the absorption of large doses of lecithin causes an over-production of uric acid, lends support to the theory that there is an incomplete and also toxic oxidation of the ammoniated base, as occurs in the case of the xanthin bases of the nucleins, which increases the proportion of uric acid in the excretions, and that the glycerophosphoric acid is directly utilised.

Danilewski, who was the first to recommend the use of lecithin, administers it pure, and chiefly in nervous disease. He has observed that, in the young and on himself, lecithin acts as a nervous stimulant, augmenting

[1] Cf. "Chimie de la Cellule Vivante."

assimilation and fortifying the cerebral functions. He has recently[1] reinvestigated the subject, and his new researches entirely confirm his first deductions. Sereno has also made use of pure lecithin; he finds that under its influence the general health is markedly improved, and that in nerve anæmia and wasting conditions the patient has a better appetite, assimilates more readily and gains weight. The number of red corpuscles increases, that of the leucocytes remaining stationary. In the urine traces of nucleo-albumin may occur, but no other disturbance.

Following Sereno and Fanelli, Muggia has employed lecithin of yolk of egg in infantile anæmia and wasting; in doses of one gramme daily in injection. This treatment is found to be well tolerated by children, even of a year, an increase of body weight and of the number of red corpuscles generally ensuing. Muggia prepares the remedy in the following manner: the yolk of a new-laid egg is placed in a glass of sterilised water containing about 150 to 200 grm.; to this is added $\frac{1}{4}$ of a solution of chloride of sodium (7·5 to 1,000). The fluid is then stirred vigorously with a glass rod, and is afterwards filtered through absorbent cotton. In the first instance 1 c.c. of the liquid thus obtained is injected, and the quantity is increased up to 10 c.c., which is the maximum dose. The treatment lasts for twenty days, and corresponds to the injection of about 100 c.c. of the preparation.

In France also lecithin contained in yolk of egg is made use of in its complex form. Colleville, who, so long ago as 1893, suggested that injections of phosphate of soda and of neutral glycerophosphates should be replaced

[1] "Neurolog. Centralblatt," 1900, No. 8.

by those of yolk of egg, which is rich in lecithin, has employed a preparation which he calls *l'huile d'œuf*. This is a solution of yolk of egg in oil of sweet almonds : 100 grm. of oil and of yolk of egg contains 0 grm. ·29 phosphoric anhydride, or 3 grm.·516 lecithin, corresponding to 0 grm. ·40 ordinary phosphoric acid, or 1 grm. ·46 phosphate of soda. According to this author, *huile d'œuf* is more efficient than are the glycerophosphates in the anorexia of lymphatism and neurasthenia, but not more than 5 c.c. should be administered hypodermically *per diem*, because more than this causes various disturbances, notably nervousness and excitement, and a diminution both in the quantity of urine passed and in the urea and phosphates contained therein. Thus Colleville considers that *huile d'œuf*—in other words, lecithin—is of value when it is desired to rapidly rouse the organism to vigorous reaction, but that the glycerophosphates are more certain in their effect, although their action is less powerful.

Quite recently Gilbert and Fournier, following the views of Desgrez and Zaky, who maintained that lecithin favours the assimilation of nitrogen and phosphorus, have given it to animals in quantities of 0 grm. ·10 to 0 grm. ·20 for long periods, and have found that this treatment considerably increases the body weight, especially in the case of young animals, whose increase in weight has greatly and rapidly exceeded that of the control animal employed. These authors have also made use of lecithin in the treatment of tuberculosis and of several nervous diseases. The results obtained would appear to be encouraging. In tubercular patients with advanced lesions, either on one or both sides, appetite has been increased as well as the body weight and the

strength generally; further, both cough and expectoration have been lessened, as also has the number of bacilli in the sputum. In neurasthenia the improvement has been less marked, although an increase of appetite and of vigour has been observed. In no case was there any evidence of lecithin exerting a toxic action and of its causing any untoward effects.

Lancereaux has also used ovo-lecithin in the treatment of various maladies of which wasting is a marked feature. In several cases favourable results were obtained, as in that of advanced pancreatic diabetes in a young man of eighteen, who was suffering from tubercular disease of the bones with amyloid degeneration of the kidneys and abundant albuminuria; also in two children who were markedly wasted. In all the instances weight was rapidly gained, and the general condition was very obviously improved.

Lancereaux gives pure lecithin in quantities of 20 centigrammes for children and of 50 centigrammes for grown-up people *per diem*.

Gilbert and Fournier have employed lecithin of yolk of egg, and have administered it, hypodermically, in quantities of 0 grm. ·05 to 0 grm. ·15 every other day, in sterilised olive oil, and also by the mouth in the form of pills containing 0 grm. ·10 to 0 grm. ·50. Danilewski, who makes use of pure lecithin, also gives it by the mouth, fasting, in doses of 0 grm. ·20 to 0 grm. ·30 *per diem*. Different specialities are also made use of which have for basis yolk of egg, and more especially extracts of sheep, pig, or calf brains, but in these the proportion of pure lecithin is not always accurately calculated.

We have recently had an opportunity of using lecithin in two forms of disease. In tuberculous

patients the results are but rarely favourable, so far as concerns an increase in the respiratory exchanges, which are very little lowered. This is not the case as regards demineralisation. Indeed, under the influence of lecithin, in doses of 0 grm. ·50 to 0 grm. ·75 and up to 1 grm. *per diem*, mineral elimination has diminished, especially as regards the earthy phosphates which have fallen from 0 grm. ·74 to 0 grm. ·70 and 0 grm. ·68, the quantity passed still, however, exceeding the normal, (0 grm ·63). It may be that this diminution is attributable to the influence of lecithin alone, the substance being considered as a fatty body, inasmuch as fatty matters are, as it were, a sort of *aliments d'épargne* for phosphates. Nevertheless, several patients have gained somewhat both in strength and weight.

In the case of scrofulous and lymphatic children, the results have been far more accurately defined. Without the weight undergoing any marked change, the general condition has materially improved. Appetite and vigour have been recovered, the skin has become healthy and clear; in three cases glandular complications have completely vanished; in another an obstinate leucorrhea has disappeared and has not returned; in yet another impetigo has cleared up. But the *chimisme respiratoire* could not be ascertained, owing to the youth of the patients; yet urine analysis has shown a distinct improvement in the balance of the exchanges, which has approached the normal, without, however, invariably attaining this point.

Finally, although the clinical observations are not numerous, it may be admitted that lecithin, regarded by itself and in the pure state, is an excitant of the general nutrition, chiefly on account of the phosphorus contained

in it, and through the action thus exerted on the nervous system; hence its administration seems desirable, especially in depressed general conditions. Yet its effects, apart from the inconveniences pointed out by A. Robin and Bardet, do not seem very superior to those of the acid glycerophosphates, and this is easily understood, inasmuch as glycerophosphoric acid is the active principle of lecithin.

B. *Nucleins.*

The nucleins, discovered in 1866, by Miescher, of Bâle, are proteids which are usually found to occur in association with albuminoids, forming nucleo-albumins. They constitute the most biologically active portion of nuclei of animal and vegetable cells (especially of chromatine), and are present, not only in milk (casein), but also in eggs and in every kind of seed. If attention is directed to the fact that these nucleins are rich in phosphorus — which represents the central nucleus around which are aggregated the xanthic bases and more complex albuminoid molecules—one is induced to attribute to the phosphorus the chief part which these substances play in the assimilative processes, and hence in those of nutrition and development. And even if this were not so, nevertheless the nucleins would not the less retain the considerable metabolic importance which necessarily results from their presence in all the chromatic elements. According to Kossel and Altmann, the constitution of the nucleins should be regarded as follows, starting from the nucleo-albumins which when decomposed yield nuclein and an albuminoid material. Nuclein in its turn breaks up on the one hand into albumin, and on the other, into a complex substance, rich in phosphorus, having an

acid property, and to which Miescher has given the name nucleic acid. When appropriately treated, nucleic acid itself breaks up into xanthic or nucleic bases—xanthin, hypoxanthin, guanin, adenin, &c., and into thymic acid (thymus), which, when treated in a state of ebullition with sulphuric acid, gives a well crystallised base, thymine, C^5 H^6 N^2 O, and orthophosphoric acid. The mean percentage composition of the nucleins is the following, according to Bunge:

C	...	...	36 to 42 p. 100
H	...	...	5 to 7
N	...	...	13 to 15
O	...	...	17, 2 to 43, 5
S	...	...	0, 5 to 1, 8
P	...	...	2 to 9
Fe	...	...	0, 2 to 0, 3

This composition proves that there must be several kinds of nucleins, which are distinguished the one from the other by their richness in phosphorus and also by the presence of iron (hæmatogen).

Hoppe-Seyler based his classification of the nucleins upon the products yielded by their disintegration, and he distributed them in the following manner:

1. Nucleins whose decomposition gives rise to albumin, to hypoxanthin and to phosphoric acid (nucleins of yeast, of pus, of the nucleated red blood corpuscles).

2. Nucleins yielding albumin and phosphoric acid (nuclein of yolk of egg, of milk).

3. Lastly, nucleins yielding only hypoxanthin and phosphoric acid (nucleins of the spermatic fluid of fishes).

As is readily seen, the first of this series alone corresponds to true nucleins, and the last to nucleic acid; as

to the second group, we do not know how Hoppe-Seyler has been able thus to classify them, considering that hæmatogen also, when decomposed, gives rise to xanthic or nucleic bases. However, certain vegetable nucleins occurring in the seeds of leguminous plants and cereals seem, indeed, not to yield nucleic bases, that is to say, that the phosphoric acid corresponding to the thymic acid of the animal nucleins would combine immediately with albumins, globulins, &c., in order to form legumines, caseins, &c.

But these facts are far from being absolutely proved, and although a distinction should be drawn between animal and vegetable nucleins—a difference chiefly based on their respective developments and on the nature of the accessory products of assimilation—it is at present difficult to say in what this difference consists, and to what molecular arrangement it especially appertains.

The nucleins are soluble with difficulty in cold water, ether and alcohol, but they dissolve in acids, and above all in dilute alkalies; they are characterised by a certain degree of acidity, and can combine with baryta to form salts. Miescher, basing his conclusions on the composition of these salts, regarded nuclein as playing the part of a tetrabasic acid whose formula is $C^{29}\ H^{49}\ N^{9}\ P^{3}\ O^{22}$; finally, according to Lubavin, the nucleins decompose the alkaline carbonates, carbonic acid being given off.

It has been supposed that these substances are only attacked with difficulty by pepsin and trypsin in a suitable medium. But if this is so it is not easy to understand how the casein of cow's milk—this milk containing especially, in virtue of the proteid matters, this casein, which is a nucleo-albumin—can be digested and

wholly absorbed by young calves, except about 1 per cent. Careful experiments have indeed led to considerable modification of our views regarding the digestibility of nucleins.

We believe that Salkowski was the first to oppose the view of Hoppe-Seyler concerning the resistance of the nucleins to the action of the digestive secretions; he has shown that the nucleins, after being partially disintegrated by the gastric juice, are finally completely transformed by the pancreatic juice. The experiments of Bovet made in the laboratory of Professor Pouchet and those of Popoff, which are still more recent, clearly confirm the observations of Salkowski. These experiments, chiefly applied to the vegetable nucleo-albumins, prove that these substances are first decomposed by the gastric juice, the albumin being converted into peptone, and the residue of nuclein, after undergoing several successive transformations, is finally digested in the duodenum under the influence of the pancreatic juice.

The digestibility of nucleins, which must therefore be henceforth regarded as proved, involves a very remarkable consequence. Salkowski, who has shown that nearly 70 per cent. of the phosphorus contained in these substances is absorbed, a fact confirmed by Gremlich, attributed to the nucleic acid—and perhaps also to the thymic acid—thus set free a very energetic antiseptic action on intestinal bacteria. Further, Altmann has ascertained that a 5 per cent. solution of these acids kills the cholera bacillus in two or three minutes; that of typhoid fever in one hour, streptococci in two hours and a half, and staphylococci in six hours. Yet Kossel thinks that these nucleic acids exert a positive chemiotactic action upon the leucocytes, which, in this way drawn into the alimentary

canal, are able to exercise their phagocytic power. The hyperleucocytosis which is clinically observed to follow the administration of the splenic nucleins of Horbaczewski seems to depend chiefly upon this chemiotaxy, as also do the obvious nutritive properties of this nuclein as regards the white corpuscles.

More difficult of explanation are the diuretic and calorificient qualities which are attributed to the nucleins. If a connection can be ascertained to exist between these properties and the elevation of temperature during the day which follows the administration of splenic nucleins, should this phenomenon be attributed to the action of these substances on the nervous centres? Diuresis would in a sense be the consequence of these phenomena, and it would convey outwards the products of decomposition and the toxins which are rendered soluble by oxidation. And Kossel has, indeed, noticed a marked increase in the excretion of urates to follow the use of nucleins. This formation of uric acid results from the oxidation of the xanthic bases of the nucleins, according to the equation

$$\underset{\text{xanthin.}}{C^5\,H^4\,N^4\,O^2} + O = \underset{\text{uric acid.}}{C^5\,H^4\,N^4\,O^3}$$

Lastly, we must remark that the pyrogenous effects, tolerably constant in the case of the animal nucleins, do not occur as regards the nucleins and nucleoses derived from the vegetable kingdom. From this difference the deduction is reasonable that the composition of the latter class of substances differs from that of the former.

As to the peptic action of the nucleoses (the complex nucleo-albumins of vegetables, nucleo-albuminoses, and nucleo-peptones) pointed out in 1895 by Bovet, it would

seem to be due to the diastases contained in these substances together with fat and sugar—the nucleoses being the elaborated materials of the seeds of leguminosæ and of cereals. These diastases, by digesting the albumins, according to Bovet, facilitate the work of the stomach and give repose to the organ, to such an extent, indeed, that the glandular function can recuperate, and the proportion of the hydrochloric acid contained in the gastric juice is thus augmented, causing a marked increase in digestive vigour. Yet the influence of these diastases, and even their presence, seems somewhat problematical, when it is a question of pure nucleins or even the nucleoalbumins, and in such circumstances it may be asked if their peptic action is not simply due to the phosphoric acid which is partially set free in the stomach, as ascertained by Popoff—inasmuch as phosphoric acid forms with the alimentary albumoses peptones of superior quality.

It remains to inquire into the employment of nucleins for the purpose of nourishing the organism. Do these nucleins, or at all events certain of their most important groups, contribute directly to the formation of the nucleins of the organism; or do they merely supply, at the end of their complete decomposition, those elementary materials which the organism unites with the foreign albumins to produce the nuclein of its cell nuclei? This question is very far from being definitely decided. If it must be maintained, with Lambling, that in certain cases the nucleins may take origin from the simple mineral phosphates, yet the comparative physiological utilisation of these phosphates and of the phosphorised nuclein combinations proves that the organism allies itself more willingly, more easily, and

more completely with these latter. Although synthetic phenomena necessarily occur in the process of the fixation of each substance in the living complex, yet each kind manufactures its own particular living material; and although, for example, human nuclein differs from that of all other animals, yet is clear that, in virtue of the principle of least resistance, the synthetic processes make use preferably of those substances whose combination can be effected with the least possible expenditure of energy. Thus it is that mineral substances, for instance, are assimilated far more easily in the organic than in the inorganic form, and this principle, consequently, should never be lost sight of in arranging dietaries, especially in the case of sick people. Finally, the observations of Miescher and of Kossel, which are wrongly cited in support of the view that crude mineral substances are directly built up in the organism, simply prove that the latter is capable of restoring complex nucleins by combining certain molecular groups of primitive disintegrated nucleins—which is a concise proof of the utility of this decomposition under the influence of the digestive juices.

The various properties of the nucleins have led to their application to therapeutics, which, although not at the present time a very extended one, would seem to be capable of considerable expansion. Up to the present time the nucleins have been made use of under four different forms. We shall say nothing concerning the *nucleins of yeast*, which are whitish powders whose therapeutic action is still undetermined, but which seems to be identical with that of the fully-fermented yeast, and which perhaps confer on the extracts of the latter those special qualities which are attributed to

them. Neither shall we speak of the *sodic nucleins*, products almost completely soluble in water and which are now being studied, the first results obtained, however, being anything but conclusive. Hence we treat only of the *nucleoses* and of splenic nuclein.

The nucleoses, nucleo-albumins or vegetable nucleo-peptones have been praised by Bovet. Under this complex form they produce a marked increase in the body weight, an improvement in the chemical functions of the stomach, and an abundant diuresis. In dyspepsia, in albuminuria, in certain cardiac affections, and especially in arterial lesions in which renal insufficiency and alimentary toxæmia play, as proved by Huchard, a preponderant part, they give very satisfactory results. In tuberculosis and in wasting maladies their utility is more doubtful, for, according to Bovet, they may when in the pure state (pure nucleo-albumose) produce wasting, increase of weight only ensuing when they are given in the complex condition, *i.e.*, with carbo-hydrates, fats, and those salts which are contained in vegetable seeds. But in this case it is obviously just as well to make use of natural aliments. On the other hand, in typhoid fever pure nucleose has induced an immediate improvement, and has initiated a rapid cure, attributed by Bovet to the diuretic and antiseptic action of nucleins. The same result has also been observed in the case of nuclein contained in splenic pulp, and Strub has thus written in connection with this matter: "Vaughan has rendered a great service in pointing out the utility of nuclein in the building up of the white blood corpuscles. Nuclein, when given in large doses during typhoid fever, increases the number of the leucocytes and furnishes them with the necessary energy to combat the typhoid poison and to rid the blood of the

same." The author, in order to explain this effect, thus makes use of the theory of hyperleucocytosis and of a more powerful phagocytic action, which is the result of the increase of leucocytes. Bovet prescribes nucleose diluted with milk in quantities of three to eight spoonfuls *per diem*.

Splenic nuclein, prepared by Horbaczewski, is a brown powder which possesses, according to this authority, calorficient properties and which induces a hyperleucocytosis which may attain even cent. per cent. Consequently it has been made use of in lupus, but unsuccessfully, inasmuch as it causes exacerbation of the local inflammation, and with greater benefit in chronic varicose ulcers of the leg, in syphilitic ulceration of wide extent, in septic ulcerations of the genital organs in women and in endometritis. In tuberculosis the effects of the treatment are still *sub judice*, although Vaughan warmly recommends the product in such cases. Finally, in typhoid fever and some other affections, the results obtained are, as has been observed, fairly satisfactory. In infectious diseases Mourek recommends the hypodermic method of treatment; up to 10 or 12 c.c. may be injected of a solution of splenic nuclein of the strength of 0 grm. ·5 to 100 c.c. of distilled water with the addition of 0 grm. ·5 carbolic acid; each c.c. contains 5 milligrammes of nuclein. The initial dose is ½ c.c. In typhoid fever Strub does not recommend solutions, but dry preparations which have been carefully protected from the effects of damp.

To sum up, the nucleins, whether regarded as a food (complex condition) or as a medicine (pure condition), are doubtless adapted, by reason of their physiological properties, to be of great service, but clinical and

experimental observations are not as yet sufficiently numerous for any definite opinion on this matter to be given. Hence it is necessary to wait for the confirmation of these views. In the meantime, it does not seem rash to hope, judging from what we already know of them, that the nucleins may become therapeutic agents of a well-marked efficiency in the *rôle* of metabolism and as a means of defence of the organism.

C. *Glycerophosphates.*

As we have already remarked, it is glycerophosphoric (or phosphoglyceric) acid which confers on the lecithins their power of stimulating the nutritive exchanges through the mediation of the nervous system. As, on the other hand, the drawbacks to this form of treatment apparently arise from the union of this acid with the toxic base, choline or neurine, the attempt has been made to substitute for this organic base mineral bases which are themselves endowed with useful properties. The salts thus obtained were in the first instance studied by Pasqualis, then in 1894 by Professor A. Robin from the therapeutic point of view.

Chemistry.—Glycerophosphoric acid is a bi-basic acid, which therefore forms neutral and acid salts, both of which are made use of in medicine, the first being reserved for hypodermic injection, while the latter are now preferred for treatment by the alimentary canal.

The acid glycerophosphates differ somewhat as regards their properties from the neutral salts of the acid. They are amorphous, while the others are often well

crystallised; they are very hygroscopic, but very stable; their alcoholic and watery solutions decompose only very slowly, and, even at the boiling point and in concentrated solution, the quantity of phosphoric acid which they furnish is always very small. Finally they are much more soluble in water than are the neutral glycerophosphates, the proportion being 30 per cent. instead of 4·5 per cent., as is the case with the last-mentioned salts.

Among the glycerophosphates of the organic bases one only—that, namely, of quinine—appears to have been successfully used in therapeutics, having given good results in malarial fever and in malarial anæmia.

Physiology and Therapeutics.—It has been long known that the mineral elements used in the process of nutrition, when present in the purely mineral form, are not absorbed, and cannot therefore be made use of by the organism. Dujardin-Beaumetz called attention to this fact in connection with the administration of phosphates which it was formerly the custom to recommend; this treatment must have been nearly entirely useless on account of the all but complete inassimilability of these salts. Bunge has proved that the mineral matters which take a share in the organic syntheses cannot be utilised, at all events in the case of the higher animals and of man, unless they take on an organic form—that is to say, unless they have already been elaborated by a living organism. Thus it has been attempted to provide natural phosphates, phosphates directly extracted from vegetables, milk, or from animals. In this way *phosphatoses* have been produced which have as a matter of fact given very good results, but which have nevertheless the drawback of not being always very accurately

proportioned, and which, moreover, when sufficiently pure, are somewhat expensive.

From this point of view the glycerophosphates offer great advantages. Their chemical composition is perfectly definite, the dose in which they are usually given is not expensive, and they furnish, like the natural phosphates, phosphorus in an organic and consequently easily assimilable, absorbable form. They are therefore true cellular aliments which exert on all the tissues, but more especially on the osseous and nervous systems, a tonic and stimulant action. This property, in connection with the facility with which they are absorbed and utilised, and with the absence of untoward effects and of toxicity when they are pure, explains and justifies the success which attends the use of these products.

According to Robin, the action of the glycerophosphates on the organic exchanges is as follows: the total urinary residue is augmented, as is the urea, as well as the quantity of sulphates and chlorides. The coefficient of nitrogenous oxidation increases from 80 to 84 or 85 per cent.—that is to say, from 4 to 5 per cent.—but the proportion of uric acid to urea is lowered, while the index of acidity of the urine is slightly increased; the urinary phosphates remain stationary, which is an important fact, proving as it does that the glycerophosphates really remain in the organism.

How is this fixation of the phosphates effected? This question is far from being completely resolved. But it would seem that there is a decomposition of glycerophosphates in the organism; the phosphoric acid and the mineral bases are separately fixed, either to the nuclei of the cells or to those elements of the tissues which include the base in question amongst their essential

mineral constituents; the glycerine being set at liberty is probably burnt up in the economy. Although this is doubtless a purely theoretical view of the matter, yet it explains in an adequate manner the causation of the remarkable clinical results which are obtained by the administration of the glycerophosphates of magnesia, soda, iron and potash, &c. It also explains the effects which ensue in certain depressed conditions of the nervous system with marked anæmia. And it is clear that, if this mode of explaining the facts be correct, the employment of the glycerophosphates imitates one of the most active modes of nuclear and nervous nutrition, and is certainly the most efficient and the best method of administering phosphatic medication.

The acid glycerophosphates have a still more energetic influence than the neutral salts of which we have just spoken. Bardet has summarised the effect of these remedies as follows:

1. In moderate doses (3 to 4 grm. *per diem*) the dynamophoric action is more rapid and stronger.

2. The urinary elimination of phosphates is not markedly increased, but the nitrogenous coefficient rapidly rises until a limit is obtained which is not afterwards passed whatever may be the doses of the glycerophosphates which are administered.

3. The index of acidity of the urine is sensibly increased, but unless very large doses and dilute phosphoric acid are made use of, it is rare for the normal acidity to be attained. In all circumstances the acid glycerophosphates are superior in this matter, as regards activity, to the neutral salts.

4. Large doses (15 to 25 grm. *per diem*) are generally well borne, but a slight purgative effect ensues, which may be

of some therapeutic value. Further, there is a marked chologogue action, which exerts a favourable influence in cases of dyspepsia due to hyperchlorhydria with defective performance of the liver functions.

It may be stated in general terms that the acid glycerophosphates have the same action as the neutral salts, but that they are more effective, more rapid in their results. They are well tolerated in most cases, even when the stomach is easily upset. They would, however, appear to be somewhat less active as regards the effect on the urine than phosphoric acid. It may be said that, under all circumstances, the clinical indications for the use of these salts, both neutral and acid, are the same.

Indications for use, and the Dose.—It may be said in general terms that glycerophosphates are indicated in all cases in which there is an excessive phosphatic demineralisation. These salts are wrongly regarded as being of exceptional and specific value in neurasthenia, inasmuch as neurasthenia, or rather all those morbid conditions which are collected together under this term, are very far from owning the same cause; different causes must obviously require different modes of treatment. Among these diverse exciting agencies, those alone should be regarded as requiring phosphatic treatment which are dependent upon nutritive disorders with a marked demineralisation; the depressing effects which accompany this loss are then naturally overcome by the use of the glycerophosphates. The glycerophosphates are further available in all maladies characterised by an increased elimination of phosphates, the dietary being, of course, left out of account, *e.g.*, diabetes, anæmia, rickets, osteomalacia,

scrofula, and lastly tuberculosis. Further, their employment is desirable in the convalescent stage of infectious maladies, when loss of mineral matters is always more or less marked. They may be made use of also, in union with lithia, in arthritis and gout.

It must not be forgotten that, in actual practice, the nature of the mineral base which is combined with the glycerophosphoric acid is not a matter of indifference. In some rare cases, it is true, loss of mineral constituents is limited to a single tissue, but not unusually such and such a tissue or a certain structure loses its mineral constituents more rapidly than another, as is shown by urinary analysis, by the relationship of the vital exchanges, and especially by the proportion of the alkaline or earthy phosphates. If, therefore, it is always advisable to endeavour to remineralise the different tissues by supplying them with the chief substances of this description which they have lost—in a word, to adopt a system of polyphosphatic medication as recommended by A. Robin and Bardet—it is, nevertheless, obvious that we must especially supply that mineral constituent of the tissues which is most completely drained from the organism. Thus in rickets or osteomalacia, for example, glycerophosphate of lime is especially indicated; in nervous affections and neurasthenia and neuranæmia the glycerophosphate of magnesia would be required; in anæmia the glycerophosphates of potash and iron will give good results, as it is probable that iron occurs in the blood corpuscle in the form of the glycerophosphate. Lastly, in gout the lithia salt is to be preferred.

When given by the mouth, as is usually the case, the acid glycerophosphates should be employed, the doses being small (3 to 4 grm. *pro die*) or in larger doses

(15 to 25 grm. *pro die*), according to the nature of the case. When there is no very special indication, as may happen in gout for example, polyphosphatic medication should be resorted to, of which the following is the formula of A. Robin :

Glycerophosphate of lime ...	0 grm. ·30
,, ,, soda ...	0 grm. ·10
,, ,, potash ...	0 grm. ·10
,, ,, magnesia...	0 grm. ·10
,, ,, iron ...	0 grm. ·05

To make one cachet, two per diem. Robin recommends that these salts be combined with remedies which exercise a stimulating action on nutrition; for example :

Nux Vomica in powder ...	0 grm. ·03
Pepsin en paillette titre 50	0 grm. ·15
Maltine	0 grm. ·05

which is added to each cachet, and especially in atonic dyspepsia. Should there be severe neuranæmia, the dose of the magnesia salt may be increased to 0 grm. ·20, just as in anæmia the quantity of the salt of iron, &c., is increased. Glycerophosphate of lithia may also be given in larger quantity, as also may the salt of quinine (even up to 1·50 to 2 grm.) in malarial anæmia, and combined with the glycerophosphate of iron, &c. All these salts may also be given in solution, which is, indeed, the most certain and efficacious way of administering them, but only a small quantity of the mixture should be prepared at one time, as the solution decomposes and soon becomes mouldy. For children a syrup may be employed; it is saturated in order to avoid

the risk of subsequent changes. Here is a formula of Robin, slightly modified:

Glycerophosphate of lime	...	6 grm.
,, ,, soda	...	2 ,,
,, ,, potash	...	2 ,,
,, ,, magnesia	...	2 ,,
,, ,, iron	...	1 ,,
Tincture of Nux Vomica	...	30 drops.
,, Kola ...	...	10 grm.
Syrup of Cherries to ...	...	200 ,,

Two or three teaspoonfuls *per diem*. Lastly, the glycerophosphates may be made use of hypodermically in the quantity of 0 grm. ·25 *pro die*, but in this case the neutral, and not the acid salts, must be employed, on account of the irritation which is set up by the latter.

4. Indirect Alterants.

A. *Phosphoric Acid.*

It is only quite recently that phosphoric acid, which has for several years been somewhat neglected as a therapeutic agent, has taken an important position as regards the newer methods of treatment. This resuscitation of phosphoric acid is due to the researches of Joulie, Cautru, and Bardet concerning the hypoacid diathesis and neurasthenia.

Chemistry.—Phosphoric acid occurs under two forms, the anhydrous acid PO^5 and the trihydrated acid H^3PO^4, which, diluted with an equal weight of water, forms the officinal phosphoric acid.

A hundred parts of the officinal acid thus contain 36·4 of anhydrous acid or 50 trihydrated acid. It is well to calculate the index of acidity of commercial

preparations in equivalents of anhydrous acid on account of their variable composition. The normal preparation has a density of 1·35 at 15°; this preparation should alone be used. Forty-five drops represent 1 grm. of anhydrous acid.

Physiology.—Phosphoric acid forms in the stomach with the albuminous constituents of the food, peptones of superior quality, and on this account it may strengthen the gastric functions when they are debilitated or abolished; further, it checks the secretion of hydrochloric acid, and in this way ameliorates more or less completely dyspeptic conditions due to hyperchlorhydria.

This diminution of the secretion of hydrochloric acid, checking as it does the decomposition of the chlorides, and especially the chloride of sodium, diminishes the quantity of soda set free, and hence indirectly increases the general acidity of the humours, thus favouring the action of the liver and consequently causing the neutralisation of the excess of alkali in the system. The bile and the pancreatic juice neutralise the phosphoric acid, which thus passes into the blood as a soda salt more or less prominently basic. Hence this treatment furnishes the economy with phosphate of soda which can be absorbed and utilised. Occasionally, when the hepatic inadequacy is strongly accentuated, neutralisation may be incomplete in the duodenum; when this is so acid diarrhœa occurs, accompanied with colicky pain.

Therapeutics.—It is generally admitted at the present time that the majority of the nervous abnormalities which are grouped together under the name of neurasthenia are caused by dyspepsia, which is latent when it is compensated by vigorous hepatic action, but becomes

immediately manifest when this liver function fails. It is generally the case that over-eating, particularly as regards nitrogenous food, is the cause of this gastric trouble, inasmuch as the immediate result of over-feeding is to induce an excessive production of hydrochloric acid. So long as the liver is healthy, this organ receives the liberated soda, and the hepatic bases neutralise the excess of acid. But when the liver becomes debilitated and incompetent to perform its duties, the free soda remains in the blood and converts the di-sodic into the tri-sodic phosphate. The result of this is that the tissues become alkalinised, an alkalinisation which is still further increased by the non-neutralisation of the acids and of the ammoniacal products of the digestive process which the liver refuses to transform.

There is thus a marked lowering of the acidity of the tissues and of the urine, and passage of an increased quantity of earthy phosphates which are soluble in the over-acid blood. It is at this period that neurasthenic symptoms make their appearance, being often accompanied with marked gastric crises. Whatever may be their cause, intellectual overwork with mental depression or primary disturbance of nutrition, these phenomena lead to the production of hypoacidity of the blood and consequently of the urine and to the hypoacid diathesis, either primary or secondary.

Those whose tissues are hyperacid, and Professor Robin has proved that numbers of neurasthenics are in this condition at the beginning of their troubles, may develop neurasthenia in consequence of considerable elimination of phosphates, and the tissues thus become hypoacid in reaction, when the liver, incapable of dealing with the blood too highly charged with fatty acids and with

acid salts, no longer converts the ammoniacal derivatives, which, passing into the blood, alkalinise this fluid.

Hence phosphoric acid is likely to be useful in maladies which are the result of hypoacidity, especially in cases of dyspepsia, when it acts as a supplement and allows aliments to be artificially digested. Although other acids may, under the same circumstances, render a similar service, yet the results obtained by the use of phosphoric acid are distinctly more satisfactory, and this acid also possesses the great advantage of compensating the loss of phosphates, should such be the case. But in certain cases to which Bardet refers it has not been necessary to resort to the use of phosphoric acid, it having been found sufficient to reduce the quantity of nitrogenous matter ingested in order to raise the acidity of the urine. According to Cautru, phosphoric acid is also useful in all the forms of arthritism, in rheumatic subjects, in eczematous patients, who are almost always hypoacid—after having passed through a stage of hyperacidity—and who prolong their malady by the use of alkaline waters, in those suffering from boils, and in diabetes. Finally, as has been already mentioned, in the several forms of neurasthenia; the acid has also been praised in the lymphatic diathesis, cancer, and in tuberculosis, maladies often attended with hypoacidity, according to the severity of the affection.

In quantity of from 1 to 6 grm. of anhydrous acid *pro die*, phosphoric acid may be taken for long periods without any unpleasant symptoms occurring; at the same time there will be observed a gradual improvement in the digestive condition and in the general health. But if this treatment is not thus prolonged it will be necessary to observe a strict rule of life and of the dietary, both of

which must be rigorously followed if no check in the amelioration is to occur. Bardet has pointed out that in gastric irritability, when the condition is chiefly dependent upon nervous derangement, treatment by phosphoric acid, even when prolonged, may not prevent the attacks of gastric trouble.

Contra-indications as regards the use of phosphoric acid are, first, local irritable conditions, ulceration and cancer of the stomach, and inflammatory lesions of the alimentary canal. Under these circumstances Bardet advises the substitution of the acid glycerophosphates, which give good results; when there is diarrhœa or chronic enteritis, phosphoric acid is equally ill-tolerated on account of its laxative action; it forms, indeed, as the result of its neutralisation in the intestine, phosphate of soda, which, as is well known, is a powerful laxative. In cases of constipation this is of course a great advantage, but this is not so in cases of diarrhœa, when intolerance of the drug may then be aroused. According to Cautru, phosphoric acid is also contra-indicated in cirrhosis of the liver, as it causes diarrhœa; in renal affections, when it increases the quantity of albumin in the urine, and, lastly, in those patients who are taking arsenic at the same time.

Formulæ.—Some of the principal formulæ for the administration of phosphoric acid are given below:

Lemonade (Bardet).

Officinal phosphoric acid (36·4 per cent.)	28 grm.
Alcoolature d'oranges	20 ,,
Sirop de sucre	250 ,,
Distilled water to	1 litre.

100 c.c. of this preparation contains 1 grm. of anhydrous acid; 1 to 3 *demi verres ordinaires.*

Elixir (Bardet).

White of egg	60 grm.
Officinal phosphoric acid	58 ,,
Distilled water to	400 c.c.

Boil in a water bath, filter, and add the following mixture:

Alcoolature d'oranges	200 grm.
Sirop de sucre	400 ,,
Distilled water to	1 litre.

This preparation contains 0 grm. ·10 of anhydrous phosphoric acid in each teaspoonful. 10 to 15 teaspoonfuls diluted with water with meals.

Joulie's Formula.

Officinal phosphoric acid	17 grm.
Phosphate of soda	34 ,,
Distilled water	250 ,,

Three to 12 teaspoonfuls *pro die* in plain water or *eau sucrée.*

Substitutes for the acid in cases in which it is not well borne (Bardet).

Acid glycerophosphate of soda à 90 p. 100	220 grm.
Officinal phosphoric acid (D = 1·35) ...	67 ,,
Boiled water to	1 litre.

2 to 3 liqueur-glassfuls *per diem.*

or

Acid glycerophosphate of soda à 90 p. 100	220 grm.
Boiled water to	1 litre.

2 to 3 liqueur-glassfuls *per diem.*

B. *Cacodylic Acid and Cacodylates.*

As might be inferred from the practice of eating the metal, arsenic has been looked upon for a great length of time as capable of modifying nutrition and blood

formation, and as a regulator of the oxidative process. Whether this opinion is justified or not, the arsenical preparations made use of therapeutically, being certainly poisonous, their employment has been strictly limited. It was known that certain modes of organic combination of poisonous substances may be harmless, and it was this idea which first suggested to Professor A. Gautier in 1897 the possibility of making use of cacodylic acid, an organic combination of arsenic discovered by Bunsen in 1843, and one which at this epoch was thoroughly studied as regards its physical and chemical properties.

Cacodylic acid $As(CH^3)^2O^2H$ is white in colour, crystalline, without smell, but with a very slightly acid taste. It is made by the super-oxidation by means of oxide of mercury of the oxide of cacodyle $As^2(CH^3)^4O$.

$$As^2(CH^3)^4O + HgO + H^2O = 2Hg + 2As(CH^3)^2O^2H.$$

Cacodylic acid forms salts, of which the one most often employed is cacodylate of sodium $As(CH^3)^2O^2Na$, a combination containing 46·8 per cent. of arsenic; it occurs in the form of a white powder, very soluble in water. It is very stable, so much so that neither fuming nitric acid nor a mixture of sulphuric acid and chromate of potash have any effect upon it, even at the boiling point. Watery solutions of this substance also keep very well, and can be easily sterilised.

As already mentioned, cacodylate of soda is usually employed, but pure cacodylic acid is equally available.

Physiology.—The cacodylates, whether neutral or pure, can be administered in several ways. Professor Gautier recommends the hypodermic method of administration, Professor Renaut the rectal, and Dalché prefers that by the mouth.

Although each of these methods offers certain advantages, yet it would seem that the hypodermic injection of the remedy is preferable, especially as it avoids to a certain extent the very serious drawbacks of cacodylic treatment. When the drug is given by the mouth, these drawbacks are obvious from the very first; they consist of colic, diarrhœa, dryness of mouth, pain in the epigastrium, loss of appetite; sometimes cutaneous eruptions break out—these are accompanied with much irritation; insomnia, acceleration of pulse, loss of strength may also occur; lastly, and by no means the least important of these troubles is the garlic taste and the odour of garlic which affects the breath, the perspiration, and indeed the whole body.

A. Gautier has explained how these unpleasant results are brought about. He says: "When cacodylic acid is submitted *in vitro* to the action of reducing agents, the acid is transformed into oxide of cacodyle, a very poisonous substance whose odour resembles that of garlic. Cacodylic acid itself is inoffensive. Cacodylic acid, when taken into the alimentary canal, comes in contact with reducing agents, microbic or otherwise, and a small portion becomes transformed into oxide of cacodyle, the odour of which is speedily obvious in the breath. This substance is not only volatile, but is also poisonous; after upsetting the stomach and intestines, it is finally eliminated by the lung, skin, mucous membranes, and kidneys, and in thus passing out of the system it may lead to the production of local disorders of these structures, which vary in different subjects, but which will certainly be more or less serious and persistent if the elimination is prolonged."[1]

[1] Académie de Médecine, October 31st, 1899.

It is on this account that Gautier recommends the exclusive use of subcutaneous injections. But even these are not always absolutely harmless: Dr. R. Simon and Dr. Burlureaux have both observed the garlic-like odour and taste to ensue after the hypodermic use of cacodylate of soda; it is true, however, that in some cases this drawback may be due to impurities contained in the drug.

Under any circumstances it seems certain that cacodylate treatment is most satisfactorily carried out by the hypodermic method. By this method, even if less pleasant to the patient, the several digestive troubles just referred to are avoided, and any symptoms of arsenical poisoning are but very slowly developed. As regards administration *per rectum*, this method does not seem to be attended with any pronounced drawback, but when thus given cacodylic acid may be partially reduced in the intestine, in which case, of course, the same unpleasant symptoms will result as when the drug is given by the mouth.

Authors seem to be nearly unanimous that cacodylic acid and its salts are but feebly toxic, which permits, in exceptional cases it is true, even up to one gramme of cacodylate of soda, corresponding to about 46 centigrammes of pure arsenic, to be administered by the stomach *per diem*. This is a colossal dose when compared with that of the old preparations of arsenic which can be given. Yet it is a mistake to suppose that the drug is devoid of all toxicity, as has been pointed out by Danlos; and certain experiments on animals, especially those of Langlois, convincingly prove this, as also do the still relatively frequent cases of intolerance. These facts sufficiently explain the necessity of the great precautions which it is right to observe in the administration of the remedy, as also

does the inherent activity of the drug itself. Though Dalché and Danlos have been able to administer fairly large doses of cacodylate to their patients almost uninterruptedly for weeks together, it has not been so with many other physicians and with A. Gautier, who have insisted upon the necessity of frequent interruptions of the treatment. Usually the drug is given for eight days and then the administration is suspended, especially if the hypodermic method is made use of, for the same period; it is then once more ordered, and so on. The continuation of the treatment must depend upon the general condition; if during its suspension and in cases in which there is no intolerance the appetite diminishes, the temperature rises, the injections may be resumed. On the other hand, they should be stopped if there are signs of saturation of the system with congestive swellings, or if shortness of breath, elevation of temperature, &c., is complained of.

It should be observed that, with A. Gautier, when the kidneys are sound, and of course far more readily when their permeability is diminished, the prolonged ingestion of cacodylate of soda may give rise to a more or less persistent albuminuria; and the administration of the drug should be suspended when there is a tendency to congestions, hæmorrhages, and to hæmoptysis, and during menstruation.

What is the physiological action of cacodylic acid and of the cacodylates? There would appear to be on this question two opposing theories.

Professor A. Gautier considers that arsenic, in attaching itself to the cell nucleus, tends to increase its vitality, its power of reproduction and of regeneration, and thus plays a very active part in the process of tissue recuperation. It

increases the number of red corpuscles in the blood—and hence is a factor in the oxidative function—and that of the lymphatic polynuclear cells which form protamines and matters destructive to the pathological ferments and their toxins. For this reason it is that the appetite increases, the body weight goes up, the strength is recovered, and the proportion of urea to the chlorides falls in the urine. The improvement thus produced is sometimes lasting. According to this theory it is obvious that cacodylic treatment is especially desirable for those patients whose assimilative functions are markedly impaired.

According to Professor Renaut,[1] arsenic attaches itself to the anatomical elements, and preferably to the neurons, in the nucleus of which it probably replaces phosphorus. The result of this fixation is a diminution in the excitability of the nerve cell, as is proved by certain observations in the field of nervous pathology. But in wasting disease, the over-activity of destructive disassimilation is the result of nervous interference. If, therefore, the activity of the nervous system can be held in check, disassimilation will also be controlled and the wasting process arrested. As a matter of fact, under this treatment the body weight increases, inasmuch as disassimilation is rendered less active, and thus a portion of the circulating nutritive matters can be fixed. At the same time elimination by the kidneys is diminished and the temperature lowered by the regulation of the oxidative process. Cacodylic medication is therefore indicated in *wasting conditions*, according to Renaut; it is, on the contrary, contra-indicated in the case of those patients whose coefficient of oxidation is

[1] Académie de Médecine, May 31st, 1899.

lowered. Also when the proportion of urea, of phosphoric acid, and of all the other stable elements are markedly below the normal in the urinary elimination.

At first glance it does not seem easy to reconcile these two theories, or to support one against the other, and this is rendered still more difficult inasmuch as the facts relied upon by A. Gautier and Renaut are well established. Hence it is possible to discuss only the interpretation of these facts. From this point of view the theory of Renaut is much more satisfactory than is that of A. Gautier. If arsenic attaches itself to the cell nucleus, if in a normal condition it is met with chiefly in the thyroid gland, the thymus, the mammary glands and the epidermic structures, it certainly nevertheless seems that in medicinal doses its place of election is the nervous system. This is proved by the sedative action which the drug exerts in the neuroses attended with excitement, neurasthenia, chorea, epilepsy, and also by the production of those arsenical lecithins which are derived from the degeneration of arseniated nervous elements. But this action shows that, whether or no arsenic replaces the nuclear phosphorus, it poisons the cell, causing it to pass from a condition of functional activity to one of degeneration. And surely this is what occurs in those who are in the habit of taking arsenic, and in some of those subjected to cacodylic treatment. The adipose tissue increases in volume, yet this is not the case with the great mass of living plastic material. Arsenical or cacodylic intoxication diminishes the trophic nervous excitations; it does not increase, but on the contrary diminishes, the activity of the synthesis of assimilation. Thus arsenic is, as stated by Renaut, a *tissue-saving drug*. This is the reason why, when patients are treated by the cacodylates,

the increase of weight (when it occurs, which is not invariably the case) appears earlier than the return of appetite, and far earlier than the recovery of strength, which is, further, uncertain and transitory.

This explanation of the facts accords well with all clinical experience. It is owing to their relative toxicity —and, indeed, chiefly through this toxicity—that cacodylates may be efficacious in wasting diseases and in infections, as well as in neuroses accompanied with excitement. It is on account of their toxicity and of their particular mode of elimination that the cacodylates, or their products of disintegration, are capable of exerting their influence in pulmonary tuberculosis and skin diseases. The arsenical preparations and the cacodylates seem to increase the number of red corpuscles, but this increase does not necessarily involve a corresponding fixation of oxygen. Indeed, Langlois has shown that, when rabbits are subjected to cacodylic treatment, the quantity of oxygen contained in the blood is lessened by 20 per cent. This observation is in accord with one made, we believe, by Renz, which goes to prove that the air expired by a person undergoing cacodylic treatment contains 17 per cent. of oxygen instead of the normal 15·5 per cent. Clearly, therefore, there is in this case also a diminution in the fixative power of hæmoglobin for oxygen.

As to the increase of the polynuclear lymphoid cells under the influence of arsenic, which was confirmed by Besredka, it would be a mode of defence, not against bacteria, but against the circulatory toxins which these cells may possibly have the power of concentrating in their numerous nuclei.

There is yet one more question. How is cacodylic

acid eliminated? Pagel[1] has made some experiments on this subject on the rabbit, and he concludes that the cacodylates pass through the economy without being either absorbed or modified chemically, since they are met with unaltered in the urine. Imbert and Bodel seem to have obtained the same results in man, and Langlois,[2] on the other hand, has observed that a rabbit under whose skin 0 gramme ·75 of cacodylic acid has been injected loses flesh and shortly dies, while if the same quantity of the drug is injected into a vein no untoward result ensues. This can only be due to the fact of the unalterability of the cacodylic acid and of its rapid elimination.

Therapeutics.—The cacodylates were used in the treatment of disease before we possessed the scanty knowledge which we have to-day acquired concerning their physiological action. It must be admitted that this knowledge is extremely incomplete, and that from it alone it is impossible to make any new use of the drug; in fact, its application is almost that of the old preparations of mineral arsenic, being used as it is in phthisis, anæmia, malarial fever, and skin disease. It may be stated generally that these are the classes of disease amenable to cacodylic medication: wasting maladies, certain neuroses, and certain cutaneous affections.

Of wasting disease, tuberculosis, and especially tuberculosis in its early stages, is the one which seems to be most amenable to cacodylate treatment. Letulle has reported three cases in which remarkable improvement occurred; but this improvement is not observed in those far advanced in the disease. Further, Dalché

[1] Union pharmac., March, 1900.

[2] Société de Biologie, April 28th, 1900.

has pointed out that there may be a want of agreement between the favourable changes and the gravity of the other symptoms of the disease. For example, certain patients, although they gained weight, nevertheless continued to lose strength and the pulmonary symptoms were even accentuated; others, again, did not increase in weight, and the tubercular lesions have rapidly advanced.

In cancer, diabetes, and Basedow's disease Renaut has observed a fairly marked improvement as the result of cacodylate treatment; the same also in anæmia according to Professor Hayem.

Three varieties of neurosis have been favourably influenced by cacodylic treatment; especially is this the case with regard to excitable neurasthenic conditions and epilepsy, in which malady, according to Renaut, the action of bromides is considerably assisted by cacodylate of soda; again, chorea of Sydenham, three cases of which have been successfully treated by Dr. Garaud, of Saint-Etienne. Danlos finds that the internal administration of cacodylates, but not their external application, will frequently cure psoriasis, but relapses are not unusual; lichen planus and lupus erythematosus are improved, but in lupus vulgaris and in mycosis fungoides the results are negative.

In wasting disease, when it is a matter of importance to keep the digestive functions in a sound condition, the method by hypodermic injection is most suitable according to the following formula of A. Gautier:

Pure cacodylate of sodium	...	6 grm. ·40
Distilled water	...	100 ,,
Alcool phéniqué ...	...	10 drops.

Each c.c. of this solution represents 5 centigrammes

of pure cacodylic acid; one c.c. of this solution may be injected once or twice daily. Not more than 0 grm. ·10 of the acid should be given *per diem*.

Professor Renaut prefers, as already mentioned, rectal injection. He gives two formulæ for this purpose:

1. Weak solution—

Pure cacodylate of sodium	...	0 grm. ·25
Distilled water	...	200 ,,

2. Strong solution—

Pure cacodylate of sodium	...	0 grm. ·40
Distilled water	...	200 ,,

Each rectal injection consists of 5 c.c.; two injections should be given *per diem* for six days; three during ten days; then a suspension for five days should follow; afterwards the series is repeated. As for the method of administration by the mouth, it has been superseded by the employment of disodic methylarsinate.

C. *Disodic Methylarsinate.*

General Considerations.—It has been recently demonstrated that the cacodylates, in spite of their great therapeutic value, are very far from being free from drawbacks, drawbacks to which we have been compelled to refer (see p. 49). Amongst these disadvantages should be mentioned the practical difficulty of their administration and the cost of treatment by the hypodermic method; further, patients do not like this mode of administration when it is of long duration. Yet this method of administration is really rendered necessary by the toxic results of treatment when the drug is given by the mouth; further, when given by the mouth after two or three months the effect of the remedy seems

to be exhausted (Pujade)—a condition of tolerance is established which renders further treatment useless.

In endeavouring to find an organic combination of arsenic free from these drawbacks, and which could be administered by the mouth for a long time without danger, Professor A. Gautier, with the aid of Dr. Mouneyrat, discovered the remarkable therapeutical properties of disodic methylarsinate. The acid of this salt—methylarsinic acid—had been previously chemically studied by Baeyer, and the salt is now known under the name of *arrhénal* in order to prevent it being confounded with methylarseniate of soda, which is extremely poisonous.

Chemistry.—Disodic methylarsinate does not belong to the cacodylate family, although it possesses analogous therapeutic properties. Its formula is $CH^3\,AsO^3\,Na^2$, it contains also 5 water of crystallisation. Thus methylarsinic acid is distinguished from cacodylic acid by the fact that one of the methyl groups of the latter is replaced by OH.

From the chemical constitution of this substance alone a first advantage arises, for, when decomposed in the body, arrhénal does not give rise to oxide of cacodyle; in order that the latter may be produced there must be two methyl groups attached to arsenic. But inasmuch as gastro-intestinal complications, congestion of the kidney and the disagreeable garlic odour of the breath and perspiration, are caused by oxide of cacodyle, there is no danger of these drawbacks occurring when arrhénal is made use of. Arrhénal is a white crystalline salt, the crystals being prismatic. It effloresces in dry air, losing its water of crystallisation; it melts at 139° to 140° C., when it is not desiccated; when this is the case, it decomposes without fusion above 300° C., giving off metalloid

arsenic. It possesses a basic reaction (reddening phenophthalein), and a taste similar to that of bi-carbonate of soda. It is soluble in water, less so in alcohol; insoluble in ether, benzine and oils. As it is very stable, its solutions can be sterilised without any inconvenience.[1]

Physiology.—We must now examine the physiological properties of this new drug, since its therapeutical application is based upon a knowledge of these properties. Although up to the present time but few conclusive experiments have been made, yet there are certain definite results which are based on recorded observations.

In the first place, it appears that this remedy exerts a controlling action upon metabolism. As is well known, most of the arsenical preparations are endowed with this property, but this remedy appears to be especially definite in this respect, inasmuch as this property is not concealed by toxic phenomena. In three cases of pulmonary tuberculosis observed by Dr. A. Robin, in which the gaseous exchanges were, as is the rule in this affection, greatly increased, disodic methylarsinate diminished the *chimisme respiratoire*, so that it became almost normal. This reduction of activity as regards the gaseous exchanges explains, as we have elsewhere shown,[2] on the one hand, the return of appetite, and on the other, the increase of body weight on the part of patients undergoing the treament.

As to the changes in the urine, Professor A. Gautier[3]

[1] Dr. Mouneyrat: "Methylarsinate de soude" (*Bull. des Sciences pharmacologiques*, March, 1902).

[2] "Physiologie générale: metabolisme" (Paris, 1897), and above, p. 53.

[3] "Sur le methylarsinate de soude," and "Sur un traitement specifique très puissant des fièvre paludeennis" (Ac. de Médec., February 11th—25th, 1902).

says: "In patients undergoing the treatment, the total urinary residue, the organic matters, the urea and uric acid, the salts, the alkaline chlorides, total phosphoric acid and total nitrogen, also the urinary acidity, rapidly increase"; but this result must be interpreted in such a manner that the relation of exchange is allowed for. This is necessary because, although tubercular patients consume a larger quantity of food on account of the return of appetite, nevertheless the coefficients of the total demineralisation and of that of the tissues are reduced, as also is the coefficient of nitrogen, and this chiefly, as is obvious, in those patients who are overfed.

From what has just been said, the conclusion may be drawn that arrhénal, like the cacodylates, is a drug which economises tissue consumption.

And yet in other maladies—in chlorosis, certain neuroses, chronic malarial affections—it would seem to act differently, inasmuch as the gaseous exchanges are increased and the nitrogen coefficient rises. But this is not so in reality, as will be seen.

The influence of arsenic in improving the condition of the blood has been long known, but it is only quite recently, and especially since the observations of Besredka, that the cause thereof has been ascertained. Arsenic, indeed, exerts an energetic positive chemiotaxis as regards the lymphocytes, and more especially the large mononuclear lymphocytes, which are not merely the phagocytes of malarial hæmatozoa, but are also agents by which toxins are seized and destroyed. By increasing the number and activity of the special phagocytic elements, treatment by arrhénal arrests deglobulisation, and thus indirectly favours the production of hæmatoblasts and of red corpuscles, and consequently increases the quantity of

hæmoglobin, as well as the consumption of oxygen and the oxidations and the gaseous exchanges. This has been confirmed by Dr. Billet and A. Gautier in nine cases of severe malaria as the result of the employment of the methylarsinate.

The mononucleosis which is brought about by the employment of organic combinations of arsenic affords an explanation of the results of treatment by arrhénal upon the nervous system and fever. A. Gautier has pointed out that arsenic should be previously appropriated and transformed by the mononuclear corpuscles before being made use of in the economy, and Professor Renaut, of Lyons, has shown that arsenic, thus modified, by preference attaches itself to the nervous system, in which it partially replaces phosphorus, whence the origin of those arsenical lecithins whose existence is well known. The consequence of this appropriation of arsenic by the neuron is clearly a corresponding modification of its functional reactions and of its properties, which is manifested also by a diminution of its excitability. But are not tubercular wasting and febrile elevation of temperature under the influence of the nervous system? Further, in moderating the excitability of the neuron and its reactional aptitude, are not at the same time both wasting and fever controlled, and indirectly regulated, as well as the oxidative and assimilative process, since, although it may at the present day be difficult to admit the existence of centres and nerves which possess trophic function, yet the nervous co-operation must surely be allowed to possess a preponderating influence on the healthy nutrition of the tissues?

Such is, then, the essential mechanism by which the action of arrhénal is carried out. And a positive proof

of the accuracy of this explanation is furnished by the satisfactory results which attend the administration of arrhénal, on the one hand, in certain neuroses, chorea, hysterical chorea and epilepsy, as also in vomiting of pregnancy of central origin, and on the other, in cutaneous affections in which nutritive troubles and those of the nervous system take part.

In fine, and apart from the very slight toxicity of the drug, which fortunately permits its continued employment, the fundamental property of arrhénal is its moderating action on the excitability of the nervous system, an action which holds in check the influence of the latter on metabolism and blood formation, reflex excitation, fever and wasting. Upon this fundamental property all the therapeutic applications of disodic methylarsinate are founded.

Therapeutical Applications.—These are numerous, but may be arranged in four groups.

1. *Tuberculosis* and the *stage preceding tuberculosis.* Even when tuberculosis is advanced and accompanied with febrile symptoms, arrhénal has given encouraging results, less certain and less satisfactory, it is true, than when the disease is in an earlier stage, for it seems that then cure, if not the rule, is at least frequent. In any case, as is proved by observations collected by Professor A. Robin and A. Gautier, the appetite and strength are increased, sleep becomes calm, night sweating is less marked, and the body weight augments. All these results are also attained when the cacodylates are made use of, but under treatment by arrhénal they become more constant, regular and progressive, instead of being more or less temporary. Not seldom fever vanishes, and, if not too far advanced, the pulmonary lesions have a tendency

to sclerose. At the same time, naturally, dyspnœa, cough and expectoration become less marked, and may even wholly disappear.

But is this improvement a permanent one? It is not easy to answer this question at the present time, for the cases hitherto observed are too few in number and their duration too short. As regards those patients who are seriously ill and in whom the temperature in the evening exceeds 39° C., the lesion being severe and widely diffused, it is clear that any improvement must be but temporary. But when the malady is apyretic and not severe and when the general nutrition is good, we have every reason to believe that it will not be the same. The ease with which disodic methylarsinate can be administered, its almost absolute innocuousness, the fact that by regulating the treatment, danger of accumulation can be avoided, certainly support the hope that definite results, indeed that actual cure, will ensue, and that the latter will be maintained by the adoption of appropriate dietetic and hygienic measures.

For these reasons Drs. Pujade and Gilbert have been able to record favourable results from the use of arrhénal in *emphysema*, *asthma*, *chronic bronchitis* and *influenza*, as also in certain cases of *ganglionic leukæmia*, and in *local and general adenopathy*, which is a frequent forerunner, especially in children, of tuberculosis.

2. In *malaria* and *malarial fevers* the result of this treatment is, according to Dr. Billet, constant, definite and decisive. Whatever may be the type of the fever, even in the pernicious forms, the attacks disappear, and do not return when disodic methylarsinate is given two or three times at most by means of hypodermic injection. The mechanism of this prompt and efficacious

action is now understood, but it is very important to know that arrhénal offers two inestimable advantages over quinine and its salts. First, the digestion is not upset, as is so often the case when large and repeated doses of quinine are given; indeed, the previously disorganised digestion becomes again normal, inasmuch as patients the day after the last attack of fever ask for food and the digestive functions rapidly become stronger. Secondly, the deglobulisation, which is increased by each attack, and by every dose of quinine, no longer occurs, as has been already referred to; on the contrary, a powerful hæmatopoietic action is exerted, so that from the very commencement of the treatment, as pointed out by A. Gautier, malarial anæmia is suppressed. These advantages, together with the phagocytic and special antipyretic action of arrhénal, must lead to the conclusion that this new remedy is the veritable specific in malarial fever.

3. Certain neuroses, and more particularly *epilepsy*, *hysterical chorea* and *hemichorea*, and the *chorea of Sydenham*, which are, according to Robin and Variot, greatly benefited and their course abbreviated. Lastly, in *vomiting of pregnancy of central origin*, which is, according to Pinard, rapidly cured.

4. In many cutaneous diseases, such as psoriasis and eczema, arrhénal has the great advantage over the cacodylate of being capable of long administration without any unpleasant effects arising; perhaps in syphilis which, according to A. Robin, is rapidly cured so far as regards its cutaneous manifestations, and those affecting the mucous membranes; and also in cancer, according to Dr. Petrini. As regards the latter malady, it should be observed that arrhénal seems to exert a sedative action on pain and general excitability, and at the same time

a stimulating effect on the appetite and assimilative functions. It appears also to retard the progress of cancerous wasting.

Mode of Administration and Dose.—The administration of arrhénal is both simple and easy, but it is absolutely essential, as will be easily understood, that the sample used should be chemically pure and free from every arsenical mineral contamination by which it could be rendered poisonous. The ordinary mode of administration is by the mouth in doses of 2 to 3 centigrammes *per diem*, 5 centigrammes at the most being given. In no case except in malarial fever and vomiting, is it necessary to exceed this quantity, because if it be thoughtlessly increased there is a great risk of inducing disagreeable complications, colic, diarrhœa, congestions, particularly of the lungs. Arrhénal is given with meals (it does not exert any inhibitory action on the digestive process) in the form of granules, each containing 1 centigramme, or in a solution[1] of which five accurately measured drops correspond to 1 centigramme of the drug.

In some cases, and especially in those of severe attacks of malarial fever and in vomiting of pregnancy in which it is desirable to give larger doses, and in which it is necessary to avoid irritating the stomach, the remedy should be given by hypodermic injection. For this purpose a sterilised solution, 1 in 40, is prepared, of which each c.c. contains 25 milligrm. of arrhénal. Of this solution 1 to 4 c.c. are administered *pro die* according to circumstances. These injections are not painful, and are always well borne.

Lastly, in carrying out this treatment, it is necessary to proceed in such a way that the daily amount of the

[1] It is a standardised solution, and the drops are calculated by the *compte-gouttes ordinaire*, or medicine dropper.

drug used is given in fractional doses, and also to interrupt the treatment in a methodical manner. The quantity of 5 centigrammes *pro die* should be taken preferably in two doses, and should not be continued for more than from four to seven days at the most (A. Gautier says five days); then the treatment should be suspended during a similar period, being afterwards resumed, and so on. If the treatment is carried on without a break for more than from ten to twelve days the results will not be satisfactory, for symptoms will arise which indicate an accumulation of the drug in the system. But if great care is taken to observe these regular interruptions and renewals in the administration of the remedy, no disagreeable symptoms will arise, neither dyspepsia nor gastritis, colic, diarrhœa, no garlic odour of the breath, sweat, or skin; no renal, hepatic or pulmonary congestion, and consequently no albuminuria; no fatty degeneration of the liver, cutaneous eruptions, nor paralysis, &c. In all cases in which there is hepatic insufficiency, cirrhosis, cardiac weakness, with intestinal hæmorrhage or hœmoptysis, the action of the drug should be most carefully watched, and only the smallest doses should be made use of.

D. *Derivatives of Vanadium.*

Chemistry.—Of late years attention has been called to the therapeutic properties of certain derivatives of vanadium, and especially of vanadic acid and the metavanadates, all of which are thought to be powerful agents in modifying the nutrition and cellular exchanges.

Vanadic acid is derived from vanadic anhydride Va^2O^5 in the presence of water, and it forms with bases a number of different salts, some of which are neutral and

others acid. These last are the bi- tri- tetra- and penta-vanadates. The first, the ortho- meta- para- vanadates, being very unstable, are easily converted one into the other, and are derived from the three allotropic forms of vanadic acid. The metavanadate alone is officinal, and metavanadate of soda is a white solid body, crystalline, tasteless, and fairly soluble in water. Nevertheless, Laran makes use of pure vanadic acid; and vanadates of lithia and of iron, phosphovanadates of soda, &c., have been prepared, but their properties are still imperfectly understood. As regards *vanadine* of Helouïs, it appears to be composed of a salt of tetroxide of vanadium allied with an oxidising substance, perhaps chlorate of soda; but, inasmuch as its composition is not accurately known, we can do no more than mention it in this investigation.

The therapeutic application of the vanadium salts was suggested by their most remarkable property, their power of oxidation in the presence of the alkaline chlorates. Hautefeuille and Bereswill, and, later, Witz and Osmond, have proved that when vanadic acid comes in contact with certain organic combinations and with an oxidising substance, it gives up its oxygen to the organic matter and is transformed into hypo-vanadic acid; then, taking up oxygen from the oxidising substance, it again becomes vanadic acid, and so on. Certain derivatives of vanadium are thus purveyors of oxygen, permanent *oxidising agents*, and this property has been successfully made use of in chemical industries, more especially in dyeing.

This carrying, or shuttle, action of vanadic acid at once suggests the same function which in the blood is performed by the hæmoglobin. Witz and Osmond thus

write on the matter: "When it is remembered that hæmoglobin normally performs in the blood that identical function which vanadium does in the preparation of aniline black by means of the chlorates, it is not difficult to realise that vanadium may possibly play the same *rôle* in causing oxidation of a special nature, of the human tissues, and may thus be possessed of very interesting and important physiological properties."

This idea has been confirmed by Bunge's researches, for he has proved that the transformations of hæmoglobin are analogous to those which ferrous and ferric oxide undergo in Nature, as also, according to Pouchet and Roux, protoxide and dioxide of manganese. The application of the idea was still further extended when Laumonier proved, with regard to hæmocyanine of the crustacea and of certain molluscs, that the sole powers of iron, copper, and manganese consisted in their marked oxidising action.

In the animal organism the to-and-fro movement of the atoms of oxygen around a body, which itself undergoes no change, supplies the economy with the amount of oxygen necessary for the production of its requisite force. But when, for some reason or other, blood formation is imperfect, when the intraorganic combinations are diminished, it may be possible to make use of the oxidising properties of certain substances, to administer purveyors of oxygen, such as iron, which may be able to supply in a certain degree the deficiency of physiological oxygen, which may contribute to increase the activity of the oxidative processes, and thus on the one hand to augment the production of energy and, therefore, the assimilative functions, and on the other hand, to weaken the virulence of certain bacteria and to diminish by

oxidation the toxicity of their secretory products. Such are the theoretical considerations which have suggested the employment of the derivatives of vanadium as therapeutical agents.

However, if the derivatives of vanadium yield oxygen to organic matters with which they come in contact, it is natural to inquire as to the source of the oxygen which they themselves contain. In the production of aniline black it must certainly be admitted that the salts of vanadium remove from the chloric acid the oxygen which they then give up to the aniline. But as regards their therapeutic action, what is the nature of the substance which thus lends itself to the cyclic transformations of vanadium? The uncertainty on this point is so complete that the inventor of *Vanadine* has associated with the salt of vanadium which is made use of, an oxidising substance, itself peculiarly fitted to give up its oxygen little by little. Leaving out of account the possible toxicity of the product thus disoxygenated, it must be remembered that the quantities of vanadium and of the associated oxygenating substance (chlorate of soda, for example) daily ingested are so small that, if the oxidation is directly brought about, that is to say is effected once and for all, there cannot be any appreciable increase in the intraorganic combustion. This aspect of the question has led the Lyons authors to adopt another interpretation of the phenomena. They regard the oxidation effected by vanadium as being indirect, this substance in infinitesimal doses acting exactly in the same manner as the oxidising ferments or *oxydases*, and, indeed, by an action whose mechanism is unknown.

But this mode of solving the problem seems to us, for the present at all events, to be useless, for, as we

shall see further on, the oxidising power of the vanadium salts in the organism is either *nil*, or at all events very limited. Perhaps this may be so because vanadium does not easily find in the bodily structures those matters which are capable of furnishing the oxygen necessary for cyclical transformations.

Physiology.—Let us now proceed to the physiological action of vanadium. In the first place the derivatives of vanadium are very toxic; when injected into a vein 17 milligrm. of metavanadate of soda will suffice, according to Lyonnet, Martz, and Martin, to kill in a few minutes a kilogramme of rabbit. When given by the mouth a much larger dose (20 centigrammes) is necessary, and death does not occur until after the lapse of twelve hours. The dog is capable of greater resistance; according to the authors named 75 milligrm. of metavanadate of soda are required in order to kill a kilogramme. Hallion and Laran find that vanadic acid kills a dog in doses of 8 milligrm. the kilogramme, and metavanadate of soda in doses of 11 to 23 milligrm., according to circumstances. Laran has shown that it is very difficult to determine precisely the lethal quantity by ingestion, inasmuch as, when more than 3 milligrm. per kilogramme are given, the animal vomits the contents of the stomach. All the animals die suffering from dyspnœa, which is usually severe; the rabbit is convulsed, and the dog often presents a marked lowering of temperature. At the autopsy nothing more than congestion of the kidneys and of the liver, sometimes fatty degeneration of the liver, more rarely of the heart, are usually to be found; but, and this is curious, the red corpuscles are never affected at any period of the poisoning process.

As Manquat has observed, the properties of the derivatives of vanadium being what they are, it is very difficult to explain the absence of any change in the red blood corpuscles.

With regard to the action of vanadium on the cardio-vascular system, opinions are not unanimous. While Lyonnet, Martz, and Martin think that neither the heart nor the general circulation is affected, and that they perform their duties quite in a normal manner, Hallion and Laran, on the contrary, maintain, following the views of Kobert, that circulatory troubles are induced which have some resemblance to those resulting from the action of digitalis. Hence it follows that the compounds of vanadium should only be used when every possible precaution is observed.

According to the authors just referred to, the following effects are noticed—first, active arterial contraction and consequent rise in the arterial pressure ; later, relaxation of the vessels and fall of pressure. As regards the heart, its contraction is in the first instance rendered more forcible ; afterwards it becomes slow and irregular, weak, and finally stops beating, but not until respiration has ceased. How is it that such important phenomena should have eluded the observation of the Lyons authorities? Can it be that, as Anceau believes, the extreme dyspnœa which animals under the influence of vanadium manifest concealed the cardio-vascular complications?

In the case of animals to which large doses have been given, but still not sufficiently large to cause immediate death, loss of appetite, wasting, and finally death ensue ; whilst when very small quantities of vanadic acid or of metavanadate are administered a marked increase of

appetite results, as well as a gain of body weight and of the general strength.

These latter phenomena have also been observed in man when therapeutic doses of the salts of vanadium have been given. But the question is, what kind of interpretation can be given to these results? It might be thought *à priori* that the phenomena are due to the over-activity of the intraorganic oxidative processes under the influence of vanadium; but this is not so, for this increased oxidation appears to be extremely problematical, at all events in practical therapeutics.

Indeed, Lyonnet, Martz, and Martin have shown that, *in vitro*, the vanadates when employed in therapeutical doses, have no appreciable influence on the digestive juices, or on the sugar contained in the blood or on yeast. Further, these salts have an extremely weak antiseptic influence, contrary to what might have been anticipated from the consideration of their power of oxidation. In the living animal this action is not more obvious; there is no alteration as regards the hæmoglobin, as has already been observed. The coefficient of nitrogenous oxidation of the urine is scarcely raised: passing from 0·76 to 0·80 and from 0·83 to 0·84, as in the cases reported by Lyonnet, Martz, and Martin, or from 0·79 to 0·82, as in the case quoted by Laumonier; Manquat has not observed any marked rise in this coefficient.

Thus from the few definite observations which have been made, it can only be concluded that up to the present time vanadium does not produce in the animal body that increased combustion of the organic matters on which, theoretically, so many bright hopes have been founded. Hence it must be that the return of appetite, the increase

of body weight, which have been so frequently observed, are the result of other causes; and it is possible that Berthail is not far from the truth when he suggests that the aperient effect of the vanadates is due to the stimulation of function which they exercise on the stomach. It follows that such a stimulation would naturally lead to an increased activity of digestion and to an increased deposit of fat, and hence to a rise in body weight. Certain circumstances would seem to support this manner of regarding the facts: thus the improvement which results only continues so long as the administration of the remedy is persisted in; there is no accumulative effect, the action being purely local and specific. On the other hand, if Lyonnet has not been able to find more than traces of vanadium in the urine of a dog poisoned by the metal, Helouïs has proved that a portion of the ingested vanadium is eliminated with the intestinal excreta and another portion by the urine. Lastly, in certain forms of dyspepsia the gastric function is certainly favourably influenced by vanadium. And it must be admitted that Berthail's theory perfectly explains the amelioration of symptoms observed in chlorosis, anæmia, and in the wasting attending nervous anorexia, &c., without the necessity of invoking the oxidative power of vanadium.

Clearly the increase of appetite and the consequent ingestion of a larger amount of food may produce an increased vigour, but this does not necessarily occur, for the matters absorbed, instead of being made use of by assimilative synthesis, may be simply deposited as reserves; this latter is, physiologically, a wholly different process.

To sum up: the derivatives of vanadium are very

poisonous; they cause cardio-vascular troubles, vomiting and diarrhœa. In therapeutic doses their antiseptic power is very weak and their oxidising properties are extremely slight; thus in serious infections, contrary to theoretical preconceptions, they are practically inert both on bacteria and their toxins. Their chief action would appear to be on the stomach, by stimulating the organ; hence appetite is increased, and increase in weight and gain of strength may result. But this action is temporary, and can only lead to a rehabilitation of health by indirect means—by superalimentation. Finally, these preparations have an aperient action. This property is a valuable one, because, although the increase of appetite does not of necessity imply a corresponding increase in assimilative power, yet it is a very encouraging factor as regards the patient's mental condition—it supports him, makes him hopeful, and hence gives opportunity for the adoption or the continuance of treatment the effects of which, if less apparent, are nevertheless more certain.

Therapeutics.—Although experimental results have only to a very limited extent confirmed theoretical anticipations, yet the derivatives of vanadium have been made use of in a large number of diseases, especially chlorosis, anæmia, neurasthenia, certain varieties of dyspepsia, albuminuria, diabetes, &c. But the results obtained are not certain; not seldom there is intolerance of the remedy, or its action may become rapidly inert. When the administration of the drug ceases so does the observed improvement of health, patients rapidly losing all that they had previously appeared to gain. Nevertheless, in the uric acid diathesis a diminution of uric acid in the urine has been observed, and in diabetes the urinary

sugar may be also diminished, but in both cases the reduction is temporary and its amount very variable. In chlorosis the tissues fairly rapidly recover their normal rosy tint. Lastly, Berthail has obtained some results in impaludism, and Laumonier has observed a definite improvement in obesity which ensued after long treatment, the patient being a man aged thirty.

But it is more particularly in the early stages of tuberculosis that the derivatives of vanadium have given the best results. Cases of this description successfully treated are already relatively numerous, and in them the improvement has been less inconstant, although still limited to the period during which the drug has been taken. In some cases loss of appetite has disappeared, the weight has increased, and the progress of the disease has been altogether favourably influenced. These results are conformable to those observed by Hallion in tuberculous guinea-pigs.

It appears to us to be very difficult to explain the effect of vanadium in tuberculosis otherwise than on the assumption of its exerting a stimulating effect on the stomach, because, if its oxidising power is appealed to, an insurmountable difficulty is immediately encountered. Robin and Binet have, indeed, proved that the ground is, as it were, cleared and made ready for tubercular infection by a severe demineralisation and by exaggerated respiratory exchanges. Hence tuberculosis has a special predilection for those persons who are wasted, those in whom the intraorganic combustions are increased.

In order to oppose an obstacle to the invasion of the bacilli or wage war effectually with them, it is necessary to diminish the need of the tissues for oxygen, to supply

this latter with combustible matters other than the tissues themselves, and to renew the supply of mineral materials (Robin). But if vanadium acts in tuberculosis solely through its power of oxidation, very far from checking tissue waste it will, on the contrary, aggravate it and will tend to make the tissues more liable than before to infection; while, if it acts simply by stimulating the activity of the stomach, the consequent ingestion and absorption of alimentary materials may to a certain extent lead to the fixation of the excess of oxygen and to the deposit of salts, thus checking both the waste and destruction of tissue. Hence the improvement sometimes observed in the case of tubercular patients who are undergoing treatment by vanadium. But it must be added that, according to Weber, this treatment is contraindicated in those patients suffering from arteriosclerosis and atheroma; in these the administration of vanadium merely aggravates the symptoms from which they are already suffering.

Administration and Dose.—Metavanadate of soda is prescribed in daily dose of 1 to 5 milligrm., the drug being given every third day, either in solution or in the form of granules of 1 milligrm., in which the quantity is calculated with exactitude. The dose of 5 milligrm. *pro die* must not be exceeded, and the treatment should be suspended from time to time. Professor Robin orders half an hour before each of the two chief meals a teaspoonful of the following solution:

Metavanadate of soda	0 grm. ·03
Distilled water	150 ,,

About 2 milligrm. *per diem*. The treatment should never be continued more than eight consecutive days,

and, if a good result is obtained, must be terminated in four or five days.

In patients suffering from rheumatism the metavanadate of lithia may be employed, the same doses being given as in the case of the soda salt. It must be confessed, however, that the quantity of lithia thus ingested is so extremely small as to be of no obvious utility.

Laran orders pure vanadic acid in quantities of $\frac{1}{2}$ to $1\frac{1}{2}$ milligrm. in the twenty-four hours; he gives it sometimes with chlorides and phosphates.

For hypodermic injection the metavanadate of soda is made use of in the dose of 1 milligrm. and vanadic acid in that of $\frac{1}{2}$ milligrm.

When these small doses are employed, treatment by vanadium is very seldom attended with unpleasant results: only quite exceptionally is slight, temporary diarrhœa set up, slight local congestion and a tendency to dyspnœa.

E. *Persulphates.*

Chemistry.—It is only during the last three years that the persulphates, and more especially the persulphate of sodium, have been regarded as therapeutic agents. R. Friedländer, in 1899, was the first to make use of the antiseptic properties of persulphate of soda. In the beginning of 1900 Dr. J. Nicolas, of Lyons, studied the toxicity and the aperient power of the salt; then Dr. Garel, physician to the hospitals at Lyons, and Professor A. Robin employed the drug in the treatment of different forms of anorexia, especially of that affecting patients suffering from tuberculosis.

Since the discovery by Berthelot of persulphuric anhydride and of persulphuric acid, the persulphates

have been chiefly made use of in photography in order to remove the hyposulphite of soda. They are white, crystalline salts, easily undergoing changes in the dry state when exposed to air and light; they are obtained by the electrolysis of sulphates to which sulphuric acid has been added (Troost). Owing to their instability, it is necessary that therapeutic solutions be prepared with great care, and they must be kept from exposure to the air in bottles made of coloured glass. But in spite of every precaution it does not appear to be possible to keep these salts otherwise than in acid solution, as has been pointed out by Crinon, and hence it is customary to add to them a small quantity of sulphuric acid. The firm Lumière, of Lyons, has prepared a solution of persulphate of soda which is known commercially as *Persodine*. But Dr. Mathieu has shown that this solution contains a quantity of free sulphuric acid greater than that which must be added theoretically in order to insure its preservation. Hence it is reasonable to think that, in spite of all precautions in preparation, the solution breaks up with great rapidity.

Physiology.—The persulphates are energetic oxidising agents, being comparable in this particular to the salts of vanadium; persulphuric acid is easily resolved into sulphuric acid by giving up oxygen. This oxidising power is connected with the antiseptic action of the acid, which has been demonstrated by Friedländer, and of which he has made use; it is so marked that this substance may be placed amongst the powerful antiseptics of Miquel. In spite of its oxidising and antiseptic properties the toxicity of the persulphates is less than might have been anticipated, and inferior to that of arsenic and vanadium, which are employed therapeutically to a similar end.

Allowing for the other pharmaco-dynamic properties, this is a difference which would appear to give the persulphates the preference, especially as they seem to be eliminated with ease and rapidity and have no marked influence on the heart or circulation.

Nevertheless, their antithermic power is very marked. All the guinea-pigs experimented upon by J. Nicolas have shown a lowering of temperature amounting to three or four degrees when the animals have died, and to one or two when they have survived, as the result of the administration of persodine hypodermically. This antithermic power is even more marked when the drug is given by the mouth.

The same power of lowering the temperature has been observed in man, but it would seem to be less marked and definite, since the fall of temperature but seldom attains and very rarely exceeds one degree. Nevertheless, there is here an indication for the use of the persulphates in the fever of tubercular cases.

We have no certain knowledge concerning the action of the persulphates on normal digestion and on the composition of the gastric juice. This is regrettable, and is in urgent need of attention. But J. Nicolas has attempted to ascertain the influence of persodine upon artificial digestion *in vitro*, diastatic, peptic and pancreatic digestion being all investigated. In every instance the influence has been practically the same, whatever the nature of the ferment. In the proportion of $\frac{1}{6}$, persodine brings digestion to a standstill, $\frac{1}{60}$ slows it materially, less markedly at $\frac{1}{120}$; $\frac{1}{600}$ to $\frac{1}{1200}$ diminishes digestive activity, but less and less markedly. But these latter proportions are those which would be realised in the stomach by therapeutic doses. But it is important

to notice that not in a single instance has persodine exerted a favourable influence on artificial digestion; it has never accelerated or increased the digestive power of the ferments; on the contrary, and even when very small quantities were made use of, it has always seemed to diminish its activity.

What is then the mechanism of the physiological action of the persulphates? It is at present extremely difficult to give a satisfactory answer to this question, because we know nothing as to the influence of these salts on gastric and intestinal digestion either in animals or man, and we do not possess any analysis of the gastric juice under such conditions. It may further be asked if the aperient action of the persulphate is not due, partially at all events, as Mathieu is inclined to believe, to the free sulphuric acid which its solution contains. The *limonade sulphurique* and the *eau de Rabel*, when diluted, have both been of service, in common with many acids, in certain cases of gastric atony and debility. There would not, therefore, be anything extraordinary in the fact of persodine exerting a favourable influence in virtue of the free sulphuric acid contained in it. The fact that persodine in the experiments of Nicolas has never increased the digestive power of the ferments, and on the other hand, the clinical observations that the persulphates increase appetite, hasten the emptying of the stomach, cause the disappearance of the sensation of weight after food, leads to the strong conviction that these drugs act as irritants to the cells of the mucous membrane and of gastric motility. This action is, therefore, comparable to that exerted by orexine and the derivatives of vanadium.[1] Consequently, whether the effect of persodine

[1] See *Nouveaux Remèdes*, June 8th and 24th.

may be due to the free sulphuric acid contained in it, or whether it is merely the consequence of the action of the persulphate of soda, the effect of the remedy on the general nutrition is secondary and cannot be considered constant. When the mucous membrane is sound and the functions of assimilation and absorption are normal an improvement in nutrition results, in consequence of the stimulating and aperient action of the persulphate, which excites a greater absorption of nutritive materials and a consequent gain of weight. But if these functions are seriously impaired, the persulphate remains powerless to influence metabolism, although, by improving the spirits of the patient by a return of the appetite, the disappearance of the oppression after eating and of the sensation of depletion and the relative euphoria which follows, it may sometimes act favourably on these functions under a nervous influence, or that of auto-suggestion, or better still if a supplementary course of treatment be adopted. This mode of regarding the question has already been referred to, and it seems needless to repeat what has previously been remarked concerning those remedies which have the power of influencing nutrition.

Therapeutics.—The antiseptic power of the persulphates was first made use of by Friedländer in 1899; he employed solutions of persulphate of soda as a gargle for sore throat and for the treatment of wounds, boils, abscesses, &c.

The physicians of Lyons, Nicolas and Garel more especially, have administered persodine in convalescence after acute disease and in the early stages of tuberculosis. The results have been on the whole favourable, and Garel has observed that, on the second or third day of

treatment, the patient experienced a sensation of hollowness in the epigastrium and the desire for an increased quantity of food; thus an increased quantity of alimentary material is ingested. Return of appetite is attended with an improvement of digestive power; patients who have long complained of slow and painful digestion have asserted that, when taking the persulphate, their troubles have altogether vanished. Further, Nicolas has proved that certain patients after some weeks' treatment have gained fifteen or eighteen pounds in weight, a conclusive proof of the beneficial, though secondary, action of the persulphate on general nutrition. In the case of tubercular patients whose temperature is raised, the remedy does not always act; but, should there be any improvement of appetite, it is by no means unusual for a more or less marked fall of temperature to occur. The improvement of the general condition is under these circumstances rendered manifest by an increase of body weight.

Professor A. Robin has made similar observations with regard to tuberculosis. But he has also had encouraging results in cases of carcinoma of the stomach, and has found that both gastric irritability and anorexia are considerably relieved. He has occasionally obtained some results even in dyspepsia due to hyperchlorhydria, whether tubercular or not.

Finally, Dr. Hirtz[1] has quite recently published the results and observations on twenty-one patients, six men and fifteen women; there was improvement in sixteen cases (three men, thirteen women). In those cases in which no improvement resulted, or in which the condition was made worse, a painful sensation in the

[1] *Vide* Société de Thérapeutique: Meeting of March 27th, 1901.

epigastric region was complained of (this is a phenomenon which in certain favourable cases gives way to a sensation of hollowness and of hunger) and diarrhoea. Further, diarrhoea is not rare at the commencement of treatment, even in patients whose appetite is increased; but it is in such cases slight and transitory—more serious gastric or digestive troubles than those referred to have seldom been observed.

In short, it may be said that persulphate of soda appears to be a very good aperient: it is indicated chiefly in the early stages of tuberculosis, in which it gives the best results; then in convalescence from acute disease, when the digestive function is slow in regaining its accustomed vigour; in dyspepsia, atony, cancer of the stomach, anæmia and chlorosis; lastly, in certain nervous affections, such as neurasthenia, chorea, and hysteria. Its indications are almost the same as those of orexine and of the metavanadates, for these remedies act chiefly by stimulating the mucous membrane of the stomach, thus increasing the secretion from its glands and favouring evacuation of the organ.

Administration and Dose.—The physicians of Lyons and Dr. Hirtz employ the solution of persulphate of soda which is known as *persodine*. It is a solution of 1 in 75 which contains 0 grm. ·20 of persulphate in 15 grm. (or a tablespoonful) of excipient. This solution is not unpleasant to the taste. Adults take a tablespoonful, children a teaspoonful, of the solution in a glass of water one hour before the chief meal. The Lyons physicians recommend its administration once only, in the morning while fasting; the aperient effect is then kept up during the day. Hirtz first prescribed 0 grm. ·50 of persulphate *per diem*, but the dose has not

produced any decided improvement, and patients have complained of a disagreeable sense of sinking in the epigastrium, the sensation persisting the whole day after the drug has been taken. He has therefore returned to the usual daily dose of 0 grm. ·20, and has obtained satisfactory results.

Professor A. Robin prescribes the persulphate of soda in the following manner:—

Persulphate of soda	...	...	2 grammes.
Distilled water	...	...	300 ,,

A tablespoonful half an hour before each of the two chief meals. The treatment should be stopped if no improvement ensue at the end of six days. But the treatment must also be suspended, even when an improvement results, at the end of three weeks to a month, in order to prevent the patient acquiring complete toleration; it must be recommenced if the appetite again fails, which is generally the case, inasmuch as the aperient action is not usually very persistent, and ceases altogether a short time after the administration of the persulphate has been suspended.

F. *Orexine.*

Chemistry.—Orexine, or dihydro-phenyl-quinazoline, C^{14} H^{12} N^2, recommended first by Penzoldt, is a derivative of quinoline (quinazoline), which is obtained by the reduction of orthonitro-benzilformanilide. It is employed therapeutically in three forms: *basic orexine*, a white fine powder very slightly soluble in water but soluble in acidulated liquid, odourless and tasteless; *orexine hydrochloride*, a crystalline powder, colourless or slightly yellow, containing two molecules of water of

crystallisation, slightly more soluble and liquefied at 80° C.; lastly, *tannate of orexine*, which is odourless, of golden yellow colour, with a slight chalky flavour, insoluble in water, but soluble in dilute acids, and especially in hydrochloric acid. This latter property renders tannate of orexine completely soluble in the gastric juice.

Physiology.—All the different forms of orexine seem to be very slightly poisonous. Animals submitted to the action of the remedy do not appear to suffer any inconvenience unless the doses made use of are much larger than those employed therapeutically. Yet Hofmann has observed that, after he had taken 1 grm. of orexine hydrochloride in a single dose, he suffered from uneasiness and a feeling of weakness, from flushing of the face as well as from giddiness; it gives rise also to a sensation of warmth, and, indeed, of burning, in the mucous membrane of the mouth and throat, this effect being due to the irritant action of the drug. Sometimes vomiting is caused by ingestion of orexine, but this seldom happens.

When basic orexine or the tannate of the same is made use of these drawbacks seldom occur. As regards the circulation and the kidneys, it does not appear that the drug exerts any marked influence; a slight increase of the force of cardiac contraction and perhaps a tendency to renal congestion may be occasionally observed, so that orexine should never be made use of in renal inappetence unless with the greatest caution. As to the route by which the drug is eliminated, the subject so far has scarcely received attention.

The action of orexine on the stomach is better known, and Penzoldt and his pupils have made careful

experiments on the matter. Hofmann has found that orexine excites secretion of hydrochloric acid in the stomach in cases in which this secretion is either absent or diminished, the acid appearing one hour sooner than usual; hence the digestion of matters contained in the stomach is rendered more rapid and easy. Munter has proved that the ingestion of 25 to 50 centigrm. of hydrochloride of orexine markedly diminished the duration of the digestive process—a half hour and more—when white bread and roast meat have been consumed. As, on the other hand, Henne and Kronfeld have proved that orexine actively stimulates the emptying of the stomach by exciting the contractility of the muscular coat, it follows that the length of time during which aliments remain in the organ is shortened, and hence that weight after food, fermentation and flatulence, are generally ameliorated or altogether cured.

Kotljars goes still further, maintaining that orexine greatly aids the assimilation of albuminoids and the absorption of fat. This opinion must, however, be corroborated by careful experiment, for, although orexine may excite the gastric mucous membrane to increased activity, it is not the same as regards its effect upon the pancreatic secretion and on the absorbing power and synthesis of the cells and intestinal mucous membrane, which, as is well known, transforms the digestive peptones into new forms of albumin. The excito-secretory action of the drug arises from a different chemical action to that which tends to produce an increase in the power of synthesis of the intestinal mucous membrane, as is observed, for example, in enterogenous peptonuria. Hence it is probable that orexine takes no part in those processes, in the absence of organic derangement, beyond

strengthening and invigorating the different digestive secretions, which, in their turn, furnish to the healthy mucous membranes more abundant and superior absorbable products.

The return of appetite, which is sometimes lasting, the result of the administration of orexine, is due to the specific action of the remedy; this nervous phenomenon is indeed partially dependent upon the emptying of the stomach. Almost as soon as the organ is empty the appetite returns, except when there is very great digestive weakness, or a profound intoxication of the system. Clearly, assimilation and elimination are closely allied, and are capable of being simultaneously powerfully influenced by the condition of the digestion. Hence a return of appetite, although it may be artificial and unaccompanied with an increase of assimilative activity and of body weight, is, nevertheless, a very encouraging symptom, and one which cheers the patient, tending also to a very beneficial effect upon the nervous system.

It must be added that Swirjetin thinks that orexine prevents constipation by softening the fæces. This action appears to be due, partially at all events, to an increased activity of secretion on the part of the glands, and partially to a more vigorous contraction of the intestinal muscular wall. It is not constant, however, but when it does occur should tend to increase appetite. By this quality, and by its aperient effects, orexine acts in a twofold sense in the treatment of auto-toxic maladies, and more especially of chlorosis.

Therapeutics.—From what has been said it will be easy to understand the therapeutics of orexine. It should be mentioned that orexine has the great advantage

of being almost innocuous, and of being well borne in the great majority of cases. Further, it can be administered with the greatest ease. In the large majority of stomach affections and in the ordinary forms of anorexia the treatment by orexine should often be continued during some time. Now it cannot be said that the specifics for this form of indigestion hitherto employed are absolutely free from injurious effects when their use is long continued, these preparations being those of nux vomica, alcoholic aromatics, and bitters. Orexine, on the other hand, in itself innocuous and devoid of cumulative effects, and not usually becoming inert through continued use, is, as regards duration of treatment, free from these drawbacks; and although it is necessary, as insisted on by Professor Robin, to suspend its administration as soon as the desired effect is produced, yet when the occasion arises the treatment by orexine may be continued for a long period without fear of ill results ensuing. It is, of course, imperative that under no circumstances should excessive doses be given and that the treatment be commenced cautiously, feeling the way, as it were, so as to ascertain the susceptibility of the patient, because, although it is unusual for patients to prove refractory to the drug, yet this does occasionally occur, and this alone renders caution necessary in departing from the ordinary modes of administration.

Orexine is indicated in all cases in which loss of appetite is a marked symptom. If a severe scrutiny of the results of treatment by orexine be initiated, it will be found that the best effects have ensued in: (1) Gastric catarrh and atony of the stomach, dyspepsia, and in those cases in which functional derangements are present

which do not arise from serious lesion of the organ. From the very outset of the treatment the action of orexine in causing increased secretion and in strengthening the muscular force of the stomach causes complaints of heaviness after meals, of eructation, of unpleasant odour of the breath to be no longer heard, and at the same time the appetite becomes greatly improved. (2) In anæmia, and especially in chlorosis, because, as already pointed out, orexine acts, not merely as a stomachic and aperient, but also as a laxative. (3) In the early stages of tuberculosis, in which malady the effects of treatment are often quite striking, inasmuch as the increased appetite brings about an increase of body weight which is also fairly permanent. Occasionally orexine, just as is the case with the derivatives of vanadium or the cacodylates, gives but unsatisfactory results, or may even be completely useless in the severe later stages of tuberculosis, and in many markedly cachectic conditions. (4) Finally, in the anorexia of convalescence, especially in children, and in the want of appetite often met with in neurotic conditions. Occasionally also here the result may appear to be uncertain, and when the desired end is obtained, although it may be fairly permanent, it is only when the treatment is continued sufficiently long.

It must be added that the administration of orexine is contraindicated in hyperchlorhydria, in ulcer of the stomach, in hæmorrhagic conditions, and in cases of recent abdominal operation (Bolognesi). In advanced heart disease and in kidney affections orexine should only be given with the greatest caution.

Administration and Doses.—The administration of orexine is easy, the drug being odourless and almost tasteless. As when some symptoms of intolerance arise

—sensations of warmth in the mucous membrane of the mouth, pharynx and stomach, giddiness, vomiting—it appears to be especially in connection with the employment of the hydrochloride of orexine, Penzoldt has given up the use of this product, and now prefers basic orexine, and his example has been widely followed. But in children, on account of their greater susceptibility, tannate of orexine must be ordered, which has never caused any phenomena of intolerance.

Whichever form of the remedy be made use of, it is necessary that when treatment is commenced, as already mentioned, the dose should be very small, 10 centigrm. for instance, two hours before each of the two principal meals. Should this quantity be well borne (and in cardiac and renal affections it is often advisable that this dose be not exceeded, especially when appetite is returning), it may then be gradually increased to the usual dose of from 30 to 50 centigrm. twice a day. Penzoldt and Krünkler advise that from 200 to 250 grm. of water be swallowed immediately after the drug has been taken, but that nothing else be ingested until mealtimes. In children at the outset the quantity must be proportioned to the age of the patient, in order to ascertain the tolerance, but afterwards up to 20 and 30 centigrm. may be given.

As a rule orexine is given in cachets, but the powder may be taken mixed with a little water in a perfectly satisfactory manner. Occasionally it may be advisable to prescribe orexine in capsules or pills, each containing 0 grm. ·10 of the drug. In children the pastilles or chocolate tablets, containing 0 grm. ·25 of tannate of orexine in each, are preferable; they are always readily taken.

5. The Yeasts.[1]

The employment of the yeast of beer as a therapeutic agent is by no means of modern date, but it was in the first instance purely empirical. Those who work in breweries had long ago observed that the administration of yeast appeared to have a favourable effect in cases of furunculosis, and hence it was quite usual for the employés to resort to this mode of treatment when occasion arose. It seems also that in the old German pharmacopœia yeast was recommended as a valuable specific in a great number of maladies, and, after certain results of this treatment were reported in 1852 by Mosse, the use of yeast, thanks to our increased knowledge of the action of micro-organisms, has of late years been greatly extended.

These various applications are based upon two properties of yeast: its undoubted glycolytic power and its phagocytic action, the latter being allied to the more questionable bactericide and anti-toxic influence. As a matter of fact, some authors have observed that bacteria are present in the interior of certain yeast cells; but it must be a question as to whether these organisms had been taken prisoner by the yeast itself in its phagocytic capacity, or whether it is that the bacteria have themselves invaded and killed the yeast. This last explanation would seem to be by far the most feasible, inasmuch as the living yeast cell is surrounded with a cellulose

[1] We have discussed the yeasts among the new agents which modify nutrition because it appears to us that the results of this mode of treatment, numerous as they are, should nevertheless be looked upon as essentially related to metabolic processes, and therefore as connected with those phenomena which characterise the exchanges of the tissue elements.

envelope, only allowing the passage of matters which are in solution and those which are diffusible, and thus opposing a barrier to the entrance of any solid body or the emission of protoplasmic prolongations. In dead yeast, on the other hand, the cellulose wall is more or less altered, and in this case it is possible for mobile bacteria to gain admission to the cell. The phagocytic power of yeast has never yet been proved to ocular demonstration, and seems to us to be purely hypothetical; the same may also probably be said of its bactericidal influence, for Lomry has shown that yeast does not check the development of cultures of microbes, and Nobécourt has even proved that the latter may actually increase the action of the bacillus of Loeffler. As regards the antitoxic power of yeast, this is less uncertain, for Nobécourt has demonstrated that yeast considerably diminishes the activity of the toxins of Loeffler's bacillus, inasmuch as doses three or four times the ordinary strength of toxin are required in order to kill guinea-pigs when yeast is made use of together with the lethal matters.

We must now consider the clinical results obtained by the use of yeast. But it is necessary to remark in the first instance that the choice of the yeast is a very important matter, as each separate product gives, so to speak, a different result. As a rule, at the period when the remedy was first made use of in therapeutics, yeast fresh from the brewery was employed, as this is always preferable to that obtained from the baker or pastry-cook. This yeast when fresh is not unpleasant to the taste, but it rapidly becomes acid and putrid; hence it is necessary to renew it every day in summer, and every other day in winter; and when it is impossible to

procure a fresh supply it must be kept on ice. At the present day dried yeast is preferred, and certain varieties of this product are known commercially as *levurine*, but they should always be tested before being made use of. Speaking generally, yeast which has been desiccated at a low temperature and in a vacuum or by inert substances is to be preferred. Under these circumstances the dried product preserves to a sensible degree its colour and normal odour.

But there are real drawbacks to the use of yeast, and some of them are serious, rendering its employment difficult. It tends to give rise to a sensation of weight in the stomach, to acidity, to eructation, these symptoms often rapidly ensuing on the ingestion of the remedy. Further, diarrhœa is likely to be set up, the evacuated matters being extremely fœtid and accompanied with abundant liberation of gas. But these drawbacks are greatly modified when good dried yeast is made use of, so that the latter may be employed in dyspepsia, dilatation of the stomach, and enteritis. Again, fresh yeast possesses a strong and by no means agreeable taste; it follows that many patients cannot tolerate this form of treatment, even when their digestive apparatus is in good order, and this particularly when large doses are given, though at the present time the tendency is to greatly restrict the quantity compared to the amount formerly given.

The chief therapeutic applications of yeast may be grouped as follows: Cassaet has made use of yeast in order to diminish or entirely remove glycosuria; the theory on which his treatment is based is that of the glycolytic action possessed by this micro-organism. Thus he gives with meals fresh yeast diluted with

water, the quantity made use of being 50 grm. *per diem*. This fairly large dose of fresh yeast gives rise to most of the disagreeable consequences referred to above, but the severity of the symptoms varies with different individuals. Inasmuch as the glycolytic ferment acts on the glucose contained in the alimentary canal, this treatment is sometimes followed by a marked diminution of the quantity of sugar contained in the urine. Further, in some cases there would appear to be an improvement in the general condition, for the body weight seems to increase; but this improvement is often only temporary. Cana and Beylot have obtained results very similar to those reported by Cassaet, and they have more than once noticed an almost complete disappearance of glycosuria. They have also applied this mode of treatment to cases of albuminuria. When the albuminuria is of dyspeptic origin improvement sometimes ensues. The results obtained by Aragon and Collet also support this conclusion. But when the albuminuria is due to renal disease, no change in the condition is usually observed.

It may be asked, in connection with this glycolytic action, whether, in the but slightly oxygenated media contained in the intestine, alcohol may not be produced; this certainly seems theoretically possible, but the fact has never been confirmed experimentally so far as we are aware.

It is especially in pyogenic infections that yeast appears to give really encouraging results. Brocq has notably succeeded in obtaining positive results in furunculosis. In carbuncle, even when fully developed, under this treatment the pain is relieved or entirely ceases after the second day, the œdema and lymphangitis

on the third or fourth, then suppuration becomes less and finally ceases, and on the seventh or eighth day the carbuncle cicatrises, leaving merely an induration more or less marked which does not entirely disappear until some weeks have passed. And if at this period the administration of yeast be abruptly suspended the carbuncle tends to relapse; hence it is advisable to continue the treatment until the induration has disappeared. In cases of simple furunculosis the cure is much more rapid. When the formation of boils is both widely spread and rebellious to ordinary measures of treatment the administration of yeast is almost immediately successful, and the boils in process of formation dry up; but, even during this treatment, some small furuncles may develop and may seem to be in process of pointing, but they remain in an immature condition and dry up. These favourable results have been noted by Lassar in cases of diabetes accompanied with an obstinate tendency to the outbreak of boils. It is clear that in this malady the result is due not merely to the anti-pyogenic power of yeast, but also to its glycolytic quality.

In phlegmonous acne, in folliculitis due to the staphylococcus, and in certain other suppurative dermatoses the action of yeast is less obvious and less sure, and the effect of the remedy is very far from constant. On the other hand, in stye in the eye (hordeolum), which has a tendency to recur, Terson has observed a constant improvement when yeast is given in cachets each containing 1 grm.·50 before meals, from 3 to 6 cachets being taken *per diem*. Even if the lesion does not resolve, the pain is nevertheless quickly ameliorated.

In furunculosis and in analogous infections yeast is

given in quantities of 3 to 6 teaspoonfuls *per diem*, according to its being used fresh or dry, and according also to the tolerance of the patient. Debouzy and the physicians of the north give larger doses, even up to 3 or 4 tablespoonfuls *per diem*. The remedy is diluted with alkaline water or beer, and the mixture is taken with meals.

Landau, Gelli, and Murer have used yeast in the treatment of infections of the genito-urinary tracts, and they regard it as a valuable agent in bacterio-therapy.

Murer treats leucorrhœa by vaginal injections containing diluted yeast and by plugging or applications to the mucous membrane. An injection must first be used at a temperature of 30° C., and afterwards a tampon of absorbent cotton must be employed for drying purposes. By this treatment the discharge is rapidly arrested, the mucous membrane becomes healthy and of a natural colour, the cervix resumes its healthy appearance, and ulcerations amend or entirely disappear. Nevertheless, after some days the action of the yeast seems to become less marked, and if an improvement be maintained, still the cure is rarely complete. Further, contrary to the opinion of Landau and Gelli, it is not unusual, in cases of vaginal gonorrhœa, to once more find gonococci. Finally, not seldom under this treatment a very troublesome vaginal pruritus is set up, and this must be overcome by means of injections of carbonate of soda.

Marie gave yeast to a patient suffering from pneumonia and also from furunculosis which was both severe and painful; although the outlook was most disquieting, the patient recovered so rapidly that the author referred to employed the same treatment in seven other cases of

pneumonia, all of whom made a satisfactory recovery, and although four of them had been in a very dangerous condition. Further, Marie and Faisans have observed cases of typhoid fever in which a very favourable influence as regards the course and duration of the malady was exerted by the administration of yeast. The same good effects have been observed by Doyen in osteomyelitis, cases of which he reports as cured by this treatment. Heer, Rieck, and Mettenheimer have called attention to the value of yeast in cholera, diphtheria, scarlatina, measles, purpura, and even cancer, although it must be admitted that the results are yet too few to permit a definite statement as to the value of the treatment being made.

Thiercelin and Chévrey have employed yeast in the treatment of children's gastro-enteritis. The child, being acted on by an aperient, is put on a fluid diet, and the intestine is then washed out by means of a tube attached to a collapsible rubber ball; then a teaspoonful of dried or a dessert-spoonful of fresh yeast suspended in 50 grm. of tepid boiled water is injected. This enema should be retained for some time, and is repeated two or three times a day. So long as the diarrhœa persists is the treatment continued, the intestinal lavage and the fluid diet being maintained. Thiercelin and Chévrey have obtained excellent results by this mode of treatment; these results have been confirmed by those of Blancher in acute and chronic gastro-enteritis and muco-membranous enteritis. In the adult, Blancher orders, by enema, 2 or 3 tablespoonfuls of yeast diluted with 150 grm. of boiled water, and, when given by the mouth, 3 teaspoonfuls of dried yeast diluted with a little water, the whole to be given in 24 hours. As regards children, he partly adopts

Thiercelin's method, but he supplements it by the addition of 1 or 2 teaspoonfuls of dried yeast by the mouth. He believes the treatment by the mouth to be more successful than that by enemata of yeast alone.

The laxative action of yeast has been satisfactorily proved; for this reason yeast has been made use of, especially by Roos, of Fribourg, to overcome rebellious constipation. This author gives 50 centigrm. of fresh yeast two or three times a day, the doses being reduced by half when dried and sterilised yeast is made use of. The latter form of the remedy is preferable in order that colic and flatulence may be avoided. Roos thinks that yeast does not act through a fermentative process or bacterial agency, but simply by stimulating intestinal peristalsis. In all cases the favourable change occurs on the second day of treatment in chronic constipation, and continues for some time after treatment is suspended.

In conclusion, the treatment of De Backer must be referred to. De Backer, considering that yeast possesses a definite power of phagocytosis, introduces it into the organism by hypodermic injection. Selected yeast is mixed with sterilised water, and is injected under the skin in quantities of 1 c.c.; De Backer states that from this treatment, called *Médécine des Ferments*, he has obtained, especially in tuberculosis, marked improvement. But both in tuberculosis, and also in cancer, which has been treated in the same way, the results are far from being entirely convincing, and the danger of embolism is no imaginary one. But Heer has already pointed out the occasional value of yeast taken by the mouth, in cases of tuberculosis.

II.

BLOOD ALTERANTS.

1. The Disturbances of Hæmatopoiesis and their Treatment.

Speaking generally, anæmia may be regarded as the diminution of the blood. When this diminution concerns particularly the number of red corpuscles (which in some cases may fall from five millions to one million per cubic millimètre), the anæmia is called corpuscular, *hypoglobulie*, *aglobulie*. This affection is due to severe loss of blood, repeated bleedings, certain infectious maladies, impaludism or malaria, lead or mercurial poisoning, iodism, and lastly tuberculosis and cancer. Chlorosis is an anæmia in which the corpuscles are, further, altered in their form and chemical composition. The pathogeny of chlorosis is more obscure; it is recognised, however, that heredity often plays a part, especially in those cases in which tuberculosis has affected immediate ancestors, by involving the hæmatopoietic organs. Apart from heredity, the most frequently observed and the most active cause of the disease is an intoxication. Chlorosis in young men is due to cerebral overstrain, in young females to physical over-exertion, to badly-ventilated rooms, to confined surroundings and workshops; these conditions lead to digestive ailments attended with constipation, and to the

action of the toxins thus generated is due the morphological and chemical alteration of the red corpuscles just alluded to. Thus there is some force in the remark made by Andrew Clark that, if he were of necessity reduced to the employment of a single remedy in the treatment of chlorosis, that drug should be an aperient. Menstrual troubles act in the same way, inasmuch as this blood is also toxic. Thus when there is delay in the appearance of menstruation, or when the function is established but scanty and then ceases, chlorosis is observed. Lastly, severe moral shocks, by the nervous reaction to which they give rise, sometimes set up chlorosis.

Both in anæmia and in chlorosis, and whether the cause may be the diminution of the number of red corpuscles, or the alteration in the quality of the hæmoglobin, there is invariably a diminution in the activity of the respiratory function of the blood, or, in other words, in its power of taking up a given quantity of oxygen. This defective hæmatosis leads to incomplete oxidation, and consequently to an increased toxicity of the products of waste, which causes all the secondary troubles, sometimes of increasing gravity (such as pernicious anæmia), of chlorosis and anæmia. The most urgent indication for treatment is therefore not merely the supply of oxygen, chiefly in the form of fresh air, inasmuch as this oxygen would not be appropriated in consequence of the altered constitution of the blood, but consists rather in augmenting the number and in renewing the properties of the red corpuscles so that their hæmoglobin contents may be increased, as this is the colouring and fixative matter by which oxygen is taken up.

But the fixative agent in hæmoglobin is the iron contained therein, and Bunge has very clearly explained the

mechanism of this fixation by proving that hæmoglobin and oxyhæmoglobin play the part successively of ferrous and ferric oxide, the first taking up oxygen in order to form ferric oxide, and this latter, yielding its oxygen to the organic matters with which it comes in contact, again reverting to ferrous oxide, and so on. It is therefore evident that it is the iron which must be renewed, since in every case of chlorosis and of anæmia it is more or less defective in quantity. Further, iron is lost in normal conditions both by the urine, bile and fæces. But iron contained in food may be present in two forms: the *mineral* form, in which it is easily detected by the usual tests; in this form (which includes the greater number of the artificial albuminates, caseinates and peptonates of iron) the metal is not assimilated, and is found in the intestinal contents. The same thing occurs when iron is injected into the blood. In the other, or *organic* form, the presence of iron is not revealed by ordinary tests, but it is assimilable, and is therefore the most advantageous form for administration. Organic iron is found in a nuclein of the yolk of egg—called by Bunge *hæmatogen*—in milk, cereals, vegetables, &c.

This conclusion seems at first sight to be at variance with the facts that chlorotic and anæmic patients derive benefit from the administration of iron in a mineral form. But the contradiction is only apparent, as will be seen immediately.

In persistent abnormal digestion, so frequently observed in chlorotic patients, when secondary fermentations so often occur, and are indeed not seldom the cause of the malady, hydrogen is formed as the result of butyric fermentation. The hydrogen is in the nascent condition which produces sulphuretted hydrogen, and then alkaline

sulphides. These latter, when in the presence of hæmatogen, form sulphides of iron, and thus the metal, having taken on its mineral form, is incapable of being assimilated. But if at the same time other ferruginous salts —medicinal preparations, for example—are introduced, sulphides are formed at the expense of these mineral materials, and not at the expense of the hæmatogen, and the latter, preserving its iron in organic form, remains assimilable, and is in fact assimilated. The ferruginous preparations which are highly valued in the treatment of anæmia and chlorosis, although not themselves assimilable, are capable of rendering great services, since by their presence they protect the organic iron and allow its fixation. And some clinicians think that ferruginous preparations only act efficiently when given in large doses, so that all the alkaline sulphides contained in the intestines may be saturated.

Yet Bunge's interpretation has been criticised by several writers, especially by Woltering and by Gaule, who have brought about a marked accumulation of iron in the liver and spleen by causing animals to ingest the inorganic salts of the metal, more especially the sulphate. Capolla and Linthicum, of Baltimore, consequently maintain that, contrary to the opinion of Bunge, inorganic iron can be assimilated and thus can be utilised in the metabolic processes, provided only that this inorganic iron does not produce secondary complications. It appears to us that Linthicum very reasonably explains the action of the so-called organic preparations of iron made use of at the present day. He does not regard these preparations as true combinations of iron and of organic matters; they are, he considers, very intricate mixtures, the most unsatisfactory of which are

probably represented by the so-called peptonates and albuminates of iron, which yield, according to Herschell, when exposed to the action of the gastric hydrochloric acid, a precipitate which is wholly insoluble. If, then, such preparations should seem to be well borne by patients, it is merely because they are practically inert.

Since in certain cases and under certain conditions inorganic iron can be assimilated, the tendency is to replace the method of Bunge—a method which is, indeed, quite a rational one, which has given surprising results, and which consists in administering natural hæmatogen in association with dilute iron combinations (ferruginous mineral waters, for example)—by other systems which are more rapid in action and which consist in making use either of mineral iron, which may be given either hypodermically or by the mouth, but in the latter case certain indispensable precautions must be taken (method of Linthicum); or blood itself deprived of its fibrine may be injected hypodermically or employed as enema; or, lastly, the derivatives of blood are made use of, and more especially hæmoglobin.

These are the different methods which we shall now briefly describe; we must remark that if these latter procedures (hæmotherapy, hæmenteroclysis) greatly resemble the opotherapeutic system, yet they are modes of genuine iron treatment, since the essential aim of their use is to supply the organism with an adequate quantity of iron—and this alone—in order that the process of blood formation may be properly carried out.

2. Subcutaneous Injection.

This method has been praised, inasmuch as by it the most unpleasant of the drawbacks of ferruginous

treatment are avoided, more especially gastric troubles and constipation. Preferably the citrate and the lactate of iron are made use of, as also the citro-ammoniacal pyrophosphate of iron and even the sulphate of the metal in alcohol. The daily doses vary from 0 grm. ·05 to 0 grm. ·10 or 0 grm. ·15 given in fractional quantities. The advantage of this method consists in the greater rapidity with which effects are induced than when iron is swallowed, but much care is necessary. The results, too, are not always constant, and in not a few cases complete failure ensues, which it is not easy to explain.

Special indications for the hypodermic method of treatment are the occurrence of a serious form of anæmia, especially pernicious anæmia and that due to severe hæmorrhage; in the latter case it is well to have recourse in addition to injections of artificial serum, care being taken to avoid a too rapid rise of vascular tension.

3. Method of Linthicum.

The method of Professor Linthicum, of Baltimore, is based upon the following considerations:

The preparation of iron should be insoluble at the time of administration, so that the teeth be not injured; this is especially important in the case of children. It should not cause nausea or digestive trouble or anorexia; it must not be forgotten that although the stomach in anæmia is very irritable, yet it is absolutely necessary that its functional powers should be in the best possible condition. The iron preparation should be easily assimilable, for the vitality of the tissues is greatly lowered, and it should not possess astringent, but purgative qualities, inasmuch as anæmia is often due to constipation, to

auto-intoxication, and to a destruction of red corpuscles by the accumulated toxins.

Linthicum[1] thinks that a preparation which answers to all these requirements is found in a German product known as *aromatine*. This consists of phosphate of iron, insoluble in water and in the gastric hydrochloric acid, suspended in glycerine and flavoured with an aromatic. The remedy is given in the following manner: A tablespoonful (about 15 grm.) is swallowed and immediately afterwards a glass of water is drunk, a tablet being dissolved in it containing phosphate and bicarbonate of soda, together with tartaric acid. In the stomach the phosphate of soda reacts on the phosphate of iron, and a soluble neutral bibasic phosphate of soda and iron is formed; this is, therefore, inert as regards the gastric and pancreatic juices; it is also slightly aperient and chologogue. This purgative action is definite, indeed it is sometimes necessary to be careful in the administration of aromatine to tubercular patients suffering from diarrhœa or with a tendency to diarrhœa. Linthicum has treated a certain number of anæmic patients during variable periods by this method, the average duration of treatment being seven weeks. He has observed a marked improvement, an augmentation of from 25 to 30 per cent. in the number of red corpuscles being recorded, and from 8 to 9 per cent. in the hæmoglobin contents of the blood. This method certainly deserves to be tried on a larger scale, for it is possible that it may give satisfactory results.

4. Use of Defibrinated Blood.

The object of both modes of applying this method is to replace intravenous transfusion of blood, an operation

[1] *New York Medical Journal*, March 10th, 1900.

always difficult to perform and often dangerous, by (A) subcutaneous injection (hæmotherapy) and (B) by enemata of defibrinated blood (hæmenteroclysis).

A. *Hæmotherapy.*

Ziemssen makes use of human blood, Dominici of dog's blood, and Hasse of lamb's blood. Under any circumstances it is absolutely necessary that the individual or animal made use of for supplying the blood be altogether free from disease (tuberculosis, syphilis, hydrophobia, glanders, &c.). The blood is usually drawn from the median cephalic vein, and is collected in a sterilised vessel, warmed in a water bath to 37° to 38° C. (not higher), and whipped with a sterilised instrument in order to oxidise and defibrinate it. Twenty-five to thirty c.c. are injected at one time, and the injection may be repeated two or three times a day; Ziemssen has made use of up to 350 grm. of blood in fourteen injections. Every possible antiseptic precaution having been taken, the blood should be deeply injected, preferably in the thigh or back; energetic massage should be performed at the same time in order that the blood may pass onwards under the skin. As the injection is painful the administration of chloroform is advisable, if this is possible. When the operation is completed, ice should be applied to the site of injection. After the operation pain may persist for some time—ecchymosis, occasionally lymphangitis, phlegmon, abscess or even temporary hyperthermia may be observed. When human blood is injected, after one or two days red corpuscles may be found in the thoracic duct and

in the lymph, and when animal blood is employed hæmoglobinuria may ensue.

The most important indication for hæmotherapy is severe hæmorrhage and syncope, which threatens life; consciousness returns, and an increase of red corpuscles, and also of their hæmoglobin contents, ensues, together with a moderately rapid recoloration of the skin and mucous membranes. The same process may be made use of in severe progressive anæmia.

B. *Hæmenteroclysis.*

This proceeding was suggested by Antiq in order to avoid the drawbacks incident to hæmotherapy (pain and abscess), and the difficulty of finding a healthy person who is willing to supply the blood. The blood of a perfectly healthy ox is used; it must be defibrinated. The quantity is from 125 grm., which is warmed in a water bath to 37° to 39° C. Some minutes before the injection is given an evacuating enema should be employed. Should abdominal pain be complained of, a few drops of laudanum may be added to the enema of blood; the latter should be retained as long as possible, and if wholly retained is still better. As a rule, an enema of blood is given every evening for eight days, then the treatment is suspended for a few days, to be afterwards resumed as before. In this way the treatment may be continued during long periods without any rectal irritation arising. The chief indication for this procedure is especially hypoglobulie, and aglobulie, and hypohemoglobie. A rapid improvement in the general health results, with increase both of red corpuscles and of hæmoglobin.

5. Employment of the Blood Derivatives.

This method corresponds in part to that which has been recommended by the supporters of Bunge's theory. The hæmatogenous elements of the food are replaced by artificial products which are still richer in iron, the latter being present in an organic, easily assimilable form. The majority of these preparations are derived from blood, and are the product of several different methods of treating hæmoglobin. The essential point of inquiry is whether this form of hæmoglobin is really assimilable; it is not unreasonable to suppose that this question must be answered in the negative. If we consider the results which are obtained from the ingestion of fresh blood in the slaughter-house, as has been suggested and practised, the results are of an unsatisfactory nature. On the other hand, it is maintained, in spite of the opinion of Professor Bergeron, that fresh raw meat pulp and fresh meat juice obtained by simple pressure may be of great efficacy in the treatment of the different forms of anæmia. There are, therefore, certain methods by which the iron of hæmoglobin can be rendered directly assimilable. Unfortunately, it does not appear that the commercial preparations derived from blood are always satisfactory in this sense; the majority of them are not organic combinations of iron, and, as Rosenstein observes, "they contain the constituents of blood only in their name." We shall, therefore, here mention those preparations only which possess real therapeutic virtue.

The most interesting of these products are essentially those of hæmoglobin, a substance rich in iron but which it is difficult to prepare and to preserve. There are,

however, many commercial preparations of this substance, among which may be mentioned the *extract of hæmoglobin* of Pfeuffer, a syrupy red mass containing 30 per cent. of hæmoglobin and traces of oxy- and methæmoglobin; the *hæmatogen* of Fortuna and the *albuminate* of *hæmoglobin* of Theuer, containing hæmoglobin and methæmoglobin; lastly the *hæmoglobin* of Deschiens, which is a syrup, but is also made up as a wine and as a lozenge, the latter being intended especially for children.

The preparations which contain large quantities of methæmoglobin are apt to cause gastric disturbance and constipation; at all events, the failures appear to outnumber the successes, and the majority of these preparations must be included in Herschell's group, containing those products which cause no harm because they are practically inert.

Genuine preparations of hæmoglobin are more active; they rarely cause constipation and anorexia, and, as a rule, they are well tolerated unless previous gastric disturbance of a certain severity is present. Encouraging results have been obtained from their employment in chlorosis, primary or secondary anæmia, and in some cachectic conditions. They seem to exert a favourable influence in some cases of commencing tuberculosis, and appear to be somewhat useful in convalescence from infectious diseases, especially in children; they are beneficial, lastly, in impaludism and anæmia of hot climates.

Amongst derived products, one should be mentioned, as it seems to be of some value: *ferro-somatose*. This is a brown powder, odourless and tasteless, soluble in water. There are two varieties on the market: one contains 2 per cent. iron, the other 3·46 per cent. The

first is adapted for children, the second for adults. The product is made by treating albumose with chloride of iron; in the stomach there is a decomposition of somatose and iron, the latter combining with the hydrochloric acid of the gastric juice. Hence the preparation is both ferruginous and nutritious. According to F. Werner, St. Klein and other clinicians, it possesses the great advantage of not blackening the teeth, of not diminishing the appetite, and of causing neither vomiting, pain, nor diarrhœa; but the latter quality is often a disadvantage in persons suffering from anæmia, and in chlorosis. The daily dose is from 5 to 10 grm. for children, 15 to 20 grm. for adults; it may be given in water, milk, soup or chocolate; these quantities represent three teaspoons, more or less full, according to age; they are divided, the proper proportion of the whole being taken morning, midday and evening. This remedy has been used with success in chlorosis and anæmia, and especially in pseudo-leukœmia (St. Klein) of children. In all cases a great and rapid improvement is observed, together with an increase in the number of the red corpuscles, in the proportion of hæmoglobin, and in the body weight. In the anæmia of pseudo-leukœmia the blood recovered its normal appearance, the volume of the spleen diminished, and in slight cases a cure was effected after one or two months. In more severe instances complications ensued by which recovery was delayed.

By the light of such cases it must be granted that ferro-somatose is a good blood restorative, yet it must be administered, especially in children, with circumspection, as in pseudo-leukœmic anæmia there is sometimes intolerance of the remedy. The observations made in

France tend to show that, especially in adults, ferro-somatose is well borne and assimilated, and that only small portions are carried off by the bowel. Hence a certain amount of iron is assimilated, but under what form or by what mechanism is unknown.

Fersan is a new product derived from the red corpuscles of ox blood; it is an acid albuminate containing iron and phosphorus in organic combination. The red corpuscles, isolated by centrifugation, are treated with dilute hydrochloric acid; the resulting compound contains all the iron and phosphorus of the corpuscles, and is a brown powder, slightly saline, of acid reaction, soluble in water and not coagulating by heat; it contains 3 grm. ·7 of iron per 1,000. Fersan is only broken up in the intestines; it causes neither anorexia, gastric disturbance nor constipation, and is well borne by patients. Further, containing as it does 80 per cent. of soluble albuminoid matters, it is more nutritious than somatose, and is almost completely assimilated. It is employed in doses of 1 to 3 teaspoonfuls *per diem*, dissolved in a small quantity of cold fluid; every kind of vehicle is available, pure water, cocoa, tea, &c. Pastilles of Fersan are also supplied containing 0 grm. ·25 for children and 0 grm. ·50 for adults—three or four may be taken *per diem;* it is also made up in the form of biscuits, chiefly for children.

In consequence of its richness in iron and phosphorus and of its great digestibility, Fersan is a valuable nutrient in chlorosis, in anæmia and in wasting diseases. Kornauth, Von Czadek, Silberstein, Kornfeld have shown that, in quantities of three teaspoonfuls *per diem*, continued for two or three weeks, Fersan considerably increases the number of red corpuscles and the proportion

of hæmoglobin. Pollak has found it very useful in early tuberculosis, and also in convalescence. Lastly, Laumonier[1] has employed it successfully in the treatment of infantile atrophy consecutive to weaning.

Glycerophosphate of iron ought to be mentioned in this connection, although reference has already been made to it when speaking of organic phosphorus (*vide* p. 41). It gives excellent results in all forms of hypohémogloblie (anhematochromie) and even in hypoglobulie, since the increase in the number of red corpuscles is closely parallel with that of the hæmoglobin. Glycerophosphate of iron is made use of in the daily dose of 0 grm. ·20 to 0 grm. ·25, and is generally associated with the alkaline and earthy glycerophosphates, as already mentioned.

6. Substitutes for Iron.

As we have explained elsewhere,[2] it is not iron, as iron, that is really essential in the process of blood formation, but only the presence of an oxidising substance which is capable of taking up oxygen in certain conditions and of liberating it forthwith, &c. It is well known that iron is not the only metal which is capable of playing the part of purveyor of oxygen. In addition to vanadium and manganese, copper also possesses this property, and this metal, as demonstrated by Frederic, replaces iron in the blood-lymph of many cephalopods and crustacea. Hence, it is justifiable to infer that substances other than iron can exert a hæmopoietic influence, and some

[1] *Bullet. de thérapeutique*, December 8th, 1900.

[2] "Physiologie générale," Chap. iv.; "Le milieu respiratoire," pp. 132 *et seq.*

experiments and interesting clinical observations confirm this manner of viewing the matter. Cervello[1] has, indeed, demonstrated that the methodical administration of copper, zinc and manganese, even of mercury, in animals, and sometimes in man, increases the hæmoglobin contents of the blood. Pitini and Messina find that cobalt and nickel possess the same property.

Mercadante has proved, on the other hand, that the increase in number of the red corpuscles is not proportional to that of the hæmoglobin, the latter seeming merely to become more concentrated in the corpuscle. However, in that form of anæmia in which the number of red corpuscles diminishes, these metals not only regenerate the hæmoglobin, but they also increase the number of corpuscles.

It is very difficult to explain these results. There is no evidence that the molecule of the heavy metals referred to above can enter into the complexus of hæmoglobin; otherwise, together with iron hæmoglobin, it would be necessary to admit the existence of a copper, mercurial, manganese, &c., hæmoglobin. The existence of hæmocyanine proves that such combinations are not impossible, but up to the present time no evidence has been brought forward of such combination existing in man.

Substitutes for iron have been especially used in malarial anæmia and in certain toxic forms of chlorosis; observations are as yet too few for it to be possible to speak definitely as to their effect, but there is here a new therapeutic departure. The substances most often employed are: sulphate of manganese (dose *pro die* from 0 grm. ·05 to 0 grm. ·20 up to 0 grm. ·50); sulphate of

[1] Soc. de Thérapeutique, meeting of January 9th, 1901.

copper (5 to 10 milligrm. to commence with, and afterwards up to 2 to 3 centigrammes *pro die*); sulphate of zinc, used by Savoca in quantities of 1 to 6 centigrammes daily. These substitutes may be very usefully combined with the hemols in the form of cuprohemol, zincohemol, &c.

III.

MINERAL MEDICATION.

1.—Mineralisation and Demineralisation.

The researches undertaken long ago in the field of biological chemistry prove that each tissue, each cellular element, has its own peculiar mineral constituent, its mineral soil, the result of a chemical adaptation, which is explained by the theory of Danilewski.[1] Thus phosphorus and magnesia are the preponderating elements as regards the nervous system, iron and potash as concerns the blood corpuscles; phosphorus and lime affect the osseous tissues, soda and potash those of the muscles, chlorine and sodium the body juices, &c. But it is necessary here to observe—speaking only of the anatomical element, of the living cell—that in this process of mineralisation there is something more than a simple adaptation to a given environment, inasmuch as the mineral elements of this environment actually enter into the formation of the complex of elementary cells (with the exception possibly of chloride of sodium) which derives a portion of its properties from the fact of the presence of certain of these mineral elements; this is clearly seen as regards the iron contained in the blood corpuscles of vertebrates, the copper of the hæmolymph of the

[1] Cf. Laumonier: "Physiologie générale," pp. 9—13.

cephalopods, the crustacea, &c. Hence, Gaube, to whom interesting researches on organic mineralisation are owing, is perfectly correct when he says: "When a tissue is functionally active, its mineral constituents do not appear in the *excreta*, especially in the urine; they are only found when the tissue is quiescent or is breaking up. When, therefore, there is an excess in weight of some mineral element in the urine, it is a clear indication that a tissue or humour of the body is undergoing a disintegrating process. When any one of the mineral constituents of the urine is continuously absent, it follows that a tissue or humour is destroyed." [1]

The importance of this idea is obvious if, rejecting the conception of Claude Bernard that functional activity denotes structural waste of an organ, it is held that functional activity of the same is inseparably connected with the synthesis of assimilation of the organ in question, and that, consequently, such activity fixes the mineral elements of the living complex (which thus are less abundant in the urine), while repose, which is a more or less slow destruction of plastic matters, or their destruction under some morbid influence, should and does cause an increase of the excretion of the special mineral elements contained in the affected organ.

Regarded in this way, the process of mineralisation—which is naturally ambient and humoral before becoming plastic—is necessary to the synthesis of assimilation, and therefore intimately connected with the healthy functional activity of organs, of cells and tissues. Hence it results that any cause which impairs the process of normal mineralisation of the body structures must exert

[1] Gaube (du Gers): "Mineralisation urinaire" (*Bull. de thérapeutique*, 1898, I., p. 241).

a consecutive influence on the functional activity and on vital resistance of the anatomical elements, since, being deprived of part of the matters which are indispensable for their assimilative synthesis, these elements can no longer discharge their function with the same vigour.

Modifications of the organic mineralisation have also further consequences. If they diminish the vital resistance by restraining the amplitude and vigour of function, they equally diminish the normal anti-toxic and bactericidal power of the humours, as also their osmotic properties, which play an important part in the elimination of toxins, both of bacteria and of the tissues. There is still, however, considerable uncertainty as concerns the mechanism of these anti-toxic processes; some would regard them as being purely chemical phenomena, while the majority of authorities look with more favour upon the existence of an antagonism of physiological origin, but which cannot be easily comprehended unless it may be reduced to an oxidative process, to a decomposition, or to a fixation of toxins, or, lastly, to an increase of their solubility under the influence of the combinations which these toxins contract. However this may be, the facts are certain. It must be added, further, that, from the point of view of defence of the organism, the alterations of mineralisation affect equally the process of phagocytosis, especially as concerns the macrophages, and the activity of diapedesis apart from the presence of pathogenic agents and of their toxins; this is not difficult to understand, inasmuch as leucocytes live in the internal medium, and are everywhere exposed to the influence of the alterations to which it is subjected as regards mineral composition. Every change in this composition diminishes the activity of the phagocytes, as it does that of all the other anatomical

elements. Thus it checks phagocytosis and diapedesis, as happens in rickets, abrupt and rapid growth, gastric affections with abnormal fermentation; and if then a bacterial infection occurs it is all the more serious, because it supervenes on a diminished resistance.

If, then, the importance of the integrity of the normal mineralisation of the body is so great, every possible cause of demineralisation or of alterations of the mineral soil of the tissues should be opposed by all available means. These causes are of three kinds:

A. *Abnormal Digestive Fermentations and Auto-toxications.*

By the incomplete evolution of ternary products, for example, instead of H^2O and CO^2 organic acids are formed—lactic, acetic, formic, butyric, propionic, &c.—which are eliminated in the form of salts, and the bases which they take up are principally soda and potash, also lime and magnesia, all derived from the tissues and juices of the organism. Hence these acids, by the mere fact of their production, involve the loss of alkalies appertaining to the organism, and their elimination leads to the evolution of what the older authors, Bence Jones in particular, called *acid dyscrasia.* But in every kind of dyspepsia there is a more or less marked production of these organic acids; and it is well known that such gastric disturbances occur in rickety children, and in osteomalacia of adults, and that they explain the phenomena of deficient or altered mineralisation or of demineralisation of the bones which these patients present, since, as shown by the observations of A. Robin, the intervention of ternary matters which have undergone a complete evolution in the body is necessary for the fixation of the mineral ingredient in

the ossein. In the larger number of cases of auto-intoxication the same series of phenomena is observed; in overfeeding, for instance, the alkalinity of the blood is more or less markedly diminished, and the same result ensues in hepatic or renal insufficiency, in pulmonary affections, and those of the skin, nervous system, in which the process of mineralisation is modified, &c.

B. *Growth.*

During growth the mineral matters, particularly phosphorus and lime, leave the plasma and certain cellular elements which are in a state of regression in order to attach themselves to the skeleton, which thus exhausts the organism to its own benefit, for at this period the alimentary matters ingested are often insufficient to supply the necessary mineral materials, and this the more because digestive troubles are not seldom present at this period of life. Hence the want of vital resistance, so often noticed during growth, the severity and frequency of infectious diseases, against which the organism, already partially demineralised, can no longer successfully contend. Lastly,

C. *The Infections.*

Infection of the organism is rendered more easy when there has been antecedent demineralisation of the same. Fodor, Lauder Brunton, Maragliano have shown that the bactericidal condition yields when the soda salts are present in too small quantity in the plasma; Calabrese, Blumenthal, Charrin, Roger have proved that bacterial infection can only flourish in those humours whose reactions have been altered, and A. Robin has rightly insisted upon the great importance of this modification in preparing the soil for the evolution of tuberculosis.

But this demineralisation, which prepares and facilitates the bacterial invasion, is increased and aggravated during the evolution of the infection itself, as is observed in tuberculosis, pneumonia, diphtheria, enteric fever, and the exanthemata. This increased activity is the result of the destruction of the tissues by the pathogenic bacteria, or, rather, by their toxins; of an excessive consumption of the nutritive reserves, which is not compensated by a sufficient reparative alimentation; and, lastly, by cellular alterations under the influence of defensive reaction. It may not, indeed, be manifest at the onset, and may only appear at the critical period; the disintegrated mineral matters are sometimes partially retained by the toxins which they help to fix, and which are only eliminated *en masse* when free urinary evacuation occurs, the latter being a favourable indication, and one pointing to the approach of convalescence. But these mineral matters, though still present in the internal medium, in the form of more or less complex combinations, have none the less ceased to play a normal physiological part.

Further, these mineral discharges are not invariably critical; they sometimes indicate, especially when occurring at a crisis, the imminence of a complication. Indeed, the weakening of the organism, the successive exhaustion of all its means of natural defence against pre-existing pathogenic parasites, may permit an invasion of new injurious bacteria which undergo their own developmental processes, and in this way a new infection may be grafted on to the previous one. And it may be that harmless bacteria become pathogenic under the influence of humoral and tissue changes which have been initiated by the previous infection. Such is the origin of associated infections (by the association of microbes) and of the

complications which ensue in the course of maladies, whether infectious or not. If, therefore, it is necessary, when demineralisation occurs apart from any morbid condition, to take measures to annul its effects and to maintain intact the vital resistance in order to avoid the danger of infection, it is certainly desirable, when infection has actually taken place, to compensate consecutive loss of mineral matters in order to prevent complications.

Long before these ideas were in vogue, bouillon and infusions and decoctions of vegetable matters, which act either as tonics and mineralising agents, or simply as diuretics, were made use of in a large number of maladies, and in an empirical manner. After a period of neglect and contempt for such means, they are to-day again in requisition, having been perfected, their value being increased by a more exact knowledge of their mode of action. Thus arise the several varieties of saline medication, some acting as restorers of the mineral waste, others influencing not only the remineralisation, but also increasing diuresis, raising the vascular tension, and acting as purifiers of the blood (artificial serum); and, finally, others increasing the nutritive activity (saline cure), or ensuring the appropriation of medicines (metatrophic method).

2. Mineralising Agents.

It is necessary that the plastic mineral constituents of the body which have been lost be renewed, in order that the functional activity of the tissues may be properly exercised and the defensive powers of the organism maintained. But the organic or inorganic nature of these mineral elements, or the source from which they are derived, are very far from being matters of indifference,

inasmuch as we are now acquainted with the fact, established by the researches of Bunge, that mineral matters in organic combination are far more easily assimilated than others, and that these alone, or almost so, are able to unite themselves to the living cell elements.

The most common and oldest of these organic mineral preparations is *bouillon*, "pot au feu," whose percentage composition is thus given by König and A. Girard:—

Albumin	0·3— 0·4
Gelatine	0·3— 0·7
Fat	0·2— 0·4
Mineral matters	1·3— 1·8
Mineral extractive	0·5— 0·8
Water	95·8—97·3

Therefore bouillon is not a food. On the other hand, the researches of Schiff and Herzen and those of Lapicque have proved that it is a valuable stimulant to the digestive secretions, to the nervous system, and to the heart. It is also, as experience proves, a peptogen, a very active and powerful eupeptic, through the presence of a variety of extractive matters. Further, owing to the mineral matters contained in it, chiefly the chlorides and potassic phosphates, it exerts a reparative influence in all forms of demineralisation, and more especially those which are consecutive to infection. It has been employed from time immemorial in all varieties of convalescence, and gives excellent results. Unfortunately the preparation of good bouillon is a long and costly process, and its preservation is difficult, especially in summer, as on account of its composition it forms a most admirable medium for the culture of micro-organisms.

At the present time, owing to its containing a relatively large amount of extractives, but only a relatively small quantity of assimilable mineral matters, bouillon is but little used in therapeutical mineralisation except as an agreeable aromatic vehicle for the artificial saline or vegetable solutions, which will be treated of later. It is often but ill-tolerated in hypersthenia and in gastric affections at the period of growth, and it is contraindicated in cases of increased vascular tension on account of its vaso-constrictive action, as also in gouty persons, owing to the uric acid which is formed by the extractives.

These remarks do not apply to *vegetable bouillon* or a decoction of cereals, the employment of which is of very old standing, and the methodical use of which has been recommended by Springer and Charrin. These decoctions are intended to replace bouillon, which does not appear to be sufficiently rich in assimilable mineral constituents, and which also contains matters which may be injurious to the patient; for these reasons Charrin advises the employment of vegetable bouillons in order to compensate that form of loss of mineral matter which occurs consecutively to infection and in growing children, and he prefers them, in an emergency, to milk itself. These decoctions are prepared in the following manner :—In a litre of water is placed a table-spoonful of cereals : barley, wheat, rye, oats, maize, and bran, the materials having been first carefully crushed and lightly browned in the oven ; the liquid is then reduced by boiling to half a litre and is strained. The mucilaginous fluid thus obtained is made palatable by the addition of aromatics, and is given in small coffee-cupful doses four to eight times *per diem*. In this way a solution very rich in phosphorus and in organic iron is consumed,

as are also physiological mineral matters, which are made more assimilable than if derived from combinations and remedies of inorganic origin; the solution is easily borne by all patients, and does not in the least fatigue the functions of the stomach or intestine. Charrin has made use of these decoctions of cereals in cases of typhoid fever and pneumonia, as well as in the eruptive fevers of childhood. In the last, when decoction of cereals has been administered, he never observed those secondary infections which so often complicate the primary disease and not seldom lead to its fatal termination.

Laumonier and, more recently, Springer, have resumed the study of these vegetable bouillons during growth, and more especially in cases of rickets. In the case of children aged from fifteen months to three years the vegetable bouillon was given diluted with milk and bouillon in the quantity of a liqueur-glassful four times *per diem*. Inasmuch as the bouillon is perfectly well borne by the most delicate stomach, and as a milk diet, absolute or mixed (milk, eggs, bouillon, rice, potatoe soup), according to the age, was strictly enforced, the gastro-intestinal troubles have rapidly disappeared, as also the rickety abnormalities, especially certain osseous lesions (bowed legs, beading of the ribs), which, nevertheless, are generally of long continuance. In children of from seven to thirteen years the vegetable bouillons are preferably given in the form of soup with yolk of egg and a little butter twice a day in quantities of one or two small coffee-cupfuls. With regard to the latter class of patient, the indication for medication by the administration of mineral matters is not derived solely from the presence of fever and inflammatory phenomena, which are often present, but especially from urinary analysis and rapid growth,

although no morbid symptom be present. Should urinary analysis show demineralisation of the tissues in favour of the osseous system, it is necessary to have recourse to artificial remineralisation, which is the more active and efficacious in proportion to the promptitude of its adoption, and in this way the infections which are so frequent and usually so serious during the period of growth may be almost certainly avoided. The glycerophosphates are also mineralising agents of the first importance, especially the acid glycerophosphates; these are at the same time more soluble, more stable, and more certain than the neutral salts. They have already been described at length (p. 38), and it is therefore unnecessary to do more than refer to the article which is devoted to the consideration of these important medicaments.

Finally, in order to complete the account of the mineralising agents properly so called, reference must be made to the physiological salt of Poehl, which in Germany and elsewhere has enjoyed a certain popularity. This is an artificial mineral combination which contains in their respective proportions the mineral elements of blood serum. Its average composition is as follows:—

Sodium	21·51
Chlorine	33·09
Soda	11·02
Potash	4·61
Lime	1·38
Magnesia	0·21
Sulphuric acid	2·39
Phosphoric acid	1·74
Carbonic acid	17·79

The preparation is made up in pastilles of 1 grm., which

are dissolved in a glass of warm water. The 1·5 per cent. solution corresponds approximately to the composition of the blood serum. It is employed either internally by the digestive tract or by enema, or is used hypodermically, or lastly by intravenous injection. The results obtained have been less satisfactory than was hoped, considering the theoretical composition of the preparation, and the mineral matters contained in the solution have almost invariably proved refractory as regards their adequate assimilation; but this is always the case as concerns the larger number of mineral matters which are not presented in the organic form.

3. Artificial Serums.

The artificial serums, which are also known as physiological serums, are usually weak watery saline solutions, of which chloride of sodium is generally the predominant, or perhaps the only, constituent. They have been employed for more than half a century, since in 1832 T. Latta, of Leith, and Magendie recommended intravenous injection of saline solution. Colson and Duchaussoy (1855), Hérard and Oulmont (1866), Lorrain (1868), Conheim, in his remarkable experiment on the frog (1869), all studied this question; but it was especially Dujardin-Beaumetz (1873) who first called the attention of therapeutists to the mode of treatment of cholera by saline injections which in their composition resemble blood serum. Hayem in 1884 made use of this method during the epidemic of cholera which occurred in France, and the same mode of treatment was successfully employed in the Hamburg outbreak of 1892. On the other hand, Jolyet and Lafont (1878) have made use of 6 per 1,000

saline solution injections (histological solution), which Kronecker and Sander in Germany found very useful in the following year in cases of severe hæmorrhage, and which Sanarelli first, Roux of Lausanne (1884), Dastre and Loye (1888—89), Sahli of Berne (1890) employed in severe intoxications and infections. Bosc and Barré have also praised bleeding-transfusion, that is to say, bleeding followed by a larger or smaller injection of serum, a method which may be regarded as supplementary to the transfusion of blood, but which appears destined to furnish better results.[1]

Physiology.— The injection of saline fluid and of artificial serums appears to be absolutely unattended with any drawback when the kidneys, which get rid of the excess of fluid, are in good condition, for Dastre and Loye have injected a weight of serum equal to two-thirds of that of the body. But although the quantity may be a matter of indifference, it cannot be said that it is the same as regards the rate of injection. When the rate of injection exceeds, for example, 3 c.c. a minute, and by kilogramme of living weight in the rabbit, serious symptoms and even death ensue. Hence Bolognesi [2] has rightly said that there is no toxic *dose*, but a very definite *toxic rate of injection*.

Speaking generally, saline injections raise the blood pressure, act as cardio-vascular tonics, and set up diuresis by restoring to the blood the volume of fluid which has been lost either by hæmorrhage or by serous effusion (choleraic diarrhœa). Such treatment prevents and

[1] Landouzy: "Les Sérothérapies," Chap. XXIV. and XXV. leçons.

[2] "Les solutions salines dans les injections" (*Bull. de thérapeutique*, 2nd series, 1898, and 1st series, 1899).

minimises post-operative collapse and the accidents which accompany shock from injury. The blood regeneration is favoured in consequence of the increased activity of the migration of hæmatoblasts ; these come to the blood rich in fibrine, and therefore serve as a point of departure for clot formation (Bolognesi). Finally, saline injections have a favourable influence on infections and intoxications—on the one hand, by aiding oxidation and dilution of the toxins which are not adherent to the tissues, as Manquat observes, acting in this way by a sort of *lavage* of the blood, less complete perhaps than was at first thought, but which nevertheless, when combined with the mineralising influence of the complex saline solutions, yet initiates a condition favourable to the restoration of the defensive power of the body humours ; and, on the other hand, by renewing and invigorating the process of phagocytosis which has been weakened by the hypertoxicity of the blood, as shown by Mourette and Salé. It must be added that in small quantities (10 to 100 c.c.) saline injections have a tonic influence on the nervous system when they are continued for some time ; this influence would seem to promote mobility on the part of the protoplasmic arborisations, and at the same time to diminish the production or facilitate the elimination of the *ponogenes* of the neurons.

As a result of the injection of artificial serum, the following phenomena are observed in man :—(1) A period of calm and of euphoria, lasting a short time (from a few minutes to an hour) ; this is particularly apt to occur in infectious cases. (2) A period of critical reaction, which presents two phases : the first is characterised by rigor or sensation of cold ; the pulse is frequent, irregular, the respiration quickened and laborious ; sometimes cramps

and spasms are complained of. The temperature rises, and in the rectum may attain 40° or 40·5° C.; the face is red and swollen, the conjunctiva injected, the pulse accelerated (150 to 180), the breathing panting, the skin very hot, sometimes smoking. The second phase is characterised by a diminution in the intensity of all these phenomena, whose total duration is about three hours; then abundant diuresis ensues, sweating, and often diarrhœa. (3) Lastly, a post-critical phase is observed, during which all the symptoms referred to pass away, the temperature becomes normal, definitely if recovery ensues, for only a day or two if a relapse should occur. Nevertheless, as Debove has pointed out, there is a rapid toleration; the critical symptoms are less and less marked, and the patient reacts less and less energetically when injections are frequently repeated.

The several organs are more or less affected by the intravenous injection of artificial serum: the vascular tension is raised, the heart's beats become more regular, the pulse becomes regular and stronger, diuresis is abundant, and the chlorides naturally, but also the urea, are excreted in increased quantities; the toxicity of the urine rises somewhat, the secretion of saliva, the perspiration (specially abundant at the period of defervescence) and glandular secretions are augmented, and diarrhœa and vomiting may occur; thirst disappears, the digestive functions are more satisfactorily performed, the respiratory rhythm becomes regular, dyspnœa ceases, and expectoration becomes more loose; in some cases uterine contractions ensue, through the intermediation of the spinal cord; and, lastly, a moderate excitement of the nervous system, amounting occasionally to temporary delirium, may arise. The same phenomena are observed after the

use of subcutaneous injections, but the reactions are delayed and less severe.

Therapeutics.—The indications for the employment of artificial serum may be inferred from their physiological action : they may be grouped as follows :—

1. Traumatic and surgical hæmorrhage, intestinal hæmorrhage (that of enteric fever, for example) ; hematemesis, intractable epistaxis, hæmoptysis, certain forms of metrorrhagia, hæmophilia, some varieties of purpura.

2. Severe losses of serous fluid : Asiatic cholera, choleraic diarrhœa, infantile cholera, and even the intestinal infections of infancy (Barbier). Hayem's serum may be advantageously used in enteritis on account of the constipating action of sulphate of soda, and Huchard's modified serum in the wasting of small children.

3. Erysipelas, measles, scarlatina, variola, influenza and influenzal broncho-pneumonia, infective endocarditis, severe attacks of malarial fever, typhoid and typhus fever, severe jaundice, tetanus and anæmia (Tuffier), alcoholic anuria (Dumont), certain cases of poisoning by fungi. In urinary infections, according to Desnos, the serum of Chéron, administered in small quantities, gives the best results, while in the acute fever which may occur in prostatic cases physiological serum is preferable. But, speaking generally, and in the absence of contraindications, the serums always give the most marked results, and sometimes are really successful in the different forms of infection.

In tuberculosis the employment of saline injections has been recommended for the purpose of confirming, by the temperature and the congestive reactions which occur,

an early diagnosis; but, as Colleville has shown, a marked rise of temperature in such cases does not necessarily imply that latent tuberculosis is present, and, although frequently met with in tubercular subjects, the serum reaction must not be looked upon as really pathognomonic. But, according to Hutinel, injections in the case of tubercular subjects are capable of reviving the activity of an old tubercular lesion.[1]

4. In neurasthenic conditions, and in the psychoses and neuroses which are accompanied with depression, very good results are obtained by the continued and fractional methodical use either of physiological serum or especially of that of Chéron in small doses (5 to 10 c.c. *pro die* or every other day).

5. Lastly, Lancereaux has spoken favourably of injections of saline fluid containing 2 per cent. of gelatine in aneurysm, and Tommasoli has employed the serum in the treatment of extensive burns on more than one occasion with much success.

Contraindications to the use of artificial serum are: heart disease, chronic myocarditis, arterio-sclerosis, vascular over-tension, œdema of cardiac origin, congestive pulmonary lesions, dropsy, renal inadequacy and sclerosis. It must be added, however, that, contrary to what might have been expected, Lefèvre, of Lyons, has never had any success in the treatment of diabetic coma by saline injection.

Artificial serums are employed either by intra-venous injection or by the method of hypodermic injection. In both cases large quantities of fluid may be administered, although obviously the subcutaneous mode of procedure

[1] Cf. Landouzy, *op. cit.*

is better adapted to the injection of smaller quantities. At the present time in everyday practice the latter method is usually employed, on account of the ease with which the operation is performed and its harmlessness. As a rule, the injections are given at a temperature of 40° C., because the necessary manipulations cause a slight fall of temperature; but they may be given without inconvenience at a higher (Richer) or even at a lower temperature (Lépine). Used as enemata, serums have been praised by Villanova, Eitz, Pauchet and Boulangier in hæmorrhages after abortion, the hæmorrhage of typhoid fever, infantile diarrhœa and the gastro-intestinal disturbances of children. Given after an evacuating enema, in quantities of 200 to 500 grm., or 3 to 5 litres *per diem*, they promote diuresis and diaphoresis.

The following are the formulæ of the principal artificial serums:

1. Physiological or surgical serum—

Chloride of sodium	...	...	7 grm. ·50
Distilled and sterilised water	...	1,000	,,

In infants 5 to 30 grm. per injection, 10 to 90 grm. *per diem*. In adults 10 to 500 grms. per injection, 10 to 3,000 grm. *per diem*.

2. Hayem's serum—

Sulphate of soda	...	...	10 grm.
Chloride of sodium	...	...	5 ,,
Distilled and sterilised water	...	1,000	,,

The doses are the same as those for physiological serum.

3. Chéron's serum—

Pure sulphate of soda... ...	8	grm.
Phosphate of soda	4	,,
Chloride of sodium	2	,,
Crystallised carbolic acid ...	1	,,
Distilled and sterilised water...	100	,,

From 5 to 10 c.c. *per diem* or every other day.

4. Huchard's serum—

Phosphate of soda	10	grm.	
Chloride of sodium	5	,,	
Sulphate of soda	2	,,	·50
Distilled and sterilised water...	100	,,	

5. Huchard's serum modified (Lyon)—

Chloride of sodium	ā ā 1	grm.
Phosphate of soda		
Sulphate of soda		
Distilled and sterilised water...	100	,,

From 2 to 3 c.c. every day.

Apart from the slightly mineralising action of the serum of Chéron and Huchard, physiological serum in the proportion of 7·5 per 1,000 appears to give the best results, especially in infections and intoxications. This is probably because the fluid is absolutely *isotonic* with the red corpuscles, for, when less concentrated, the latter become spherical and lose their hæmoglobin, and at a higher concentration the corpuscles break up and shrink, whereas when the proportion is at 7·5 to 1,000 they undergo no change of form and retain their hæmoglobin.

Quite recently Quinton[1] has proposed to replace the injections of saline fluid by those of sea water. As a matter

[1] Soc. de Biologie, May, 1898.

of fact sea water is isotonic, and it is the only artificial medium in which the leucocytes can live for more than twenty-four hours; further, its salts are those found in the organism and nearly in the same proportions, except as regards the magnesia. However, Bosc and Védel have shown that sea water, when injected pure, is slightly toxic, and is therefore inferior to physiological serum. Although the experiments of Julia and of Hallion have shown that sea water is not really toxic, yet this method has not been adopted clinically.

De Renzi, some years ago, advocated the use of an iodised serum in the treatment of surgical tuberculosis; its composition is as follows:

Pure iodine	1 grm.
Iodide of potassium	3 ,,
Chloride of sodium	6 ,,
Distilled and sterilised water ...	1,000 ,,

It is given subcutaneously in quantities of from 200 to 300 c.c. *per diem*. According to De Renzi, the results obtained are satisfactory if the use of the serum be continued sufficiently long, and if a tonic and nourishing *régime* is also adopted. Quite recently Buvat[1] has studied a new method of treating mental maladies by means of serums containing bromides and iodides combined with chlorides, and this method, although still in quite an early stage, seems destined to give very interesting results.

The bromide serum has the following composition:

Bromide of sodium	6 grm.
Chloride of sodium	1 ,, ·50
Distilled and sterilised water ...	1,000 ,,

[1] Thèse de Paris, 1901.

It has a markedly sedative action in melancholia accompanied with anxiety, in maniacal delirium of senile subjects; in epilepsy it rapidly diminishes the number of attacks and stimulates all the physiological functions.

Iodide serum is composed of:

Chloride of sodium	6 grm.
Iodide of potassium	2 ,,
Sulphate of soda	2 ,,
Distilled and sterilised water ...	1,000 ,,

It is an extremely active anti-sclerotic agent, which gives results, more especially in syphilitic general paralysis and in specific mental cases. It rapidly checks wasting and considerably diminishes the tendency to febrile and congestive attacks; but as regards the mental disorders, and those of speech and of vision, the results are usually *nil*.

All of these serums are innocuous; they may be given hypodermically in the large quantity of 500 c.c. every day or only every two or three days, according to circumstances. The contraindications for their use are the same as for ordinary serums.

Lastly, the serum of Trunecek has recently been advocated in the treatment of arterio-sclerosis. Its formula is:

Sulphate of soda	0 grm. ·44
Chloride of sodium	4 ,, ·92
Phosphate of soda	0 grm. ·15
Carbonate of soda	0 ,, ·21
Sulphate of potash	0 ,, ·40
Distilled water q.s. ad	100 c.c.

This serum represents the composition of the alkaline salts of normal blood serum, but in ten times more concentrated solution. Levi uses it subcutaneously in

doses of 2 c.c. at the commencement, gradually increased by 1 c.c. every second day until 5 c.c. are attained; he maintains this dose unless pain is too severe. This serum may also be made use of in enemata in the daily quantity of 35 c.c. According to Mathieu, some success has followed its use in arterio-sclerosis and in chronic rheumatism.

4. The Metatrophic Method.

This method has been suggested by Richet and Toulouse, in order to avoid the drawbacks attending bromide medication, which is, of course, very efficacious in epilepsy, but apt to lead to bromism through the employment of the large doses (10 to 15 grm.) which are necessary in order to lengthen the interval between the attacks and to cause their cessation.

The metatrophic method consists in gradually depriving the organism of alimentary alkaline salts, and particularly of chlorides, so as to render the nerve cells, thus partially demineralised, able to appropriate certain medicinal substances which possess similar properties. Richet and Toulouse have thus treated thirty epileptic women who were placed on a diet very poor in chlorides. It was found that daily doses of 2 grm. of bromide of sodium alone were sufficient, sometimes in less than a week, to cause the disappearance of the attacks when this method was adopted. When the convulsive attacks were replaced by those of *petit mal* it was sufficient to increase the daily quantity of bromide by 1 to 2 grm. in order to relieve the symptoms. Yet in these doses, on account of the greater activity of the remedy, it may happen that symptoms of bromide intoxication supervene; further, it is advisable not to abruptly

cease the treatment, in order to avoid, at the time of the cessation, a return of the seizures, which may then be still more frequent than before. The diet to which the patient must be submitted for this method to be carried out is quite harmless.

IV.

RESPIRATORY ALTERANTS.

1. Elements and Factors of Respiratory Disturbances.

In disease of the respiratory apparatus it is necessary to consider, from the therapeutic standpoint, several conditions: the respiratory function, cough, bronchial secretion, and local infection. All the drugs which exert an influence on one of these conditions or on several of them jointly are capable of modifying respiration.

A.—The investigation of the *chimisme respiratoire* affords a means of examining the modifications of the respiratory function. This mode of research has led Robin and Binet to the verification of very important principles concerning the treatment of pulmonary affections. These authors have shown that the respiratory exchanges and the pulmonary ventilation are both considerably increased in tubercular phthisis, while they are, on the contrary, markedly diminished in bronchitis, simple pleurisy, pneumonia, and maladies of the same class. Influenza, when affecting the lungs, forms the only exception; the exchanges in this malady have much in common with those of phthisis, but they are far less marked.[1]

Without stopping here to consider the consequences of

[1] Robin and Binet: "Conditions et diagnostic du terrain de la tuberculose pulmonaire" (Ac. de Méd., March 19th, 1901).

this discovery from the point of view of prophylaxis and of the early diagnosis of tuberculosis, it is enough to remark that in the one condition the therapeutic indication which arises from it is the employment of remedies which are capable of increasing the respiratory exchanges, and thus to combat the defective hæmatosis; and, in the other malady (tuberculosis), to retard these processes in order to check consumption.

Amongst the respiratory stimulants, it must unfortunately be admitted that, except pure oxygen given by inhalation, which has been long known and which renders inestimable services whenever hæmatosis and the gaseous exchanges are defective, we do not possess any really efficacious remedy, and the majority of those recommended as such are, on the contrary, respiratory sedatives, or simply agents which modify the bronchial secretions. The researches of Impens prove that in this matter there is a true therapeutic void. The experiments of this author have included a very large number of substances: he found that caffein caused a slight acceleration of the frequency of respiration, yet the volume of air introduced is not increased, but is, on the contrary, diminished. Camphor and oxycamphor diminish the excitability of the respiratory centre and the frequency of respiration, and they slightly increase the total volume of air, which accounts for their use as antidyspnœics, but their effects are inconstant and transitory. It is the same as regards strychnine, and, apart from its action being very temporary, it is necessary to employ dangerously large doses in order to obtain any definite results; hence it is not a remedy that can be confidently recommended. As regards the salts of ammonium, the acetate seems to be the least inactive, but it is very uncertain; the sulphate

increases the amplitude of the respiratory movement, but not the ventilation of the lung. Thebain, picrotoxin, aspidospermine, and tropococain have no sort of influence: lastly atropine increases the frequency, the volume of each respiration and the total volume; but it causes distress, and this distress, as Impens observes, is doubtless the cause of the increased frequency. Further, atropine is much too poisonous to be safely employed in daily routine.

The respiratory sedatives are, on the other hand, both numerous and efficacious, and among these remedies may be cited arsenic, the tannates, the iodides and bromides, cod-liver oil, and finally the vegetable essences, spirit of turpentine and its derivatives (terpine and terpinol), eucalyptus, niaouli, &c., which act chiefly by modifying the pulmonary secretions and the area of infection; we shall study these later on. It should be noticed that the vegetable essences act more directly than do other respiratory sedatives upon the gaseous exchanges, inasmuch as they are eliminated to some extent by the pulmonary mucous membrane, and they take part in the metabolism of the anatomical elements of the organism, while the preparations of arsenic and of iodine, &c., do not modify the respiratory activity, as we have seen in studying the *cacodylates* (p. 52), except by delaying and moderating the general metabolic exchanges, whose diminution naturally involves a smaller need of oxygen.

B.—Cough is due to a succession of short, sudden, frequent expirations, which cause a characteristic sound in consequence of the passage of air through the bronchi and trachea, thus expelling foreign bodies and accumulated mucus. Cough is a reflex action due to the

irritation of the terminations of the pneumogastric nerve in the larynx. Hence it is a defensive action, and hence, also, it should not be treated without good cause. In the majority of pulmonary affections cough merely detaches and removes expectoration, and in this case is generally *loose;* it arises from direct irritation, and should be encouraged by appropriate drugs; the derivatives of turpentine—terpinol especially—are here very useful, as they liquefy the mucus and thus help its expulsion.

Dry cough, on the other hand, is useless and even injurious; it does not encourage expectoration, and arises from inflammation, or in tuberculosis from the presence of tubercles. Sabourin has shown that dry cough simply excites irritation, and that the more the patient coughs the more he desires to cough. Hence it ought to be treated. There are two methods of effecting this. The first consists in making use of substances which diminish sensibility and the excito-motor power of the spinal cord, and thus check the cough; such remedies are morphia and its derivatives, peronine, dionine, and more particularly heroine, which will be considered later (*vide* p. 249). Further, atropine must be included, as it exerts a marked effect on the *chimisme respiratoire.* Codeia is less efficient. Morphia and atropine diminish bronchial secretion.

The second method, of recent date, is more original; it has been devised by Lalesque, of Arcachon, and consists in *controlling the cough by discipline.* Supported by Sabourin and Detweiler, Lalesque recommends the following method: just at the moment when laryngeal irritation, ending in a dry cough, is noticed the patient must gently close the mouth and make a series of inspirations through the nostrils; these inspirations

must be deep, slow, and calm, and should be continued till the laryngeal irritation ceases. After a few days' practice the patient will be able to suppress the dry useless cough, and in future will only cough in order to expectorate.[1]

C.—Pulmonary infection and secretion are the causes and the effects of the morbid process. But although it may be right to control the first, it is not always prudent to overcome the second, for secretion is really a defensive action, and is the result of excessive activity on the part of the mucous cells and of phagocytosis.

Hence it is very often desirable to encourage pulmonary secretion, that is to say, to arouse and maintain the activity of the agents of internal defence, but it is at the same time expedient to facilitate the elimination of the secretions by rendering them more fluid, by which process not only are the pathogenic elements got rid of, but also toxins which, if absorbed, may give rise to more or less serious disorders. From this point of view certain drugs are very valuable; such are eucalyptus, goménol, and the derivatives of turpentine, terpine and terpinol. It should be remembered that the remedies which cause elimination both by lung and kidney have also a satisfactory action upon the genito-urinary secretions.

In addition to these properties, the vegetable essences possess an antiseptic power with regard to certain non-specific pathogenic bacteria and to certain micro-organisms, such as those of malaria and marsh fever. But as regards antisepsis of the respiratory tract, the first place belongs without doubt to the derivatives of creosote, guaiacol, phosphotal, thiocol, which drugs are especially active against the tubercle bacillus.

[1] *Journ. de Méd. de Bordeaux*, March 10th, 1901.

The antiseptic method of combating infection may be carried out either by means of inhalation and atomisation, and by intra-pulmonary injections, or by internal administration which causes elimination by the lungs. The latter method, which was formerly the only one made use of, and which was chiefly confined to the administration of the balsams (balsam of tolu, for example), some of which are slightly antiseptic, does really effect a disinfection of the pulmonary alveoli. But the process is often inefficiently carried out, the quantity of the remedy which escapes through the lungs and to the seat of the lesion not being sufficient to exert an efficacious germicide action on the organisms therein contained. Further, a distinctly injurious effect may ensue as regards the general health by the absorption from the digestive tract of substances which are detrimental to the economy; thus in some cases really serious effects may be induced. But this method has the advantage over that by inhalation and pulverisation of reaching the alveoli of the lungs, for vaporisation, if it acts on the broncho-pulmonary mucous-membrane, yet does not reach the pulmonary alveoli on account of the presence of residual air. Thus the mode of treatment by the mouth has a distinct advantage over that by inhalation. Intra-pulmonary injections certainly bring the remedy into direct contact with the disease; but their performance unfortunately involves a delicate and difficult technique, and the results obtained are by no means constant. Further, they are painful and liable to set up inflammatory phenomena and febrile reaction.

We shall only consider those drugs which are made use of in the new methods of pulmonary therapeutics—

namely, on the one hand, terpine and terpinol, eucalyptol, goménol; and, on the other, creosote and its derivatives, phosphotal, guaiacol, and thiocol.

2. Vegetable Essences.

A. *Derivatives of Turpentine, Terpine and Terpinol.*

Terpine has been studied by Professor Lépine, of Lyons, since 1885. It is a bihydrate of turpentine, having the formula C^{10} H^{16} 3H ^{2}O. When pure it occurs in the form of upright rhombic prisms, pellucid, readily soluble in alcohol (1 to 7) and ether, less so in boiling water (1 to 22), and scarcely soluble in cold water (1 to 200).

Terpinol is a dehydrated terpine whose formula is $(C^{10}\ H^{16})^{2}\ H^{2}O$. It is a very mobile liquid, volatile and colourless; it possesses an odour which suggests that of hyacinth or jasmine. Bouchardat and Tanret have obtained it in the crystalline form. It it soluble in alcohol and ether, but insoluble in water.

Terpine and terpinol are eliminated partly by the lung and partly by the kidney; they have an influence upon the bronchial secretion, and that of the urinary tract, not merely on account of their slight antiseptic endowment, but also from their power of stimulating the glandular and mucous elements. But terpinol is much more active on the bronchial secretions than is terpine, and the latter has more effect on the urinary secretions, as proved by Dujardin-Beaumetz; this depends upon the greater volatility of terpinol. Hence in pulmonary affections the latter is to be preferred, but it may sometimes be advantageously combined (for example, in influenza with pulmonary complications) with terpine, which, in small doses, increases the urinary secretions.

Further, neither terpine nor terpinol appears to be markedly toxic, as Guelpa has given up to 4 and 6 grm. to a healthy man without any obvious disturbance arising. Nevertheless, in bronchitis and phthisis, a marked slowing of the respiration and a diminution in the gaseous exchanges are initiated by the use of these drugs, but to a lesser extent than occurs when oil of turpentine is employed in toxic doses. Lastly, contrary to the latter, it does not seem that terpine and terpinol have more than a very slight action on the temperature and on the nutritive exchanges. It should be remarked that when a patient is taking these drugs, and more especially terpine, when cold nitric acid is added to the urine a slight cloud occurs at the point of contact of the two fluids; this must not be mistaken for albumin.

Terpine and terpinol are employed in most pulmonary and vesical affections, but more frequently in the first than in the second, because in bladder troubles essence of turpentine is more efficacious. Under the influence of these remedies the bronchial secretions are considerably modified; they become more fluid and are consequently more easily expectorated, and their disagreeable odour is removed. When administered continuously in small doses in early tuberculosis they effect a considerable change both in the stethoscopic signs and in the appearance of the expectoration, which becomes more mucous in character.

Terpine may be given in cachets in doses of from 10 to 20 centigrammes, four to eight *pro die*, or in the following manner:

Terpine	0 grm. ·50
Alcohol	20 ,,
Syrup of tolu	30 ,,
Distilled water	100 ,,

To be taken in the twenty-four hours. But, without inconvenience, up to 1, 2 or 3 grm. of terpine can be given *per diem*. Terpinol, owing to its insolubility, must be given in capsules each containing 10 centigrammes, or it may be ordered in pill form. The following formula is proposed by Tanret:

Terpinol...	ā ā 0 grm. ·10.
Benzoate of soda ...	
Sugar	q.s.

In one pill, 6 to 12 *per diem*. On account of its slight volatility, terpine is not made use of either by inhalation or by atomisation; but terpinol may be employed in this form when combined with tincture of eucalyptus and alcohol:—

Terpinol	ā ā 10 grm.
Tincture of eucalyptus ...	
Alcohol	200 ,,
Water	800—1,000 ,,

This preparation may be vaporised in a hand-atomiser and be made to impregnate the air breathed by a patient in a small room or in an enclosure formed by white curtains with which the patient's bed can be surrounded, 100 to 150 grm. being employed every two or three hours. From time to time, of course, the air must be renewed, curtains being drawn back. This mode of treatment, in which moisture of atmosphere is united with the action of essences, gives very good results in the pulmonary affections of childhood and in fœtid bronchitis; in the latter malady the odour is very rapidly removed. Lastly, terpinol may be employed as a rectal injection in the form of medicated vapour. This is absorbed by the mucous membrane and eliminated by the lungs, whose

secretion it influences in the same way as when it is taken up from the alimentary canal.

B. *Eucalyptol and Eucalyptus.*

Eucalyptol is an essential oil derived from a myrtaceous plant, the *eucalyptus globulus*. Its formula is $C^{12}H^{20}O$. It is a yellowish liquid, distilling at 175°, very soluble in alcohol, but slightly so in water. It acts like terpine, but its antiseptic powers are more marked, and are very well defined in respect of the micro-organisms of malarial fever. According to Gimbert and Binz, eucalyptol exerts but a trifling and transitory irritating action on the skin and mucous membrane, it moderates nervous action; when given in larger doses it causes drowsiness and intellectual prostration, slows the respiration, diminishes the gaseous exchanges, and slightly lowers temperature and vascular tension. Like terpine and terpinol, it is partially eliminated by the lungs and partially by the kidneys, giving to the urine, like turpentine, the odour of violets.

Eucalyptol and the preparations of eucalyptus (powdered or entire leaves, tincture, &c.) were at first made use of in bronchitis and genito-urinary catarrh. But when in 1865 Tristan showed their value in intermittent fever, the preparations of eucalyptus were freely given in such cases and with very satisfactory results, as proved by the statistics of Keller. These results were in part attributed to the antiseptic power of the essential oil, and it was therefore attempted to make use of this product in the treatment of tuberculosis and of serious pulmonary affections, more especially as it exerts a powerful action on bronchial secretion. Besides phthisis, pneumonia and broncho-pneumonia, chiefly in children, have been

also treated in the same way, as have pulmonary gangrene, bronchial dilatation, fœtid bronchitis, and pleuro-pulmonary fistula in empyema. It has also been made use of, in combination with benzoic acid, as an antiseptic for the mouth and throat (Gillet).

Owing to its penetrating taste, eucalyptol is given by the mouth only in the form of capsules, in doses of 50 centigrammes to 1 grm. ·50 *per diem*. It is ordered also in the form of tincture of eucalyptus, combined with syrup of turpentine, syrup of tolu, or syrup of cachou, in doses of from 5 to 20 grm. *per diem*. A eucalyptus wine and an infusion of the leaves are also employed, but the aromatic taste of these preparations is disagreeable to many patients. Eucalyptus and eucalyptol are most often employed by inhalation and vaporisation, not merely in pulmonary diseases, but also in those of the upper respiratory and digestive tracts, on which they exert an antiseptic influence, and this more especially in sore throat, both simple and complicated, in laryngeal diphtheria, tuberculosis, syphilis and cancer of the larynx. The following is a formula for the drug used by inhalation—

Eucalyptol	20 grm.
Essence of turpentine	20 ,,
Creosote	20 ,,
Ether	5 ,,

and by vaporisation (Smith)—

Tincture of eucalyptus	10 grm.
Essence of turpentine	10 ,,
Alcohol ā 65°	200 ,,
Distilled water	780 ,,

Lastly, in the case of children, it is often sufficient to

cover a few handfuls of eucalyptus leaves with boiling water and to cause the resulting vapour to be inhaled.

The use of hypodermic injections of eucalyptol has been recommended (Roussel) in tuberculosis, from 15 to 30 centigrammes being used *per diem* in an appropriate vehicle. But the results obtained do not appear to be superior to those which ensue from the method of ingestion or inhalation, so far, at least, as the stethoscopic signs and the expectoration are concerned, but the *chimisme respiratoire* seems to be checked and the temperature lowered to a greater degree.

C. *Essence of Niaouli: Goménol.*

The essence of niaouli, first investigated by Dujardin-Beaumetz and Main, and which is derived from the *Melaleuca viridiflora*, possesses properties which are comparable, from the point of view of their action upon the bronchial secretions and impaludism, to eucalyptol; but, owing to impurities contained in it, this essence has sometimes proved inefficacious, and has been replaced by goménol, an essence obtained from the *Melaleuca viridiflora*, which flourishes in the Gomen region of New Caledonia, by special processes which ensure constancy of composition.

Goménol is a yellow volatile liquid, of aromatic odour and burning taste, which is insoluble in water, but soluble in alcohol, ether and in oils. According to Bertrand, it contains eucalyptol, terpinol, citrene and, lastly, traces of aldehydes; hence its composition resembles that of the synthetic terpinol of List, although it contains a higher percentage of eucalyptol (66 per cent.). Although goménol appears to be still less toxic than terpinol and

eucalyptol, since 4 grm. of the active principle per living kilogramme do not, according to Main, exert any deleterious influence on the rabbit, yet it possesses definite antiseptic properties; indeed, 3 per cent. solutions of goménol retard in a marked degree the development of the bacillus of Koch, and 5 per cent. solutions stop the growth entirely. The same effect is produced on the growth of staphylococci and of gonococci, but the growth of streptococci is only arrested when 8 per cent. solutions are employed.

Goménol does not seem to influence either the heart or the circulation, but it has an analgesic effect on the nervous system. It diminishes the number of paroxysms of cough, even in pertussis, moderates their violence, checks nervous vomiting; and, according to Dubousquet-Laborderie, it assuages rheumatic and influenzal neuralgic pains when used as a liniment and paint in oily solution. Lastly, although it seems to be less efficacious than oil of turpentine and terpinol in controlling the secretion of the genito-urinary mucous membrane, it has, on the other hand, a powerful influence on bronchial secretion, and on the appearance and tenacity of the exudation, and it lowers in a marked degree the *chimisme respiratoire*, which tends to approach the normal, in the early period of phthisis, as Laumonier has proved. Along with this diminution of the gaseous exchanges there is a return of appetite and an increase of body weight.

Goménol was originally employed in the treatment of wounds, both accidental and operative, in solutions of 2·5 to 3 per 1,000, and also in burns; further, as an oily preparation, in the treatment of neuralgia and of uterine catarrh, as an injection of 2 per cent. strength in prostatitis, cystitis and blenorrhagia, in which it has

given good results. In pulmonary disease and especially tuberculosis goménol acts well and is superior to terpinol, which Dujardin-Beaumetz places at the head of the list of remedies available in bronchial affections. Not only are the secretions generally influenced, but the cough and expectoration and dyspnœa are all diminished; further, the abnormal auscultatory sounds are changed in character, the crepitations lose their consonating quality,leading Laffont to believe that there is a tendency to the cicatrisation of the lesions. It has been noticed by Dubousquet that the number of bacilli in the expectoration diminishes and that they may entirely disappear. Lastly, as the night sweats cease there is sometimes a tendency for the temperature to become normal.

The remedy is employed, internally, only in capsules, on account of its aromatic taste; each capsule contains 0 grm. ·25 goménol, 4 to 10 *pro die*. When there is gastric disorder the hypodermic method is preferable; the injections are composed of:

Pure goménol...	10 grm.
Sterilised olive oil	40 ,,

From 1 to 10 c.c. are used; but not more than 1 c.c. should be employed in the first instance, especially in patients in whom there is a congestive or erethitic tendency, tubercular or not, in order to ascertain the sensitiveness to the treatment. In torpid forms the dose may be rapidly raised, and may be carried to 20 c.c., being the equivalent of 4 grm. of goménol *pro die*. This is the maximum dose. Lastly, goménol may be employed by inhalation and atomisation, and used in this way it may replace eucalyptol or tincture of eucalyptus in the formulæ already given (p. 148).

3. Creosote and its Derivatives.

A. *Creosote.*

Creosote is a yellow caustic liquid but slightly soluble in water, but soluble in alcohol. It is obtained from the distillation of tar derived from beech-wood. Creosote contains from 60 to 90 per cent. of *guaiacol*, and to this constituent a portion of its active properties appears to be due.

Amongst these properties the most remarkable is its antiseptic power. This is greatly superior to that of phenol, since, according to Guttmann, 0 grm. ·25 per 1,000 of creosote checks the growth of cultures of tetragenes of staphylococci and of the cholera bacillus; according to Bouchard the quantity required lies between 0 grm. ·50 and 1 grm. per 1,000 to arrest the growth of Eberth's bacillus and that of Koch, but Marcus and Pinet find that the lethal dose for this purpose is not less than 10 per 1,000. As a result of this antiseptic power there is a marked toxic effect, for when injected into a vein a fatal dose of creosote is 0 grm. ·17 per living kilogramme; when injected hypodermically it is about 2 grm. according to Main, in the rabbit and the guinea-pig. In man the toxicity varies, but with quantities less than 0 grm. ·10 per kilogramme marked symptoms of poisoning occur—giddiness, profuse sweating, difficulty of breathing, hypothermia and torpor, &c.; however, it is shown by the method of Burlureaux that in certain cases, and when the kidneys are healthy, 15 grm. of creosote *pro die*, corresponding to 0 grm. ·25 per kilogramme on the average, may be tolerated. Lastly, creosote is strongly caustic, and, although when dissolved in oil it may be fairly well borne, it not seldom causes erythema and abscess, sometimes also lymphangitis, and

more rarely gangrene. In therapeutic doses (2 to 3 grm. *pro die*) it seems to have but slight effect on the circulation, nutrition and the nervous system, but it tends to reduce the frequency of respiration. It is eliminated to a moderate degree by the lungs, much more freely by the kidneys. In the urine it appears as creosol-sulphate and guaiacol-sulphate of potash, and it imparts to the urine a black or greenish-black colour, which is frequently an evidence of a special intolerance, or that the dose administered is too large, approaching that which is toxic for the organism treated.

Since the researches of Bourchard and Gimbert, creosote has been more especially employed in pulmonary tuberculosis. As Berlioz says: "The favourable influence of creosote in pulmonary tuberculosis is firmly established; at present it is the best remedy which we possess for this malady, and I affirm that those phthisical patients in whom the lesions are not irreparable, and who are able to take creosote in the requisite quantities, and also to live in the open air, have a very good chance of being cured." Creosote may also be employed in pulmonary gangrene and in fœtid bronchitis.

Internally a good preparation of creosote is creosoted cod-liver oil in the proportion of 2·50—5 per 100, and this more particularly in children; 4 to 6 teaspoonfuls daily or more may be given if well borne. It may also be ordered in the form of pills, each containing 0 grm. ·10, or in that of enemata (1 grm. ·50 creosote dissolved in oil and a yolk of egg added); the latter especially in those cases in which the stomach cannot tolerate the remedy. But the best mode of administration appears still to be that by hypodermic injection, according to the method of Burlureaux.

This method is founded on the principle that, as regards both creosote and other antiseptics, large doses must be employed if the maximum effect is to be obtained. In order to avoid gastric intolerance, which is rapidly induced, large hypodermic injections are made use of. As a matter of fact, the affected tissues in consequence of the local changes in the vessels do not permit the remedy to penetrate with facility, but, as Peter has observed, the impregnation of neighbouring regions which are still healthy opposes an obstacle to the extension of the tubercle bacillus.

Burlureaux makes use of the following formula:

Beech-wood creosote	... ...	10 grm.
Sterilised pure olive oil	...	150 ,,

which is injected hypodermically by means of an apparatus which bears his name, or by some other mechanism which ensures a continuous pressure. The method is based on the principle of the manometer, and the instrument is furnished with a tap, which allows the liquid to flow or to be arrested at pleasure. The skin must be most carefully rendered aseptic, as also the needle and apparatus; care must be taken not to wound the vessels, or otherwise serious accidents may occur. The back, or a locality in which there is loose connective tissue, is selected, and from 50 to 150 c.c. of the oily solution are slowly injected at one sitting; it seems to us scarcely possible to exceed this quantity, although Burlureaux has been able to go up to 250 c.c. At least half an hour should be spent in injecting 100 c.c. The operation is somewhat painful and tedious, and it may cause erythema or abscess, as also symptoms of intoxication. Hence it is well to proceed with circum-

spection, and only to employ large doses by gradual increase of the quantity.

Given in this way, creosote is eliminated by the skin (hence cutaneous complications), by the kidneys (so that occasionally pain in the renal region occurs, and even slight albuminuria when the doses are too large), and by the lungs. If the remedy is well borne localisation of the pulmonary lesion ensues. The latter tends to cicatrise, and a general improvement of health is observed ; sometimes, indeed, a complete cure is established, according to Burlureaux.

Amongst the derivatives of creosote may be mentioned *creosotal*, or carbonate of creosote ; *creosocamphor*, or camphorate of creosote ; *creosol*, or tannate of creosote ; *tophosol*, or tannophosphate of creosote ; *eosote*, or valerinate of creosote ; *phosote*, or phosphate of creosote, &c. We shall only consider *phosphotal*, or phosphite of creosote, as this remedy has given really interesting results.

B. *Phosphotal.*

Phosphotal is the neutral phosphite of creosote, which is used in the same way and for the same purposes as creosote itself ; it is less irritating than the latter and less caustic. Phosphotal is but slightly soluble in water, and is given in capsules containing 0 grm. ·20 of the remedy ; it may also, and preferably, be administered in emulsion. This preparation contains 9·5 per cent. of phosphoric acid, which is set free in the intestine, and which is by no means without effect in the treatment of tuberculosis.

It is from the latter aspect that the action of phosphotal has been carefully investigated. The effects

obtained are both uniform and satisfactory. As a result of the administration of phosphotal, two principal facts stand out prominently: the first is that a very definite effect is exerted on the *chimisme respiratoire*, although only a small quantity of creosote is eliminated by the lungs; the pulmonary secretions are favourably influenced, the expectoration loses its purulent aspect, and when the disease is not in an advanced stage amelioration of the stethoscopic signs is observable. The second fact is that a general tonic effect is elicited, which is no doubt due to the influence of the phosphorus contained in the preparation. The appetite is often improved and the body weight steadily increases. As the result of bacteriological examination, Laumonier has found that, in four cases, there was a marked diminution in the number of associated bacteria, which would explain the improvement that was observed, the reduction of temperature, the favourable change in the expectoration and the return of appetite. The only drawback to the use of this remedy is its tendency in some cases to cause vomiting when taken by the stomach, but this objection can be overcome by administering the emulsion of the drug by enema.

C. *Guaiacol.*

Guaiacol is the active principle of beech-wood creosote, of which it contains from 60 to 90 per cent. That portion which distils between 200° and 205° C. is collected, but this product is generally more or less impure, and the crystallised synthetic guaiacol is usually preferred. Natural guaiacol is a colourless liquid with an aromatic odour; both varieties are but slightly soluble in water, but are soluble in alcohol and the fixed oils.

Guaiacol possesses the same general qualities as creosote, but, when pure, it is less irritating, and has a strikingly defined anæsthetic and antipyretic quality when painted on the skin. Unfortunately the antipyretic action, which commences from fifteen to twenty minutes after the application, and lasts several hours, may be attended with disagreeable sensations and sweating, which are very unpleasant to the patient, and the fever may then return and be accompanied with shivering.

The antiseptic power of guaiacol resembles that of creosote; its toxic equivalent, ascertained by Main, is 1 grm. ·87 for each living kilogramme, in the case of the rabbit and guinea-pig, when the drug is injected subcutaneously. Hence its toxic power is scarcely inferior to that of creosote. Guaiacol is very rapidly absorbed by the mucous membranes and the skin; it is eliminated especially by the urine in the form of a sulpho-conjugated combination, which occasionally gives a black colour to the secretion. Only a small amount of the guaiacol taken is got rid of by the lungs—from 30 to 40 per cent.

The local analgesic action of guaiacol has been utilised in the treatment of neuralgia, rheumatism, inflammatory pain, and more particularly in that of orchitis, but it is now little employed as an antithermic. On the other hand, it has been substituted for creosote in the treatment of pulmonary tuberculosis, on account of the fact that it is far better tolerated, and because the same clinical effect is produced by smaller doses. In every case an improvement is observed in the *chimisme respiratoire*, the number of attacks of coughing is diminished (Goldammer), the expectoration and the pulmonary added sounds are

favourably influenced, and there is a return of appetite and strength. Both untoward and poisonous effects are far more seldom observed than in the case of creosote.

Guaiacol is given in doses of from 0 grm. ·50 to 1 grm. *per diem*, in the form of pills and in solution with cod-liver oil. The latter method is preferable for children; when given hypodermically oil containing guaiacol (5 per cent.) may be employed in quantities of from 1 to 4 c.c. *per diem*.

D. *Thiocol.*

Thiocol or sulphoguaiacolate of potash ($C^6H.OH.CH^3O.SO^3K$) is a fine white powder, of bitter, saltish taste, but leaving a sweet after-taste, without smell, which is soluble in four parts of cold and in one part of hot water. This drug contains 52 per cent. of guaiacol, according to Schnirer, 60 per cent. according to Schwarz. Its great advantage over the other guaiacol or creosote preparations is that, even in concentrated doses, it causes no irritation of mucous membranes, and is very easily absorbed. According to Rossbach, 72 per cent. of the ingested thiocol is absorbed, which is a distinct advantage over similar products. Further, it is not markedly toxic, for this author has given up to 20 grm., and even more, of thiocol daily to dogs without any untoward results ensuing; on the contrary, the animals increased in weight. Its action on the heart and circulation is nearly *nil*. As regards its antiseptic power, it does not appear that any special researches have been undertaken.

The action of thiocol depends upon the guaiacol and sulphur combination contained in it. It has been recommended not only in the treatment of chronic bronchitis, of

enteric fever, and of enteritis, but especially in that of tuberculosis. This product has been chiefly employed in Germany; it is but little known in France, and deserves to be more so. According to Schwarz[1] thiocol never sets up vomiting or diarrhœa in tubercular patients; it markedly increases appetite, and has a favourable influence on the general health, increasing weight and diminishing the number and severity of the attacks of coughing. At the same time the cough becomes easier and the purulent expectoration gives place to that which is sero-mucous only, while the night sweats become less severe and finally disappear. When the temperature has been febrile before the treatment, it is not unusual for it to become normal without the necessity of any antipyretic being made use of. Lastly, when tuberculosis is not very far advanced, the crepitation first of all diminishes and then disappears and the percussion dulness is less marked.

Thiocol is given internally in cachets, of 0 grm. ·25 to 0 grm. ·50, and up to 6 may be ordered *pro die;* or in solution. In the case of children it is advisable to make use of a quantity of 0 grm. ·20, which is put, just before use, into a warm, sweetened liquid, so that the slightly bitter taste may be disguised. In Germany from 10 to 15 grm. of thiocol are given daily; but it is unnecessary to resort to the use of such large quantities, for 3 to 5 grm. generally suffice, in order that satisfactory results may be obtained. Thiocol may also be used by subcutaneous injection in an appropriate vehicle (water, glycerine, oil) which has been carefully filtered and sterilised, in the daily dose of from 1 grm. ·50 to 3 grm. No inflammatory or toxic accidents have been observed.

[1] Vratch. XIX., 1898, No. 12, p. 569.

4. Intra-Pulmonary Injections.

It has been thought that by the method of intra-pulmonary injection it may be possible to bring the bactericidal agent into the very heart of the lesion and of the infected tissues, and in this way to kill the pathological virus and to arrest the effects to which it gives rise. Further, it has been hoped to produce by the same method a sclerosis and cicatrisation of the developed lesions.

Fernet and Comby, who have spoken highly of this method of treatment, especially in tuberculosis, make use of β naphthol, aristol, or of beech-wood creosote as antiseptic agents; in Germany guaiacol, and more especially thiocol, are preferred.

The following formulæ are suitable for this method of treatment:—

β Naphthol	0 grm. ·40
Tragacanth	0 ,, ·20
Distilled and sterilised water	20 ,,

30 centigrammes for each injection (Fernet).

Beech-wood creosote	1 grm.
Sterilised oil	15 ,,

1 to 2 c.c. at the most for each injection (Comby). Three to four injections to arrest the progress of the lesion.

Thiocol	1 grm.
Oil or sterilised water	10 ,,

The same quantities as above (Schwarz).

It is obvious that these injections should not be employed unless the lesion is limited and of small extent, otherwise it would be necessary to occupy the lung with

the remedy. Hence it follows that a most important contra-indication is the absence of this limitation of lesion; a second contra-indication is a too violent reaction to the treatment which is manifested by some individuals, or the occurrence of profuse hæmoptysis (Gilbert).

In order to carry out the treatment a Pravaz syringe is employed, but in the first instance the needle only should be introduced, in order to be certain that no vessel has been pierced, as otherwise embolism is possible; the needle should not be inserted to a greater depth than from 3 to 4 centimètres, and the proximity of vessels must be avoided.

The effect of this treatment is usually very marked. The injection causes severe pain, in consequence of the irritation of the local nerve filaments: this pain is not always localised; it may extend to the neck, shoulder, and arm. The added sounds in the neighbourhood of the area injected disappear, but soon return, finally ceasing altogether. Sometimes fine crepitations indicate the onset of local congestion, and in some cases signs of pleuro-pneumonia supervene, with crepitation, pleural friction, and dulness on percussion; but in all cases such forms of inflammation only last two or three days. If the injection penetrates a bronchus severe fits of coughing ensue, accompanied in some cases by the voiding of a portion of the injection with the expectoration. Consecutively to these results the crepitation and friction sounds disappear and the expectoration ceases to be purulent; loss of resonance on percussion and cicatricial contraction of the lesion ensue.

As regards general effects, an elevation of the temperature is noticed in the first instance; the fever rarely exceeds 39° C., and generally disappears after twenty-

four hours: it may be attended with palpitation and with an increase of dyspnœa; but when these symptoms have passed away a gradual improvement in the general health is observed, which is especially marked after each series of injections, and at the same time the reaction consecutive to the operation becomes less prominent. In the most favourable cases, when the lesions are not too extensive and are localised, a marked increase of strength is observed, the body weight rises, the fever disappears, together with night sweating and diarrhœa. In a word, the patient is on the high road to recovery, and this may be perfected by means of an appropriate diet, rest and out-of-door treatment. But it must be admitted that these very successful cases are few and far between, for this method is not often employed on account of the comparative difficulty attending its technique. It is chiefly adopted when other means have failed, and then the lesions are too widespread for the treatment to have any definitely good results.

V.

RENAL ALTERANTS.

1. Urinary Toxicity and the Eliminative Agents.

The reactions of the synthesis of assimilation and the destruction of tissue of which the economy is the seat give rise to the production of useless or toxic matters, which must be got rid of, inasmuch as these products—excepting some which are partially utilised (some secretions, fats, &c.), or which, being almost insoluble, are normally deposited in the tissues (*albumoïdes*, mineral matters, &c.), and form the resisting portion of the body, the skeleton, which are pathologically crusted over certain tissues (ankylosis, atheroma, &c.)—do not enter into the constitution of the living complex, being *anisotonic* for this latter, and consequently hinder the manifestation of its elementary life, its functional activity. Physiologically, these products are soluble, either intrinsically or in consequence of the changes which they undergo in the organism in the healthy condition, and they are eliminated more or less rapidly, their temporary accumulation causing merely local fatigue, when it is limited to a single organ, or general exhaustion ending in sleep, when it results from prolonged functional activity of the whole body.[1]

These products, with the exception of carbonic acid and

[1] Cf. J. Laumonier: "Physiologie générale," pp. 403 *et seq.*; and "La fatigue et le sommeil" (*Révue Universelle*, October 9th, 1902).

certain biliary matters, are got rid of chiefly by the urine, and hence it is easy to understand that the latter is normally toxic.

In morbid conditions the urinary toxicity varies within wide limits. When this toxicity is least marked it often happens that the patient is most seriously ill, either because in this event the toxic matters are to a great extent insoluble, or because the kidney is more or less impervious to the passage of poisonous matters. On the other hand, defervescence in acute disease and in the infections is accompanied, and, indeed, preceded, by the discharge of urine, which contains a large amount of toxins. It is obvious that in some conditions the production of toxins and the urinary toxicity follow a parallel course.

It follows from the preceding considerations that it is very useful to be acquainted with the degree of toxicity of the urine. This toxicity has three chief sources: alimentation and gastro-intestinal fermentation, the accessory products of assimilation, and, lastly, disassimilation or tissue destruction. Several methods have been devised to determine the degree of this toxicity.

The method of Bouchard consists in collecting and filtering the total urine passed in twenty-four hours; this is then injected, at a constant rate, into a peripheral vein of a rabbit. The animal dies, and the quantity of the urine introduced is divided by its body weight. The lethal quantity thus determined per kilogramme is a *urotoxie*. In a healthy man 40 c.c. of urine are required to kill a kilogramme of the animal experimented upon; the total quantity of urine (about 1,200 c.c.) thus kills 30 kilogrm., and corresponds to 30 urotoxies. The *urotoxic coefficient* is obtained by dividing the number of urotoxies accumulated in twenty-four hours by the body

weight. The average coefficient is 0·461. Clearly, as already shown, severe infections diminish the toxicity of the urine during the height of the fever, but increase it at the period of impending defervescence. In the same way a milk or a vegetable and milk diet lowers the toxicity, while a meat diet, and above all the abuse of viands which are "high," increases it. Severe cerebral strain also increases the urinary toxicity, as does muscular overwork, this being proved by the researches of Tissié and Sabrazès on the urotoxic coefficient of cyclists, in the race from Paris to Bordeaux, a coefficient which has amounted to 2·35 (Roger).

The objection has been made to this method that the osmotic tension of urine is variable, and that the injection of the urine in any considerable quantity when its osmotic tension is very high into the veins of a rabbit must affect the osmotic tension of the blood plasma in a corresponding degree at the expense of the blood cells, and this in such a way that the toxicity of the urine would be due in reality to the isotonic variations, and only partially to the toxic chemical action of the urine. It has also been further objected that, in this method, regard is not had to the volume of the urine, which must obviously have a direct influence on the urinary toxicity apart altogether from the difference of osmotic tension which results in the concentration of the fluid. If it is assumed that an individual passes in 250 c.c. of urine the same quantity of toxic matters which another passes in 2 litres of urine, the urotoxic coefficient of the latter will obviously be much lower than that of the former, although as a matter of fact the elimination of toxic material is the same in both. It is partly to reply to these objections that Bouchard has endeavoured to

determine the weight of the *average elaborated urinary molecule*. "The determination of the weight of the average elaborated urinary molecule is important, says Bouchard, not perhaps as regards the diagnosis of the illness, but in order to ascertain to what extent the disturbance of nutrition has been carried through the illness, and, above all, to discover how far an apparently healthy individual, or at all events, one who is not yet or no longer ill in any way, is removed from a condition of perfect health. It would tell us, perhaps, whether an *apparent* convalescence is but apparent, or whether behind the seeming recovery there may not be some latent pathological condition. It may also inform us whether a man who believes himself to be, and seems to be, in perfect health is not already in the grasp of some hidden disease, such as tuberculosis, syphilis, or nephritis."[1] But, as Bouchard[2] adds, the practical applications of the method of determining the toxicity of the average elaborated molecule are not very obvious.

More useful in clinical work would seem to be the coefficient of urinary toxicity arising from the relationship of the extractive matters to the total nitrogen of the urine. This method A. Robin substitutes for that which relies upon the determination of the urotoxies. What in reality are these extractive matters? They are the incompletely elaborated products which, as a matter of fact, confer on the urine its more or less marked toxicity, that is to say, creatin and creatinine, the xanthic and the sulpho-conjugated bodies; the amidated acids and complex amides; the different ammoniacal constituents;

[1] Bouchard: "Traité de Pathologie Générale: Troubles préalables de la Nutrition," t. iii., p. 249.

[2] *Op. cit.*, p. 280.

the colouring matters, &c., and occasionally the tox-albumins and true toxins, or, to speak more accurately, their derivatives. These several matters, whose nature and proportions vary according to the illness, the condition of the digestion, and that of the liver and kidneys, cause, when they accumulate in the organism, for some reason or other, the phenomena of auto-intoxication. The proportion of the extractives to the total nitrogen gives then, more or less correctly, making allowance for the uric acid, the coefficient of urinary toxicity. In this way it is possible to avoid the experimental determination of the urotoxie and the relatively complicated and delicate technique which it requires.

The conception of the urinary toxicity and the knowledge of the causes which produce variations in its degree emphasise the importance which attaches to those drugs which act on the elimination of these toxic matters, inasmuch as they remove from the organism noxious substances and thus prevent the possibility of auto-intoxication. Further, these remedies act either upon the toxic material itself, or upon the eliminating organ, or kidney, and consequently upon the passage of urine.

As usually it is the size of their molecules which hinders the elimination of toxic matters or of incompletely elaborated waste products in the economy, all the substances which diminish the dimension of these molecules by decomposition or by oxidation, or which render them more soluble, may be regarded as active agents in modifying urinary elimination, and as possessing a kind of specific action.

But urinary elimination may be modified by other causes; in the first place, by a purely mechanical

influence, that, namely, which increases the blood pressure. This increase of pressure may be the result of increased impulsive action of the heart, or it may arise from the volume of the circulatory area being diminished, either by the action of the vaso-constrictor nerves or by contraction of the smooth fibres of the walls of the vessels; it may again be the consequence of an augmentation in the volume of the blood through absorption of a certain quantity of water. It must be remembered that, in order to act diuretically, the drugs which contract the circulatory area should not act on the vessels of the kidney, otherwise anæmia of this organ will ensue, and its functions will be languidly discharged, thus leading to a diminished quantity of urine being secreted. It is easy to understand, when the histological structure of the kidney and the differential calibre of the afferent and efferent vessels of the Malphigian glomeruli are considered, that an increase of pressure in the afferent vessels necessarily leads to an increased elimination, and consequently to increased diuresis. However, the increase in the amount of urine only affects the absolute quantity of the water, and does not materially alter the amount of the residue, except so far as the holding of chlorides is concerned, for this latter constituent is naturally increased when absorption of œdema or of effusions such as occurs in ascites, cardiac dropsy, &c., takes place. But it is proved that those diuretics which act by increasing the volume of the blood—water, injections of artificial serum, &c.—by diluting to a certain degree some constituents of the blood, augment the solubility of these constituents, and consequently aid their elimination. Amongst the mechanical diuretics (those which act by increasing the blood pressure) may

be mentioned veratrine in minute dose, digitalis, theobromine, ergot of rye, and the various so-called *dialytic* diuretics, thus named because they attract to themselves the extra-vascular liquids and thus increase the volume of the blood; these are the carbonates, chlorides and alkaline nitrates, &c.

In the second place must be considered the irritant diuretics; these act more particularly by stimulating the kidney and thus exciting its functional activity, probably by a reflex which ends in the vaso-motor, and perhaps special *secretory* nerves of the kidney. The mechanism of the action of these substances, turpentine, terpine, copaiba, cubebs, broom, and probably the salts or strontium, is still very obscure; but it seems certain that these remedies are capable of effecting more or less marked alteration as regards the secretion of urine, and, consequently, of the nature and quality of the matters eliminated, not merely by their presence, which is discovered in the urine and which causes the renal irritation, but also by their elective action on certain of the histological elements which either excrete or which select the matters eliminated.

2. Urinary Alterants.

A. *Spermine.*

For some time spermine was confounded with piperazine, but the researches of Pœhl especially have proved that the substances are distinct the one from the other in the chemical sense, and therefore also therapeutically.

The formula of the spermine of Pœhl is $C^2H^{14}N^2$, and differs from that of synthetic piperazine, or the double ethylenimine of Ladenburg, which is $C^4H^{10}N^2$. It is

met with, according to Pœhl, in most of the body tissues, and especially in the prostate and ovaries, pancreas, spleen and thyroid gland, and lastly in the testicle, whence it has been thought to be the active principle of orchitine. This nitrogenous base is a whitish powder, very soluble in water and in artificial serum. When a solution of a spermine salt is treated with phosphoric acid in the presence of alcohol, an insoluble phosphate of spermine is formed which is precipitated in crystals. It seems that the crystals may be met with in certain diseased states in the body humours, and more particularly in some serous secretions, the semen and blood, where they have been described as Charcot-Leyden crystals.

Spermine, therefore, would appear to form one of the normal constituents of the blood and one of the active principles of all the organic extracts (see *Opotherapy*). It plays the part of an energetic oxidising agent, and behaves like one of the oxydases, as is proved by the experiments of Pœhl. This author has indeed shown that solutions of spermine, even in small quantities, transform considerable amounts of metallic magnesium into the oxide of the metal, restore the oxidising power of the blood which has been diminished or abolished by chloroform, or carbonic oxide, and raise the rate of oxidation in the urine of those who make use of the remedy. In the latter case, however, the oxidising power of spermine only declares itself so long as the remedy remains soluble, and the diminution of the alkalinity of the body juices and of the blood appears to cause the transformation of soluble into insoluble spermine—in other words, leads to the formation of phosphate of spermine or Charcot-Leyden crystals. Hence it follows that

every influence which tends to alter the normal reaction of the organic media lowers the oxidative power, leads to an accumulation of leucomaines and of similar products of decomposition, and hence to auto-intoxication.

According to Pœhl, spermine takes its origin in the nuclein, and more especially in the nuclein of the leucocytes. This oxydase, which appears at the same time as the xanthic bodies, by oxidation of these latter, leads to the stage of urea formation, but should the alkalinity of the plasma be diminished, then uric acid is produced; should the alkalinity disappear, spermine becomes insoluble, and the nuclein bases are no longer transformed or oxidised. Hence it follows that the toxic troubles which may occur under these circumstances may be annulled by administration of spermine, as has been observed by F. Richter and Lœvy in Senator's clinic. The hyperleucocytosis, which does not delay its appearance, is followed by a renewed alkalinity of the plasma and by a proportional increase of urea.

From what has preceded it will be obvious that the administration of spermine is indicated in any malady in which there is insufficient oxidation, and when auto-intoxication threatens. Hence, such treatment may be serviceable in anæmia and chlorosis, in arthritic disease, in alcoholic poisoning, and lastly in the infections, inasmuch as spermine accelerates oxidation and consequently the elimination of bacterial toxins. In all these affections the use of spermine diminishes the proportion of uric acid and of the extractives contained in the urine, while it increases that of urea and chlorides. Pœhl, Hirsch, and M. Salomon record cases of scorbutus, rickets, of the uric acid diathesis and of anæmia which have been very favourably influenced, and even cured,

by the use of the remedy. In anæmia and chlorosis Hirsch suggests that iron or hæmatogen be administered together with spermine.

The remedy has also given excellent results in the treatment of organic disease of the nervous system, neuritis, paralysis, tabes, neuroses, as also in hysteria and epilepsy, and above all in severe neurasthenia. Max Salomon has published[1] observations on this point which are absolutely conclusive, and which tend to corroborate the earlier researches of Ewald, Eulenburg, Medelet and Seuston. But the manner in which spermine acts (it contains no phosphorus) in these maladies remains so far altogether undetermined.

Spermine is given by the mouth in the pure condition in the form of cachets, containing from 0 grm. ·30 to 0 grm. ·50, two to three *pro die*. It may be administered hypodermically. Pœhl recommends the use of a double salt, chloride of spermine and of sodium, which is given by the mouth in aromatic alcohol solution of 4 per cent. strength; twenty to thirty drops are ordered two or three times a day in a warm alkaline mineral water. It may also be given hypodermically in sterilised aqueous solution of 2 per cent.; injections of 1 to 2 cubic centimètres are administered two or three times a day, preferably in the vicinity of the spinal column.

B. *Piperazine.*

Synthetic piperazine is the double ethylene diamine of Ladenburg, or the diethylene-diamine of Hoffmann. Its formula is $C^4H^{10}N^2$; it occurs as a white crystalline powder, soluble in water. It is a strong base, combining

[1] Cf. *Berlin. Klin. Wochenschrift*, No. 31, 1899.

easily with acids; its combination with uric acid forms urate of piperazine, which is soluble in 44 parts of water, that is to say, is much more soluble than urate of lithia ($\frac{1}{360}$), which is, however, the most soluble of the salts of uric acid. Hydrochloride of piperazine is also made use of; it crystallises freely and is very soluble; further, the tartrate of dimethylpiperazine is employed and known as *lycetol*.

Piperazine is but very slightly toxic, and in 2 per cent. solution it never causes irritation of the mucous membranes. *In vitro* it rapidly dissolves uric acid crystals, but, according to Van den Klep, it acts less rapidly on uratic calculi. According to this author, it possesses the property of retarding and arresting the deoxidation of oxyhæmoglobin, a quality which seems to be contradictory to the other known properties of the drug. When injected subcutaneously it considerably diminishes the proportion of urates, as Bardet has shown, and proportionally increases the urea eliminated. But, contrary to what has been maintained in Germany, it does not appear to cause an increase of the general metabolic changes and a stimulation of nutrition comparable to that induced by spermine, a substance with which piperazine has been erroneously confounded, as we have seen.

The indications for the administration of piperazine are all those nutritive disturbances in which an excess of uric acid is formed, gout, gravel, rheumatism—in a word, the arthritic diathesis. Under the influence of this remedy a marked change occurs in the quality of the urine; the coefficient of nitrogen increases, and there is a speedy disappearance of the effects of the presence of uric acid in the blood (attacks of gout, &c.). But in some cases

a discharge of urates has been noticed at the commencement of treatment, which has caused the proportion of nitrogen in the urea to the total nitrogen to fall below 80 per cent.

Piperazine and its salts (especially the hydrochloride) may be given in solution or in cachets in quantities of 1 grm. *pro die*. This dose should not be exceeded when pure piperazine is given, but if the hydrochloride or lycetol is used, up to 2 grm. may be ordered. Most frequently the remedy is employed by hypodermic injection. The solutions used are of 1 in 10 strength for pure piperazine, 1 in 5 for the hydrochloride; 1 or 2 cubic centimètres of the solution are given *per diem*, a quantity which represents 0 grm. ·10 to 0 grm. ·20 of pure piperazine, and 0 grm. ·20 to 0 grm. ·40 of its hydrochloride. Lastly, alcoholised solutions of 10 or 20 per cent. strength have been recommended for local application in the form of Priessnitz's compresses to gouty swellings, and this mode of treatment seems to act successfully.

C. *Sidonal.*

Sidonal, or quinate of piperazine, is a synthetic drug, which occurs as a whitish powder with slightly acid taste and which is very soluble in water.

This new drug appears to be altogether devoid of poisonous properties, for its employment, even in large doses, causes no unpleasant symptoms, either as regards digestion or circulation; and it combines the valuable properties of its two constituents—quinic acid and piperazine.

Quinic acid in the organism becomes in the first instance quinone, as Weiss has shown, and then forms

benzoic acid, which in presence of uric acid (whence glycocoll arises) may give origin to considerable quantities of hippuric acid. These facts, discovered by Lautemann in 1863, have been denied by Rabuteau, who maintained that quinic acid, like all the organic acids, burns up in the economy in forming alkaline bicarbonates. But if this were so, as Bardet remarks, quinic acid having been administered in too large doses would not meet with sufficient glycocoll in the economy to supply a proportional quantity of hippuric acid. Further, the recent researches of Adoue and Brissemoret fully confirm the theory of Urr and Keller, according to which hippuric acid is formed at the expense of benzoic acid and of glycocoll, which is derived from the uric acid. Thus, while quinic acid destroys a portion of uric acid formed in the body, the base—that is to say, piperazine—carries away in the form of soluble urates the proportion of uric acid which has not been decomposed (Bardet). The combination of these two substances, far from altering their respective properties, on the contrary develops the latter by causing a different physiological action to concur in effecting a given result. And all clinicians, especially Leyden and Blumenthal, are agreed that by the employment of sidonal uric acid is in great part replaced by hippuric acid in gouty urine, this latter acid being very soluble in water and not giving rise to any of the evil results which ensue from the accumulation of uric acid. Hence it is more especially in the uric acid diathesis in its various manifestations—in gravel, gouty rheumatism and in typical gout—that sidonal is of service. In these maladies the administration of quinate of piperazine shortens the duration of the attacks, alleviates the inflammatory phenomena, the

swelling of the articulations, and checks the formation of tophi, while it attacks and quickly renders more soluble renal concretions. Bardet[1] has shown that, although there may not be a marked increase in the quantity of urine passed, yet the proportion of uric acid in the urine steadily diminishes and soon approximates the normal. It must be mentioned that this diminution in the proportion of uric acid is not preceded by a discharge of urates, as is observed in the case of other drugs possessing similar properties, such as piperazine, lithia, &c.; on the contrary, from the outset of treatment there is a definite and progressive diminution in the quantity of uric acid excreted.

Sidonal is given in quantities of from 3 to 5 grm., or even up to 8 grm., *per diem* without any unpleasant symptoms arising. It may be administered in cachets, each containing 0 grm. ·50, or dissolved in water; the treatment should be continued on the average for a week. Bardet advises that the treatment should be persisted in for about one month after the cessation of all painful symptoms.

D. *Quinoformine.*

In connection with sidonal a very interesting substance must be referred to, the uratolytic qualities of which have been recently pointed out by Dr. Bardet: this is *quinoformine*.

Quinoformine is a combination by substitution of quinic acid with hexamethylenetetramine, or *formine* (known abroad as *urotropine*). As already mentioned,

[1] "Traitement de la goutte et du rhumatisme goutteux par le sidonal" (*Bull. de thérapeutique*, April 15th, 1901).

quinic acid is transformed in the economy into quinone, which supplies benzoic acid, the latter hindering the formation of uric acid by making use of the glycocoll (the combination produces hippuric acid), which is necessary to the uric acid in order that it may come into existence. As to the formine, it represents a base belonging to the same family as *piperazine* (*vide* 172), and which possesses nearly the same properties. It has, further, the merit of being a very efficacious antiseptic of the urinary tract, kidney and bladder.

As Bardet has shown, the first effect of quinoformine is the production of an abundant emission of hippuric acid, and also of urates, very soluble in combination ; this elimination of urates is a genuine discharge, to such an extent indeed that, after some days, the proportion of uric acid in the urine may fall below the normal. When inflammatory affections of the kidneys and bladder are present, pyelitis for example, it is found that the continued employment of quinoformine causes all troubles to disappear, and prevents their return. In gout it lengthens the intervals between the attacks and suppresses the latter, provided, however, that a severe *régime* free from chondrogens and poor in nucleinic elements be adopted.

Hence quinoformine is indicated in the different manifestations of the uric acid diathesis, gout and rheumatism in gouty subjects, and in gravel, particularly if there is reason to fear the occurrence of inflammatory phenomena affecting the urinary apparatus. It is made use of in the quantity of from 2 to 4 grammes *pro die*, 6 grammes at the most in gout, although the remedy is quite inoffensive. It is given in cachets containing 1 gramme, or dissolved in a little water.

E. *Theobromine.*

Theobromine, the active principle of cacao, the fruit of the *Theobroma Cacao*, one of the Malvaceæ, is a genuine diuretic. An inferior homologue of caffeine, theobromine ($C^7 H^8 N^2 O^2$) possesses well-marked diuretic properties which make it actually preferable to caffeine and digitalis on account of its more rapid effect and of its superior activity. Further, it does not increase the tension of the cerebral arterial system as does caffeine. Hence, where there is increase of arterial tension, theobromine is preferable to caffeine.

Huchard and Robin recommend the use of theobromine in ascites and anasarca of cardiac origin, as also in parenchymatous and interstitial nephritis. Owing to the tonic action of the drug œdematous fluid is rapidly absorbed and afterwards eliminated, the proportion of chlorides in the urine is increased, but that of albumin is but little affected. At the same time a rapid improvement in the general condition is observed, as also the disappearance of dyspnœa and the return of refreshing sleep, &c. But if these favourable symptoms do not make themselves evident after five or six days' treatment, the administration of theobromine should be suspended, for it is then certain that no good result will ensue from the use of the remedy.

Huchard advises that theobromine be given pure; as it is but slightly soluble, it must be ordered in cachets in doses of from 2 to 3 grm. *per diem;* sometimes the desired effect may be obtained by doses of 0 grm. ·50 to 0 grm. ·60.

More frequently a mixture of salicylate of soda and theobromine, known as *diuretin*, is made use of; being

easily soluble in water, it can be given in solution. The following is a suitable formula :

Diuretin	5 grm.		
Syrup of oranges	25	,,	
Distilled water	60	,,	(Bardet).

A tablespoonful every two hours, each dose containing about 0 grm. ·40 of theobromine. Diuretin should always be given with circumspection in renal disease on account of the presence of salicylic acid, which has a strongly irritant action on the kidneys.

F. *Salts of Strontium.*

The salts of strontium seem to have been first used therapeutically by the homœopaths in 1830. During more than fifty years these experiments remained isolated or unknown, and it was not until 1885 that Hassan in his thesis called attention to the researches of Vulpian on the employment of large doses of nitrate of strontium (15 to 20 grammes *pro die*) in the treatment of articular rheumatism. Lastly, Laborde having in 1891 proved that the salts of strontium are harmless, G. See, Dujardin-Beaumetz, C. Paul, Féré, &c., introduced these remedies into the domain of practical therapeutics.

It is essential that the salts of strontium employed in medicine (the bromide, lactate, tartrate, &c.) should be pure. By this is meant that, considering the difficulty which is experienced in separating the salts of baryta from those of strontia, it is necessary that the salts of strontium should contain less than $\frac{1}{1000}$th part of barium salts as an impurity. This result can be achieved by treating 1 grm. of the given salt dissolved in 10 c.c. of

distilled water with 1 c.c. of the 10 per cent. solution of bichromate of potash. If a perceptible cloud results it is proof that the salt of strontium contains more than $\frac{1}{1000}$ part of salts of barium, and it should therefore be rejected as impure.

The bromide, iodide, lactate and tartrate of strontium are very soluble in water; these salts are alone employed therapeutically, the phosphate of strontium being almost insoluble.

The experiments of Laborde have shown that the salts of strontium are almost completely innocuous and that their toxicity is invariably markedly inferior to that of the salts of potash. Animals have been found to endure treatment with strontium salts for months without manifesting any disturbance. It is the same as regards man, in whom, further, an increase of appetite appears to result. Lastly, the diuretic action of the remedy, although variable in its intensity, is always well marked.

The different salts of strontium have different applications. The bromide has been praised by Féré as a substitute for bromide of potash; it is given in the large quantity of 15 grm. *per diem*, without signs of intolerance or any appearance of the symptoms of bromism. The action on the stomach is less marked. In Basedow's disease this salt as well as the iodide has seemed to give good results in the dose of 1 grm. of the bromide or of 2 grm. ·50 of the iodide.

Nitrate of strontium has well-marked diuretic properties, being as active in this respect as the alkaline nitrates; it is useful in articular rheumatism, and particularly in gouty rheumatism, in quantities of 10 to 15 grm. *pro die*.

Lastly, the lactate of strontium possesses the property,

unexplained, but nevertheless demonstrated by Dujardin-Beaumetz and C. Paul, of diminishing the quantity of albumen in Bright's disease. Under the influence of this remedy, when taken in quantities of 6, 8 or 10 grm. *per diem*, "albuminuria rapidly diminishes to a point below which reduction cannot be effected" (Bardet), and at the same time an increased diuresis appears. But in interstitial nephritis the action of the lactate of strontium is less definite. It must be mentioned that the administration of lactate of strontium occasionally seems to cause violent pain in the nape of the neck.

Bromide of strontium is given in the form of syrup:

Pure bromide of strontium...	...	30 grm.
Syrup of oranges	...	150 ,,
Syrup of bitter orange peel	...	150 ,,

A teaspoonful contains 1 grm. of bromide.

Iodide, lactate and nitrate of strontium are given in solution; solution of the iodide:

Pure iodide of strontium ...	...	20 grm.
Distilled water	...	300 ,,

1 grm. of iodide in 1 tablespoonful.

Solution of nitrate of strontium:

Pure nitrate of strontium ...	...	40 grm.
Distilled water	...	275 ,,

2 grm. of the nitrate in 1 tablespoonful.

Solution of lactate of strontium:

Pure lactate of strontium ...	50 grm.	
Distilled water ...	... 250 ,,	(C. Paul).

3 grm. of lactate in a tablespoonful, 2 or 3 spoonfuls *pro die*.

VI.

VASO-MOTOR ALTERANTS.

1. Hypertension.

Vascular tension is dominated by three factors: the total mass of blood, the cardiac impulse, and the peripheral resistance. This resistance is in large measure regulated by the contractile elements of the arterial wall—contractile elements which are particularly closely connected with the great sympathetic, whose nerve filaments, some being vaso-dilator and others vaso-constrictor, maintain *vascular tone*, that is to say, the condition of varying contraction of the vessels. This tone may also be acted upon by the bulbar and medullary centres. This contractile property regulates the calibre of the arteries, and the dilatation or contraction of the artery under the influence referred to produces hyper- or hypo- nutrition of the organs which these arteries supply; on the other hand, diminution or increase of tension causes increase or diminution of the capacity of the circulatory field. Repeated exercise of function and a pathological or purely senile deposit may modify vascular tone or may almost abolish it, while causing hypertension, which may be more or less permanent, in consequence of sclerotic or atheromatous thickening of the vessels and of their consecutive tendency to obliteration.

Pressure steadily diminishes from the aorta to the arterioles, but the tension in the latter is by no means *nil*. Normal pressure in man is equivalent to 110 to 120 m.m. of mercury. But it must be remembered that the mean pressure includes two factors: the one invariable, the pressure which exists before the passage of the blood wave (arterial systole); the other which is the pressure at the moment of transmission of this wave or *pulse* (arterial diastole), depends not merely on the ventricular systole, but also upon the elasticity of the arterial walls. The arteries are capable of tolerating pressures greatly superior to those which are normal; thus Gréhant and Quinquaud have proved that the human carotid artery can, in health, resist the pressure of eight atmospheres.

In the capillaries the pressure is weaker than in the arterioles. Ludwig and von Kries estimate this pressure at 20 to 40 m.m. of mercury. Owing to the elasticity of the arterial tree there is no capillary pulse, except when some obstacle to the venous circulation, with resulting increase of pressure, exists.

But a capillary pulse is found normally in the fœtus, because the arteries have not yet acquired their elasticity, and also in the old, the arteries having lost this important quality owing to atheroma or sclerosis. Finally, in the veins the normal pressure is still lower, 5 to 10 m.m. of mercury, although these vessels are particularly contractile and resistant on account of the presence of muscle elements in their walls; but it must not be forgotten that the area of the venous is double that of the arterial cone, and that the pressure in the veins does not vary with the different stages of the cardiac cycle, the course of the blood having been rendered uniform by the elasticity of the

arteries. Further, there is no venous pulse except when the capillary system is much dilated, for the *venous pulse* of Potain is the result of the reaction of the auricular systole on the pressure in the veins which approximate the heart (jugular); it does not cause a reflux of blood, but it produces a momentary retardation in its arrival.

To sum up, it may be said with Claude Bernard that the circulation of the blood is presided over by a double apparatus: the one, peripheral, regulates the resistance; the other, central, or the heart, initiates and regulates the blood movement. With Huchard it may be said that there are three kinds of hypertension, according to the cause and the localisation of the resistance: arterial, pulmonary, and portal. In this place arterial hypertension will alone be considered, this form of excessive pressure being well recognised and controllable by certain new medicaments.

Arterial pressure is modified but slightly by the volume of the whole mass of blood, by what was known as plethora, as is proved by the fact that arterial tension is affected only in a slight and temporary manner by bleeding. Frederic has shown that after venesection pressure is quickly recovered, unless the bleeding be to the extent of 2 or 3 litres; this, it need scarcely be said, would be dangerous. The contraction of the heart acts probably more efficaciously, but to a much slighter degree, than the vascular tone, in maintaining pressure, for whenever the vaso-constrictive nerves and the vaso-motor centres are irritated, the peripheral resistance increases, the arterial tension rises, and this increase of pressure causes corresponding reactions, as Huchard has well shown. "Other things being equal," he says, "and the quantity of blood and the force of the heart remaining

normal or constant, vascular pressure can be raised by a mere increase of the peripheral resistance; further, the peripheral resistances act upon the motor centre, whose systolic force is thus increased, and also upon the volume of blood, whose quantity tends to increase in the locality situated above the obstacle. Thus this single factor—an increase of the peripheral resistance—brings into action the two others, and it is thus that the state of the arterial circulation is chiefly responsible for vascular hypertension."[1]

Consequently, along with valvular heart disease and myocarditis, both of which lead to hypotension and asystole, and which therefore require cardio-tonic, vascular-tonic, hypertensive treatment, it must be allowed that there occur also arterial cardiac diseases tending to ischæmia of organs, to hypertension, and to intoxication by early insufficiency of the kidney and liver, and which are, on the contrary, in need of treatment by eliminative, antitoxic and hypotensive measures.

Arterial hypertension, the gravity of which is so much the greater in proportion as the histological integrity of the vessels is the less complete, is dangerous in a large number of maladies, among which may be mentioned the pre-sclerosis of Huchard, coronary angina pectoris, uricæmia and gout, hereditary aortic disease, excess in the use of tobacco and alcohol, interstitial nephritis, local syncope of the extremities, Stokes-Adams disease or permanent slow pulse, aneurysms, excessive consumption of animal food, and, lastly, the infections, the effect of bacterial toxins being usually vaso-constrictive, as in

[1] Cf. Huchard: "Traité des maladies du cœur," 3rd ed. (Paris, 1899—1901). Cf. also Huchard: "Les trois Hypertensions" (Soc. de thérapeutique, June 12th, 1901).

scarlatina. These toxins may induce tachycardia and acute dilatation of the heart (Federn, of Vienna).

But in all these affections or diseases which result in an almost permanent condition of vaso-constriction, of hypertension, the proper treatment consists, as Huchard well points out, not in modifying the action of the central heart, itself more or less seriously affected as regards its contractile force, but rather in influencing the condition of the peripheral heart, in other words, of the arterial system, the morbid contraction of which should be combated in order to relieve and assist the cardiac action.

There are several ways of modifying hypertension, some of which exert a rapid action upon acute hypertension, which they rapidly relieve, while others, whose influence is slower, gradually relieve the condition of high pressure, reducing it to the normal. Amongst the first class may be mentioned *trinitrin and erythrol tetranitrate* (*tetranitrol*), then the organic extracts of liver, thymus, pancreas, testicle and ovary, all of which, as shown by Livon, of Marseilles,[1] are capable of lowering the tension (the extracts of the supra-renal capsule, kidney, spleen, pituitary body, thyroid, and parotid gland are, on the other hand, productive of increased tension). Amongst the second of these methods massage may be mentioned, for the muscular contraction causes five to nine times as much blood to pass into the muscles as in the state of repose circulates in these structures, so that massage helps the peripheral circulation and relieves the heart, exerting also an eliminative and antitoxic action of some importance, since, according to Zabludowski, the wearied

[1] Livon: "Action des sécrétions internes sur le tension sanguine" (Congrès de Méd. de Montpellier, 1898).

muscle eliminates its waste products far more rapidly and completely when it is massaged than when it is left in repose. A milk and vegetable diet may also be included amongst the methods in question, as it is at the same time eliminative, hypotensive, and antitoxic, the latter in consequence of the small amount of vaso-constrictive toxic matters it produces in the animal economy. Inasmuch as trinitrin is already well known, and the subject of massage is not included in the purview of this work, tetranitrol will alone be referred to. As regards the lacto-vegetarian treatment, reference may be made to my work on "Hygiene of Alimentation."[1]

2. Erythrol Tetranitrate.

Erythrol tetranitrate, or *tetranitrol*, is a member of a series of bodies which have been known for some years to possess vaso-dilatory powers which are more or less energetic and temporary. Leech in 1893 spoke favourably of the nitrites and of nitro-glycerine (trinitrin) and Matthew Hay of the nitrate of ethyl and of nitro-cellulose. Still more recently Lauder-Brunton made use of the hydrochloride of hydroxylamine, but this had to be given up on account of the unpleasant effect which it produced on the stomach. Bradbury and Broadbent studied the nitrates of alcohol of multiple equivalence, and finally Leech, Marshall, and especially Huchard, definitely determined the properties and the mode of employment of erythrol tetranitrate.[2]

Tetranitrol belongs to the group of nitric ethers. These

[1] V. 2nd ed. Paris, Alcan, Voy.; also J. Laumonier: "Le régime vegetarien" (*Bull. de thérapeutique*, No. 15, July, 1902).

[2] "Tetranitrate d'erythrol" (Ac. de Méd., March, 1901).

are formed by the action of concentrated sulphuric acid and nitric acid upon an alcohol. The chemical preparation is therefore simple, but it requires the greatest precaution, as the substances produced are powerfully explosive. They decompose with a slight elevation of temperature, and give off nitrous vapours; when struck, they explode with great violence. Tetranitrol is solid at ordinary temperatures, but it melts towards 60° C.; it is insoluble in water, and but little soluble in alcohol and ether, which considerably limits its therapeutic employment. It possesses vaso-dilatory and consequently hypotensive properties, which are more pronounced as regards duration than intensity; it is thus clearly distinguished from trinitrin, for example, whose action is immediate and intense, but fleeting.

As a matter of fact, if, by the aid of the sphygmograph, the action of the remedy be studied, it will be seen that the effect does not commence until after the lapse of 20, 30, or even 50 minutes; the arterial tension then falls slowly and continuously for about an hour and a half, and perceptibly tends to approach the physiological normal. It may remain stationary for nearly an hour, and even for a longer period, and may then rise, but so slowly that not seldom even six hours and a half after the administration of tetranitrol the pressure has not obtained its previous force. It may be stated in general terms that the fall of pressure continues from three to four hours. Indeed, as Huchard points out, by giving a centigramme of the remedy every three or four hours (six times a day) the arterial pressure may be kept almost permanently lowered, especially if, before tetranitrol is given, 3 to 4 drops of a 1 per cent. alcoholic solution of trinitrin be administered, the action of which

is far more rapid than is that of tetranitrol. Further, at the same time as the pressure falls, the frequency of the pulse increases, and may attain 90, 100, and even 110 beats a minute. It should be observed that the action of tetranitrol is purely on the vascular system, and not on the heart; the effect produced on the latter is merely secondary and consecutive to the vaso-dilatation.

The employment of this new remedy is indicated whenever the arterial tension is raised in the maladies referred to above, and more especially in angina pectoris, aneurysm and the dyspnœa of nephritis, when it gives constant and very satisfactory results, amounting to an almost immediate and lasting relief. Migraine and certain neuroses are also sometimes benefited by this form of treatment. Further, the drug does not appear to cause gastric disturbance; its only drawback is a tendency to produce a kind of throbbing headache and a feeling of heaviness in the head, but these sensations do not often occur, and when they do are transitory.

Huchard gave in the first instance 5 to 6 milligrm. of tetranitrol *per diem;* he now finds that from 1 to 3 centigrammes may be given with better effect in one dose, and up to 6 to 8 centigrammes may be administered *per diem*. The drug may be given in compressed tablets, or in pills, both preparations being, of course, accurately proportioned as regards the quantity of the drug—1 centigramme in each. This mode of administration, which is certainly not the most desirable, is rendered necessary on account of the insolubility of tetranitrol, for Brissemoret has not succeeded in obtaining a concentrated standardised solution of the medicament, which would be more manageable.

VII.

OPOTHERAPY.

OPOTHERAPY (Landouzy, 1895), or *organotherapy*, is a new therapeutic departure in which a variety of *juices* (ὀπὸς), glandular extracts, parenchymatous animal tissues, are made use of, and are employed with the object of annulling the morbid phenomena arising from the absence, the alteration or the insufficiency of the corresponding organs or tissues in man, or of supplying a deficiency as concerns physiologically co-operating organs (thymus and thyroid glands, for example).

1. Principles of Opotherapy.

This mode of treatment is very ancient, for from time immemorial savage and barbarous peoples have been in the habit of eating certain so-called noble organs (heart, brain, &c.), these organs being those of animals killed in the chase or of conquered enemies. By thus consuming these organs it was considered that the predominant qualities of which they were the seat would be transferred to the consumer. The present custom of administering blood and ox bile in chlorosis and biliary lithiasis respectively, of sheep's kidney in cases of renal disease and of the lungs of the calf in pulmonary affections, may be regarded as a survival of these primitive notions as to a therapeutic correspondence between

animal and human organs. These ideas thus obscurely handed down were of course based entirely on empirical considerations, until in 1889 Brown-Séquard, making use of the views of Cl. Bernard and Schiff as to internal secretion, established the method on a strictly scientific basis, and this in spite of many hindrances and much ridicule.

According to Brown-Séquard, not only do the closed glands, but those also which are furnished with an excretory duct, and in the latter case apart from their external secretions, elaborate and give up to the blood substances which take an important part in the general nutrition, inasmuch as the alteration, the inadequacy, or the absence of these substances cause intoxications and organic disturbances. If, then, certain of these glands should be injured or destroyed, the resulting deficiency or loss of internal secretion may be supplemented or supplied by introducing into the organism thus affected either the glands themselves or their active principles in the form of extracts. And the results of experimental and clinical observations tend to confirm this manner of regarding the matter.

But the question has been carried a step further, and now it is maintained that, not merely the glands, closed or not, but also the whole of the organs and tissues, elaborate and pour into the general circulation products which are not wholly waste, inasmuch as they take a more or less important part in maintaining the life of the individual. But if this is so, by what mechanism do these internal secretions act? and, further, by what mechanism the opotherapeutic agents which are intended to replace them? These questions are still moot ones, and all the more so, in the case of matters introduced,

because it is necessary to make allowance for the differences resulting from remoteness of species and for the condition in which the substituted matters are introduced. Nevertheless many theories based on the results of physiological experiment and clinical and therapeutical observation, and on the chemical analysis of organs and of their active principles, have been proposed, and these theories may be grouped, according to Hillemand,[1] in three classes :—

1. These opotherapeutic substances may act as modifying agents of the nutrition, either directly or through the nervous system.

2. Opotherapeutic materials may have an antitoxic influence, acting as a means of defence against noxious matters which are the result of organic exchanges. It may be that they convert these toxins, in proportion to their production, into harmless, inoffensive substances.

3. Lastly, these substances may be active, some in modifying nutrition, others as antitoxic agents, and it may be that the same substance acts in both ways. Or, perchance, certain of these matters unite, with a protective power against auto-intoxication, the faculty of aiding in opposing a resistance to infection, and in furnishing immunity.

It must be observed, also, that the idea of functional substitution has occurred to some in the case of organs possessing a certain or possible co-operative action ; thus, a give-and-take action has been held to occur between the thyroid and thymus on the one hand and the pituitary body on the other, &c.

If none of these theories exactly explains the disorders

[1] "Organothérapie ou opothérapie" (Paris, 1899).

which follow pathological changes in an organ, which disorders vary according to the function of the gland in question, and the variable therapeutic effect of the different opotherapeutic agents, this is due to the fact that the part played by internal secretion in the general co-ordination of the bodily functions has up to the present time been inadequately determined.

As a matter of fact, the medium in which all our anatomical elements are immersed is a limited medium, in spite of the fact of its more or less rapid and complete renewal by the ingestion of food and elimination of waste products. But, in consequence of this limitation of the medium, the alterations which ensue in the manner in which the functions of certain elementary cells are performed—whatever may be the causes of these alterations—react on all the other anatomical elements by modifying in a perfectly definite manner the constitution of the medium which, in consequence of the strict adaptation of the multitude of highly differentiated cells which flourish in it, is capable of variations only within very narrow limits. It thus follows that the consequent modifications are necessarily *correlative*. The result is the production, in the normal condition, of what was formerly known as the *organic equilibrium*, that is to say, a condition of balance between the functions of different organs according to their importance to the individual. Hence, if an organ is very active, this activity is maintained at the cost of other organs, whose repose, induced by the limitation of the medium and the accumulation of waste products, causes atrophy, and *vice versâ*. Since, in the normal condition, the different organs of the human body perform their functions and persist, they enter—the cellular elements of which they are formed,

and the different products which they secrete and which diffuse into the internal medium—into the general co-ordination, and their disappearance or the alteration of their function must necessarily break up, and does break up, this co-ordination. Thus arise the general disturbances which accompany local functional disorders, and which may be the manifestation of the effort made by the organism to regain its equilibrium. Thus also arises the necessity of supplying the animal economy with that which is either wanting, or is, at all events, insufficient to re-establish the functional balance; and hence, lastly, the therapeutic effect, which is often marked, of animal extracts, or, in other words, of opotherapy.

Such considerations as these also explain the fact that, not seldom, the effect of the suppression or insufficiency of such and such an organ is far from being obvious clinically, and thus many physicians deny the existence, or, more exactly, the therapeutic action of internal secretions of certain organs and tissues, such as the lungs, the bone marrow, the nervous tissue, the muscles, &c. If it is maintained with Le Dantec and Laumonier,[1] that the internal secretions are accessory products of the synthesis of assimilation, it follows of necessity that every organ, tissue and cell, yields an internal secretion, as is proved further by the toxicity of all tissue extracts, and that this secretion plays an important part, as we have seen, and in consequence indeed of its ponogenic and toxic influence, in general co-ordination of function. This influence is, on account of the limited power of adaptation possessed by the elementary cells, the real

[1] Cf. F. Laumonier: "Physiologie générale" ("Sécrétions"), pp. 418 *et seq.*

source of the disturbances which arise when certain internal secretions are diminished or vitiated, troubles which are the more marked in proportion to the ponogenic power of the secretion. From this point of view the nutritive, antibacterial or antitoxic defensive reaction is no longer a paradoxical occurrence, inasmuch as the functional equilibrium and vital resistance are both the results of co-ordination. Every disturbance of this co-ordination, by suppression of one of its conditions, may thus induce either a trophic change or a lessening of defensive power. This is particularly evident as concerns certain glands, the testicle and ovary, for example, whose internal secretions are nevertheless not admitted to exist, although their suppression causes physiological and morphological alterations which are universally recognised. Obviously the importance of disturbances which are consecutive to an alteration is subordinated to the more or less limited specific action of the organ, or to the abundance of tissue affected. And although the fact of the existence of internal secretion—and consequently the therapeutic efficacy of the restitution of this secretion when from any cause it is no longer produced in the organism—is admitted as regards the thyroid gland, the liver, the thymus, the pituitary body, possibly also the pancreas, yet it is denied as regards the kidney, the prostate, the mammary gland, and especially the lungs, the bone marrow, the muscular and the nervous tissues, &c., simply because, as regards the organs specified, experiments and observations have not yet enabled us to discover the part played by their internal secretion in co-ordination, and the mode in which their therapeutic influence may be exerted. And it is a singular fact that, at the very time in which the value of

the internal muscular secretion was altogether denied, Richet and Héricourt made use of muscle extracts with most satisfactory results, thus establishing the fact of a metabolic power being possessed by this extract (*vide* "Zomotherapy," p. 215). It cannot, therefore, be considered rash to assume that it may be the same with regard to internal secretions of other tissues and organs.

2. Administration of Opotherapeutic Agents.

Whether the whole organ be administered, or merely its extract, the animal which is selected to furnish the organ in question must be most carefully examined; it is not enough that it is free from any infectious disease, it must be in perfect health. According to the nature of the organ required, young animals are chosen (thymus, thyroid, suprarenal capsules), or those in full sexual activity (testicle, ovary), or those which are muscular (muscles, nerves, nervous tissues). The horse ought not to be included in the list, as it is almost invariably killed when in bad condition, and the ox is not desirable when the suprarenal capsules are desired. For the latter the calf is preferable, for the thyroid the sheep, for the liver the pig, and the kidney the pig, sheep, &c.

The organ to be administered may be given fresh or desiccated, or in the form of an extract, whole or partial. There are several modes of administering opotherapeutic matters. The following methods have been made use of:—

1. The glands or tissues taken from living animals or those recently killed have been grafted either subcutaneously or by the intraperitoneal method, and this especially in those cases where the opotherapeutic action cannot be conveyed by extracts, or when the action is

modified by the digestive process. This method is, however, seldom employed on account of its difficulty and other drawbacks.

2. When the juice is altered by the digestive ferments (which seldom happens), or when it is desirable to ensure the maximum efficacy and rapidity of action, extracts may be injected by the intravenous or by the intra-peritoneal matter, or, especially, hypodermically. The hypodermic injection of the extracts has been recommended by Brown-Séquard, and has been frequently employed.

3. Lastly, the fresh or preserved organ or its active principles may be taken either by the mouth or by the rectum; in the latter form of administration, which is made use of especially when there is intolerance on the part of the stomach, only those juices which are rendered soluble by the proteolytic ferments or by certain mineral salts should be employed in most cases. The method of ingestion by the mouth, formerly neglected but now recommended by Howitz, Fox and Mackenzie, is by far the best; it simplifies the treatment by animal juices, and in this way enables this therapeutic method to be more widely employed.

3. Opotherapeutic Substances.

A. *Thyroid Body and Parathyroid Glandulæ.*

Experimental thyroidectomy is followed by the same train of consequences as are observed consecutively to the surgical removal of the thyroid gland, or to the functional inadequacy and degeneration of the same organ, which may be either congenital or acquired. In cases in which the gland is degenerate, the consequences may

be less marked and slower in declaring themselves than when it is artificially removed. These consequences are of two kinds: some are of toxic origin, and consist chiefly in cerebral disturbances, which may be of a paralytic or more often of a convulsive nature, the latter closely resembling tetany; others are connected with disorders of nutrition, consisting in slowness of metabolism, diminution of the urinary exchanges, of the *chimisme respiratoire*, in intellectual feebleness, lowering of temperature, and, in young people, in arrest of growth and of the process of ossification.

Gley has pointed out that the thyroid gland must be distinguished from the parathyroid glandulæ. And this distinction seems to be the more satisfactorily established, inasmuch as the experiments of Moussu and Charrin tend to prove that the internal secretion of the thyroid gland differs from that of the glandulæ—to the first would appear to belong all those trophic disturbances which are brought about by a removal of the gland, to the second the acute convulsive phenomena already referred to. These things being so, it follows that the secretion of the thyroid gland has to do with the nutritive exchanges, while that of the glandulæ is antitoxic in function.

As a matter of fact, two active principles have been isolated from the thyroid apparatus: *iodothyrine* of Baumann, which exerts an influence in the disturbed metabolism and the toxæmia which occurs in cases of hypothyroidism; and *thyreo-antitoxin* of Fraenkel, which acts on the convulsive disturbances just mentioned. Clinically both of these substances act as complete thyroid extracts.

But these facts do not furnish us with any precise information as to the mechanism of the action of thyroid

secretion. It has been thought that the antitoxic secretion may have the power of neutralising or destroying the toxic matters which are the result of the assimilation of albuminoids—those matters which should possess the property of stimulating the action of the nervous system, and particularly of the motor nerves; and that the metabolic secretion, on the other hand, has a stimulating effect on the trophic centres. It must be admitted that these explanations are far from satisfactory, and that they do little more than point out the importance of correlation and the disturbances of equilibrium which follows its overthrow.

In whatever way the effect may be produced, the administration of thyroid gland certainly causes the gradual disappearance of the symptoms which are due to athyroidism and hypothyroidism. The nutritive and gaseous exchanges recover their normal activity, the percentage of oxyhæmoglobin increases, the power of bearing fatigue becomes greater, and, in children and adolescents, the processes of ossification are more energetically accomplished. As would be anticipated, the acute disturbances, convulsive or paralytic, are the first to disappear. In order that these desirable results may ensue, it is necessary to avoid too prolonged or too energetic treatment, for if this precaution is not taken disturbances will arise, which are due to an excess of thyroid secretion entering the system and which are by no means unlike the symptoms of Basedow's disease. In other words, nervous excitability arises, accompanied with phenomena which are generally associated with vaso-dilatation; marked loss of flesh and increased size of the neck may be observed, and trembling as well as exophthalmos may make their appearance. Further,

gastro-intestinal troubles may arise, and also albuminuria. It is obvious, therefore, that thyroid opotherapy must always be undertaken with the greatest prudence.

Indications for this treatment are: first, the different forms of athyroidism, infantile and adult myxœdema, cachexia-strumipriva, endemic cretinism; these are the affections in which thyroid treatment has proved most effectual, rapid and durable; goitre and chronic affections in which the secretion of thyroid juice is defective, with the exception of cystic goitre, vascular or cancerous. In the second place, cases of infantism and of arrested growth, obesity, diabetes—sometimes benefited, sometimes, but more rarely, made worse—rickets, osteomalacia, hæmophilia, some cases of metrorrhagia, psoriasis, eczema. Finally, epilepsy, tetany, eclampsia of infants, sclerodermia, and even exophthalmic goitre (J. Voisin, Mossi, Mairet, Burns, &c.). Contraindications are hyperthyroidsm, fatty degeneration of the heart, disease of the liver and kidneys.

Fresh thyroid gland may be made use of, that of the sheep being preferred, or the substance may be given in the form of extract (opothyroidine). Grafting of the gland is now practically abandoned, as is also the method of hypodermic injection of the extract. The fresh gland is given in quantities of 0 grm. ·50 to 1 grm. at the beginning of treatment in the adult; as much as 3 or 4 grm. *per diem* may be administered, according to the effect. Afterwards, at longer or shorter intervals, quantities are given sufficient to maintain the improvement (2 grm. every three days in cases of myxœdema and 4 grm. twice a week in obesity). It is, of course, necessary to immediately suspend the treatment if symptoms of intolerance arise. The complete extract is given in

single doses of from 0 grm. ·05 to 0 grm. ·10; or from 0 grm. ·15 to 0 grm. ·60 *per diem*. Children are very sensitive to the treatment, and therefore in them, as also in cardiac, renal, and hepatic cases, careful watching is necessary. Bedart and Mabille have suggested that Fowler's solution be associated with thyroid treatment, in order to avoid any of the unpleasant consequences which may accompany this form of medication.

B. *Thymus.*

The thymus is a vascular sanguineous gland which is first observed during fœtal life, and which only begins to atrophy from the second or third year; it may, however, persist for long periods, but when this happens, there is frequently atrophy or insufficiency of the thyroid gland. Hence it has been thought that the function of the thymus is ancillary to that of the thyroid. The gland extract contains iodised combinations analogous to those of thyroidine. Although hardly anything is known as to the pathology and physiology of the gland, yet it is thought to play an active part in nutrition, and on this account its use has been suggested in imperfect development of the new-born infant, in wasting, in hereditary syphilis, in chlorosis, anæmia, leucocythemia, and, above all, in goitre, in which disease Mikulicz finds that it gives good results. It has also been employed in exophthalmic goitre, but with no definite effect.

The thymus of the calf or of the lamb is given by the mouth in quantities of 10 to 15 grm. *pro die*. The extract (opothymine) is also administered in tablets in quantities of 0 grm. ·2 to 0 grm. ·5 for one dose, or from 0 grm. ·6 to 3 grm. *per diem*.

C. *Pituitary Body.*

The pituitary body, or hypophysis cerebri, would seem to be supplementary in function to the thyroid gland, inasmuch as Combe has shown that, when the thyroid is atrophied, the pituitary body is frequently enlarged. Further, there would seem to be an analogy between the two glands as concerns their antitoxic action. Lastly, Sarda has shown that there are tolerably constant relations between pituitary lesions and acromegaly. It is particularly in this latter malady that the gland has been employed, and Lyon, Mendel and Marinesco, have shown that this treatment relieves the headache and the paræsthesia of the hands, which are characteristic of the disease.

The gland is given by the mouth either fresh or dry; sometimes the extract obtained by Lyon is administered; it is found to exert a stimulating action on the pneumo-gastric nerves. More frequently the pure extract is employed (opohypophysine) in the single dose of 0 grm. ·05.

D. *Suprarenal Capsule.*

The suprarenal capsules supply an internal secretion which seems to have the power of exciting muscular contractility, especially affecting the heart muscle and the muscular wall of the vessels, and also to possess the property of destroying or of neutralising certain poisons, especially muscular poisons. The extract of the gland acts as a vaso-constrictor, and causes a temporary increase of the blood pressure by acting at the periphery upon the smooth fibres and the nerve endings. This effect appears to be due to the adrenalin, the active

principle of the suprarenal capsules, which will be considered later.

Suprarenal opotherapy was first made use of in Addison's disease, because in this malady there is frequently a marked alteration in the suprarenal capsules. Further, in bronze diabetes, in which affection many of the phenomena met with in animals from which the capsules have been removed are observed, such as muscular weakness, fall of arterial pressure, &c. If a cure is but rarely effected by this treatment (Béclère's case), yet certain symptoms are markedly relieved, such as asthenia, darkening of the skin, &c. Suprarenal extract has also been administered in diabetes insipidus, in cardiac weakness, neurasthenia, hæmorrhages (on account of its vaso-constrictive properties, which are due to the adrenalin), and the troubles complained of during the menopause.

The glands of oxen, of calves, and of sheep are taken by the mouth either fresh, or dried in powder, tablets, &c. The extract (oposuprarenaline) is given in quantities of 0 grm. ·2 to 0 grm. ·4 in one dose, or 0 grm ·4 to 0 grm. ·8 in twenty-four hours. Should there be gastric intolerance of the remedy when thus given, the glycerinated extract may be administered hypodermically.

E. *Adrenalin.*

Adrenalin, the active principle of suprarenal extract, was discovered by Takamine (of New York) in 1901. Neither its chemical constitution nor its molecular weight are yet known; but it nevertheless possesses remarkable and constant qualities. First, its toxicity is about 0·0015—0·0020 (Chevalier)—it declares itself by intense

dyspnœa and symptoms of prostration : convulsions only occur at the end; at the autopsy, as a rule, merely trivial congestive lesions are observed. When injected into the veins of a dog, the toxic dose is, according to Chevalier, from 0 grm. ·0036 per kilogramme of the animal's weight.

Intravenous injection of adrenalin causes, in the first instance, as Chevalier has shown, slowing of the cardiac contraction, lowering of the arterial pressure, and slowing of respiration. But very soon afterwards the pressure once again rises by wide oscillations, and exceeds the normal, the heart beats rapidly and becomes irregular, and the depth of the respiration increases, Thus spasms of the heart and vessels supervene, which explains the increase of arterial pressure by intense vaso-constriction of the peripheral circulation. But this vaso-constriction and this augmentation of pressure are of short duration, and the condition rapidly becomes normal (6 to 8 minutes). Reichert has detected, further, that the temperature is raised and the exchanges are increased, but it is difficult to determine these phenomena experimentally.

When injected subcutaneously in the dose of 0 grm. ·001 per kilogramme body weight adrenalin seems to have only a slight effect upon arterial pressure. When given internally the results are very uncertain, inasmuch as it loses nearly all its properties when brought in contact with the tissues, and more especially the glandular structures.

It should be added, in conclusion, that when adrenalin is injected in large doses into the peritoneal cavity of dogs, glycosuria results (Herter and Richard).

Adrenalin is an astringent and energetic hæmostatic,

its effect being very rapid in action (in from one to two minutes). It is successfully made use of in keratitis, iritis, and glaucoma for the purpose of assuaging the ciliary pain, reducing the ocular tension and clearing corneal opacity consecutive to injury; in swelling of the lachrymal canals and in cases of buzzing in the ears (1 or 2 drops of adrenalin solution in the Eustachian tube); in the minor ophthalmic operations, as well as those of rhinology in which, by inducing anæmia of the area operated upon (tampons suffice), the risk of hæmorrhage is avoided. It is equally useful in operations upon the nose and tonsils and in dental surgery. Lastly, it is successfully employed in severe and rebellious epistaxis and in the inflammatory congestions of the upper respiratory or digestive tracts, laryngitis, pharyngitis and tonsillitis, in coryza and hay fever, according to Vignes. Further, it has been recommended in cases of opium and morphia poisoning and in collapse following anæsthesia.

The remedy is contra-indicated, however, on account of the abrupt increase of vascular tension which it causes, in all cardio-vascular cases.

Adrenalin is employed in solution of 1 in 1,000; to the solution is usually added a little chloretone in order to preserve it. But it must be pointed out that from the physiological point of view this is illogical, inasmuch as chloretone is a hypotensive agent and a vaso-dilator. Only freshly-prepared solutions should be made use of, for adrenalin undergoes oxidation and is converted into oxyadrenalin. The small phials containing 5 cubic centimètres of the solution should be preferred, as this quantity is amply sufficient for all occasions in which adrenalin is indicated.

F. *Spleen.*

The spleen apparently plays an important part in hæmatopoiesis. Its extract is extremely rich in nucleins, phosphorus and iron; according to Schiff and Herzen it transforms protrypsine into trypsine. Danilewski considers that it increases the number of red globules and the hæmoglobin, and Wauters is of opinion that it contains bactericidal substances. Hence spleen has been administered in impaludism and malarial cachexia, in which maladies it is sometimes successful; it has also been given in leukæmia and pseudo-leukæmia, in splenic hypertrophy, in rickets, and even in exophthalmic goitre (Wood).

Internally, spleen of the pig or of the sheep is made use of, either in the fresh condition or desiccated, or the extract (opolienine) is employed in doses of 2 to 6 grm., or from 4 to 12 grm. *per diem*. Hypodermic injections of the watery or glycerinated extract are also used, but more rarely.

G. *Testicle.*

Brown-Séquard was the first to employ testicular juice (in 1889). The importance and value of this substance is deduced by this physiologist from the bodily changes which ensue after removal or atrophy of the testicles, and which are also sometimes observed in crypt-orchidism and in senile degeneration. Brown-Séquard held that these phenomena, as well as the connection which undoubtedly exists between the testicle and the development of the larynx, of the hair and of the muscular system, could be explained only on the assumption of the existence of an internal secretion of

the gland. Of late this explanation has been criticised, and the phenomena consecutive to castration and those of anorchidism have been held to be the result of hereditary correlations. But in order that these correlations may become active, an excitant is necessary, which can only be the internal secretion of the testicle, the effect of which is to provoke the appearance of the observed correlations.

The success of the method employed by Brown-Séquard, and which has been confirmed by a number of observers, has also been called in question, or has been explained on the assumption that it is the result of suggestion (Gilbert and Carnot). The truth is that it has been attempted to make of orchitic medication a universal remedy, but as a matter of fact it is only of use in the treatment of certain well-defined cases, more especially all forms of neurasthenia, nervous asthenia, cerebral depression, failure of reproductive power, and premature senility. In these maladies it frequently gives good results by stimulating the nervous system, and by increasing the power of work, both intellectual and physical, and also the secretions and diuresis, the proportion of hæmoglobin, the vital resistance, &c. These results may be explained, in part at all events, by the chemical composition of testicular extracts, which are rich in organic phosphorus, and whose action is exactly comparable to that of the lecithins and glycerophosphates, which have been already studied and which give, under the same circumstances, altogether similar results.

Testicular opotherapy has been successfully employed in neurasthenia, and the neuroses with depression; in melancholia and mental alienation; in paralysis agitans

and general paralysis and senile decay and premature senility; in tuberculosis, cancer and malarial cachexia; lastly, in anæmia, impotence, and in the disturbances which ensue after castration.

As a rule the juice of the testicle is made use of; this is prepared by the maceration of the gland in glycerine, the organ being previously cut into small pieces. The testicles of bulls and of rams are exclusively used. The macerated mass is filtered and sterilised under pressure of carbonic acid; it is employed by hypodermic injection in quantities of 1 to 3 c.c. The dry extract (opo-orchidine) may also be given by the mouth in doses of from 0 grm. ·5 to 0 grm. ·8, or 1 grm. ·5 to 3 grm. in the twenty-four hours. Sometimes the fresh organs are made use of either reduced to pulp or lightly roasted.

H. *Ovary.*

The changes which ensue consecutively to disease or removal of the ovaries are almost the same as those which follow atrophy or removal of the testicles. And it seems probable that the menstrual blood carries out of the system a portion of those toxins which have accumulated in the female organism. As, further, the investigations of Etienne and Demange would seem to prove that the active principle secreted by the ovaries, *ovarine*, contains an oxidising ferment, an oxydase, analogous to Pœhl's spermine (see p. 169), it would follow that atrophy of the ovary must cause disorders which are the result of auto-intoxication (by want of the oxydase), as also those of nutrition (by rupture of co-ordination), which declare themselves: (1) During growth and development by chlorosis; (2) at the menopause, and as

the result of double ovariotomy, by congestive seizures, nervous troubles, vertigo and attacks of syncope, as well as by pelvic and cephalic neuralgia.

These latter disorders are also observed, but in a less marked form, in amenorrhœa and even in dysmenorrhœa.

Hence ovarian opotherapy has been sometimes successfully employed in chlorosis, in the nervous symptoms which are often complained of at the menopause and after surgical removal of the ovaries, in amenorrhœa, and also in neurasthenia, hysteria and osteomalacia.

The ovary of the cow or sheep is made use of in dried powder, or in tablet form. The dose varies from 0 grm. ·10 to 0 grm. ·30 *per diem*. The extract of ovary (opo-ovarine) is also employed in the dose of 0 grm. ·2 to 0 grm. ·8, or 0 grm. ·6 to 3 grm. *pro die*. Sometimes the glycerine extract is injected hypodermically.

I. *Liver*.

The internal secretions of the liver have been specially studied by Gilbert and Carnot, who have shown that they increase the production of urea and stimulate the bile-forming, glycogenic, and antitoxic functions. Further, internal secretion exerts a very well defined coagulating influence. Hence these authors regard the part played by internal secretion as a very important one, and they consider that hepatic opotherapy has a great future, although it cannot be denied that the results of this mode of treatment seem to be contradictory.

Gilbert and Carnot recommend hepatic opotherapy in the treatment of atrophic and hypertrophic cirrhosis of the liver, icterus—in both of which affections cases of remarkable improvement are detailed, while Laudouzy

and Dieulafoy report others in which no amelioration ensued—in diabetes and gout, in biliary lithiasis, and, lastly, in hæmorrhages, hæmoptysis, epistaxis, purpura, &c. In no case has any untoward toxic effect ensued from the treatment.

Either the fresh liver of the calf or pig, or the total fresh or dried extract of the same, is made use of when the remedy is given by the mouth. The quantity of opohepatoidine is 1 grm. ·50 to 4 grm. *per diem*, the single dose is 0 grm. ·5. Different aqueous, alcoholic, or peptic and papaine extracts are also employed, whose activity varies. These may be administered hypodermically or (the last) by the rectum.

J. *Pancreas.*

The researches of Lancereaux, Mehring, of Minkowski, and, later, those of Lépine, Heydon and Gley, have shown that the internal secretion of the pancreas controls either the moderating function of the liver as concerns sugar formation or the activity of glycolysis. This control is effected either by the action of the secretion upon the nervous centres or by the glycolytic ferment which it contains (Lépine), and which it would give up to the blood.

Hence pancreatic opotherapy has been employed in those cases in which diabetes is associated with lesions of the pancreas. It must be admitted that the results obtained have been by no means uniform; the failures have been attributed by some observers simply to the fact that diabetes other than pancreatic cannot be reasonably expected to yield to the treatment. Rummo has extolled the use of pancreatic extracts in all functional digestive disturbances, on account of the energetic

action which the ferments contained in them exert when care is taken to convert artificially the pro-ferments into active ferments.

In diabetes the active fresh gland is preferably administered *in toto;* but the extract (opopancreatine) may also be given by the mouth in single doses of 0 grm. ·2 to 0 grm. ·8, or from 2 to 8 grm. *per diem*. The extract may also be given either hypodermically or in the form of enema.

K. *Prostate.*

Prostatic opotherapy is yet in its infancy, and has only been employed by Reinert and Bazy in hypertrophy of the prostate gland. They have obtained some definite results. Minced bull's prostate is made use of, or the extract (opoprostatine) in single doses of 0 grm. ·2, or 0 grm. ·8 *per diem*.

L. *Mammary Gland.*

According to Danhardt, this gland contains a substance which is capable of converting albumin into casein. Further, this substance depresses the heart's action. Bell and Shober have praised the extract in uterine myomata; it seems that the volume of the tumour is diminished and that metrorrhagia ceases. It is employed in the form of a dry powder (opomastine), in quantities of 0 grm. ·75 to 1 grm. *pro die*.[1]

M. *Kidney.*

From the fact that when the ureters are tied animals live longer than when the kidneys are removed, Brown-Séquard has drawn the inference that there is an internal

[1] Hillemand, *op. cit.*, p. 43.

secretion of the kidney different from the urinary function.

This secretion would appear to be at one and the same time antitoxic, capable of stimulating nutrition or of moderating the process of disassimilation, and finally, according to Gilbert and Carnot,[1] of exerting a coagulating influence on the blood analogous to that of the internal secretion of the liver. But these several properties would appear to be present together only in the living organ, inasmuch as Bunge and Schmiedeberg have not succeeded in arriving at the synthesis of hippuric acid by the aid of kidney extract.

Renal opotherapy has been made use of since 1893 by Dieulafoy, Teissier and Fraenkel in uræmia, chronic nephritis and in albuminuria, and by Gilbert and Carnot in several cases of hæmorrhage in Bright's disease. The results have been extremely variable, and in as many cases as have been relieved uræmic symptoms have been aggravated rather than benefited. Sheep's and pig's kidneys are employed, or the extract of the same (oporenine) in single doses of 0 grm. ·5 to 0 grm. ·8, or 1 grm. ·50 to 3 grm. *per diem*. Hypodermic injection of glycerine extract may also be used.

N. *Lung*.

Trophic disorders affecting the extremities, which are not seldom observed in the course of pulmonary lesions, and especially in those which are due to micro-organisms, first suggested the possibility of there being an internal secretion on the part of the lung. This secretion possesses an antitoxic action according to Wauters, a

[1] Rapport du Congrès de Médecine Interne (Montpellier, 1898).

metabolic action according to Demons. Pulmonary extract has been employed in phthisis, chronic bronchitis, bronchicetasis, in *osteoarthropathies hypertrophiantes pneumiques*, as also in empyema and mediastinal abscess, in which it would seem to have occasionally caused some marked improvement. The total extract (opopneumine) is made use of in daily amounts of 1 to 2 grm., administered by the mouth, or by hypodermic injection.

O. *Bone Marrow.*

Just as is the case with the spleen, so does the bone marrow appear to take a part in the elaboration of the formed elements of the blood. As Knoll has shown, it invariably contains a variety of hæmatogen and a substance resembling the glycerophosphate of lime. Hence medullary opotherapy has been essayed in a certain number of affections, and in these it increases the number of red corpuscles and of the hæmoglobin content and thus considerably ameliorates the symptoms. In some maladies, such as rickets and osteomalacia, the yellow marrow gives the best results; in others, such as severe anæmia, chlorosis, leukæmia and pseudo-leukæmia (Combe), neurasthenia, the red marrow seems to be preferable. Critzmann in impaludism combines splenic and medullary therapy.

The fresh marrow of the calf or ox is made use of in daily quantities of a teaspoonful for children, from 50 to 100 grm. for adults; the latter doses sometimes have a slightly purgative effect. The extract of yellow marrow (opoossiine) and that of red marrow (opomedulline) are given in doses of 0 grm. ·2 to 1 grm., and up to 6 grm. may be administered in twenty-four hours.

P. *Nervous Tissue.*

When the nervous structures are modified, either functionally or structurally, the deficiency of the normal accessory product of their activity tends to give rise to disorders of general co-ordination. It has, therefore, been proposed, in morbid nervous states, to practice opotherapy, or *nervous transfusion*, by means of extracts of cerebral or meduliary substance of animals which are strong and healthy. Babès, and especially C. Paul, have made use of this material in neurasthenia, epilepsy, melancholia, acute mania and tabes dorsalis, as well as in chlorosis and depressed general conditions consecutive to serious infections.

In some cases the results have been satisfactory. The effects of the extracts of nervous tissue, and especially of the grey substance (cellular portion of the neurons), have, however, been but slightly different from those which are the results of treatment with Séquardine, or testicular juice.

Recently Wassermann and Takaki have discovered that nerve extract neutralises tetanic toxin, and this has been confirmed by the researches of Courmont and Doyen, of A. Marie, of Brouardel and Thoinot, and of Roger and Josias. Lastly, Babès and Riegler have proved that the medulla oblongata of healthy sheep is antagonistic to the infection of rabies in dogs which have been inoculated after they have been trephined.

The glycerinated extract is preferably employed, and by hypodermic injection at the rate of from 4 to 5 grm. of the 1 in 10 extract per week or every third day. When dried extract (opocerebrine) is made use of by

the mouth the single doses are from 0 grm. ·2 to 0 grm. ·4, or from 0 grm. ·4 to 0 grm. ·8 in twenty-four hours.

4. Zomotherapy.

Just as happens with regard to other tissues, the muscles furnish accessory products by their activity which without any doubt take part in the general co-ordination of function. Hence muscle extracts have also been employed in opotherapy in spite of their toxicity, which does not, however, seem to be more marked than is that of other animal extracts. These muscle extracts have been made use of by hypodermic injection, especially in the primitive myopathies, but without any marked success; yet Hammond has employed extracts of heart muscle (cardine) in chronic disease of the myocardium and in asystole, and with some benefit.

But muscle extract has recently (1900), in the hands of C. Richet and Héricourt, given unexpected and very remarkable results in the treatment of tuberculosis. Raw meat has for long been employed in the treatment of wasting and debility of children, as also in prolonged convalescence, and in most cases this treatment is followed by very rapid improvement, in spite of the opinion which once prevailed, and of which Bergeron has been a supporter, that the only effect of the raw-meat treatment is the production of worms. It was these clinical facts which led Richet and Héricourt to make use of raw meat in the treatment of tuberculosis. Dogs fed chiefly or entirely on raw meat did not become tubercular, while the control animals inoculated in precisely the same conditions all died. Further, the ingestion of raw meat induced a condition which was inimical

to the production of tuberculosis, for it was found that dogs submitted to this treatment for some months and then again placed on ordinary diet and inoculated were incapable of being infected and gained weight, although other dogs which had not been thus fortified against tubercular infection succumbed more or less quickly.[1]

Richet and Héricourt have gone yet further, and have proved that muscle extract, or *muscle serum*, obtained by submitting meat to strong pressure possesses exactly the same properties as raw meat, and that the serum given in quantities of 20 c.c. per kilogramme weight of the animal cures tuberculosis experimentally induced on dogs. In the early stage of tuberculosis the minimum dose which is requisite in order that positive results may follow would be 15 grm. of serum per kilogramme of the patient's weight at the beginning of treatment.

This method was immediately applied to the treatment of human tuberculosis and tried by a large number of physicians, particularly by Josias and Roux. These authors[2] have proved that zomotherapy is very efficacious in the first stage of tuberculosis, in which it causes rapid and lasting improvement, the diarrhœa, night sweating, cough, febrile and stethoscopic signs of the disease all disappearing. Further, body weight increases. But when the disease is in the second or third stage the case is widely different: when improvement results, it is temporary only, and usually the fever does not yield, neither does the diarrhœa; the pulmonary lesions, too, extend and become more severe. Josias and Roux conclude: "When the case is one in which the lesion is the result of the activity of the tubercle bacillus alone, the muscle serum

[1] 1 Soc. de Biologie, June 2nd and 8th, 1900.

[2] Soc. de Thérapeutique, February 13th, 1901.

treatment may be followed by the amelioration or even by the cure of the malady. But when the tubercular lesion is complicated by the invasion of the secondary microbes which flourish in the lungs in the stage of softening and of cavity formation, treatment by raw meat juice has only a relative therapeutic action."

It must be remembered that these results have been obtained in hospitals, which are by no means a favourable locality for the cure of infections, on account of the numerous contaminations which must inevitably be present. In private practice better results have been obtained. Duhourcau has reported several satisfactory results, some cases being really cured. But this author, sharing the opinion of A. Robin, does not make use of the large doses of muscle serum which have been recommended by Richet and Héricourt, and he admits the use of the darker meats in the treatment, these being forbidden by the latter authors. Too energetic serum treatment may, owing to the toxins contained in the fluid, cause accidents due to auto-intoxication, and even irreparable lesions of the kidney. Duhourcau never orders more than 150 to 200 grm. of meat juice *pro die* (corresponding to 250 to 300 grm. raw meat), and 150 to 200 grm. of raw meat pulp.

There is much difference of opinion as to the manner in which, in favourable cases, muscle serum acts. Duhourcau seems inclined to admit with Rey Pailhade the influence of a hydrogenous ferment (philothion), which stimulates the chemical activity of the cells of the organism. Laumonier thinks, on the contrary, that by superalimentation with meat and by the use of muscle extracts tissue changes are brought about resembling those of arthritism. Urinary analysis under this

treatment reveals a marked increase in the proportion of uric acid to urea, at the same time that a diminution in the relation of uric acid to phosphoric acid of the alkalies occurs, which would clearly tend to show that the system is passing into a condition of uricæmia, unfavourable to the evolution of tuberculosis, or in which sluggish, slowly developing forms of tuberculosis are alone observed. Josias and Roux have proved, what Héricourt had already observed, in animals, that zomotherapeusis, when tending to a favourable issue, may cause benign local tubercular lesions, which, however, become cured without any complication.

Héricourt has constructed[1] the following formula for antitubercular zomotherapeusis: fresh beef, preferably beef steak, is minced and freed from fat, and is then macerated for two hours in one-fifth of its weight of sterilised cold water. The mass is then placed in a strong cloth and submitted to methodical pressure in an appropriate machine, which should be cleansed with boiling water before and after each operation.

The quantities of muscle juice ingested are as follows, regard being always paid to the drawbacks already referred to:—

1. In early or latent tuberculosis 200 to 400 grm. of the liquid, which corresponds to from 500 to 1,000 grm. of meat before pressure.

2. In tuberculosis which has reached the second stage, 400 to 800 grm. of juice, corresponding to from 1,000 to 2,000 grm. of meat.

3. In tuberculosis which is advanced, or in miliary tuberculosis, 800 to 1,200 grm. of the juice, representing

[1] *Révue de la Tuberculose*, 1901, No. 2.

from 2,000 to 3,000 grm. of meat. Muscle juice decomposes with great rapidity, and should be taken as soon as it is prepared. It should be given about half an hour before food, in order that the appetite may not be destroyed. If the taste is objectionable a little salt, seltzer water, or syrup of orange peel may be added.

As soon as possible cooked meat should be replaced by that which is raw, and if the patient cannot take the latter, cooked dark meats should at least be forbidden. When there is no tendency to congestion or hæmorrhage the juice may be entirely replaced by raw meat, of which, in early tuberculosis, 300 to 400 grm. may be given, and 500 to 800 when the disease is in its later stages. If the risk of the production of tape-worm is dreaded, then mutton may be substituted for beef.

Lastly, zomotherapy requires that all other medication be suspended—except the administration of cod-liver oil—and the treatment should be continued during six months at least after the disappearance of threatening symptoms.

VIII.

SEROTHERAPY AND VACCINATION.

1. The Defensive Reactions of the Organism and Immunity.

The organism is possessed of numerous and efficacious means of defence against the invasion of infectious germs, of pathogenic bacteria.

The skin forms the first line of defence, for if the intact skin does not appear to offer so effective a resistance to microbes as to foreign bodies in general, yet microbes are rarely found in it on account of its thickness, of its but slightly raised temperature, of its structure, and of the absence, therefore, of conditions favourable to their development. This is not the case as regards the mucous membranes, which are far more permeable, although their secretions are frequently endowed with germicide properties. When these barriers are once surmounted, the genuine defence of the organism commences by a congestive reaction which is accompanied by diapedesis and phagocytosis—phagocytosis to which we shall speedily return at greater length on account of its importance. A local lesion arises which represents a new effort to limit the bacterial invasion, since, along with the damaged cells which succumb, there is a proliferation of others which regain the power of phagocytosis (macrophages).

In some cases this means of protection would seem to fail in the case of very virulent bacteria whose toxins appear to have a negative chemiotactic action on the phagocytes; then a tendency to general infection arises. Happily these are not the only means of defence, and the lymphatic ganglia, the single and aggregated follicles, the tonsils, the serous membranes, all exert an action in arresting or retarding the general invasion of the system. This is effected by the blood, either directly, or after the lymphatic ganglia are surmounted. But the blood possesses bactericidal powers, or at least presents a medium little favourable to the evolution of microbes, since they rapidly disappear (possibly mechanically) and localise and fix themselves in the different organs. In the course of this circulation they encounter the last barriers to their progress. The liver seems to be especially powerful against bacteria and the staphylococcus, but as regards the streptococcus and the bacterium coli this organ is not defensive; on the contrary, it increases their virulence. The lung is the most efficacious barrier against the streptococcus. The kidney, like the liver, seizes upon many micro-organisms, and thus exercises really protective powers.

Lastly must be mentioned the genital organs, and especially those of the female, which, very permeable to microbes and continually infected, secrete by their mucous membranes a germicide liquid; further, at the time of lying-in this resistance to microbes is markedly increased. The same mode of defence is met with in the digestive tract, especially the stomach, on account of its acidity, &c.

To sum up, in all the different organs the means of defence are of the same order; disregarding any

mechanical influence, they act through their special or accidental (phagocytes) constituents upon pathogenic bacteria and their toxins. By what mechanism? This question must be briefly considered. Apart from the tentative inquiries of D'Auzias-Turenne and of Maurice Raynaud, the researches of Richet and Héricourt in 1888 and 1889, and those of Bertin and Picq in 1890, were the starting point of serotherapy, and they showed to a certain extent that injections of the blood of an animal which was refractory as regards any special infection into animals liable to the same infection rendered the latter more resisting. Then the memoirs of Behring and Kitasato in 1890, and of Roux in 1894, definitely established the principles upon which serotherapy is based, these principles being developed and rendered precise by the work of Metchnikow, and of Salimbeni and Roux. From this time the fact of immunisation in certain cases appears to be indisputable, but the explanation of the same, and consequently the manner in which serum acts, still seems to be very variable. However this may be, it appears that the theories put forward to interpret the mechanism of immunity may be divided into two chief groups: in the first are included the views of those who think that the destruction of bacteria and the neutralisation of their toxins are the effect of a passive resistance which is the result of the peculiar properties of the body humours; in the other is contained the doctrine that they are the result of an active offensive resistance exerted by certain cellular elements, the phagocytes.[1] Thus is renewed the

[1] Cf. Bourcy: "Prédisposition et immunité" (Path. gen. de Bouchard, Vol. I., pp. 438 *et seq.*); Landouzy: "Les Sérothérapies" (Paris, 1898).

old quarrel between humourists and solidists; but it will be obvious presently that this conflict of opinion is only apparent, inasmuch as it arises simply from an imperfect interpretation of the phenomena of reaction, of which the economy is the seat. The humoral theories would explain immunity either by a bactericidal condition, or by the attenuating properties of the internal humours, or by the antitoxic influence of the same humours.

The bactericidal condition of the humours has been chiefly dwelt upon by Fodor, and later by Flügge, Nuttal, Nissen, Buchner, and Behring himself, all of whom have maintained that the serum of immunised animals kills bacteria, or more or less retards their development. The experiments of Behring and Nissen on this point seem to be very conclusive. As a matter of fact the guinea-pig is very sensitive to bird septicæmia, and in a normal condition its serum does not exert any action on the microbe (*vibrio-Metchnikowii*) of the disease, while, if the animal has been vaccinated, its serum is definitely bactericidal. The fact is true; but by what mechanism does the serum become bactericidal? It can only be assumed that it is the result of a chemical change, itself the effect of an influence conveyed from without, or due to the altered activity of the elementary tissues. Since there is no sufficiently potent exterior agency, it is not possible to explain the fact otherwise than by the assumption that the cause must reside in the histological elements of the tissue, and more especially in the phagocyte. Further, the bactericidal condition of the humours does not necessarily produce immunity. Human serum, as a matter of fact, is bactericidal as regards Eberth's bacillus, and yet man contracts typhoid fever. On the other hand, the serum

of the dog is in no degree lethal as regards the anthrax bacillus, and yet the dog does not contract anthrax. It should be added that a serum when heated to 55° C. loses its bactericidal power, but retains its immunising properties. As regards the *phenomenon of Pfeiffer* (disorganisation and dissolution of the cholera vibriones when the latter are introduced into the peritoneal cavity of immunised animals), Metchnikow and Bardet explain it through the intervention of phagocytes.

The unsatisfactory nature of the bactericidal theory has led Bouchard, Charrin and Roger to maintain that the juices, without necessarily killing infectious germs, may yet diminish their virulence. From this point of view pathogenic bacteria, although still living, would undergo a change in their functional activity under the influence of the humours, by which their virulence would be checked and they would be rendered inoffensive. But there is really no proof of this being so, so far as concerns natural immunity, since, as Roux has shown, the virulence of bacteria, far from being diminished, seems to increase on their being passed through a refractory animal. In the case of vaccinated animals, as concerns their consequent immunity, an attenuation of virulence is, however, sometimes observed, as Charrin and Roger, Metchnikow and Courmont have noticed as regards the bacillus pyocyaneus, the streptococcus of erysipelas, the bacteridium, and the pneumococcus and the staphylococcus. But the attenuation is far from being constant, and, further, this explanation is attended with the same difficulties as are the bactericidal theories.

As the result of their researches on diphtheria and tetanus, Behring and Kitasato, having remarked that

the serum of vaccinated animals neutralises the corresponding microbic toxins, although not possessing any bactericidal or attenuating property, formulated a new theory of immunity according to which the humours, without killing or attenuating the virulence of bacteria, yet contain *antitoxins* which neutralise the bacterial toxins. This theory, as is well known, has led its authors to make use of antidiphtheritic and antitetanic serums, and is, indeed, the fundamental principle upon which serotherapy is based. But if, as concerns acquired immunity, it is assumed with Ehrlich and C. and F. Klemperer that antitoxins are sometimes formed in the humours, this is not the case as regards natural immunity, since the blood of animals which are spontaneously refractory has no antitoxic property. And as we have seen, the blood of vaccinated animals may be bactericidal without being antitoxic, and *vice versâ*, and Calmette, Phisalix and G. Bertrand have shown that a mixture of antivenomous serum and venine, warmed at a temperature of 70° C., loses its antitoxic power while maintaining its toxic properties. Hence there is no neutralisation of the toxin by the antitoxin in the chemical sense, and consequently acquired immunity would not exclusively depend upon the antitoxic property of the humours. This property exists, but it is a secondary adjunct subordinated to other conditions rather than to the presence of bacterial toxins, and this is the reason why it is both inconstant and variable.

The cellular theory of immunity, that is to say, the theory that the innate or acquired resistance of an organism to a given infection is due to certain histological elements of this organism, appears to have been first put forward by Grawitz, who formulated it since 1881.

But it is Metchnikow and his pupils who have brought forward the most striking facts and arguments in support of this explanation.

This theory may be briefly stated as follows: certain cells, and notably the polynuclear leucocytes (neutrophiles or pseudo-eosinophiles) or microphages, and, further, the lymphatic cells, the fixed elements of the connective tissue, the cells of the bone marrow, of the spleen, tonsils, isolated follicles, Peyer's patches, glands, lung, pulmonary alveoli, &c., or macrophages, are capable of playing a double part in the defence of the organism against infections, on the one hand by enveloping and dissolving the pathogenic bacteria (phagocytosis), on the other hand by secreting *antibodies* (*alexines* and *antitoxins*), some of which kill bacteria and also check or stop their development, while others neutralise bacterial toxins. When the organism is refractory, the bacterial toxins exert a chemiotactic action of a positive nature upon the phagocytes, which, impelled by diapedesis, destroy the bacteria and neutralise their toxins. When, on the contrary, the organism is in a receptive condition the toxins exert a negative chemiotaxis, there is neither diapedesis nor phagocytosis, and the infection runs its course. Yet a first attack of the disease or a vaccination renders the phagocytes capable of reacting upon the toxins, that is to say, a negative is turned into a positive chemiotaxis, and the fact of this transformation occurring really constitutes the acquisition of immunity.[1]

At the Congress held at Budapest in 1894 Buchner, endeavouring to connect the antitoxic power of the body

[1] Cf. Metchnikow: "Leçons sur l'inflammation et l'immunité dans les maladies infectieuses" (Paris, 1902).

tissues with the activity of phagocytes, suggested that natural and acquired immunity are under the control of matters originally diverse, the first being the *alexines*, which are substances produced by the action of the leucocytes, and which are soluble, bactericidal and globulicidal; the second the *antitoxins*, modified bacterial products, non-toxic, non-bactericidal, not globulicidal, and which act far more by diminishing the receptivity of the organism and by stimulating its natural powers of defence than by neutralising or destroying the bacterial toxins. Here also the bactericidal and antitoxic power of the humours is evident, but it appears to be due either to the activity of the phagocytes or to the defect of function on the part of the microbes.

The cellular theory of immunity is generally accepted at the present time in spite of its many weak points, but it must be remembered that it furnishes a far more satisfactory explanation of the facts than do the different humoral theories. Yet certain points remain very obscure, and particularly the change in the nature of the chemiotaxis exerted by the microbic toxins, according to the state, refractory (naturally or by acquisition) or otherwise, of the organism. Further, it is possible that defensive reactions are not confined to the phagocytes, which seem to be actively defensive, while the tissues exert a passive defensive action; at least this would seem to result, from an interesting experiment of Roger on two guinea-pigs, one of which was intact, while the other was vaccinated against symptomatic anthrax. The tissues of the latter had been freed from the humours, which they contained, by means of a current of saline solution sent through the aorta, the veins being opened. The resistance of the muscles of the vaccinated guinea-pig

to the anthrax infection proves that the tissues are capable of destroying microbes even in the absence of the humours and phagocytes which they contain. It would seem, therefore, that in order to comprehend the mechanism of immunity, whether natural or acquired, the amplitude of the defensive reactions must be generalised, and they must be regarded as a means of adaptation in connection with general co-ordination.

As a matter of fact, in susceptible subjects, the toxins on entering the circulation modify the nutritive medium of the anatomical elements, and consequently the reactions of the synthesis of assimilation, for the first effect of a toxin is to impair the process of assimilation. Then one of two things happens : either the change induced is insupportable by the cell, which ceases to assimilate, and dies, or the change induced does not alter its plastic qualities, and it therefore remains capable of elementary life. In the latter case the cell has clearly undergone a change corresponding to that of the surrounding medium, the waste products of the synthesis of assimilation will not be the same as formerly, and will yield substances which may be lethal to bacteria, or, at all events, inimical to their development. Hence it is said that cells secrete antitoxins, that the humours possess antitoxic or bactericidal properties. The change may affect all the anatomical elements, but some of them are more sensitive to it than others ; these are the phagocytes, which is proved by the fact that these cells have a negative chemiotaxis as regards bacterial toxins, the organism being intact and fresh, while they have a positive chemiotaxis when the organism has successfully passed through a first attack of infection. But for such a result to be obtained the modification induced may be only of a chemical nature,

thus corresponding to the chemical adaptation of Danilewski, in virtue of which the entrance of elementary material belonging to a toxic group into the molecular complex suppresses the anisotony of the group. When our anatomical elements are victorious over an infection it is an evidence that this toxin, or certain of its molecules, has entered into a combination with the living complex without modifying its quality of plastide capable of elementary life. Thus our anatomical elements are no longer affected by this toxin—they are adapted to it, they are immune to it, at all events for a time, until a new adaptation replaces that brought about by the toxin in question. This new adaptation may, further, be simply a more or less incomplete return to the pre-existing condition. In all cases the elements of the tissues clearly participate, in varying degree, in this adaptation by means of the general co-ordination, and it is in this way that the experiment of Roger just referred to is explained. Thus immunity, whether innate or acquired, consists essentially in adaptation; but the result of this adaptation may be either an indifference to toxins and bacteria (bacteria only being capable of existing in the internal medium of an organism in virtue of the composition of this medium), or it may be an increase, under the influence of selection, which is established by the very fact of adaptation, of the positive chemiotactic and phagocytic properties. The latter is observed much more frequently in acquired than in hereditary immunity, as is easily understood, and thus an indirect support is accorded to the views of Buchner relative to the distinction between the *alexines* of spontaneously refractory organisms and the *antitoxins* of organisms which have been made artificially refractory.

From what has preceded it is easy to understand that the essential process of defence against the attacks of infection is an adaptation. This adaptation is the most constant, efficacious, and the most durable means of protection, and it is by this alone that it is possible to explain either the condition or the modes of immunity. Thus certain infections are only undergone once because the organ is then adapted, immunised in a definite manner. Other infections may be repeatedly experienced, but generally each successive attack is milder than the previous one, the chemical adaptation and the phagocytic selection being progressive. The latter infections, too, are only suffered from in youth; this period having passed, they do not attack the organism which has become progressively adapted to them. Thus when an infectious disease attacks populations hitherto free from the malady, it makes the most terrible ravages and seizes upon all the people indiscriminately, since none are protected by preceding adaptation. The well-known epidemic of measles in the Faroe Islands is perfectly convincing on this point.

Such are the facts and such the conceptions on which serotherapy and vaccination are based. But there is this difference between serotherapy and vaccination, that the first only aims at supplying, as a therapeutic agent, the soluble waste products of the synthesis of assimilation with elementary materials adapted to certain toxins, while the second introduces directly into the organism either bacteria themselves, attenuated or not, or their toxins, in order to procure adaptation. In the first, therefore, there is not in reality an adaptive reaction of the organism, while there is such in the second. This is the reason why vaccination is more

active, more efficacious and more constant, furnishing an immunity which has a much longer duration.

2. Antitoxic and Anti-infectious Serums.

A. *Antitetanic Serum.*

Cultures of the bacillus of tetanus in bouillon of peptonised beef to which 0·5 per cent. of gelatine has been added are made use of; this culture is placed in the incubator and kept at a temperature of 37° C. during two or three weeks. These cultures when filtered furnish the test toxins, which are very active, and can kill a mouse in quantity of $\frac{1}{4000}$ c.c. The horse is the animal chosen in order to obtain immunisation and the therapeutic serum, because the healthy serum of the horse is almost harmless to man, and also because the animal is capable of supplying large quantities of blood. In the first instance the horse is injected with $\frac{1}{2}$ c.c. of a mixture of equal parts of toxin and of Gram's or Lugol's solution; the injections are continued in gradually increasing quantities. On the seventeenth day 10 c.c. of a mixture of two-thirds toxin and one-third iodised solution is injected; the proportion of the iodised solution is diminished up to the thirty-fifth day, and then 10 c.c. of pure toxin are injected. This quantity is now injected every two or three days until the seventy-second day, according to the intensity of the reaction, when 150 c.c. of pure toxin are injected at once. At the end of some days the immunity is at its maximum, and the serum of the animal may be employed therapeutically; but in order to support the production of antitoxic substances, which otherwise rapidly decreases, it is well to administer from time to time a new injection of pure toxin.

The blood of a horse thus immunised is drawn from the jugular vein, all necessary precautions being observed, and is received in a glass bowl, in which it is left for a day or two; then the serum which has separated is decanted into bottles each containing 10 c.c., and these are placed upon the market. All the bottles, corked and sealed, are put for some days into an incubator at a temperature of 37° C., and those whose contents become cloudy are rejected.

Serum thus prepared (and every variety of serum is obtained by nearly the same process) will keep perfectly well for a whole year if it is properly corked and not exposed to the light. In Germany a small quantity (0·5 per cent.) of formol, or of carbolic acid, is added; at the Pasteur Institute tyndallisation at a temperature of 56° C. is considered sufficient, as it suffices to cause perfect sterilisation, and enables the serum to be made use of without any risk of accidents arising from the presence of antiseptics. At the Pasteur Institute serum in powder is also prepared; this is obtained by the desiccation of liquid serum *in vacuo*. The powder is almost as active as fresh serum; in order to use it it is dissolved in eight to ten times its weight of filtered and sterilised water.

The activity of serum may be estimated both as regards its *immunising* and its *antitoxic* power. According to Roux, a serum is active to the millionth degree when 1 c.c. of the serum immunises 1,000 kilogrm. of mouse weight, that is to say, it is sufficient to inject on a mouse a quantity of serum equal to $\frac{1}{1000000}$ of its weight in order to protect it against a mortal dose of toxin. Behring, who introduced this method of estimation, has abandoned it for another which calculates the

antitoxic power, and which consists in fixing, *in vitro*, the quantity of serum necessary to render inoffensive a given volume of a toxin whose activity is known.

The discovery of an antitetanic serum is due to the researches of Behring and Kitasato (1890); as a preventive it is very active, but its curative power is far less reliable. This appears to arise, according to the researches of Metchnikow, Marie, Roux, and Borrel, from the fact that the tetanic toxin attaches itself very closely to the nervous system, and that the antitoxin is powerless to neutralise the toxin when thus fixed. Roux and Borrel have, indeed, recommended the intracerebral injection of serum, but this method, which has given some results in the guinea-pig, is so inconstant in man that it cannot be considered satisfactory. To sum up, when the symptoms of tetanus are fully developed antitetanic serum is almost useless; hence it should be employed when the malady is suspected. When the treatment is inaugurated before the medulla oblongata is involved recovery is probable.

As a preventive, and in the event of slight injury, an injection of 10 c.c. generally suffices; if the wound is extensive, contaminated, and difficult to clean, a second injection should be employed about eight days after the first. Lastly, when the symptoms of tetanus rapidly develop 50 to 100 c.c. of serum, given in one or two injections, are necessary; but these injections, it must be clearly understood, by no means dispense with the necessity of a strict employment of the usual methods of treating a wound. It must be added that the period of immunity conferred by the serum varies from fifteen days to one month at the outside.

Occasionally some sequelæ of the treatment are

observed: erythema, arthralgia, myalgia, sometimes albuminuria. But these complications have no real gravity, and disappear after some days. They seem to be due, not to the antitoxin, but to the horse serum.

B. *Antidiphtheritic Serum.*

This is prepared nearly in the same way as antitetanic serum, with Loeffler's bacilli in Martin's medium; at the end of thirty-six hours the surface is covered with a film. The toxin employed, which should in doses of $\frac{1}{10}$ c.c. kill 500 grm. of guinea-pig in forty-eight hours, is injected into horses in the following manner in order to obtain immunisation: the first day $\frac{1}{4}$ c.c. of toxin mixed with $\frac{1}{10}$ Lugol's solution; second day $\frac{1}{2}$ c.c. of the same mixture, and this injection is repeated every day up to the eighth; then the quantity of iodised solution is diminished up to the seventeenth day, on which $\frac{1}{4}$ c.c. of pure toxin is given. By this treatment œdema is produced, but no fever. From the twenty-second day increasing doses of pure toxin are given every second or third day, in such a way that on the fiftieth day 30 c.c. are employed, 60 c.c. the fifty-fifth day (up to the sixty-seventh day), 90 c.c. the seventy-second day, and, lastly, 250 c.c. the eightieth day. Before being bled the animal is allowed a respite of twenty days. As is obvious from the mode of procedure, the process of immunisation is slow, requiring four months. Landouzy[1] has proposed another and more rapid method adopted by Parodlorsky and Maksutoff, by which a horse can be immunised in forty days. By this method the antitoxic

[1] Cf. "Les sérotherapies" (Paris, 1898).

serum is first injected into the horse, and afterwards the diphtheritic toxin in increasing doses up to 1,200 c.c. It appears that the serum obtained by this method is not inferior to that which is made by the slower process.

The activity of antidiphtheritic serum is measured in almost the same way as that of antitetanic serum, but the values are somewhat different. If $\frac{1}{100}$ c.c. of serum protects a guinea-pig of 500 grm. weight, the serum is active up to $\frac{1}{50000}$; in other words, a quantity of serum equal to $\frac{1}{50000}$ body weight of guinea-pig is sufficient to protect it against infection. This method, employed by Roux, thus estimates the preventive power of the serum. The serum of the Pasteur Institute possesses a power above $\frac{1}{100000}$. In Germany, Behring and Ehrlich employ the method of mixture which, on the contrary, estimates the antitoxic power. The serum, of which 0 c.c. ·1 exactly neutralises 1 c.c. of the toxin, that is to say, one hundred times the dose which is fatal to the guinea-pig, contains in each $\frac{1}{10}$ c.c. an *antitoxic unit*, or an *unit of Ehrlich*. But if a serum neutralises 1 c.c. of the standard toxin, in the dose of $\frac{1}{1000}$ of 1 c.c. (0 c.c. ·001), it contains 100 antitoxic units. It is allowed that the $\frac{1}{100000}$ serum of the Pasteur Institute is equivalent to about 250 Erhlich units.

Antidiphtheritic serum is endowed with well-marked antitoxic powers. It gives very remarkable results, results which have been confirmed by a large number of observers, since the general mortality of diphtheria, which was formerly about 60 per cent., has fallen to 15 per cent., and even to 5 per cent., if those cases are omitted in which the treatment was commenced too late. As a matter of fact, the serum is almost powerless when the bacterial toxin is diffused through the body, when there

is paralysis, irregularity of pulse and respiration. This is indicated by Bouchard's statistics:

Children treated on the			1st	day of	illness,	mortality,	0	per 100.
,,	,,	,,	2nd	,,	,,	,,	3	,,
,,	,,	,,	3rd	,,	,,	,,	13	,,
,,	,,	,,	4th	,,	,,	,,	23	,,
,,	,,	,,	5th	,,	,,	,,	40	,,
,,	,,	,,	6th	,,	,,	,,	51	,,

These figures prove that the early administration of serum when the clinical signs are affirmative, or even doubtful, is absolutely necessary. If the serum is given, a marked improvement in the general condition quickly ensues, and the false membranes are more or less rapidly detached. But when the streptococcus or staphylococcus is associated with Loeffler's bacillus, the effect is less constant.

Lastly, this serum is also preventive, as Landouzy has proved, for of 12,426 persons who underwent preventive injection only 53 contracted diphtheria, or 1 in 235. The immunity conferred lasts about three weeks.

In mild diphtheria 5 to 10 c.c. of serum suffice at the commencement; when the illness is several days old, or when it presents severe features, then 10 to 20 c.c. must be injected, whatever the patient's age. But, in very severe cases, and especially when the disease involves the larynx and bronchi, up to 30 to 50 c.c. may be used. And it is better to give a large dose at an early stage than to employ repeated smaller quantities of serum.

The injections of antidiphtheritic serum have certain drawbacks, the importance of which, however, seems to have been exaggerated. Some days after the injection

an urticarial eruption, with slight elevation of temperature, is often noticed; both symptoms are of short duration. More rarely polymorphic erythema and fever have occurred; and, quite exceptionally, painful swelling of joints complicates the eruption, more especially in grown-up people, and when the streptococcus is present in addition to Loeffler's bacillus. Under these circumstances the fever may last some days, but these affections are not in any way serious.

C. *Antivenomous Serum.*

The venins are probably analogous to bacterial toxins; they are not altered by Lugol's solution or by the iodine trichloride, but they are very sensitive to chloride of gold or to the hypochlorites, and this property has been made use of, as will be seen, in the preparation of serum. Their toxicity is considerably diminished by ptyalin, pancreatin, papain, less markedly by pepsin, rennet and amylase; this is why snake poison, when taken by the mouth, is usually harmless, the toxins being rendered inert by the digestive ferments.

Calmette maintains that the venins have a hæmorrhagic property which is distinct from their toxic property; the first marked attribute is destroyed by heating to a temperature of 70° C. Phisalix and Bertrand think that the venom of the viper contains two substances, one phlogogenous, which disappears at 80° C., the other toxic, which attacks the nervous system and causes considerable depression of temperature. But, contrary to what these authors have maintained, the action of heat does not transform the venin into vaccine; it merely diminishes its toxic properties. It must be mentioned, finally, that, as

Calmette has observed, the venin, when it is deprived by heat of its albumin, is neither retained nor modified on its passage through the "bougie" of a Chamberland filter.[1]

Antivenomous serum was simultaneously discovered by Phisalix and Bertrand (February 2nd, 1894) and Calmette (March 27th, 1894). For its preparation three principal methods are employed, all of which make use of the horse by preference. The first, adopted by Phisalix and Bertrand, consists in injecting venin which has been modified by heat; it is a very rapid method, for only forty-eight hours are required, but is insufficient. The second consists in inducing immunity by introducing small and repeated doses of venin; the procedure is long and the manipulations delicate. Finally, the third method, so far the most usually adopted, consists in inoculating a mixture of venin and of hypochlorite of soda or lime conformably to the procedure employed by Roux and Vaillard, who mix the toxins both of tetanus or of diphtheria with Lugol's solution.

Calmette at Lille makes use of the dried venin in quantities of 1 grm. dissolved in 100 c.c. of distilled water, which has been heated for half an hour at a temperature of 78° C. in order to get rid of the phlogogenes, and is mixed with decreasing quantities of hypochlorite of lime of $\frac{1}{60}$th strength. An injection is made on the animal every four or five days. At the end of two months a dose is tolerated which is capable of killing 100 kilogrm. of rabbit, no reaction ensuing. At the end of six months the serum is sufficiently active to be employed therapeutically.

Calmette measures the value of his serum by *anti-*

[1] Cf. Grimbert: "Les serums thérapeutiques" (Paris, 1899).

venomous units. The serum, of which 1 c.c. protects 1,000 grm. of rabbit against the fatal dose of venin, contains 1,000 antivenomous units. As regards the *toxic unit*, it is represented by two-tenths of 1 c.c. of a 1 per cent. solution of dried venin, which kills by intravenous injection a rabbit of 2 kilogrm. in twenty minutes. The serum prepared by the Pasteur Institute at Lille has an antitoxic value of 40,000 antivenomous units per ten cubic centimètres.

The immunity conferred by repeated inoculations of non-mortal doses of venin is of long duration: it may extend to eight months after the last inoculation. When the serum is made use of the immunity is fleeting, not exceeding two to four days, but is very powerful; even when injections are repeated daily, the refractory condition does not last after 20 or 30 days. The antivenin serum is efficient against the poison of all snakes and scorpions. Ten c.c., representing at least 20,000 antivenomous units, are sufficient in the majority of cases. But when the snake is a very dangerous one and treatment is commenced late, it is necessary to inject simultaneously two or three doses of 10 c.c. each. In spite of these injections it is necessary to apply a ligature or compression of the limb so as to hinder venous return, to wash the bites carefully in chromic acid in 1 per cent. solution, or with chloride of gold in 1 per cent. solution, or, lastly, above all, with hypochlorite of lime in 1 to 60 solution. The solution should be recently made. At the same time the patient should be roused by means of moderate friction, but it is useless to attempt to restore animation by alcohol or coffee. The serum is absolutely harmless; no complication occurs, and under its influence the condition of the patient improves in some hours.

D. *Antistreptococcic Serum.*

This serum has been studied since 1891 by Roger; in 1895 this author and Charrin published a new work on this subject almost contemporaneously with the memoir of Marmorek upon the serum which bears his name.

Roger and Charrin contented themselves with filtering and heating the cultivation of streptococci to 110° C. Marmorek commences by increasing the virulence of the streptococcus. In order to do this he cultivates it in human serum, or in ascitic fluid to which two parts of peptonised bouillon have been added: and he increases its virulence by passing it from rabbit to rabbit; after two months the virulence becomes so great that "a single microbe, so to speak, introduced beneath the skin of the rabbit suffices to kill it. An infinitesimally small quantity (c.c. 0·000000001) inevitably causes death" (Marmorek). It is essential, on account of the difference presented by the several varieties of streptococcus, as is pointed out by Courmont, Van de Velde, Lignieres, that a large number be cultivated together, so that a *polyvalent* serum may be obtained, which is applicable to the majority of cases.

Marmorek, instead of immunising animals, as Roger and Charrin, with warmed cultures, employs small doses of natural cultures of a very active streptococcus. The horse, ordinarily made use of, shows a very energetic reaction, and a new injection is given only when the health of the animal is completely restored; and more than a year must elapse before a really satisfactory serum can be obtained.

The serum is particularly efficacious in infections caused by the pure streptococcus; its action is less

energetic and less constant when the streptococcus is associated with other pathogenic bacteria. And in order to obtain satisfactory results in diphtheria, croup and scarlatinal angina, in which diseases the streptococcus is associated with the bacillus of Loeffler, it is necessary that a simultaneous injection of Marmorek's serum and that of Behring-Roux be made. In erysipelas the serum of Marmorek gives, according to Chantemesse, very gratifying results (the mortality falls from 3·8 to 1·5 per cent.) when its activity is from $\frac{1}{10000}$ to $\frac{1}{30000}$, calculated according to the method of Roux. In scarlatina, which is often complicated by streptococcic infection, Josias and Berginsky have observed that the use of this serum, without influencing in any marked degree the progress of the disease, yet acts very satisfactorily upon its complications, not only upon the sore throat, but also upon the adenopathies, &c.

In puerperal fever the results are less constant; yet Pinard finds the injection of the serum a valuable preventive when infection threatens. According to Landouzy and Claisse, this serum is also very efficacious in broncho-pneumonia of streptococcic origin; the temperature rapidly falls and cure follows. Lastly, in variola and in epidemic cerebro-spinal meningitis Lindsay, Wallach and Einsler have obtained unexpected cures by the injection of Marmorek's serum.

However, speaking generally, it may be said that the therapeutic properties of this serum are less pronounced than its preventive power. And it is necessary that it be used as soon as the suspicion of streptococcic infection arises. The quantity given is 20 c.c. at all ages, even in the youngest patient; should danger be imminent 50 c.c. should be injected at one operation, and this should be

repeated every twelve or twenty-four hours until the symptoms have entirely disappeared. After the injection a fugitive erythema may appear, but it is not accompanied by any serious symptoms.

The Pasteur Institute supplies serum desiccated *in vacuo* in sealed tubes, the contents of each of which correspond to 10 c.c. of liquid serum.

E. *Antiplague Serum.*

Yersin, in order to prepare this serum, injected a culture of a virulent bacillus upon gelose. To increase the virulence of the micro-organism, Roux cultivates the bacilli in capsules of collodion shut up in the peritoneal cavity of rabbits; afterwards he sows Kitasato's bacillus in a culture containing $\frac{1}{2}$ per cent. gelatine. The culture thus obtained is injected into horses, an intense febrile reaction ensuing; when the animal's health is restored, *i.e.*, after twenty days, the procedure is repeated, and so on. The horse serum only commences to possess preventive properties after six weeks, but a whole year must elapse before a serum can be procured which is both preventive and curative. The serum which Yersin made use of in Amoy (China) during the epidemic of 1896, and the preparation of which occupied a year, yielded twenty-one cures in twenty-three cases of the disease, while that which he employed in Bombay the following year, and which had been supplied by animals in process of immunisation, was really preventive, but did not reduce mortality more than 48 per cent., instead of 70 per cent.[1]

[1] J. Laumonier: "La Peste" (Paris, 1897); and "Mesures prophylactiques contre la peste dans l'Inde" (*Bull. de thérap.*, September 30th, 1901).

As shown by statistics, the serum is particularly efficacious in the early stages of infection; hence it must be injected when the first symptoms appear, and from the first large doses must be employed (20 to 30 c.c.). As a preventive 10 c.c. suffice, but as the immunity obtained is not of long duration it is advisable to renew the injection every ten days. As a curative agent, 20 to 30 c.c. must be injected and renewed several times if necessary until the fever, as well as the local and general symptoms, have disappeared. When the infection is taken in time, before the heart fails and the respiration and pulse become irregular, the fever generally yields in some hours and the swelling of glands (buboes) rapidly diminishes. The serum is by itself innocuous.

F. *Anticholeraic Serum.*

Cholera may be regarded as an acute poisoning due to the absorption of a toxic substance elaborated in the intestine by the comma bacillus. Therefore it is the toxin upon which it is necessary to act, and it is the toxin which must be procured in order to obtain a therapeutic serum.

For this purpose Metchnikow, Roux and Salimbini impregnate small capsules of collodion containing 2 per cent. peptone with virulent vibriones and place them in the peritoneal cavity of a guinea-pig. When the animal is dead, the contents of one of these capsules are sown upon a 2 per cent. solution of peptone to which 2 per cent. gelatine and 1 per cent. chloride of sodium have been added. After three or four days the virulence of the cholera toxin is at its maximum, and it is then used for the immunisation of the horse. The first injection of 10 c.c.

of toxin causes a rise of temperature to 40° C. and a considerable swelling at the seat of the inoculation. When these symptoms have disappeared, at the end of fifteen or twenty days, a fresh dose is injected which is stronger in toxin content, and so on. An intense reaction invariably occurs, but its duration becomes shorter and shorter. After six months it is possible to inject 200 c.c. at one sitting. The serum thus obtained is preventive and antitoxic; in the dose of $\frac{1}{150}$ c.c. it protects a guinea-pig against the lethal dose of living cholera culture.

There is yet another method, by the aid of the injection of living or dead bacilli; this is a real vaccination. This procedure was suggested by Ferran, of Barcelona, in 1885. In India from 1892 to 1895 Haffkine has employed cultures whose virulence has been increased by successive passage from guinea-pig to guinea-pig, and then diminished by exposure to the air at 39° C. In the first instance attenuated vaccine was inoculated, then after five days the stronger variety. Immunity was acquired after eight days, and the results thus obtained were very favourable. Yet it must not be forgotten that an animal immunised against the microbe is not necessarily so against its toxin, and hence it yields a serum which, though preventive, is not antitoxic.

G. *Antityphoid Serum.*

Chantemesse and Widal have made use of cultures deprived of the bacillus of Eberth by heating to 128° C. in order to prepare an antityphoid serum (1888). In 1892 the same authors, and also Sanarelli, endeavoured to render animals permanently immune by injecting into them cultures of increasing virulence which had been sterilised at 100° C. Lastly, in 1897 Chantemesse

recommended a new method which yields a serum capable of being used therapeutically.

Chantemesse employs typhoid bacilli whose virulence has been increased by a long sequence of transmission (nearly two years) from animal to animal, and which have been cultured in cold maceration of spleen and of bone marrow, to which a small quantity of defibrinated human blood has been added. After five or six days the filtered culture obtains its maximum virulence. The very active toxin contained in it is liable to change when exposed to air and light, but is not affected by heating to 58° C., even for an hour.

The toxin acts as an immunising agent on the horse; the immunisation is very slow, requiring about eight months, on account of the intense reaction which follows each inoculation.

The serum thus obtained has been made use of for the treatment of typhoid fever in the human being. It appears to exert a favourable influence on the temperature curve and the general condition, but observations are not yet sufficiently numerous to enable a definite conclusion to be drawn.

H. *Various Serums.*

In addition to the serums which have now been considered, many others have been suggested, and more especially the antipneumococcic serum of Issaeef (1893), the antitubercular serum of Maragliano (1895), the hydrophobia serum of Babès and Talasescu (1894), the leprosy serum of Carrasquilla and Laverde (1895), the antistaphylococcic serum of Viquerat (1895), the antisyphilitic serum of Richet, Héricourt and Tommasoli (1895), the

anticancerous serum of Ch. Richet (1895), the serum for relapsing fever of Gabritschewsky (1896), the anti-typhus serum of Raynaud (1896), the antirheumatic serum of Weiss (1896), the serum against scarlatina and whooping cough of Kélatidès (1896), the serum against the coli-bacillus of Salvati and Gaetano (1896), the yellow fever serum of Sanarelli (1897—98), the serum against pseudo-tuberculosis of Ledoux-Liebard (1897), &c. But not one of these preparations has yet been proved to be of real service; thus it is only necessary to mention them. However, it may be noted that the serum of Maragliano, if it is antagonistic to tuberculin, does not seem to have any influence on the infection, whose development it does not arrest, nor on all the toxins of the tubercle bacillus. Further, antipneumococcic serum has, according to Landouzy, given satisfactory results when employed by G. and V. Klemperer, Goa, Janson and De Renzi.[1]

3. Vaccinations.

The method of vaccination has been proposed in a certain number of diseases: in cholera, as already described, by the measures of Ferran, of Gamaleia, of Brieger, of Wattermann and of Haffkine; in whooping cough by Celli's process (vaccinal lymph, on account of the influence which the vaccine appears to exert on pertussis); and, lastly, in variola. But in the latter instance, for *variolisation*, or the inoculation of the virus of small-pox, has been substituted *variola vaccine*,

[1] Cf. Grimbert: "Les serums thérapeutiques" (Paris, 1898). For the bibliography of serums the complete and excellent work of Professor Landouzy may also be consulted: "Les sérotherapies" (Paris, 1898).

which consists in passing the variola virus through an animal (preferably the calf), and then in inoculating the product of the inoculation on man. But the question to be determined is, if there is identity between variola and vaccinia, and, on the other hand, if the variola virus is capable of causing an eruption of vaccinia in an animal. In spite of the experiments of Haccius, Eternod, Hime, and others, this question is very far from being decided, and the results do not seem to be superior to those obtained from Jennerian vaccination. We shall only discuss here the subject of anti-hydrophobia vaccination.

Antirabic Vaccination.

This method was devised by Pasteur, who maintains that the hydrophobia virus is localised in the spinal cord, and that the latter, in an animal suffering from rabies, contains at the same time both the virus of the disease and its vaccine. In order to attenuate the virus, the spinal cords of rabbits inoculated with the very active virus of rabies are desiccated: this drying process, when complete (thirteenth to fourteenth day), destroys the virus, retaining intact all the properties of the vaccine; hence the virus is more and more attenuated as the expiration of this period is approached.

At the Pasteur Institute the following method is adopted: The desiccated spinal cord is pounded with salted and glycerinated sterilised water, the whole is filtered and then injected under the skin in the quantity of 1 c.c. For the first injection the spinal cord of an inoculated rabbit dried to the fourteenth day is made use of, and this is therefore deemed to contain vaccine only. For the second injection, made two days later, a spinal

cord of the thirteenth day is employed, and so on. Towards the end of treatment, which lasts on an average twenty days, spinal cords which are continuously more recent are made use of for injection every day until the one is arrived at which is that of the day. These injections cause a little diffuse œdema, but when antiseptic precautions are taken no untoward results ensue.

The statistics published by the Pasteur Institute are fairly satisfactory, for it is necessary to make allowance for those cases in which hydrophobia is uncertain, particularly when the treatment is carried out immediately after the bite of the rabid dog. But when bites of other rabid animals (wolves, cats) are submitted to treatment the results are far from being so encouraging, and this lends force to the assumption that, in these animals, hydrophobia is more virulent, and thus resists the action of the vaccine which is efficacious in cases of canine hydrophobia.

IX.

NERVE ALTERANTS.

1. The Neuron and the Nervous Reactions.

The nervous system, the instrument by which several portions of the organism are brought into mutual relation and into that with the external world, is composed of special elements called *neurons*, a variety of cells which present, in addition to the nucleated cell body, ramified prolongations or *arborisations of protoplasm*, and one single prolongation, the *axis cylinder*, whose dimensions are sometimes considerable (1 mètre or more). The neurons are connected both with non-nervous anatomical elements and also with other neurons. In the first case the connection is established either by the protoplasmic arborisations—these are the *peripheral sensory neurons*—or by the termination of the axis cylinder—these are the *peripheral motor neurons*. In the second case, the connection is always heteronymous, *i.e.*, it is effected between prolongations whose characters differ (axis cylinder with protoplasmic arborisations), and never between those of the same nature (axis cylinder with axis cylinder, or arborisations with arborisations); and the neurons which are only connected in this manner with other neurons are called *central neurons*. Under the name of *associating neurons* are classed those neurons which connect the different levels, or the several layers, or the different

grey nuclei of the spinal cord, the medulla oblongata, the cerebellum and the cerebrum.

The neurons are no more endowed with spontaneous activity than are the other elements forming the bodily structures. In order that their activity may be roused, it is requisite that an excitation be applied to them, or, to speak more clearly, that they undergo a chemical change which is the result of external actions.[1] This change, which passes from neuron to neuron always in the same direction (that is to say, from the protoplasmic arborisations to the terminations of the axis cylinders in the same neuron, and inversely from one neuron to another), constitutes the *nervous influx*, is of a disorganising nature and analogous to that which passes, according to Grothus, in the electrolysis of water, where the constituents of a molecule of water are liberated at two points far removed from each other, without each atom being compelled to proceed a greater distance than that which separates two neighbouring molecules.[2] The reactions which follow the passage of the influx depend, therefore, directly upon the intensity of the excitation, or, in other words, on the importance of the molecular destruction set up by the excitant. When the excitation is feeble, the change does not reach the nerve centres, and there is no sensation; when it is sufficiently strong, the centres are affected, and sensation follows; when it is very strong, there is not merely sensation, but also *pain*, *i.e.*, consciousness of an abnormal destruction of nervous elements. Hence, pain is the result of every strong excitation which disorganises or destroys these elements. Although this is the case when an injury or

[1] Cf. J. Laumonier: "Physiologie générale," pp. 467 *et seq.*

[2] Cf. le Dantec: "Théorie nouvelle de la vie," p. 137, note.

burn, the action of caustic, &c., is in question, it does not seem to be the same when we suffer from neuralgia, cramp, or colic. But we now know, thanks to progress in microscopical technique, that under all circumstances definite alterations of the nervous elements are present.[1] The passage of the influx only occurs if the terminations of the axis cylinders and the protoplasmic arborisations are in direct contact, touching one another. The recent researches of Bethe and Apathy would tend indeed to prove, if confirmed, that there is not merely contiguity, but sometimes even *continuity*. As the terminations of the axis cylinders are, by themselves or by their adventitious fibres, in contact with a great number of protoplasmic arborisations, the influx, according to the adaptation of the neurons, may in the nervous system follow very different paths.

But however different they may be, these paths are not arranged haphazard. Indeed, although the ends of the axis cylinders may seem to be immobile, this is by no means the case as regards the protoplasmic arborisations. According to the researches of Rabl, Lépine, Duval, Demoor, Pupin, &c., these arborisations may execute restricted movements of expansion and retraction, but which are yet sufficient to break or to establish the contiguity, to hinder or prevent the passage of the influx, and are altogether analogous to the movements executed by the pseudopodia of an amœba. This property has therefore been called the *amœboism of the neurons*. This faculty does not exist, at all events in a definite degree, in all the nerve elements. Repeated and severe functional activity diminishes or suppresses it; an act

[1] J. Laumonier: "La douleur et ses remèdes" (*Rev. du monde moderne*, April, 1899).

which is at first conscious and voluntary, becomes, when frequently performed, instinctive and mechanical. The property, probably, is the appanage of the nerve cells, which are relatively the least active and the youngest, and, consequently, of the central neurons whose function is inaugurated very late, which are still being developed in the adult and which are far from being mature, *i.e.*, not unalterably connected, in the aged person.

From what has been said, it is possible to comprehend the difference between a reflex and a voluntary act. The reflex act concerns adult neurons only, those which are practically free from amœboism and in which, consequently, the nervous influx always pursues the same course. To a given excitation the response is therefore always the same, and it can be accurately anticipated. On the contrary, the voluntary act concerns neurons which are not adult, which are endowed with amœboism, and in which, consequently, the path of the impulse is extremely variable and cannot be anticipated. The response to a given excitation is therefore not always the same, and the act, differing according to circumstances, is called *voluntary*, because, although in reality rigorously defined, it nevertheless seems to be the result of a deliberation.[1]

Under what circumstances do the protoplasmic arborisations of the neurons undergo retraction and expansion? Under chemiotrophic influences. It is known from experiments upon algæ, bacteria, amœbæ, &c., that certain substances attract these unicellular organisms, while others repel them. It is the same as regards the arborisations of the neurons, and, according as the substance is positively

[1] J. Laumonier: "La fatigue et la sommeil" (*Rev. Univers.*, October 19th, 1901).

or negatively active, their arborisations extend themselves or retract. The effect exerted by substances which are positively chemiotactic, is to maintain, and even to increase, the connections of the neurons among themselves, and to open multiple and new paths to the influx. The effect of negative chemiotactic substances is, on the contrary, to break connections and to prohibit the passage of the influx, thus causing the centres or the portions of the nervous system whose neurons have retracted their arborisations to pass into a state of repose.

Amœboism, the existence of which experiments and observations both confirm,[1] is the condition of the normal or pathological nervous reactions. Indeed, if the influx which sets up, as we have seen, every excitation causes the reactions by promoting amœboism, or the expansion of the protoplasmic arborisations, it may be that the positive chemiotaxis exerted by the influx as concerns the arborisations is annulled by the stronger negative chemiotaxis of the matters which are accidentally present in the interior intercellular medium. In this case no remote action ensues, because, at certain levels, the influx is no longer transmitted on account of the retraction of the nervous network of prolongations. But it may also happen that the substances accidentally present in the interior medium may, on the contrary, favour amœboism by exalting the influx, *i.e.*, by increasing the molecular destruction which it transmits. In the majority of cases, the positive or negative chemiotaxis which sets up amœboism is localised in certain groups of neurons, and does not transgress their limits. Thus if cold water be applied, a contraction of the vessels of

[1] Cf. pour la démonstration de l'amiboisme: Mathias, Duval: "Précis d'histologie," 2 ed. (Paris, 1900).

the refrigerated region occurs, and of this region only. An irritation of a definite locality produces active congestion, followed by œdema, diapedesis, &c. In the same way intense and prolonged activity of an organ induces fatigue of this organ, which finally ceases to act, because, owing to the accumulation of waste products, particularly of the ponogenes, the cells become poisoned, and the arborisations of the neurons retracted.

The reactions vary according to the intensity and point of origin of the excitation; they may be symmetrical and homologous, as in the experiment of Brown-Séquard and Tholozan, or on the contrary, compensatory, as when a species of balance between the central and peripheral circulation occurs. Lastly, they may generalise themselves, and in this way obtain their maximum importance, whether they result from amœboid expansion, as in shivering, pain, delirium, convulsions, fever, &c., or whether they indicate, on the contrary, retraction of the protoplasmic arborisations, the momentary or definitive rupture of the central nervous connections, of co-operation, as in nervous shock, syncope, and death. Sleep is nothing more than a temporary rupture of co-operation, of the connections between the cerebral and reflex centres. We may add that age, sex, and heredity act in the same way as the point of departure of the excitation.

Thus it is evident, and hence it is unnecessary to labour the point, that amœboism is modified by changes, as also are the influx and reactional phenomena. Hence, when acting upon the centripetal paths, these changes induce retardation, abnormalities of reaction, or even entire absence of reaction (perceptions, mental operations); when they affect the centrifugal routes, there may be

an exaggeration, or suppression of motor, secretory, &c., reactions, contractions, cramps, trembling, disordered movements or paralysis, &c.

These considerations prove that certain causes influence amœboism and therefore the reactions which arise therefrom. The nervous influx is, speaking generally, a hyperæmia; an abundance of nourishment for the neuron in the intercellular medium increases amœboism, favours, by its positive chemiotactic influence, the expansive power of the arborisations. Hence frictions, sinapisms, warmth, massage by drawing blood to the skin, increase the *excitability* of the centripetal nerve terminations; on the contrary, fatigue (through intoxication the result of the accumulation of the waste products of functional activity), prolonged repose (through atrophy of the nerve elements), and cold (by inducing anæmia), diminish amœboism. Many poisons and toxins, both those of bacteria and of the tissues, have also an influence on amœboism, either increasing it, as is the case with the toxin of tetanus and of rabies, or, on the contrary, diminishing or suppressing it, as occurs with the toxins of diphtheria, ethyldiacetic acid, &c.

Inasmuch as abnormal materials, or those which are foreign to the organism, are capable of influencing the amœboism and the resulting nervous reactions, it is possible to combat the latter, when they have a morbid character, by the aid of matters which are endowed, so far as concerns the neurons, with antagonistic qualities. As a matter of fact, it is only in recent times that this mode of reasoning has been possible, and that it has been feasible to undertake the rational investigation of remedies which will counteract such and such a nervous change. For a very long period the treatment of nervous

disease was purely empirical, and the therapeutists who made use of this medication were scarcely acquainted with the mechanism of its action, and consequently with the strict indications for the employment of the long list of different products which is formed by the drugs having an action on the nervous system. At the present day, as we have already seen, our knowledge is somewhat more advanced, and we are able not only to choose, amongst those which are well known, the remedy which is best adapted to combat such and such a symptom, but further, and it is in this especially that real progress consists, to select artificially the remedy which is exactly antagonistic to such and such a reaction, as is strikingly shown by the law of Dujardin-Beaumetz and Bardet relative to the properties of the derivatives of the aromatic series, whether methylated or amidated.

The remedies which act on the nervous system are divided into two chief classes according to the views enunciated above.

The first group contains the nervous excitants, which stimulate the nerve centres and favour amœboism; these are divided into two categories: the trophic excitants, lecithins, the glycerophosphates, alcohol, tea and coffee; and the functional excitants, strychnine, brucine, ammonia, camphor. It should be noted that, these substances being toxic, large doses of them produce paralysis, and that hence they act as stimulants only in small or therapeutic doses.

The second group includes the nervous sedatives, and is by far the fullest. These remedies must be divided into: 1. Those which diminish nervous excitability and sensation and induce sleep, *i.e.*, those which exert a retractive action upon the neurons; examples are opium

and certain of its derivatives, morphia, codeia (other derivatives of opium, thebaine, papavarine, &c., resemble excito-nervins in their properties, such as strychnine), atropine, aconitine, conicine (or cicutine), &c. To them must be added the remedies which modify nutrition; these act much more feebly, and do not induce either total insensibility or sleep, but have a sedative influence on the whole nervous system, such as the bromides and the organic derivatives of arsenic (see "Cacodylates," &c., pp. 47 and 57). 2. The general anæsthetics or hypoanæsthetics, which cause insensibility, muscular flaccidity and sleep, such as chloroform, ether, nitrous oxide, &c. 3. The hypnogogues, which induce sleep and diminish reflexes, but which have only a slight influence on sensation, such as chloral, sulphonal, trional, acetophenone, urethane, chloralose, chloralamylene, paraldehyde, &c. 4. The local anæsthetics, which locally act on sensation, and the analgesics, which act on general sensibility, but neither by themselves induce sleep. Among local anæsthetics may be cited cocaine and the eucaines, orthoform, nirvanin; among the analgesics, antipyrin, exalgin, phenacetin, acetanilide, &c. Only the most recently discovered drugs, and those which are of real therapeutic value, and especially the new morphia derivatives, will be considered here.

2. Recently Discovered Derivatives of Morphia.

A. *Dionin.*

Dionin, or hydrochloride of ethylmorphine is represented by the formula $C^{19}\,H^{23}\,NO^3\,HCl,H^2\,O$. It is a white, crystalline powder, without smell and bitter to the taste, which melts at 123°—125° C., and is tolerably

soluble in water; at 15° C. 100 parts of water dissolve 14 parts of dionin.

Physiologically dionin appears to be intermediate between morphia and codeia, which is methylmorphine. Nevertheless, the very marked narcotic properties of dionin render its resemblance to morphia very close, while on the other hand its weaker influence on the spinal cord reflexes would approximate it to codeia, the latter being, as Bardet has pointed out, a very distinct depressant remedy. But the properties which have been the most thoroughly investigated are those which it exerts on the respiratory function. Winternitz has shown (*Therap. Monatsh.*, September, 1899) that, in the normal subject, the excitability of the nervous centres, the frequency of respiration and the amplitude of the same are in no degree influenced by doses of 0 grm. ·06 of dionin when given hypodermically. The experiments have been made on fasting persons with the apparatus Zuntz-Geppert.

Dionin is sedative, analgesic and hypnotic in action, and it has therefore from the first been used in a variety of ailments. Korte of Danzig, Bornikoel of Berlin, and Heim of Vienna have more especially experimented with it. It gives good results in the acute and chronic affections of the respiratory tract, in bronchitis, bronchiectasis, pulmonary emphysema, asthma, pneumonia, and pulmonary tuberculosis. It checks the paroxysms of painful cough, facilitates the respiratory movements, without making the expectoration more copious; it soothes patients without apparently affecting the respiratory exchanges. As hypnotic its action is sometimes, contrary to that of codeia (Bardet), more energetic and sure than that of chloral, sulphonal, or trional,

and it may succeed in cases in which these latter drugs have failed. As an analgesic dionin is also useful, it checks the most violent pain and thus induces sleep. Heim has succeeded in producing absence from pain in hepatic colic, in neuralgia and migraine, in gastralgia of nervous origin, and in ulcer and carcinoma of the stomach; similar results have ensued in parametritis and in uterine carcinoma, as also in painful acute rheumatic affections from Bornikoel's use of the remedy. This author also reports cases in which dionin has been completely efficient in removing the shooting pains of tabes and in the gastric crises of the same disease. The analgesic effect of the drug is first noticed about a quarter of an hour after its administration. As a rule, no unpleasant effects are induced, and no secondary disturbances ensue, such as headache, nausea, vomiting, heart trouble, suppression of urine, &c. It is true that digestive disturbances, and notably constipation, may be induced, but these are of far more rare occurrence than after peronin.

Dionin is made use of just as is this latter remedy as a local anæsthetic, especially in ophthalmic practice. Wolfberg has thus successfully used it. The presence of dionin in the eye causes at first the unpleasant sensation due to a foreign body; afterwards a slight sensation of burning and lachrymation ensues; all these disagreeable phenomena soon pass away, and the subsequent anæsthesia is fairly durable. Wolfberg makes use of solutions of 2·5 to 10 per cent., but he advises that these be prepared as wanted, inasmuch as the active agent is rapidly deposited. Lastly, it does not appear that the use of dionin causes injurious drug habit, and as its toxicity is relatively weak it may be employed in the treatment of morphinism, for it alleviates the

symptoms of abstention and hastens the invigoration of the mental faculties of the patient.

Dionin is given by the mouth, by the rectum or hypodermically; the daily amount is from 1·5 centigrammes to 3 centigrammes in a draught, in syrup, or in pills; 1 to 2 centigrammes in enema or suppository; 1 to 2 centigrammes hypodermically, but in the latter case the quantity of 2 centigrammes should never be exceeded *pro die*.

B. *Heroin*.

Heroin is the diacetic ether of morphine. Its formula is C^{17} H^{13} NO 2 ($CH^3CO.O$). It is a white crystalline slightly bitter powder, which melts at 173° C.; it is slightly soluble in water, but freely so in alcohol.

A large number of observers have investigated heroin and have determined as follows its chief properties. After its absorption it does not seem that heroin undergoes any decomposition in the animal economy; it is not acted upon either by the gastric or intestinal juices. It produces its effect in doses far smaller than those of morphine and codeine, and the medicinal dose is much less than that which proves fatal. Thus 1 milligrm. of heroin will cause a marked diminution in the frequency of respiration, while 1 centigramme of codeine phosphate will be required to produce the same result. On the other hand, the fatal dose of codeine in the rabbit is 1 centigramme per kilogramme, while that of heroin is 12 milligrm. Hence heroin is ten times more active therapeutically, and, at all events in man, is a little less toxic. But in animals, according to Guinard,

this toxicity is in certain instances more pronounced, those namely in which the animal has been excited by morphia. This circumstance is so obviously advantageous that it is unnecessary to dwell on the point.

Different explanations have been offered as concerns the action of heroin upon the phenomena of respiration. But it is incontestable that it diminishes the respiratory volume and frequency. Dreser has shown, from experiments on animals, that though the drug diminishes the frequency of respiration, yet the sensitiveness of the respiratory centre with regard to the chemical relationship of respiration and the contents of carbonic acid and of oxygen contained in the respired air, remain invariable. However, the researches of Winternitz have proved that what is true as regards animals does not always hold good in the case of the human being. He has shown that heroin markedly diminishes the excitability of the respiratory centre, and consequently diminishes the amplitude and frequency of respiration; this confirms what experiment had already pointed out, that heroin acts in the same way as morphia, but more powerfully.

According to Bougrier, heroin diminishes the frequency of respiration, but increases the length of inspiration in such a manner that more time is given to the air to enter the pulmonary alveoli. Further, the depth of the respiratory movement is considerably increased. Consequently, the frequency of respiration diminishing and the respiratory amplitude, on the contrary, increasing, the ventilation of the lung must be deeper and more effectually carried out. On the other hand, the actual work performed by an isolated inspiration has been proved to be slightly increased; hence it follows

that in administering heroin to debilitated patients there is no risk of weakening the muscular force and of thus causing an accumulation of secretion within the bronchial tubes. It is also proved that the consumption of oxygen is sensibly diminished, and the cause of this diminution would appear to be the suppression of those muscular movements which are useless or accessory. Further, the saturation of the blood by oxygen is not hindered, as happens in the case of those accidents which sometimes occur when morphine is made use of.

The sensitiveness of the respiratory centres as regards the chemical excitants, oxygen and carbonic acid, remains invariable, but the reaction to mechanical stimulation, although not abolished, is yet considerably diminished. This diminution of excitability to mechanical irritation explains the fact that patients are enabled to breathe freely, to take deep inspirations, and yet do not suffer from attacks of coughing, attacks which are really due to hyperexcitability of the damaged lung. Further, heroin is a mild hypnotic causing calm sleep, especially in children. In some cases this sleep is not so heavy as that induced by morphia; not seldom it is rather a condition of drowsiness and lethargy than of true sleep. Finally, in a dog, according to Guinard, as soon as the quantity reaches 1 centigramme per kilogramme of body weight the calm repose gives way to great excitement, although the resulting movements may be embarrassed by the paralysing effects of the drug.

Heroin does not seem to influence the heart, the circulation, nor therefore the blood pressure; hence it may be employed without fear of secondary troubles resulting in patients whose heart and arteries are weakened, and who in consequence cannot tolerate morphia. It does not

markedly cause constipation and does not interfere in any way with the appetite or with gastric or intestinal digestion. And Lépine has shown that it is endowed with anti-thermic properties which are more marked than are those of morphia, and that this influence is not accompanied with disagreeable or dangerous factors such as cramp, &c.

In consequence of these different properties, more especially of the influence on the consumption of oxygen and the reduction of fever, heroin is particularly useful in phthisis, in which disease it checks exaggerated combustion, reduces the tendency to sweating and calms the cough. It also gives excellent results in asthma and bronchial affections, as also in laryngitis, pharyngitis and catarrh. Its action is very rapid, being perceptible about half an hour after it has been taken. Kandel has made use of heroin, and with success, in the treatment of morphinism.

It may also be employed in children in obstinate and rebellious cough, and in the paroxysms of whooping cough; in the latter malady Runkel has obtained good results in three out of four cases. But in children the hypnotic action is paramount, and twenty or thirty minutes after the drug has been given the child falls into a deep sleep. For children the following is the posology recommended by Runkel of Bonn, who has especially studied the action of heroin from this point of view:

A child of 6 weeks	...	$\frac{1}{4}$— $\frac{1}{3}$	milligramme.
,, 3 months	...	$\frac{1}{4}$— $\frac{1}{2}$	,,
,, 7 ,,	...	$\frac{1}{4}$— $\frac{2}{3}$	,,
,, 10 ,,	...	$\frac{1}{2}$—1	,,
,, 15 ,,	...	$\frac{1}{2}$—$1\frac{1}{4}$	,,
,, 20 ,,	...	$\frac{1}{2}$—$1\frac{1}{2}$	,,

For adults the average dose is 5 milligrammes three or four times a day. In asthma up to 1 centigramme may be given. The drug may be taken in pills, cachets, or alcoholic solution, for heroin is soluble in alcohol. In watery solution hydrochloride of heroin must be employed, as it is soluble in water. It may also be made use of by hypodermic injection, of which the dose is 3 milligrm. to 1 centigramme, not more under any circumstances, two or three times *pro die*.

3. Local Anæsthetics.

A. *Eucaines.*

The eucaines, first recommended by Vines, possess the same composition as cocaine, one atom of hydrogen being replaced by a methyl group. Their formula is $C^{19}\ H^{27}\ O^4\ N$; they are obtained by treating ecgonine with acid carbonate of oxypiperidine. Eucaine A. and eucaine B. are isomers of *position* which only differ in the degree of their toxicity; these bases are but slightly soluble in water, but their salts are more soluble. As a rule, hydrochloride of eucaine B. is employed; it is a white crystalline powder, very soluble in warm water; the solution does not change in consequence of successive elevations of temperature, so that it can be readily sterilised.

The effects of eucaine B. are almost the same as those of cocaine; this drug causes anæsthesia, but according to Pouchet, Reclus and Schmitt, this loss of sensation is less durable and slighter; on the other hand, Lewis S. Somers finds that, although anæsthesia may be slower in its production (8′), yet it lasts longer than that of cocaine. Further, contrary to the effect of

cocaine, which produces mydriasis and anæmia of the tissues, eucaine has no action on the pupil and is a vasodilator. On the other hand, it slows instead of accelerating the pulse, but does not appear to affect the vascular pressure. As regards its general action, eucaine B. does not seem to be much less dangerous than cocaine; as does the latter, it causes excitement, clonic convulsions, and its action on the heart may lead to dangerous syncope. But these drawbacks are only to be feared when too large quantities of eucaine are incautiously employed. As eucaine B. is about 3½ times less toxic than is cocaine, all danger can be avoided by employing a 5 per cent. solution for local application and a 3 per cent. at the most for hypodermic injection in quantities of 1 to 4 c.c.

Eucaine has been particularly recommended for the production of local anæsthesia in dental operations, in which it gives good results, provided, of course, that the operator never neglects any precaution which is necessary in making use of this class of drug. Lewis S. Somers has also used eucaine as a local anæsthetic in nasal operations, and others have employed the drug in operations on the œsophageal and rectal mucous membrane. Berger, Legueu, Belt, Fuller, Schwergger, &c., recommend the combination of cocaine and eucaine B. for minor operations. This combination appears to bring out the virtues of each of these remedies, and at the same time to suppress their drawbacks. The following formula may be used for hypodermic injection in doses of 1—2 c.c.:

Hydrochloride of eucaine B. ...	}	0 grm. ·20
,, ,, cocaine ...		
Boiled and distilled water ...	20	,,

B. *Nirvanin.*

Nirvanin, first recommended by Einhorn and Heinz in 1898 as a substitute for orthoform, being capable of hypodermic use, is the methylic ether of diethylglycocoll-amido-oxybenzoic acid. It occurs as a white powder which crystallises in small prisms; it is odourless, but possesses a taste recalling that of iodide of potash. It melts at 185° C., is very soluble in water, slightly so in alcohol, and is almost insoluble in ether. It is neutral in reaction, but gives a violet colour with perchloride of iron. Finally, its solutions are very stable and can be several times re-sterilised without deterioration.

Five per cent. solutions are free from causticity, any local irritation produced by them is quite transitory. The toxic power of this drug is feeble, as shown by the figures of Joanin reproduced below, being the numbers which represent toxic equivalents in the same experimental conditions:

The toxicity of	holocaine	is	0·07	per kilogramme of animal.
,,	,,	cocaine	0·08	,,
,,	,,	eucaine A.	0·10	,,
,,	,,	eucaine B.	0·30	,,
,,	,,	nirvanin	0·70	,,

Consequently nirvanin is eight or nine times less toxic than cocaine.

But although nirvanin is but feebly toxic, its anæsthetic action is slow, very limited and not sufficiently well marked to allow the tissues to be cut without pain, even when 5 per cent. solutions are made use of. On account of the diffusive power of nirvanin being feeble and markedly inferior to that of cocaine,

small injections have been employed very close together, so that the anæsthetic solution is brought into immediate contact with the sensory nerve elements. If this method is not made use of and care is not taken to proceed from the periphery towards the painful centre by successive injections, sensation will remain almost uninfluenced, and indeed at the periphery a very sensitive, painful zone may be found. This phenomenon is connected with the property which nirvanin possesses of increasing the excitomotor power of the spinal cord, as also, according to Reynier, of causing, trembling, epileptiform convulsions, paralysis with visceral hyperæmia (cerebral, pulmonary, hepatic, &c.), which latter may be met with at *post-mortem* examination. The period of hyperexcitability and of reflex excitement is followed by that of clonicotonic convulsions. According to Joanin, there is also a slowing and diminution in the number of cardiac beats, the heart finally stopping during systole; according to Dumont and Legrand death is due to paralysis of the respiratory centre. The drawbacks to the use of nirvanin, in which must be included its slowness in producing anæsthesia which only ensues in ten minutes (cocaine causes anæsthesia in five minutes), are compensated, on the one hand, by its feeble toxicity, and on the other by the much longer continuance of the anæsthesia; the insensibility with a 2 per cent. solution of which 4 c.c. are made use of lasts for twenty minutes, or even for three-quarters of an hour or an hour, without its being necessary to renew the injection, so long as the ligature is kept in place. It may be mentioned, further, that nirvanin is slightly antiseptic, and that in a 2 or 3 per cent. solution it checks the growth of the staphylococcus.

Nirvanin is used in minor surgery in such operations as the opening of abscesses, whitlow, &c., and in dental cases. The results obtained are very satisfactory, especially in those cases in which it would be risky to make use of cocaine. In minor surgery 4 per cent. solutions are employed, in dental practice 2 per cent. solutions. In the manner already described, from 2 to 10 c.c. of these solutions may be injected. No accidents have, so far as can be ascertained, been recorded after operations.

C. *Orthoform.*

Orthoform, or methylic ether of metamidobenzoic acid, is a crystalline white powder, without smell and insipid, little soluble in water, but soluble in alcohol, ether and fatty bodies, and also in certain organic liquids, such as serous fluid.

This substance is a local anæsthetic and analgesic whose action is slow and progressive, but lasting. It is successfully employed in cases of painful wounds, where its action, although only developed after a lapse of a certain time, is prolonged for twelve or even twenty-four hours. It acts especially on mucous membranes, yet also on the skin, but only when the surface is cut or when there are erosions ; because, on account of its feeble solubility, its analgesic power can only be exerted when it is brought into immediate contact with the nerve elements.

Its toxicity is very feeble ; in the dog, when swallowed or injected into a vein, it amounts to 1 grm. per kilogramme of body weight, but when injected into the peritoneum 0 grm. ·50 produces decided effects. When the toxic dose is reached or is exceeded spasms supervene, as well as contractions and loss of equilibrium,

followed by coma. As a rule orthoform causes no irritation, yet Wunderlich and Vogt have found its application to be followed by slight erythema. Lastly, according to Mosse, the absorption of the drug is very rapid, for half an hour after it has been taken into the stomach, its presence can be detected in the urine in the form of a diamidophenol combination.

Orthoform gives good results in painful wounds and ulcerations of the tongue and larynx, of the stomach, in chancre, cancer, varicose veins, burns of the third degree, in excoriations and fissures of the lips, nipple and anus, and in dry and painful hæmorrhoids.

Orthoform is made use of either as ointment, pommade, or powder. In rebellious fissure of the nipple, Bardet recommends the following formula :

Orthoform	...	...	5 grm.
Sulphuric ether	...	...	q.s. to dissolve.
Oil of sweet almonds		...	20 grm.

To be painted on the affected part. It is necessary that the nipple be carefully washed with water alkalinised to a fifth before putting the infant to the breast, as orthoform is poisonous to babies. In fissure of the anus and dry hæmorrhoids, Bardet combines orthoform with Lutz's pommade of oxide of zinc and introduces the whole into the rectum by the aid of a canula attached to a bladder containing the mixture. In excoriated hæmorrhoids he uses also a powder formed of equal parts of orthoform and iodoform, which is applied by means of insufflation, and which induces rapid cicatrisation. The disagreeable smell of iodoform is thus rendered less perceptible.

Internally, orthoform is employed in the treatment of

ulcer and cancer of the stomach, and whenever there is erosion of the mucous membrane. The quantity made use of varies from 0·50 to 1 grm. *pro die.*

A combination of orthoform and hydrochloric acid, or of hydrochloride of orthoform, which is soluble in water, is employed in the same class of case as orthoform, except for analgesia of the conjunctiva and of the mucous membrane of the upper digestive and respiratory tracts, and as a hypodermic injection, on account of its acid reaction, which causes much irritation of the tissues. Yet in gonorrhœa urethral injections of this preparation have occasionally given good results.

D. *Salicylate of Methyl and Ulmarene.*

We shall study briefly in this place these two bodies, in spite of the fact that they belong to a different series, on account of their local and general anæsthetic and analgesic properties.

Salicylate of methyl has been known for some years; it is the active principle of essence of wintergreen. It is a yellow, volatile liquid, possessing a peculiar, slightly insipid, but very tenacious and disagreeable odour, and it contains about 90 per cent. of salicylic acid. The most characteristic property of this substance is the facility with which it is absorbed by the skin; indeed, after being painted on the skin it appears in the urine in less than a quarter of an hour. The maximum elimination is attained after six to eight hours, and elimination is generally complete after forty-eight hours. But this elimination, which is chiefly effected (80 per cent.) by the urine, must obviously affect the kidney in the same way as salicylic acid.

As a substitute for salicylate of soda, salicylate of

methyl is made use of in rheumatism, rheumatic arthritis, both acute and chronic, in rheumatoid pains, in which maladies it is of great value as a local analgesic, rapidly assuaging the pain. It has also succeeded in cases of torticollis and of rebellious zona. It is only employed externally as a paint, in quantity of from 4 to 16 grammes *per diem*. A more efficacious result may be obtained by pouring some grammes of the liquid on the painful part and then covering it with cotton wool and oiled silk or gutta percha.

When the renal permeability is impaired it should not be made use of, or, if so, only when great precautions are taken.

One of the greatest drawbacks of this remedy is, as already mentioned, its persistent and disagreeable smell, which is unendurable to many patients. Hence another substance has been sought for, which, while possessing the same therapeutic virtues, might yet be free from this objection. This substance has been found by Bourcet, and has been studied by Bardet and Chevalier; it is *ulmarene*.

Ulmarene is a mixture of salicylic ethers of alephatic alcohols of high molecular weight. It occurs in the form of a heavy, refracting, slightly rose-coloured liquid, which is almost completely odourless; it is insoluble in water, but soluble in alcohol, ether and chloroform, and it contains 75 per cent. of salicylic acid. It possesses exactly the same analgesic properties as salicylate of methyl, and is absorbed by the skin with the same facility. But it is got rid of more slowly; its elimination may be prolonged for 3 or 4 days after the cessation of the administration of the remedy. But its toxicity is markedly less, and it can be taken in quantity up to

5 grammes *pro die* without causing accidents. Finally, it does not seem to affect the temperature, but its influence on the kidney remains sensibly the same.

Hence it follows that ulmarene, almost free from unpleasant odour and less toxic, though possessing equally defined analgesic powers, may advantageously replace salicylate of methyl as regards all its therapeutic purposes. It is made use of in the same manner, and in the same quantity as is the last-mentioned medicament.

X.

THE ANTIPYRETICS.

1. Fever and its Indications.

Of all abnormal phenomena affecting the human body fever is perhaps the most common. Hence all the different schools of medicine, both ancient and modern, have endeavoured to explain its mechanism and its meaning. But in spite of the great number of theories and researches we hardly know anything, even at the present time, of the real nature of fever, and are still in need of a rational therapeusis for the same.

So far as we are aware, fever is but a symptom, and a complex one, whose most striking and constant character consists in abnormal elevation of the body temperature, *hyperthermia*.

But there is a real difference, although one often difficult to appreciate, between fever and *hyperthermia*, since in fever the existence of hyperthermia is accompanied with disturbances of secretion, respiration, of the heart's action, and of that of the nervous system.

When the causes of fever are left out of account, it is clear that febrile hyperthermia is merely an exaggeration of the normal thermogenetic processes. It will, therefore, be advisable to briefly recapitulate the principal features of physiological thermogenesis.[1]

[1] Cf. J. Laumonier, "Physiologie générale": "Thermogenese," pp. 491 *et seq.*

In adult man the mean temperature in repose is 37° C., but in the same person this temperature is not absolutely invariable. Under normal circumstances, it alters according to the part of the body considered and certain external conditions. From the point of view of the locality, the temperature of the periphery is obviously lower than that of the deep parts, and that of the extremities than that of the trunk. According to Cl. Bernard, the deeper regions may be divided into three zones in accordance with the temperature of the blood: the peripheral zone, in which the venous blood is colder than the arterial; the central zone, in which the venous blood is warmer than the arterial; the pulmonary zone, in which the arterial blood of the pulmonary veins is colder than the dark blood of the arteries. The rhythmical daily variations of temperature, observed by Jürgensen, Billet, Ch. Richet, &c., must also be noticed. According to these authors the minimum temperature of the twenty-four hours is observed in man at 4 A.M. (36°·5), and the maximum towards 4 P.M. (37°·5). Richet does not attribute this rhythmical variation to digestion, nor to the surrounding temperature, nor to the effects of work, but he thinks that it has a nervous origin. It may be, too, as in the periodicity of sleep, that the accumulation of certain waste products (hyperthermisants, convulsivants), which are met with more especially in the urine, may also have an influence in this matter. These waste products are found in the morning's urine, and it may be that they awake the patient. They are not wholly eliminated until the afternoon, while the waste matters which induce sleepiness are particularly prominent in the evening urine and that of the early night hours. However this may be, we have observed that in persons who work

during the night and rest during a portion of the day, the hours of maximum and minimum temperature change markedly. Lastly, the temperature varies according to age (the average is 37°·5 in the child, 37° in the adult, 36°·5 in the old), but less markedly according to sex and race.

As regards external conditions, alimentation does not seem to have any definite influence, for an evening meal does not prevent the fall of temperature which begins at 4 P.M. Nevertheless, after a full meal, a marked peripheral vaso-dilatation is sometimes observed. In inanition the temperature falls in the first instance and then remains stationary, and it is only shortly before death that a marked and abrupt fall takes place.

The variations of the temperature of the surrounding medium do not affect in any marked degree the physiological temperature in warm-blooded animals and man, owing to the phenomena of nervous auto-regulation which manifest themselves in order to counteract these variations of temperature when they attain a certain amplitude. When the external temperature rises, the influences by which a loss of bodily heat is effected come into action, *i.e.*, dilatation of peripheral vessels, sweating and evaporation by the skin and by the lungs, the latter being particularly active in those animals which do not perspire, in whom a marked acceleration of respiration occurs (*thermic polypnœa* of Richet). Obviously, under these circumstances, the movements of the air and its hygrometric condition favour or hinder evaporation and consequently refrigeration. On the contrary, when the temperature of the surrounding medium falls, vaso-constriction occurs peripherally; there is further an increase in the activity of the exchanges and of the

nervous reaction upon the muscular system, which is expressed by *rigor* or a generalised muscular contraction.

The controlling apparatus may also be put into action by an excitation of central origin, and in this case peripheral excitations do not take any part, or at most only a secondary one, in the appearance of the reactional phenomena ; hence it is the thermic elevation or depression of the interior medium and of the tissues which initiates them.

Thus the rigor may be of peripheral origin, and be simply produced by the external impression of cold upon the centripetal nerve-endings ; but it may also be of central origin, and be provoked by the direct excitation of the nerve centres by chilled blood. In the latter case the rigor occurs later than in the former ; in the same way the cooling which is manifest through the secretion of sweat, the abundant evaporation of water at the cutaneous surface, and vaso-dilatation, may be of peripheral origin when it is excited by elevation of the surrounding temperature (if the air is not saturated), and may also be of central origin when the internal elevation of temperature is provoked by excessive muscular activity, by excessive oxidation, over-activity of the glandular functions, or of those of the liver, &c., all these being normal factors of thermogenesis.

This regulative mechanism is, however, only capable of strictly maintaining the *physiological* temperature if the excitations are not too strong, for if this is the case the consequent reaction exceeds the normal limits. Thus a prolonged cold bath, which has reduced temperature by 2° or 3°, is followed, after some hours, by a reaction in which the temperature exceeds the normal. Professor Bouchard cites the case of certain patients

who, having swallowed carbolic acid, experienced a fall of temperature at first to 34°·8, with coma, and then after a few hours the temperature rose to 41·8, returning the next day to the normal. In the same way, after hard work, or after vapour baths, the temperature may in the first instance rise to 38° or 39°, then a progressive fall, sometimes below 36°, may ensue, to be followed only later by normal temperature. These facts show that the variations of temperature, when they attain a certain amplitude, have a tendency to compensate themselves, and this has been stated by Jürgensen in his *Law of Compensations*, which may be thus formulated: "The compensatory effort and the amplitude of the oscillations are proportioned to the extent of the first deviation."[1]

These abnormalities of the regulative mechanism are genuine *reactional fevers*, and they enable us to gain an insight into the mode of production of morbid elevations of temperature. In fever, whether nervous or toxic, the regulative mechanism is interrupted, according to Traube, who thinks that it is due to the constriction of the peripheral vessels and to the suppression of cutaneous evaporation, *i.e.*, to a diminution of the normal loss of heat by radiation. On the other hand, Regnard and Richet have shown that in fever, inasmuch as there is also an increase in the production of heat by increase of the deep oxidations, it is not merely a question of a diminution in the activity of the cooling process, but that as the deep oxidations involve an augmentation of respiratory exchanges, it follows that fever tends to spontaneously increase (Ch. Richet). Thus in fever there would be both diminution in the process of

[1] Guinon: "De la fièvre" ("Pathol. générale de Bouchard," tome III., p. 14).

refrigeration and increased heat production; the first would explain the secretory troubles, the second, the respiratory abnormalities and the frequency of the pulse. As the result of their researches on the *chimisme respiratoire*, and the urinary exchanges, chiefly in typhoid fever, Robin and Binet have arrived at the conclusion that there are two types of fever which differ in their symptoms, prognosis and treatment. The first type is that form of fever in which the hyperthermia is accompanied with an increase of oxidations and of the exchanges; the second is that in which the hyperthermia is, on the contrary, attended with diminution in the oxidations and exchanges. The first form is purely reactional; it should not be combated, but encouraged, for it points out that the natural defences of the organism have come into action; its prognosis is favourable. The second variety is, on the contrary, toxic; all its symptoms must be combated, and an endeavour made to restore the oxidations, by cold bathing for example. Its prognosis is much more serious. But it must be remembered that this arrangement is by no means absolute, since in tuberculosis, in which fever is accompanied with an increase of all the exchanges, indeed with a veritable consumption, it is necessary to moderate the hyperthermia and the oxidations.

The evolution and the course of the fever are subordinated to its cause and to the intensity of the defensive reaction. This is so obvious that it is needless to dwell upon the fact. Fevers are divided into two classes from the pathogenic point of view: those which are functional, nutritive and nervous and due to exaggerated functional activity, the result of intense excitation; and those which are toxic, being the result of auto- or hetero- intoxication.

Amongst the functional fevers must be mentioned: muscular fever, which is fleeting and slight; it is due to considerable muscular exertion, and Guinon allies to it the fever of child-birth of Pinard; digestive fever, and secretory fever (milk fever?); and, lastly, the various nervous fevers of reflex or central origin, such as those which are caused by emotion in certain debilitated subjects and which follow quite trivial causes, such as hysterical fever and neuro-traumatic fever, which occasionally follows slight traumatism of certain nerve centres, and the fever which sometimes attends severe paroxysms of pain, apart altogether from septic influence (hepatalgia, nephritic colic, &c.).

The toxic fevers are usually of longer duration and are more severe and numerous. The fever of auto-intoxication results from the accumulation of waste products of functional activity which act on the thermogenetic centres, or which, in order to become soluble or to be eliminated, appropriate a large quantity of oxygen. Gouty fever, that of chlorosis, of constipation, of overfeeding and of growth are included in this category, as is also the fever of asphyxia, and the pyrexia which accompanies the absorption of extravasated blood from traumatism.

The fevers due to hetero-intoxication are divided into two groups; the first, rare however, contains those which are caused by the ingestion of a poison possessing the power of inducing pyrexia. These poisons are strychnine, eserine, nicotine, picrotoxin, caffeine, curari, certain tissue poisons of serum, urine, &c. The second group is made up of those fevers which own a toxic microbic origin, *i.e.*, are due, not to the presence of the microbe itself, but to that of its soluble products, its toxins. In other words, these are the fevers of all the infections. In order

to explain them, Roger has propounded an ingenious theory. According to this author, the microbic poisons are really apyrexial in large doses, inasmuch as they cause death by collapse. Hence, infective fever is not due to the direct action of these poisons, but rather to a reaction of the organism, a reaction which, in conformity with Jürgensen's law, exceeds the physiological limit, and raises the temperature to a greater or lesser extent. The proof of this statement is that toxi-microbic hyperthermia is usually preceded by rigors—a reaction against hyperthermia whose meaning we are acquainted with—and which would be useless and inexplicable if toxins were really thermogenous. Further, in those infections which are serious and rapidly fatal, as in cholera, there is a fall of temperature, and fever, when it does occur, is a favourable symptom. In other infections, at an early stage while the vital forces are still active, fever is observed; but later, when death is approaching, when the economy is altogether ruined, and its defensive reactions are exhausted, the temperature falls below the normal because the only forces left in action are the apyrexial toxins.[1]

Although this is a very attractive explanation, it is yet far from being applicable to every case; for certain toxins of microbic origin have marked pyrexial powers, and further, in infectious fevers, the defensive reaction is no longer the sole cause of the hyperthermia. This explanation is not, however, unconnected, at all events from the therapeutical standpoint, with that of Robin and Binet, since it shows, as does the latter, that there are cases in which it is not desirable to oppose the fever, and others in which on the contrary it should be actively

[1] Cf. Roger: "Introduction à l'étude de la médecine" (Paris, 1899).

combated. As a matter of fact, reactive hyperthermia is due to abnormal metabolism, and to an increase in the activity of the exchanges which modifies nutrition and stimulates phagocytosis, the antitoxic power, the vital resistance, as has been shown by the experiments of Walther, Loevy, Richter, Filhene, Hildebrand, and Cheinesse. But pure toxic fever, where reactional pyrexia does not occur—as in serious cases of typhoid fever in which all the exchanges are diminished—or only occurs secondarily—as in febrile tuberculosis, when all the exchanges are, on the contrary, augmented—is far from indicating the vital resistance, the struggle of the organism, but, on the contrary, it points out the continually increasing power of the toxic element.

Hence the conflict must be waged with this latter, and for this purpose certain means are at our disposal of which some act by favourably influencing the exchanges, while others are adapted for the treatment of the fever itself, especially affecting the hyperthermia, which they reduce. We shall here leave on one side the first (stimulants, oxidising agents, baths, wet packing, &c.), and shall confine our attention to the most interesting of the new antipyretics.

2. New Antipyretics.

A. *Euquinine.*

The formula of euquinine is $CO<^{O\,C^{20}\,H^{23}\,N^2\,O}_{O\,C^2\,H^5}$; it is ethylcarbonic ether of quinine, and is therefore a synthetic product resulting from the treatment of quinine with ethylcarbonic acid. It forms fine, white needles which melt at 95° C., is soluble in alcohol, ether and

chloroform, but little so in water. With litmus paper it gives a basic reaction, and it combines with acids to form crystalline salts. It is almost tasteless, which gives it a marked advantage over the usual salts of quinine, and is but faintly bitter, the bitterness being easily covered by syrup, milk, cocoa, and broth. But the hydrochloride has a more marked and disagreeable taste, while the tannate of euquinine, sometimes employed, is free from all unpleasant savour.

Euquinine is well borne by the stomach; it causes neither vomiting nor dyspeptic symptoms, and those characteristic of quinine poisoning—headache and buzzing in the ears—never ensue. Its ingestion is followed by two different series of phenomena, of which the one is quickly developed and the other only appears after some time. The first group includes the fall of temperature which has been recognised by all authors, von Noorden, Overlach, Galiner, Thomas, Panegrissi, Fauser, Mori, Bianchi, Bardet, &c., as occurring in every case of pyrexia, whether the fever is periodic or not. But the very remarkable power of this drug over malarial fever and other kindred affections proves that the antipyrexial qualities of euquinine are partially united with its antiseptic influence with regard to the microbes of malarial fever.

The second group, containing those results which are observed only after a lapse of time, when euquinine is given for long periods, includes an increase in number of red corpuscles and of the hæmoglobin contents of the blood, as observed by Overlach. In connecting this action with the antibacterial influence of the remedy, Bianchi draws the conclusion that this drug acts in a special manner upon the spleen, and generally upon the

hæmatopoietic organs. In small doses euquinine exerts the tonic effects which follow the administration of similar doses of quinine. Lastly, according to Panegrissi and Gammarelli, the elimination of euquinine by the urine commences half an hour after its ingestion; the elimination attains its maximum in seven hours, and after forty-eight hours no trace of the drug can be detected in the urine.

From what has just been said, it is easy to gather the therapeutical indications for the employment of euquinine. According to the Italian physicians, who are in a position to form a competent opinion on the subject, euquinine is the best antimalarial drug, particularly in the case of young people, as is maintained by Bianchi, and a dose of 1 grm. to 1·50 as a rule suffices to bring the attack to an end. In the several varieties of intermittent fever, the same satisfactory results follow the use of the remedy. Its antipyrexial action is not less well defined in other fevers, and this is the more satisfactory, inasmuch as the remedy, even in large doses, does not cause any secondary accident or untoward symptoms. Von Noorden, who was the first, in 1896, to investigate euquinine, considers that 2 grm. of this remedy correspond exactly, as regards results, to 1 grm. of a soluble salt of quinine. And in pneumonia, typhoid fever, and hectic fever of tuberculosis the same satisfactory results have been obtained by the use of this drug as when quinine was employed. But euquinine possesses the incontestable advantage of being almost devoid of bitterness, so that, as Bardet has observed, the drug may be added to fluid aliments or fruit syrups, and consequently may be administered in small doses frequently repeated. This advantage, when taken in connection with its slight toxicity and with the

fact that it is well tolerated by the most feeble stomach, and further that no head symptoms follow its use, renders euquinine an extremely useful drug in the pyrexia of children. In whooping-cough its use causes an improvement which is often positive. Lastly, Overlach has obtained excellent results from its prolonged administration, in small doses, in chlorosis and anæmia in consequence of its hæmatopoietic action.

Euquinine is generally given in cachets of from 0 grm. ·25 to 1 grm. for adults once or twice a day; the smaller doses are used in cases of continued fever, while the larger are employed in those of malarial fever. For children doses of from 0 grm. ·10 to 0 grm. ·15, repeated several times *pro die*, are administered; the drug may be given with syrup or in water, milk or broth, &c. When thus used euquinine is always well taken by children.

B. *Pyramidon.*

Pyramidon is a once amidated and twice methylated derivative of antipyrin; it is dimethylamido-antipyrin or dimethylamido-phenyldimethylpyrazolon, to which Filhene, of Breslau, who made use of it for the first time, has given the name by which the drug is at present known. Pyramidon is a crystalline powder of a yellowish white colour, tasteless, and soluble in 10 parts water.

As regards its elimination, Hoffmann has demonstrated that pyramidon breaks up in the organism; in tubercular subjects not a trace of it can be detected in the excreta, but in health the remedy is never totally decomposed, about 1 per cent. being detected in the urine. Further,

in animals subjected to the toxic influence of the drug the author has detected pyramidon in the alcohol extract of the blood, liver, kidney, and small intestine, as also in the muscles, but he has not succeeded in ascertaining in what locality of the organism the drug is decomposed.

The properties of this new remedy are very interestingly elucidated by the law established by Dujardin-Beaumetz and Bardet.[1] It is proved by this law that the amidated derivatives of the aromatic series are endowed with marked antipyretic powers, while the methylated derivatives act as powerful analgesics. And, indeed, pyramidon, conformably to this law, is a very active antipyretic in virtue of its amidated molecule, and at the same time is also an effective nervine in right of the two methylated groups which have been integrated in the molecule of antipyrin.

It seems that pyramidon acts almost in the same manner on the nervous system as does antipyrin; it also increases the blood pressure, and markedly lowers the temperature; but this reduction of temperature appears to be due to the regularisation and augmentation of the loss of heat rather than to a decrease in its production, because, as will be shown further on, pyramidon seems to exert a positive influence on the nutritive exchanges. From this point of view it follows that pyramidon is all the more useful, inasmuch as no fears need be entertained during its administration that those secondary effects will be induced which are the result of diminished oxidation, the integrity of the

[1] Dujardin-Beaumetz and G. Bardet: "Note sur l'action physiologique de la methylacetanilide et sur l'action comparée des composés de la série aromatique" (C. R. Ac. des Sciences, March 23rd, 1889).

oxidative process being a most important factor in the struggle with febrile activity.

Yet it cannot be said that in all respects pyramidon exactly resembles antipyrin in its action. In the first place, if given in the same dose, it is more than three times more powerful than the latter drug in man ; in the second place, its action is slower, about two hours being required for its power to declare itself. But although slower in its evolution, its action is much more durable than is that of antipyrin. Thus it may be affirmed that pyramidon acts more gently and more temperately than does antipyrin, and that its effect is also far more lasting.

The analgesic properties of the drug manifest the same peculiarities ; slower in their development, they yet persist for a longer period. Lastly, pyramidon would appear to possess the very important quality of not inducing any untoward secondary effect: neither vomiting nor marked uneasiness follows its administration ; it seems to be endowed with diuretic qualities, and heart affections do not contraindicate its use.

Researches undertaken by Wihl, Spiro, and Filhene on the blood of animals treated by pyramidon have not revealed the presence of any material alteration in this fluid ; neither the blood corpuscles nor the hæmoglobin were modified or altered. *Post-mortem* examination of animals to which toxic doses of the drug have been given does not reveal the presence of hæmorrhages, or of fatty degeneration of organs, or of any obvious changes in the vascular system. Bertherand has occasionally noticed profuse sweating to follow the employment of the drug, but this chiefly in tubercular subjects ; and Gérest and Rigot in typhoid fever have observed slight

sweat rashes as the result of its administration. These trifling drawbacks, which are always most marked in phthisical patients, have suggested to Bertherand the propriety of making use of combinations of camphoric or salicylic acid with pyramidon. The bicamphorate of pyramidon has been successfully employed in tuberculous patients, and salicylate of pyramidon in those suffering from rheumatism. Once only when this salt was employed has a trifling urticarial erythema been observed.

To sum up, it may be said that the antipyretic and analgesic action of antipyrin and of its amidated and methylated derivative are nearly allied; but that, at the same time, each has its own influence, peculiar to itself, on the nutritive exchanges, as has been demonstrated by Robin and Bardet. In fact, antipyrin checks the respiratory exchanges, while pyramidon appears to increase them, and sometimes to a fairly marked degree. Antipyrin diminishes the amount of urea as compared with the total nitrogen; pyramidon increases it from about 10 per cent., according to Bertherand. The effect of camphorated pyramidon is similar, for this drug in a case of influenza observed by Bardet caused an equivalent elevation of the coefficient of nitrogenous metabolism. The antagonistic powers of these two drugs on the general metabolism are of great therapeutic value, for while pyramidon, in consequence of its influence in increasing the organic exchanges, is greatly superior to antipyrin in the treatment of febrile maladies, it is yet much inferior to the latter drug in simple diabetes, as has been shown by Robin and Bardet.

In diabetes there is no sluggishness of nutrition; on the contrary, the nutritive processes are all too actively

carried out. Thus it follows that pyramidon should increase, and as a matter of fact it does increase, the quantity of sugar passed in the urine. Hence the use of the remedy is contraindicated in saccharine diabetes and in azoturia, while antipyrin, by its power of diminishing nitrogenous metabolism, is a preferable drug in these maladies, the result of vices of nutrition. Thus these two substances, so similar in appearance and possessing antipyretic and analgesic properties, yet manifest specific modes of action which are not merely interesting, but are also of great value in practice.

Apart from this formal contraindication in diabetes and azoturia, pyramidon gives very satisfactory results, on the one hand when made use of as an antipyretic in simple or complicated pyrexia, and more especially in the hectic fever of tuberculosis, in peritonitis, typhoid fever (Gerest and Rigot), bronchitis, pneumonia, pleurisy, influenza, erysipelas, and the infectious fevers.

On the other hand, the drug may be advantageously employed as an analgesic in anæmic headache, toxic polyneuritis, intercostal neuralgia, the painful symptoms in pseudo-leukæmia, in those of rheumatic origin, in neuralgia, particularly in the obstinate relapses of trigeminal neuralgia, and finally in the lightning pains of tabes dorsalis (Legendre and Dubois). It should be mentioned that, for antipyretic purposes, the bicamphorate of pyramidon is preferable in tuberculous cases, while, when analgesic effects are desired, the salicylate of pyramidon gives the best results, assuming, of course, that there is no counter objection to its use. In any case, whether pyramidon or its salts are employed, the drug should be administered at the very commencement of the symptoms, or even before this time if their occurrence can be

foreseen, on account of the relatively slow development of the analgesic action of the remedy.

Pyramidon and its salts may be administered either in cachets or in solution, the average dose being from 0 grm. ·25 to 0 grm. ·60 *pro die*. But the dose may be fractionally increased up to 1 grm. or 1 grm. ·50 *pro die;* Legendre and Bardet have given up to 3 grm. of pyramidon in one day without accidents arising. In solution of the strength of 1 in 60 the remedy may be given in tablespoonful doses, three or four *pro die*, for adults, and in teaspoonful doses, three or four *pro die*, for children. For children this is the preferable form of administration of pyramidon, for the drug is not only soluble in the ordinary vehicles, but is also not unpleasant to the taste and is well borne.

Finally, the hypodermic method of administration has been made use of by Bertherand, more especially in sciatica, with satisfactory results, at the rate of 10 centigrm. per injection, of which one or two are administered *pro die*. The effect obtained is quite as definite as when larger doses are given by the mouth.

C. *Acetopyrin.*

Acetopyrin is acetylsalicylate of antipyrin, or, in other words, a kind of combination of aspirin and of antipyrin. It occurs in the form of a white crystalline powder with a faint odour of acetic acid or of vinegar, fusible at 64°—65° C., very slightly soluble in cold water, more so in hot water, and soluble in alcohol and chloroform.

It gives the same reactions as antipyrin, and turns red when treated with perchloride of iron.

This new product seems to possess the same properties as its constituents, salicylic acid and antipyrin, and it has therefore antiseptic, antipyretic, and analgesic virtues. Its toxicity is less than that of salicylic acid, for even when given in large doses no serious accidents occur.

Vollmann, of Berlin, has shown that acetopyrin is but feebly decomposed in the gastric juice. In the intestines, that is to say in an alkaline medium, it is dissolved and broken up into its elements, with liberation of salicylic acid. From this point of view acetopyrin exactly imitates the behaviour of aspirin: thus, when the gastric secretions are healthy, the ingestion of this remedy is not productive of any disturbance, and neither loss of appetite, nor vomiting, nor pain in the stomach, nor heartburn arises; there is, further, no buzzing in the ears, and deafness is not complained of. Lastly, no untoward symptoms seem to occur as regards the kidney, for analyses of the urine carried out each day of treatment have never shown either albumin or sugar to be present.

Acetopyrin is a fairly good antipyretic, causing on the average a fall of one to one and a half degrees in the temperature; it acts well in typhoid fever, pleurisy, influenza, and epidemic cerebro-spinal meningitis. Further, owing to its antiseptic properties, it seems, in certain cases, to favourably influence the duration of the disease. But in septicæmia it does not appear to favourably affect the septic phenomena, and in febrile pulmonary tuberculosis along with a fall of temperature, which may attain two degrees, profuse sweating and great depression are observed.

Like aspirin, acetopyrin is particularly efficacious as

regards pain. According to J. Winterberg, Braun, and Bolognesi, it gives satisfactory results in neuralgia, sciatica, polyneuritis, and migraine. But it is chiefly in acute articular rheumatism and in muscular rheumatism, according to Bolognesi, that acetopyrin produces the most markedly successful effects; as the result of its administration both pain and swelling rapidly leave the affected joints, while the rate of both pulse and respiration frequently diminishes. Further, the profuse sweats which are observed at the commencement, both those which are natural to the disease and those caused by the drug, promptly disappear, and a cure results in from four to ten days. In chronic cases which have been treated by the salicylates, acetopyrin is markedly superior in its action, and the disagreeable symptoms which are so often caused by the salicylates, such as abdominal pain, nausea, buzzing in the ears, soon disappear. Finally, Bolognesi recommends acetopyrin, on account of its antiseptic properties, as a good anti-blennorrhagic, this remedy, as we have already seen, producing no bad effects on the renal parenchyma.

Acetopyrin is preferably given in cachets containing 0 grm. ·50; one of these is taken every hour and up to 3 grm. may be given *pro die*. Winterberg and Braun have gone up to 7 grm. *pro die* in cases of neuralgia, sciatica, and polyneuritis without the least disturbance of bodily function being induced. Bolognesi usually limits the administration to three to four doses of 0 grm. ·50. The remedy may also be given in a syrupy solution, slightly alcoholised to dissolve it. As the taste of acetopyrin is agreeably acid, the drug is always well taken.

D. *Citrophen.*

Citrophen, discovered by J. Roos, of Frankfort, is a combination of one molecule of citric acid with two molecules of paraphenetidine. It is a white crystalline powder, tasting and smelling slightly of citric acid, and melting at 181° C. It is soluble in aerated water. Alkalies and acids decompose this product into its constituents; it is resolved in the same way in the economy, and its therapeutic virtues are those of the substances of which it is composed. On the one hand, the citric acid exerts a favourable effect on rheumatic affections, and on the other the paraphenetidine acts beneficially on pyrexia and neuralgia.

Thus citrophen is at the same time an antipyretic and an analgesic, and it has also a refreshing effect in virtue of its acidity. This preparation does not appear to be toxic, or at all events its toxic qualities are very feeble. Yet Schotten cites a case of a young woman, aged 20, suffering from rheumatism who, having taken 1 grm. of the drug, presented marked symptoms of intolerance of the remedy: there was severe head-pain, noises in the ears were complained of, profuse sweating ensued, and cyanosis of the face, lips, and hands was observed.

The rheumatic pains were not influenced by the administration of the drug.

But this is clearly an isolated case, for the majority of authors who have made use of citrophen—Benario, Kornfeld, Hirschkorn, Bolognesi—have found that it causes no untoward symptoms, neither nausea, nor vomiting, nor heat of the stomach; neither cyanosis of the face, vertigo, noises in the ears, nor a sense of emptiness of the head, which has been noticed to follow

the use of similar preparations. As much as up to 6 grm. of citrophen have been given without any unpleasant consequences. Lastly, citrophen does not lose its effect by repeated use, and it has been shown by Kornfeld that it is well borne by patients suffering from heart disease.

When used for its antipyretic effects, it is found that citrophen causes a drop in the temperature of from two to three degrees, and this about two hours after it has been taken. But this antipyretic action is often accompanied, in febrile maladies, with sweating of variable intensity, which may in febrile tuberculosis be very debilitating. But in enteric fever, gastritis, and influenza citrophen yields satisfactory results, and in rheumatic affections, rheumatic polyarthritis, and chronic arthritis the fever, according to Kornfeld and Bolognesi, rapidly falls, the pains cease, and the joint-swelling disappears. Kornfeld has also made use of citrophen in morphinism. In the headache of chlorosis and anæmia, in facial neuralgia, lumbago and sciatica, a very rapid amelioration of pain has been induced, and when citrophen is given in the evening the patient passes a quiet night, as Benario has pointed out. Finally, according to Hirschkorn, citrophen is often useful in hysteria, but its effects are less certain in hysterical neuralgia.

In children, citrophen gives very good results in quinsies and in certain of the febrile exanthemata, according to Kornfeld; it is useful also in whooping-cough. Tihel, of Vienna, has pointed out that, in the last-named malady, citrophen diminished both the intensity and duration of the attacks; but Bolognesi has not found that the drug has a reliable power of diminishing the number of attacks, or that it is efficacious

as regards the spasmodic element of the affection. It should be added that this drug is very valuable in children's practice, on account of its agreeable and refreshing taste.

Citrophen may be prescribed in cachets, each containing 0 grm. ·50, of which from two to four or even six may be given *pro die*. In children the dose must be reduced, from 0 grm. ·20 to 0 grm. ·30, which may be ordered in cachet or water, the latter being sweetened if necessary, several times a day. A 2 per cent. solution, of which two to four tablespoonfuls can be taken *pro die*, may be prescribed.

XI.

ANTISEPTICS.

1. Antisepsis.

Pasteur and the micro-biologists, by proving that a very large number of diseases are due to the presence and development of certain micro-organisms, have rendered great service, not merely to prophylaxis, but also to therapeutics. In truth, the very simple conceptions of the early period of research, according to which each pathogenic bacterium has its own definite mode of action, which determines, from the simple fact of its development in the organism, such and such a well-defined infection, have given place to a far more complex manner of regarding the matter, which, at the present day, inclines to emphasise the importance of the field in which the micro-organism develops, the vital resistance and the integrity of the natural means of defence on the part of the economy. But the therapeutic measures adopted have not materially changed since the theory of Pasteur was first promulgated, and it is only quite recently that a tendency has arisen to substitute asepsis for antisepsis, or to combine asepsis with those measures which are calculated to increase the vital resistance to the attacks of microbes. The therapeutic methods which are founded on micro-biology are, at all events theoretically, of very easy application, inasmuch as they consist in introducing into the medium in which pathogenic bacteria develop

antiseptic substances, *i.e.*, matters which are capable of arresting the development, and even of killing, the injurious elements. And the efficacy of this method cannot be gainsaid, as its employment in practical surgery has rendered it possible to produce statistics which show that mortality decreases, even in those cases in which surgical interference is considered to be most dangerous.

The antiseptic treatment of internal maladies has made less rapid progress; it has not, however, been neglected, but the results have been but moderately satisfactory. But the difficulties encountered in endeavouring to procure internal antisepsis are almost insurmountable, and have only recently been fully appreciated, for the antiseptic employed must not only arrest the development and weaken the vitality of the pathogenic organism in question, but must be so diluted as not to exert any injurious action on the cells of the economy, inasmuch as this antiseptic passes into the circulation and penetrates all the tissues, in order to exert its disinfecting properties wherever these are required. Now, it is obviously very difficult to meet with a substance which shall be endowed with offensive properties as regards microbes, and at the same time be perfectly innocuous to the tissue elements. So difficult is it to meet with such a substance that, so far, not one has been discovered, for all the antiseptics which are of any value are also toxic as regards the organism, although the degree of toxicity varies; but this toxicity, even though it may vary, is nevertheless sufficient to upset the metabolism of the tissues, and to diminish their power of resistance and their natural means of defence. Thus quinine, regarded as the accepted antiseptic for hæmatozoa and malarial fever, and for long years looked

upon as harmless, is nevertheless, when given in doses which are necessarily frequently repeated, a very active poison as regards certain anatomical elements, and particularly the red corpuscles, and a deglobulising agent. It is the same as regards carbolic acid, salicylic acid, creosote, iodine, mercury, and arsenic, although the two last-mentioned drugs would seem to possess, in small doses, the property of arousing the activity and increasing the number of phagocytes. Further, a recent observation of A. Robin[1] concerning the case of a syphilitic woman who was being actively treated with mercury, and who succumbed to an attack of typhoid fever, inasmuch as mercury was found in the liver and other organs, tends to prove that these substances are not only toxic to the organism, but are altogether powerless to kill many pathogenic bacteria.

The drawbacks to this method, which are innumerable, have led to the adoption of a new procedure, *the aseptic method*, which does not aim at combating infection, but rather tends to avoid it. Unfortunately this method, which does not poison the organism or injure its resisting power or its means of defence, is applicable only when the infected focus, or that which is liable to infection, is directly and immediately accessible, as in the case of superficial wounds, surgical injuries, the mouth, the nasal fossæ, the intestine, the urethra, the vagina, &c. Hence surgery has profited far more than medicine from this method, because accidents due to the absorption of iodine, carbolic acid, and mercury are much less likely to happen when the remedies are applied locally than when given medicinally, although it must be allowed

[1] "Dangers de l'antisepsie interne" (*Bull. de thérap.*, April 30th, 1902).

that by the latter mode of administration good results have sometimes been obtained, especially in gastro-intestinal affections.

Is this equivalent to saying that the employment of antiseptics is always injurious, or merely useless? Certainly not. They are, on the contrary, capable of rendering, and do render, when the affection is localised and its seat accessible, very real service. But for success to be obtained it is necessary that certain conditions must be fulfilled.

First of all, as concerns a given antiseptic, it is necessary to distinguish between the *inhibitory* power and the *microbicide* power of the given antiseptic; the first arrests the development and the vitality of the infecting germs, but does not kill them; the second kills them outright. It is obvious that the quantity of antiseptic required will be less in the first case than in the second. As regards the microbicide power, further, account must be taken of the time which is necessary for the production of genuine sterilisation, *i.e.*, for the death of the microbes; clearly the more concentrated the solution of the antiseptic, the more rapid the death of the micro-organisms. As Berlioz has well pointed out, the quantity of the antiseptic which is lethal to the microbe has no value unless the time required is indicated. Thus perchloride of mercury is fatal to the streptococcus, according to Tarnier and Vignal, in two minutes in 1 in 1,000 solution, but only in fifteen minutes in 1 in 10,000 solution. Thus it is essential, in practice, that the conditions referred to should be accurately stated. The following tables are taken from the work of Tarnier and Vignal,[1] and give for some of the principal antiseptics the

[1] *Archives de Médecine Experimentale*, July 1st, 1890.

inhibitory quantity and that which is microbicide, as well as the length of time required for the efficient action of the latter.

Antiseptics.	Quantity inhibiting. Grammes.	Quantity microbicide. Grammes.
Bichloride of mercury	0·015	0·05
Biniodide of mercury	0·040	0·15
Oxycyanide of mercury	0·050	0·75
Sulphate of copper	0·74	0·95
Thymol in soda solution	0·165	0·50
β. Naphthol	0·70	1·00
Salicylic acid	0·70	0·835
Phenol...	2·00	3·25
Boric acid	3·335	7·60
Hydrate of chloral	4·00	10·00

If it is assumed that the length of application, by lavage for example, does not exceed five to ten minutes, it is obvious from a glance at the appended tables that very few antiseptics can be successfully employed, and the more so because with many of them the proportion per 1,000 parts cannot be considerably increased without danger of accident on account of the toxicity and causticity of the drug. Further, even in the smallest quantity, especially in the case of young children and sensitive persons, toxic symptoms have been often observed, especially as regards perchloride of mercury, carbolic acid, and iodoform.

The drawbacks obviously are far less frequent and serious when the inhibitory power is alone needed, for in this case, speaking generally, a quantity ten times less than that necessary to produce microbicide action is required. But this inhibitory action only gives satisfactory results when the greater number of the pre-existing

Antiseptics.	Duration of contact in minutes.	Quantity microbicide. Grammes.
		per 1,000.
Bichloride of mercury	2	1
Do. ,, ,, ...	3	0·50
Do. ,, ,, ...	5	0·20
Do. ,, ,, ...	15	0·10
Biniodide of mercury	9	1
Do. ,, ,, ...	22	0·50
Do. ,, ,, ...	26	0·25
Iodine	8	3
Do.	15	2
Do.	60	1
Carbolic acid	15	30
Do. ,, ...	18	20
Permanganate of potash	30	0·50
Sulphate of copper	27	10
Do. ,, ,, ...	40	2
Salicylic acid	35	2·50
Thymol in soda solution	35	1
Oxycyanide of mercury	+ 60	1
Sulphate of copper	+ 60	5
Hydrate of chloral	+ 60	20
Boric acid	+ 60	30
β. Naphthol	+ 60	0·40

infectious germs have been killed by a previous dose of the microbicide, as is the case when wounds and surgical injuries are dressed. It must be added that the alkaline antiseptics are generally preferable, as they dissolve fatty matters, together with mucus and other products of secretion, and thus come into more intimate contact with the pathogenic bacteria, which are often protected by being covered up or by the medium in which they develop.

From what has been said it will be obvious that, if the difficulties attending direct antisepsis are great, those of internal or indirect antisepsis are still greater, because the antiseptic employed in this case can only reach the

infectious germs which are lodged in the deep organs, such as the heart, liver, and brain, by passing into the blood and into the internal intercellular medium, the lymph. But should the antiseptic be poisonous, this passage of the disinfectant becomes dangerous to the organism, and grave accidents may ensue. Hence it follows that, as Bouchard has pointed out, the inhibitory dose as regards bacteria must be less than the quantity which is toxic to the economy. Further, the effects of accumulation must not be overlooked, and these are not uncommonly observed. They are injurious to the economy, of which some organs may become seriously affected, but they do not seem to have a prejudicial influence on the parasites, because the amount of antiseptic material contained in the interior medium varies relatively little.

Lastly, it must not be forgotten that heat, the combination or mixture of the antiseptics, the nature of the vehicles employed, all influence the action of these substances. It is admitted that warmth increases their effect, and that when several antiseptics are combined, the product is more active than any one of the ingredients when used separately. But it must be particularly remembered that an antiseptic, when in the presence of living tissues, does not behave as it does *in vitro*, in the laboratory; for the vital activity of the tissues sometimes decomposes it, and the products thus yielded do not possess the properties of the original substance, either the antiseptic power being diminished or the toxic influence being increased. Further, this tendency of the body to decompose substances in contact with it is often made use of, especially in intestinal antisepsis; it is in this way that iodine is disengaged from iodoform, that salol yields

carbolic and salicylic acid, and that benzo-naphthol is decomposed into benzoic acid and naphthol, or phenol into naphthalene. It is sometimes maintained that these antiseptics are insoluble; in reality they are soluble, but very slowly, in organic liquids, and to this slow and slight solubility is due the possibility of employing them without serious drawbacks. In the second place, the properties of antiseptics are modified by the vital reactions, which weaken in a greater or lesser degree their disinfecting power. The fact is certain, but the mechanism by which it is effected remains obscure. It may possibly be due to phagocytosis, by which a portion of the antiseptic is appropriated, and in this way its quantity in the medium diminished. If this were so, it follows that internal antisepsis, though by itself of no direct value, would, by encouraging phagocytosis, in a round-about way lead to the destruction of infectious germs.

However this may be, internal general antisepsis is too uncertain and unreliable, and has given but very problematical results, as is proved by the fruitless endeavours to control tuberculosis, enteric fever, cholera, septicæmia, &c., by this method. Hence it is more and more neglected in favour of simple asepsis, the washing out of organs, evacuants, and more particularly of those methods which arouse and increase the natural means of organic defence and supplement them when they are abolished. General antisepsis will not recover its former position until we are in possession of antiseptics which are free from toxicity of every kind, and with the mechanism of whose action on the economy we are perfectly familiar. But of antiseptics of this nature we do not at the present time possess one, and it is not probable that many will ever be available,

inasmuch as, with regard to this order of chemical action, almost all forms of protoplasm, cellular and bacterial, react almost in the same manner and are equally sensitive.

As already mentioned, local antisepsis has remained more in favour because it is easy of application and more certain, and because it seldom leads to a general intoxication; and, further, when microbic infection is strictly limited, it has given positive results. And the number of local antiseptics is constantly increasing. We shall here only consider those which have been most recently introduced, and which appear to be really useful in the treatment of wounds, suppurations, and localised infections.

2. Derivatives of Silver.

Nitrate of silver possesses a powerful antiseptic action, especially as regards the gonococcus. This action does not seem to be the exclusive result of the coagulation of albumin and of the precipitation of the products of union between silver and albumin, but is also due to the presence of the silver itself, which appears to be *anisotonic* to a very high degree for certain pathogenic bacteria. Thus the possibility of preparing a large number of derivatives of silver has been entertained, these products being more or less completely free from the drawbacks of nitrate of silver, while yet preserving its disinfecting power. We shall consider here three of the newest and most interesting of these products.

A. *Argonin.*

This is a caseinate of silver which occurs as a white powder containing 4 per cent. of the metal: it is soluble in warm water, but less so in cold water; it is also

soluble in albuminous solutions, especially serum, is of absolutely neutral reaction, but is sensitive to light, so that preparations of argonin must be kept in bottles made of dark-coloured glass.

Argonin has been praised by Liebrecht and by R. Mayer, who have shown that it is endowed with genuine antiseptic properties, especially, like the other silver salts, as regards the gonococcus. If these properties are less active than those of nitrate of silver and of argentamine, yet, on the other hand, argonin is far less caustic than these latter; further, argonin possesses the advantage of losing to a far less degree than these antiseptics a portion of its disinfecting power when it is added to albuminous liquids. As regards activity, 15 parts of argonin are equivalent to 1 part nitrate of silver.

This remedy has given very good results in gonorrhœa and also in gonorrhœal and purulent ophthalmia; its use is attended with no drawback, it is not caustic, and does not irritate the mucous membrane. In one case of chronic urethritis a cure ensued in less than fifteen days, and from the first week gonococci disappeared from the discharge. It is employed in solutions of 1 in 50 to 1 in 100; it is advisable to add, as suggested by Bardet, one or two drops of ammonia to 100 c.c. of the solution in order to increase the activity of the remedy.

B. *Largin.*

Largin is a combination of silver and of nucleo-albumin, containing 11·1 per cent. of silver. It is a greyish powder, somewhat soluble (10 per cent.) in water and glycerine, but insoluble in alcohol and ether. The

clear, watery solution has a slightly alkaline reaction; it is not precipitated by chlorides or albumin.

Largin was called attention to by Pazzoli in 1897. All those who have made use of the remedy attribute to it an antiseptic power which is very real, and especially active against the gonococcus; indeed, in this connection the action of largin is scarcely inferior to that of argentamine. And it is well known that, when employed as a lethal agent of the gonococcus, argentamine is superior to all the silver combinations of the same kind. Yet largin has one drawback—its slight causticity, which makes the use of protargol preferable in cases of great sensitiveness.

Largin is especially useful in gonorrhœa, in which it gives satisfactory results. It is employed in solutions of increasing strength from 0·25 per cent. to 2 per cent., of which 10 c.c. are used as an injection three times a day, the strength of the solution being increased by 0·25 per cent. every three or four days. At the commencement of the treatment, which continues for four to five weeks, 0·25 per cent. injections of protargol may be employed; these accustom the patient to the use of injections of largin, which are more painful and can be administered later. When the gonococci disappear from the discharge and the urine is once more clear, it is advisable to associate with the largin an astringent solution, that of Ultzman, for example:

Sulphate of zinc ...		
Alum	ā ā 0 grm. ·25.	
Carbolic acid ...		
Distilled water ...	200 c.c.	

Lastly, it is important that the urethra be carefully

cleansed by two or three injections of previously boiled water, which are immediately returned, before making use of the largin injection; the latter should be administered very slowly. If these conditions are observed, a cure of even the most obstinate chronic urethritis is assured; the discharge rapidly diminishes, the gonococci disappear, and there is no risk of any complication arising.

C. *Colloidal Silver, or Collargol.*

Colloidal silver is an allotropic modification of silver; it was discovered by Carey Léa, and was first made use of therapeutically by Crédé, of Dresden. It was first introduced under the form of a blackish powder, forming, when dissolved in water, a dark brown opaque solution, which behaves, as shown by Lottermoser, like all other solutions of colloidal substances. Iodine, chlorine, and bromine form with this substance iodides, chlorides, and bromides.

Danlos and Cothereau have recently explained the mode of preparation of this product—its preparation being based on the reduction of a solution of nitrate of silver by citrate of iron. The product thus obtained is similar to the German collargol, introduced by Crédé. It occurs in small fragments having a metallic reflection, which is the more brilliant in proportion to the extent to which desiccation *in vacuo* has been carried. It contains 97 per cent. of silver, together with traces of iron and citric acid.

But as the result of researches undertaken by Hauriot on collargol made in Germany by the firm Heyden, it appears that this product contains an acid, *collargolic acid*, and that silver enters into the radical of this acid,

which is united to a base, probably ammonia. Hence collargol is not a simple reduction of silver to the metallic condition, but a collargolate or *argentate* of ammonia.

Colloidal silver is, it seems, a very active antiseptic, almost as energetic as perchloride of mercury as regards the majority of the pathogenic bacteria; this has been proved by Thiele and Wolf, but it has the great advantage of being neither irritant, nor caustic, nor toxic in the quantities which are required therapeutically. These antiseptic properties have been made use of both externally and internally.

It was first chiefly used in the form of soap or ointment, known as *Crédé's ointment*, containing 10 per cent. colloidal silver, in the treatment of a large number of diseases and of bacterial infection. Schirmer, Wolfram, Schlossman, and Thiele have used it successfully in furunculosis, septicæmia, osteomyelitis, fœtid bronchitis, erysipelas, endometritis, and cerebro-spinal meningitis. In the disinfection and antisepsis of deep surgical wounds, of cavities, of fistulous tracts the ointment of Crédé may be employed in the form of ovoids and bougies, each containing from 0 grm. ·05 to 0 grm. ·1 of colloidal silver. In otitis, cystitis, gonorrhœa, conjunctivitis, and gonorrhœal ophthalmia, particularly of new-born infants, a 1 per cent. solution may be advantageously used.

The solutions of colloidal silver are so slightly irritant and so little toxic that they may be used internally without inducing disturbance, either hypodermically in 1 per cent. solution (but these injections are sometimes painful), or preferably by the mouth, as this solution does not irritate the mucous membranes whether healthy or inflamed, and its use has never been followed by any

untoward results; it is well borne by all patients, even by children.

This mode of treatment has yielded very good results, especially in gastro-intestinal affections of childhood, chronic enteritis, and intestinal maladies generally. Klein gives the following formula for the administration of colloidal silver:

Colloidal silver	...	0 grm. ·5 – 2 grms.
Distilled water	...	50 ,, – 200 ,,
Fresh white of egg Neutral glycerine	...	ā ā 0 ,, ·5 – 2 ,,

Three teaspoonfuls a day in a glass of water or milk, preferably taken half an hour before meals.

The remedy may also be given in pills:

Colloidal silver	...	0 grm. ·5
Lactose ...	...	5 ,,
Neutral glycerine Distilled water	...	â â q.s.

To make 50 pills; two to be taken before each meal.

Netter, who, in France, has warmly supported the internal administration of collargol, has made use of the remedy in a large number of infections, and especially in pneumonia and the pulmonary complications, and even the broncho-pneumonia of influenza; the results have been fairly satisfactory, but unfortunately they do not appear to be constant, inasmuch as other observers have not been equally successful. The result seems to be less uncertain in typhoid fever (as the observations of Klein would indicate), but the observed facts are not yet sufficiently numerous for a new and more efficacious treatment, based on this method, to be inaugurated.

3. Derivatives of Mercury.

What has been previously said concerning silver (p. 303) may here be repeated with regard to mercury. But while silver would seem to be the specific in the case of gonococcic infections, mercury is, as is well known, the most active and the most certain agent against syphilis and its different manifestations. Among the new derivatives of mercury we shall only refer to *hyrgol*.

Hyrgol is colloid mercury, that is to say, mercury in an allotropic form which renders it soluble. It is a black, granular powder, insoluble in ether and alcohol, but soluble in water, forming a dark-coloured solution of neutral reaction—a solution in which the acid salts of the heavy metals and the alkaline earths form an insoluble precipitate by the displacement of the mercury. Hyrgol contains about 80 per cent. of mercury; sometimes impurities are contained in it, particularly salts of ammonia and soda.

This preparation, which was first studied by Lottermoser and later by Hœhnel, Neisser and Friedman, seems to be superior, when pure, to other derivatives of mercury, inasmuch as it is absorbed more rapidly and more certainly, is not irritant and is not liable to cause symptoms of mercurialism, salivation, gingivitis, gastro-intestinal derangement, &c. Therefore it may be of great service in the continued treatment of syphilis and of its different complications. It is made use of in several ways: first, as a hypodermic injection, an aqueous 1 per cent. solution being employed in quantities of 1 to 2 c.c.; but when thus used it is absolutely indispensable that the product be chemically pure. It may be given in pills,

each containing 1 centigrm. of hyrgol, one to two of which are taken daily for a month. It may also be ordered as an ointment of 10 per cent. strength. The method of Friedman, in which this ointment is made use of, consists in employing 5 grammes of the ointment as an inunction daily for six days; on the seventh no inunction is administered, but an ordinary full bath is taken, and then the treatment is recommenced as above. This method lasts from four to five weeks, and has always given extremely satisfactory results. The 10 per cent. ointment is also used for the purpose of making plasters with which ulcerations and indurated glands are covered. Lastly, the drug may be supplied in compressed tablets of 1 grm. each, which may be used either for mercurial baths, or for general disinfection.

4. Derivatives of Iodine.

Iodine is remarkable not only for its marked antiseptic power, but also for its property of neutralising bacterial toxins. Unfortunately this substance is too caustic and irritating to be employed in adequate doses, and this is the reason why attempts have been made to discover products, of which iodoform is the type, which are capable of slow decomposition in the organism and thus of releasing iodine, so that the valuable properties of the drug may be available, yet without danger arising from the causticity of the remedy. But iodoform, which fairly fulfils these conditions, has one great drawback—the extremely unpleasant and tenacious smell, which is difficult to conceal; several substitutes have recently been recommended which are free from this drawback. We propose to consider two of the most important of these preparations from the therapeutic standpoint.

A. *Di-iodoform.*

Di-iodoform has been prepared by Maquenne and Taine. It is a yellow powder, composed of prismatic needles, in the cold and in darkness being devoid of smell, but giving off a slight odour of iodine when exposed to light, which also causes it to darken in colour. Hence it is necessary to keep di-iodoform in red or yellow bottles and to take care, during its manipulation, that it is not too long exposed to the light. It is insoluble in water, and but slightly soluble in alcohol and ether, but is soluble in chloroform, benzine, and especially in warm toluene. It is very stable, and resists the action of concentrated and boiling nitric acid, but it is decomposed by warm alcoholic potash. It melts at 192° C., giving off fumes; when rapidly heated it resolves itself into its elements, carbon and iodine. When analysed it yields 4·62 per cent. carbon and 95·28 per cent. iodine, corresponding to the formula C^2I^4. Thus it may be regarded as the result of the union of two molecules of iodoform with a loss of hydroiodic acid, whence its name di-iodoform: $C^2I^4 = 2CHI^3 - 2HI$. Thus di-iodoform is, of all the derivatives of iodine, with the exception of iodoform, that which contains the greatest quantity of iodine, and it is to this circumstance that its remarkable antiseptic properties are due. Further, as iodine is given off very slowly, no irritation of the tissues results, and symptoms of iodism occur far more rarely, and only with larger quantities, than when iodine is made use of. Lastly, far from causing pain it seems, as shown by Mayet, to possess a genuine analgesic action in painful hysteria, in uterine anteversion and retroversion, and in cervical endometritis.

The indications for the employment of di-iodoform are the same as in the case of iodoform; but it possesses the great advantage over the latter of being almost odourless. Hallopeau, Brodier, and Regnauld have used it successfully in simple and ulcerated chancre, in boils, carbuncle, burns, and for the antiseptic treatment of wounds of all kinds. It may be dusted on to the affected surface, or it may be applied, as Bardet recommends, upon a tampon of absorbent cotton. In gynecological affections the following ointment may be used:

Di-iodoform	2 grm. ·5
Hydrochloride of cocaine	0 ,, ·5
Olive oil	2 ,,
Sterilised vaseline ...	50 ,,

Tampons to be smeared with the ointment and applied as directed.

B. *Traumatol.*

Traumatol, or *iodo-cresine*, prepared by A. Kraus, is a combination of iodine and cresylic acid which contains 54·40 per cent. iodine. It is a violet-coloured powder, insoluble in water and but little soluble in alcohol and ether, with a faint odour, but still weaker and less persistent than that of iodoform. Although containing less iodine than the latter substance, traumatol possesses almost equally powerful antiseptic properties; it is not irritating, and does not induce symptoms of iodism. It should be preferred to iodoform, particularly in children's practice, and may be regarded as being of the same value as di-iodoform.

Perier, Lyon, Petit, Tison, and Reynier have used it successfully in the dressing of wounds, whether of old

standing or fresh, in varicose ulcers, in soft and hard chancre, and in discharging lesions of the skin. When it is applied to moist surfaces its curative action becomes manifest. Laumonier, who has used it with good results in the treatment of wounds, has remarked, however, that traumatol, after a cure has been effected, leaves pigmentation of the skin behind it, but a different mode of preparation has led to the possibility of avoiding this drawback.

Traumatol is employed in powder to sprinkle over wounds; the remedy may also be incorporated in vaseline in the proportion of 2·5 per cent., or in glycerine and collodion 10 per cent. Further, traumatol gauze is also prepared for dressing wounds. Ladevie, Tison, and Kaminski have praised the use of iodo-cresine internally in the early stage of tuberculosis, from 10 to 20 centigrammes being given *pro die* in pills; these authors have found that the remedy is not only well tolerated, but that its use has been followed by a great diminution of the expectoration and in the number of bacilli, and by a general improvement of health.

5. Formol and its Derivatives.[1]

A. *Formol.*

Formol, formaldehyde, or formic aldehyde (CH^2O), although long known, has only recently been introduced into therapeutics on account of its very remarkable antiseptic properties. We are indebted to the researches of

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[1] It must be observed that the term *formol* is also used as a synonym for *formalin*. This is the commercial name of a 40 per cent. aqueous solution of formic aldehyde.

Trillat for the ability to manufacture the preparation. Commercial solutions of formol are of 40 per cent. strength. Formol possesses a very irritating odour: it is soluble in water; it coagulates albumin and hardens the tissues. When the solution is concentrated formol undergoes polymerisation and yields *triformol*, or trioxymethylene $(CH^2O)^3$, which possesses the same properties, and which can be easily obtained as a white powder, insoluble in cold water but soluble in warm water, by allowing the commercial solution of formol to evaporate.

The experiments of Trillat, Berlioz, Aronsohn and Schmitt have proved that formol is inhibitory to the growth of pathogenic bacteria in quantity of 0 grm. ·05 in 1,000, so that it stands almost on a level with corrosive sublimate. Unfortunately its microbicide power seems to be much less marked, inasmuch as Berlioz and Schmitt have shown that 1 in 1,000 solutions only kill pathogenic bacteria in six hours, and that the 1 per cent. solutions require not less than ten minutes for the same purpose to be effected. But the latter solution is too strong to be tolerated by the tissues. The considerable disproportion between the disinfecting power, the microbicide influence, and the irritating and caustic properties of formol specially stamp this product as very well adapted for the disinfection of instruments, clothing, &c., and this still more markedly as the vapour of formol is extremely bactericidal and its pressure allows of its penetrating very rapidly (two to four hours) everything contained in a dwelling-house.

According to Trillat and Berlioz, Buck and Vanderlinden, the toxicity of formol is 0 grm. ·07 per kilogramme in the dog and 0 grm. ·09 in the rabbit when given by intravenous injection, and 0 grm. ·8 when given

hypodermically. The vapour of formol is not toxic except in large quantities, but its irritating action on the eyes, nose, and throat prevents its use.

Formol has been employed in surgical practice and recommended by Le Dentu, Valude, and others. Winckel has also treated vaginitis and blennorrhagic and catarrhal endometritis by vaginal injections and cauterisation of the cervix and of the intra-uterine mucous membrane with water containing formol. As a rule solutions of 1 or 2 in1,000 are used. It must, however, be remembered that, in this strength, formol is inhibitory to the growth of bacteria, but not bactericidal, and even in 2 per 1,000 watery solution formol is very irritating.

Thus formol is especially employed for disinfection on a large scale; dressings, compresses, and bandages treated with formol are of great use, inasmuch as they are invariably sterile; and as in cotton dressings with formol the remedy is present as triformol (1·5 per cent.), becoming formic aldehyde when in contact with moist wounds, an antiseptic medium results, which is particularly favourable to cure. In the disinfection of clothing, bedding, and of dwellings, formol may advantageously be substituted for corrosive sublimate, for it is far less dangerous than the latter; it has but a fleeting odour, can be easily used, leaves no trace of its presence, and impregnation is aided by the high pressure of the vapour. In a few hours clothing, mattresses, &c., can be completely disinfected.

Berlioz has succeeded in effecting the antisepsis of the upper respiratory passages, by enabling the patient to breathe the much diluted vapour of formol; but treatment by pills of triformol has not been successful in tuberculosis, for the remedy is too irritating, and has never yet been tolerated by patients.

B. *Iodoformine.*

Iodoformine is a derivative of formol, which may be regarded as a very useful substitute for the latter.

This substance contains 80 per cent. of iodine; it is insoluble in water, in ether and cold alcohol, slightly soluble in warm alcohol, and soluble in acetone. When heated to 100° C. it decomposes, giving off iodine vapour.

Iodoformine is a very remarkable antiseptic, whose properties have been investigated by Bardet, Reynier, and Dignat. Being but slightly irritating and toxic and free from disagreeable odour, it may be advantageously substituted for aristol and iodoform in the treatment of ulcerations of the mucous membrane, of suppurating, and of surgical wounds, and of chancres. Its powerful antiseptic action is due to the iodine and the formol which iodoformine gives off, but it would further seem to possess the power of accelerating the cicatrisation of wounds. This beneficial influence would appear to be due, according to Bardet, to the formol, which seems to possess the property of stimulating the vitality of the tissues.

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THE END.

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