Collected papers on pharmacology and therapeutics.

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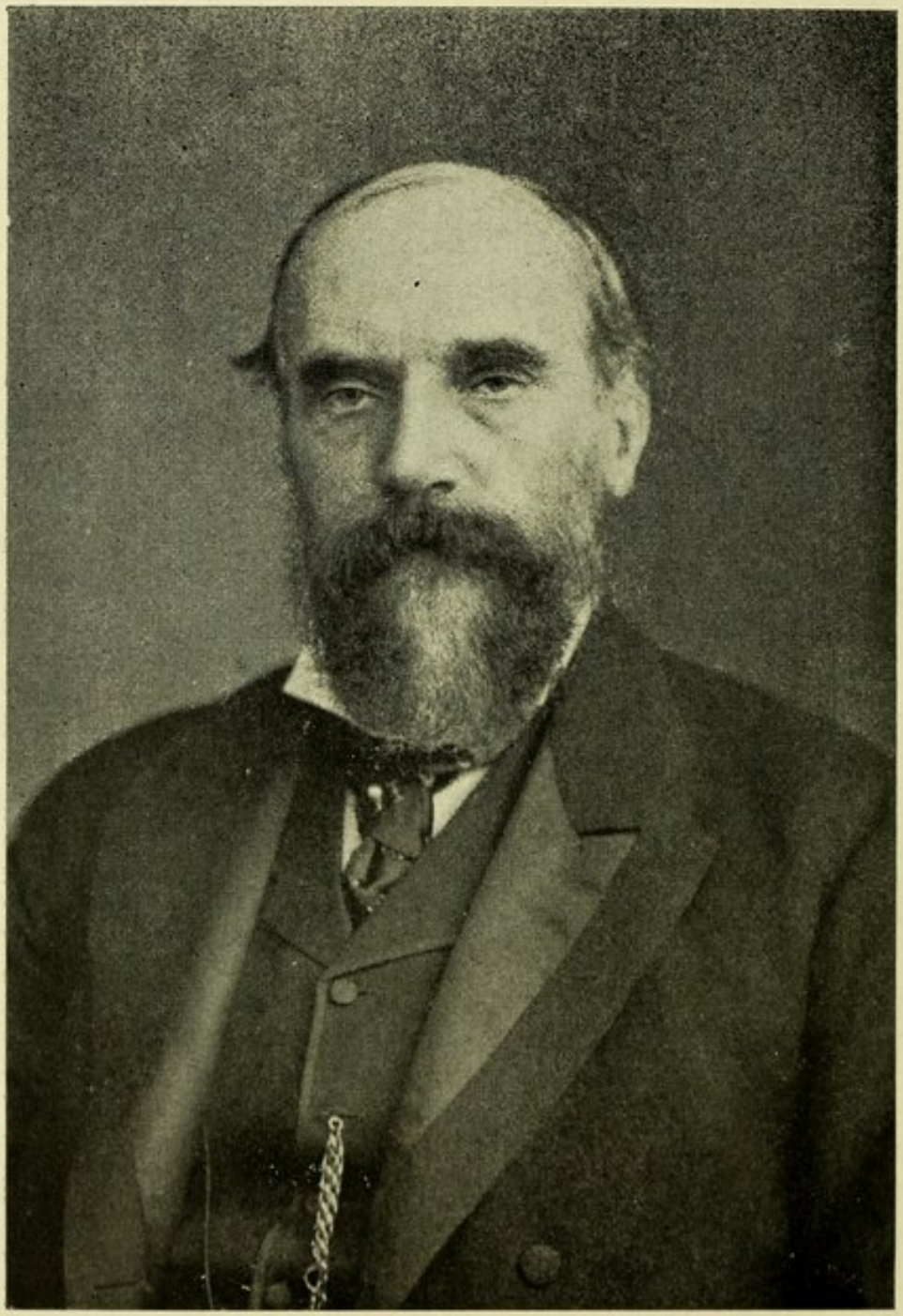
ON

PHARMACOLOGY AND THERAPEUTICS



Charles D. F. Phillips, M.D.

COLLECTED PAPERS

ON

PHARMACOLOGY AND THERAPEUTICS

BY

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INTRODUCTION.

Dr. C. D. F. Phillips was the fifth son of Captain Robert Phillips, who fought all through the Peninsular War and also at Waterloo.

Dr. Phillips was the author of a well-known work on *Materia Medica and Therapeutics*. The first volume was published in 1884, the second in 1896 and the third in 1903, only a few months before his death.

He qualified at Aberdeen in 1852, and commenced practice in Manchester in that year. In 1867 he moved to London where he soon created a large practice, but in 1878 he met with a serious railway accident, from the effects of which he was completely paralysed for five years. After two prolonged trials, he obtained from the Railway Company £16,000 damages.

In 1883 he gradually resumed practice at Henrietta Street, Cavendish Square. He was very popular with his patients and did a large consulting practice all over the country, and was several times sent for abroad.

He was an indefatigable worker and for many

years rarely slept more than five hours out of the twenty-four.

In addition to his work on Materia Medica, he published in conjunction with Dr. M. S. Pembery, of Guy's, a textbook on the *Physiological Action of Drugs*, which is especially valuable from the large number of tracings it contains.

He was an active member of the Therapeutic Committee of the British Medical Association, and published under its auspices a paper on " Hydrastis and Hydrastine Hydrochlorate ". He retired from active practice about a year before his death, and was appointed Chairman of the Universities of Glasgow and Aberdeen Unionist Association, being invited to represent the joint Universities in Parliament, an honour which, however, he declined. He died in November, 1904, deeply regretted.

After Dr. C. D. F. Phillips's death these Papers were found, most of them in manuscript. The editing of them was kindly undertaken by an old friend of Dr. Phillips, to whom Mrs. Phillips is greatly indebted.

STARDENS,
NEWENT,
GLOUCESTER.

CONTENTS.

AN INVESTIGATION INTO THE MODES OF ACTION OF THE GROUP OF ANTISEPTICS.

In this paper it is not proposed to deal with the relative value of different antiseptics, a subject on which there must of necessity be much difference of opinion, but to discuss generally the mode of action of a well-recognised group of therapeutical agents.

The etiology of disease having been practically revolutionised during the last few decades by the rapid advances made in pathological research by Koch, Pasteur and others, and the "germ theory" having been established as the true explanation, not only of putrefactive or septic changes, but also of many specific forms of disease—these two facts have naturally directed therapeutists to look for assistance in the treatment of such morbid conditions by means of the remedies known as antiseptics or germicides.

This large group embraces all those chemical and physical agents which can exert a detrimental or deterrent effect upon the growth and develop-

ment of micro-organisms, and can bring about their ultimate disintegration.

The value of many of the antiseptics has long been recognised, and although their employment has been entirely empirical, their efficacy has been none the less marked or appreciated. Recently, however, large additions have been made to our knowledge of the more special characteristics of this extensive class, and since fresh methods of observation have been introduced and elaborated, more exact researches have been conducted with the view of throwing fresh light upon the manner in which these substances effect their germicide action.

Our knowledge concerning them is as yet vague and fragmentary, and the therapeutist, in directing his attention to their study, is met at the commencement by a series of important problems which it will be necessary here shortly to discuss under the following heads :—

I. What is known regarding the biological history of micro-organisms as a class ?

II. What is known regarding the action of the microbes upon the tissues as well as upon the great physiological processes of the body itself, whether in a normal or abnormal state ?

III. What is known regarding the action of those physical or chemical reagents which are called germicides upon the organisms themselves ?

IV. What is known regarding the action of

germicides whether exhibited externally or internally upon the tissues and functions of the body itself ?

1. In considering the first problem, as it presents itself before us here, only a brief review of the ascertained facts can be submitted.

Although numerous and valuable results have been gathered from the careful exertions of many reliable observers, who have devoted much time to the study of the life-history and special characteristics of these micro-organisms, as well as to the differentiation of the individual members of the vast phalanx of which they consist into groups and families, the difficulties of making a suitable and satisfactory classification are extremely great.

One group of germs (saccharomyces cerevisiæ) are seen to luxuriate, where another (bacillus anthracis) will not be able to show any signs of vital activity, and upon some such peculiarity methods of classification have been adopted.

Pasteur suggested one based upon the necessity (or the reverse) of the presence of oxygen in the surrounding media ; and he accordingly divided all germs into two great classes : The ærobic—those which require the presence of oxygen ; and the anærobic—those which can flourish without oxygen. For the present purpose, however, such a system of classification is of no value. A more satisfactory basis has been offered by pathologists, who classify germs according to the physiological

effects they produce upon the system of more highly organised beings, into two great divisions, the putrefactive or septic, and the pathogenic or specific.

The latter, the pathogenic, are those that act upon animals so as to produce special forms of disease; they do not flourish in acid media, nor in the absence of proteids and certain inorganic salts; whereas the former exert no specific influence upon the body, and do thrive in acid media, as well as in the absence of proteids. This classification is not quite satisfactory, however, since septic organisms do, in some instances, thrive in alkaline media also, and sometimes vary in their reactions.

For instance, a bacillus supposed to be that of leprosy, although resistant to acids when grown in gelatine and bouillon, loses this resistant power when grown on agar-agar.

Certain conditions are now recognised as being essential to such an environment as will allow of the development, growth and multiplication of micro-organisms. Thus they must be situated in a suitable soil, from which the necessary nourishment may be obtained for their subsistence; they must enjoy certain ranges of temperature, and lastly, there must be a certain amount of moisture in the surrounding media. The deprivation of one or all of these conditions, or, in the case of some (as will afterwards be discussed), their presence

in excess, will arrest the growth and development, or if carried further, bring about the degeneration and ultimately the complete disintegration of the organisms themselves.

Their growth and multiplication, when placed in a suitable soil, and under favourable conditions, is extremely rapid, and the media soon become teeming with the microbes, but it is an interesting fact to observe that there comes a time when, in spite of the favourable conditions for growth, and regardless of the remains of undevoured stores of nourishment, they degenerate and die; they are no longer able to proliferate, and they become not dormant, but extinct.

Wernich, Burdon-Sanderson and others established the fact in regard to putrefactive ferments that certain complex chemical compounds are produced as the result of their vital actions; and that these substances, which mostly belong to the aromatic series, have, when produced in sufficient quantity, themselves a powerful deterrent and destructive effect upon the vital activity of the organisms which have produced them, and thus, by their own increased growth and multiplication, their own destruction is brought about. Koch and others have given greater prominence to those products in relation to pathogenic organisms of tubercle and malarial fever, and considerable light has been thrown upon the etiology of these diseases by such observations.

Again, the chemical compounds produced by one species of micro-organism are often baneful in their effects upon those of another species, so that the appearance of one kind of organism in a cultivation of another may keep, during its presence there, the original growth in check, or even destroy it. This peculiar effect is due, in all probability, to the antiseptic action of the ptomaine produced being more marked upon the *foreign* germ than upon itself, but considerably more information is needed to supplement our knowledge in this important detail.

A fact even more interesting and remarkable is recorded by Brieger and Fraenkel with reference to diphtheritic bacilli, *viz.*, that they produce two substances, one *toxic* to an animal, the other *protective;* the former destructible by a temperature of 55°-60° C., the latter resisting a temperature little below boiling point. These substances are otherwise closely allied, and possibly one is transformable into the other.

2. The relation between the micro-organisms and the tissues of the body in which they are found affords a very interesting study, and is a necessary factor for consideration.

That germs are found in enormous numbers in the blood and in the tissues of the body in some specific diseases is an indisputable fact, but the exact relation that they bear to each other is not well known.

Virchow has pointed out that there appears to be a perpetual warfare going on between the micro-organisms and the cells of the tissues with which they come in contact. The microbes attack the cells in their immediate neighbourhood, and the cells, in their turn, react upon the microbes and cause their disintegration, and thus an antagonistic process is being carried on between the two with a continuous struggle for the ascendency.

The result of this process is the formation of ptomaines similar in character to those already described as formed in pure cultures apart from the body altogether, but differing, apparently, in the case of different organisms.

Thus, where these microbes become situated (and some appear to affect one organ while another group infect another), considerable local irritation is set up with its concomitant processes, but how the great symptomatic changes are brought about which are regarded as indicative of their presence in the system and the precise relationship of the germs to the diseases with which they are associated, is at present not satisfactorily explained.

Several theories have been advanced to afford a possible basis for rational appreciation of their import.

(*a*) Is it that micro-organisms, having once become introduced into the system, find a suitable nidus in the blood and tissues for their development, grow and multiply with such rapidity that

they come to interfere by their *physical* properties with the great physiological functions of the body? or (*b*), Do they, by the vital requirements of such an enormous number, abstract from the tissues and juices of the body those materials which are essential for their growth, and without which abnormal conditions of so extensive a nature become established? or (*c*), Is it that they are of themselves innocuous, and cause their virulent effect by the chemical metamorphosis over which they preside in the presence of certain complex compounds (but in which they themselves are not influenced), or by some poisonous secretion or excretion emanating from themselves?

This last, the ptomaine hypothesis, in all probability, is the most likely to afford a satisfactory explanation. It is a recognised fact that ptomaines are present wherever there is a manifestation of vital activity by microbes (though how they are formed is not fully appreciated), and further, other researches have clearly shown the exceedingly toxic nature of their effect upon the general system, since they produce all the effects of severe fever when introduced into the circulation, even in very small quantities.

3. What is known regarding the action of those physical or chemical reagents which are called germicides upon the organisms themselves?

Concerning the influence of variations of temperature many observations have been made with

the result of showing that some kinds of germs, and even different stages of development of the same germs, can resist higher or lower degrees of temperature than others, and in most instances the high degrees of heat are more effective as germicides than the low degrees of cold, for, although the latter do very markedly diminish vital activity, this is only temporary, unless the exposure be prolonged over very considerable periods of time.

External applications of cold have been recommended, in some cases, to diminish the activity of germs in some local affections, but it will readily be seen that, owing to the normal temperature of the body, the application of cold has to be limited to the surface and to localised areas.

The higher degrees of temperature have undoubtedly a wider sphere of application, because of both the greater efficacy of their action, and also the greater readiness with which such high temperatures are obtained. Dry heat is not found to be so effectual as heat with moisture, since it appears that this renders the germs more readily affected.

The rise in temperature in cases of fever may be regarded in this connection as a recuperative attempt on the part of nature to hinder the development, and check the further multiplication of the micro-organisms within the system. Koch has clearly shown that a temperature of 105° F. is

sufficiently high to check the further development of tubercle bacilli, and that if these bacilli be exposed for three weeks to a temperature of 107° F., they will be killed. He has also found that the bacillus of cholera was prevented from further growth by a temperature of 104° F., and the bacillus of anthrax by one of 109° F.

This elevation of temperature in specific fevers has a close connection with the renewed activity of the colonies of germs within the body, and is generally regarded as due to an increased formation of ptomaines, which, finding their way into the general circulation, react upon the central nervous system, and cause the rise in temperature.

Moreover, the elevation of temperature has a further beneficial action, since the ptomaines produced exert a more deterrent action upon the growth of the microbes in the presence of increased heat. Heat is of great service in sterilising instruments and purifying air contained in closed vessels, and also solutions which may form suitable nidus for germs, but the high degrees of heat and the prolonged exposure required render its application inconvenient.

In accordance with these experiments, inhalations of hot air, both moist (Krull) and dry (Sormani and De Toma), have been recommended in cases of tubercle of the lung and in diphtheria, on the theory that the growth of the microbes

will be checked by such temperatures, but it is difficult to follow the arguments advanced by the above-named observers, and their conclusions are by no means convincing.

In discussing the large group of chemical substances, the claims of which to be recognised as germicides have from time to time been brought prominently forward, it will not be possible to review them at any length, but it is important to understand how they have been tested and how certain conclusions have been reached.

The method of observation first employed to recognise the value and power of an antiseptic was introduced by Koch, and has since been followed by many other observers.

It consists in observing the degree of concentration required for a given substance in order to prevent the development of a particular organism in a suitable nutrient medium.

Active spores of the bacillus anthracis were for that purpose transferred to media to which known quantities of the chemical had been previously added, and the whole placed under favourable conditions for growth. If this growth was hindered, or prevented, the germicide was proved to produce a positive result.

TABLE I.

GROWTH OF ANTHRAX SPORES IN A GELATINE MEDIUM.

Chemical Agent.	Hindered.	Completely Arrested.
Sublimate Solution	1 : 1,600,000	1 : 300,000
Oil of Mustard	1 : 330,000	1 : 55,000
Allyl Alcohol	1 : 167,000	1 : —
Potassium Arsenite	1 : 100,000	1 : 100,000
Thymol	1 : 80,000	.....
Turpentine	1 : 75,000	.....
Hydrocyanic Acid	1 : 40,000	1 : 8,000
Oil of Peppermint	1 : 33,000	.....
Osmic Acid	1 : 6,000	.....
Oil of Cloves	1 : 5,000	.....
Potash Soap	1 : 5,000	1 : 1,000
Iodine	1 : 5,000	.....
Salicylic Acid	1 : 3,300	1 : 1,500
Hydrochloric Acid	1 : 2,500	1 : 1,700
Camphor	1 : 2,500	above 1 : 1,250
Eucalyptol	1 : 2,500	above 1 : 1,000
Borax	1 : 2,000	1 : 700
Benzoic Acid	1 : 2,000	.....
Potassium Sulphate	1 : 2,000	.....
Bromine	1 : 1,500	.....
Chlorine	1 : 1,500	.....
Potassium Permanganate	1 : 1,400	.....
Boracic Acid	1 : 1,250	1 : 800
Carbolic Acid	1 : 1,250	1 : 850
Chloral Hydrate	1 : 1,000	1 : 400
Quinine	1 : 830	1 : 625
Calcium Sulphate	1 : 350	.....
Potassium Chloride	1 : 350	1 : —
Sodium Sulphate	1 : 250	.....
Acetic Acid	1 : 250	.....
Sodium Benzoate	1 : 200	.....
Alcohol	1 : 100	1 : 125
Sodium Chloride	1 : 64	.....

In reviewing these experiments, valuable as they indeed are, it must not be concluded that the degree of concentration given is sufficient to produce a complete antiseptic effect. Undoubtedly the growth and further development of the micro-organisms have been prevented for the time being, and although their death *may* have been caused,

yet no such conclusion can be arrived at, unless the germs thus exposed to the antiseptic be transplanted into a suitable soil, under conditions favourable for growth if the vitality be not lost.

This method has, accordingly, been modified by Klein and others, who have adopted the plan of first bringing a small quantity of an organism (either in the culture-fluid or upon sterilised silk thread) into contact for a variable time with a relatively large quantity of the chemical agent to be investigated, and then the vitality of the organisms thus treated is tested after various periods of exposure by placing them in a suitable medium and observing if they still possess the power to grow and multiply; and in the case of those organisms which gives rise to specific diseases inoculation of suitable animals is made. The advantages of this latter method are obvious, and the accuracy of the results is insured by further cultivation.

It may be pointed out that De la Croix, Miguel and others have followed the line of observation laid down by Koch, and, as they have experimented with the same chemicals, but with a different micro-organism (*viz.*, the non-specific bacterium termo cultivated in meat infusion), a comparison of the results thus gained is interesting :—

TABLE II.

	Koch.	De la Croix.	Miguel.
Sublimate Solution . .	1 : 300,000	1 : 30,208	1 : 14,300
Oil of Mustard . . .	1 : 33,000	1 : 3,353	.....
Iodine	.....	1 : 5,020	1 : 4,000
Salicylic Acid . . .	1 : 1,500	1 : 1,003	1 : 1,000
Boracic Acid	1 : 800	1 : —	1 : 130
Carbolic Acid . . .	1 : 800	1 : 669	1 : 313
Alcohol	1 : 12·5	1 : 21	1 : 105

Klein, in an elaborate and exhaustive inquiry into the antiseptic properties of phenylproprionic and phenylacetic acid, has, in a yet more striking manner, shown that any generalisation from results of the germicide action of one chemical agent on one form of micro-organism to its action upon another is not admissible.

For instance, he finds that a non-specific micrococcus and bacterium termo requires one to two hundred phenylproprionic acid to destroy its vitality, whereas bacillus anthracis requires a solution of one to eight hundred only, both being exposed for the same length of time, and under similar conditions; and again, the virus of tubercular matter requires to be exposed to a solution of one to two hundred for ninety-six hours before it loses its activity, whereas that of swine plague is destroyed by being exposed to one to eight hundred for twenty minutes.

Marteris, Weeks, Yerson and others have compiled long series of tables as to the results gained by exposing various micro-organisms to the

action of different antiseptics for variable lengths of time, but our ignorance of many of the fundamental laws which govern the growth and development of these germs, and their adaptability to altered conditions, must make us very cautious in accepting observations which differ so widely from each other, though performed apparently under similar conditions.

In such experiments the chief sources of possible inaccuracy appear to be due to :—

(i.) The fact that some forms of micro-organisms appear to be more virulent than others, though both are of the same species. As an illustration of this may be quoted the fact, that if a healthy mouse be inoculated with the blood of a sheep suffering from anthrax, death results in the course of twenty-four to thirty-six hours, but the converse proposition does not hold good ; to a healthy sheep, which is inoculated with the blood of a mouse affected by anthrax, the disease is not communicated from the mouse.

(ii.) The *spores* of those organisms which produce them are much less vulnerable than the *bacilli ;* and

(iii.) The bacillus of cultivations is not so well calculated to resist the action of the antiseptic, though equally well able to reproduce the disease. For this reason, therefore, it is most desirable that the micro-organisms thus experimented with, if of a specific character, should be passed from

time to time through an animal that is capable of inoculation by the disease, in order to increase and refresh their power and virulence.

Much valuable knowledge may be gained from perusing these results, which distinctly indicate the great service germicides are able to render when direct application is possible to those sites where the septic or zymogen processes are taking place; through their deterrent effect the process may be checked or entirely arrested, either by placing the organisms under such untoward circumstances as to render their further life impossible, or by poisoning the nourishing media, so as to kill the microbes completely.

But these are not the only factors to be taken into consideration, even in regard to the external application of antiseptics, and highly important is the following problem, *viz.* :—

4. What is known regarding the action of germicides on the tissues of the body?

The local action of many of the antiseptics is that of an irritant, even of an escharotic, if used in a sufficiently concentrated form, and there seems but little doubt that a germicide may not only prevent the activity of the microbes present, but, by its stimulating nature, may also act upon the cells of the tissues, and thus produce a more healthy and vigorous condition, which renders them better able to disintegrate the enfeebled germs by which they are infested.

Many of the antiseptics already tabulated are so destructive in their action to living tissues (when sufficiently concentrated to show a germicide action) that they have to be abandoned for all practical purposes, and it does not, with our present knowledge, seem possible to recognise to which reagents the cells of the tissue or the micro-organisms themselves are the first to yield, although it is a most important point to appreciate.

Difficult as the subject is in relation to the *external* application of antiseptics, the difficulty is tenfold increased when we come to consider the value of antiseptics administered *internally*, whether when given by the mouth and absorbed from the alimentary canal, or exhibited by subcutaneous methods.

Under these circumstances the problem of the reaction between the cells of the tissues and the antiseptic is of vital importance, and still it is one of which little practically is known. In considering the internal administration of antiseptics it will be necessary to approach the subject under three heads :—

I. Do the antiseptics, when administered internally, produce an antiseptic condition of the blood, and the tissues of sufficient concentration to check or arrest the growth of micro-organisms?

II. Do they produce this effect by reacting upon the tissues themselves, and thus enabling them to resist the attacks of the germs?

III. Do they produce their effect by neutralising the toxic products of the microbes?

1. The internal administration of antiseptics in sufficiently large doses will undoubtedly produce a marked antiseptic action in the alimentary canal, prior to the time when they become absorbed into the blood capillaries and lymphatics, but some of them are very diffusible, and soon make their appearance in the urine, by which channel most of them are very rapidly eliminated. Take, for example, sodium salicylate, which will appear in the urine in from five to eight minutes after administration by the mouth. Thus it will be recognised that the length of time taken by the absorption and the rapidity of elimination of a drug must exert a very distinct effect upon any possible degree of saturation to which the system may be subjected by its exhibition.

This, however, is not the only view to be considered in this relation, for although absorption of an antiseptic may take place, yet during that process there appears to be a very great chemical change brought about in the substance ingested.

The great difficulties which beset such a line of observations are, with our present limited knowledge of physiological chemistry, almost insuperable. Baumann has pointed out that carbolic acid, if administered by the mouth, may be found in the blood as sulpho-carbolates, chiefly of sodium, which, though they still possess an antiseptic

power, is of a very much milder nature than that from which they have taken origin; similarly, salicylic acid is transformed into salicylate of sodium, and is eliminated as such.

With the view of comparing the power of higher forms of life with the power of *germs* to resist the action of antiseptics, even in very dilute solutions, Richet conducted some interesting observations upon fish. He placed fishes in salt water, to which had been previously added sufficient organic matter to allow germs to grow and multiply, but not enough to interfere with the well-being of the fishes. The degrees of concentration of the various antiseptic metallic compounds which could be resisted by the fish, and the effect of the same upon the germs employed, was observed, with the following results:—

COMPARATIVE TOXIC INFLUENCES OF THE METALS IN COMBINATION UPON MICROBES AND FISHES.

Metal.	Minimum Dose expressed in Pounds per Litre.	
	Arrests Putrefaction.	Kills Fish in less than 48 Hours.
Mercury	0·0055	0·00029
Zinc	0·026	0·0084
Copper	0·062	0·0033
Cadmium	0·040	0·017
Iron	0·24	0·014
Nickel	0·18	0·125
Barium	3·35	0·78
Lithium	6·9	0·3
Magnesium	7·2	1·5
Ammonium	18·7	0·064
Calcium	30·0	2·4
Sodium	43·0	24·0
Potassium	58·0	0·10
Manganese	7·7	0·3
Cobalt	.....	0·125

Medium employed—

Sea Water	900 grammes.
Neutralised Urine	100 grammes.
Peptone	1 gramme.

at 20° C.

The results thus gained indicate clearly that the more active antiseptics are much more fatal to the fishes than to the germs, and that in solutions of such concentration as would kill the fish, germs would not even be impeded in their growth.

Too much reliance, however, must not be placed on these results, for although it may not be possible to so saturate the blood, lymph and tissues with an antiseptic as to kill any microbes that may be present, still sufficient may be absorbed without disastrous effect to check and hinder, to some extent, the growth and development of the micro-organisms.

The experiments of Chamberland and Roux have pointed out that very small quantities of some chemical reagents (carbolic acid and potassium bichromate) added to culture media, though not in sufficiently concentrated solution to arrest, but only in some degree to inhibit the growth of the bacillus anthracis, may alter its morphological appearances. This does not appear to be due to any real alterations in the specific characteristics of this organism, but merely a general weakening of its vital power, for no reliable observations have yet been made which will allow the conclusion to be arrived at that by alteration in the processes of culture, or in the nature of the culti-

vating media, one specie of micro-organism can be merged into and acquire the characteristics of another.

It is, therefore, not an unreasonable hypothesis to adopt that by the continued administration of a suitable antiseptic the blood and lymph, though the latter not so readily as the former, may be brought into such a condition of saturation with an antiseptic that, though the antiseptic may not be present in them in sufficient quantity to arrest the growth, it may be able to inhibit or to alter the vital activity of the micro-organisms, so as to render them less virulent, or even innocuous.

The fact is well established that certain chemical preparations, when administered by the mouth, are to be found being eliminated by the various channels of excretion, and, in the case of some of the simpler inorganic salts, unchanged. Hence we are led to the conclusion that they have, in all probability, been absorbed, circulated and discharged without their chemical combination having been broken up. Though this view may hold good for the more simple, it certainly does not for the more complex compounds, the organic combinations being subjected to very elaborate changes when within the circulation, with the result that many varied derivatives are produced from them.

It is also not at all unlikely, as has been mentioned already, that those reagents which exert a

marked antiseptic action outside the body may, when absorbed, form some entirely different and feebly germicide product, or even a neutral compound with some of the albuminates or salts of the blood, and so render no material assistance to the object in view.

2. Do antiseptics react upon the tissues of the body, and thus enable them to resist the attacks of the germs?

A large share of the work of destruction of microbes within the body has, rightly or wrongly, been attributed to the white cells of the blood, and with the inference that a small increase in the activity of their functions may cause a more rapid diminution of the microbes. Very little attention has yet been devoted to the study of the action of antiseptics upon the activity of these cells, but Pohl has, in an elaborate research, shown that an increase at any rate in number of the white cells could not be noticeably traced to those antiseptics which have the most prominent position as such. Much more work is needed under this head before any satisfactory facts can be advanced.

3. Concerning the last theory of the possible power that the antiseptics administered may neutralise the toxic effects of the ptomaines produced, anything that may be said is merely a question of speculation.

It is fully recognised that these ptomaines are

produced, and that they check the further progress of the germs that produce these is also appreciated, but when they are developed within the body, in many instances at least, they appear in such quantities that the system falls a victim to their presence before the micro-organisms can be affected.

MANGANESE AND ITS SALTS.

THERE is no doubt that in the domain of *materia medica*, manganese occupies a somewhat anomalous position. The therapeutical value of its salts is well established, but its pharmacological actions have not yet been worked out with that completeness of detail which has been observed in the case of other drugs such as aconitine, digitalin and strychnine. The deep-rooted belief that manganese is in some way related to iron and that it is useful in anæmia may have something to do with the false position assigned to this useful remedy. A reputation of this kind is eradicated with difficulty, although numerous observers have shown that manganese is of no value in the treatment of either common anæmia or the pernicious variety.

The preparation of manganese commonly employed is the permanganate of potassium, although this cannot be regarded as typically representing the manganese action. The same may be said of the permanganate of sodium and the permanganate of calcium. The binoxide of manganese is insoluble in water, but dissolves readily in hydrochloric acid, so that it is therapeutically active. The citrate is soluble and there is a double salt with sodium

citrate. There are various combinations of the citrate of manganese with iron, quinine, strychnine and other bases, but these are outside the scope of the present investigation, which is largely pharmacological. With respect to the permanganate in which the manganese occurs in the acidic radical there is reason to think that it is decomposed in the stomach, forming a salt of manganese, so that its further action may be attributable to the manganese-ions. Its utility is due to its capacity for parting with oxygen to albumin or other organic matter. It is used as a disinfectant and deodorant, but its power in this direction is limited, for when it yields up its oxygen it becomes inert.

The literature of manganese is tolerably extensive, although it must be confessed that the conclusions arrived at are not always reliable or at all events conclusive. Such discrepancies are not unusual in the case of salts presenting a complex chemical composition.

Sir William Turner, of Edinburgh, found evidences of manganese in the urine of a diabetic patient who had taken potassium permanganate for three weeks, showing that that salt was absorbed and eliminated by the kidneys. These observations were made more than forty years ago. Traces have been found in the urine of man and more than traces in the urine of herbivora; these are derived from vegetable food, hence there must

be some absorption, and therapeutical effects confirm this.

The presence of manganese as an essential element of the corpuscles has been relied on as a guide to its action, but it seems to be rather an accidental than a normal constituent of the blood. Wurzer first announced its presence, and Millon, Hannon and Burin-Dubuisson corroborated this, while Melsens, Bonnewyn and others could find no manganese on repeated analysis. Melsens operated on seven kilogrammes of blood from twenty-one different persons. Glènard analysed in various ways blood from forty subjects of varying ages, and found the metal in one case only. He concluded "that manganese is not an essential element of human blood; it may be found accidentally, but only in minute amount; it does not enter by the lungs or skin, as proved in the case of miners". Riche detected minute quantities in the blood of bullocks and a trace in human blood.

According to Laschkewitz, the organic salts of manganese in moderate doses (subcutaneously) slow the pulse and the heart-action, and cause lowering of the blood-pressure with paralysis of muscles and nerves; after death from manganese poisoning the heart is found dilated and does not respond to electrical stimulation. This may be the case in laboratory experiments, but in a case of acute poisoning (thirty-five minutes) from a large dose of permanganate taken in beer the heart was

arrested in systole. Professor Kobert finds that the intravenous injection of manganese salts first transiently stimulates the vaso-motor centre, then paralyses it; later the heart itself is depressed and finally paralysed; the cardiac nervous centres suffer first and later the muscle.

Certain nervous phenomena are determined by manganese salts. Toxic doses cause death with convulsions, and one-half to one gramme injected into the veins of rabbits or dogs produces cramp and death from heart-palsy, or else faintness and weakness and slower death with fatty degeneration. The pupils are dilated; the temperature is unaffected. Rabuteau injected a little more than one gramme into a vein of a dog, and at first there were no symptoms, but on the following day tetanic convulsions set in with trismus and opisthotonos, and death followed shortly; the white substance of the spinal cord was shrunken, the grey matter congested. Kobert states that rabbits after large doses subcutaneously die in epileptiform convulsions; after non-lethal doses they suffer from diarrhœa, loss of appetite, and great depression of the function of the spinal cord, the transverse conducting power being destroyed, though the longitudinal conduction remains intact. In dogs excessive vomiting and great nervous depression are seen after hypodermic injection; there are no convulsions, but jaundice and renal inflammation are striking symptoms always present. It must

be remembered that rabbits cannot vomit, hence the difference in symptoms.

Large doses given for a long period induce effects analogous to those of zinc—progressive wasting and feebleness, a staggering gait and paraplegia. Kobert states that chronic poisoning can only be induced if the salt is administered by subcutaneous or intravenous injection. Cases of chronic poisoning observed in man have been reported by Couper in workers in manganese. The symptoms were muscular wasting and paralysis, which may have been due to other metallic admixtures.

The sulphate has been credited with the power of stimulating the secretion of bile since the observations of C. G. Gmelin, who found in animals poisoned by large doses inflammation of the stomach and intestines, and "so large an amount of bile poured out that the whole tract was coloured like yellow wax". He reported a less degree of the same effect in man, and Ure found that sixty to one hundred and twenty grains acted as a cholagogue purgative. Goolden took various doses from one up to thirty grains before vomiting occurred, but states that as a rule ten to twenty grains will cause nausea and purging with a copious secretion of bile. Professor Rutherford, however, failed to corroborate this experience, at least in animals, for after giving sixty grains to a dog, the biliary secretion was at once lessened,

and severe diarrhœa occurred. After death the mucous membrane of the small intestine was found pulpy, "as if the epithelium had been dissolved by caustic". In another dog a dose of twenty grains caused lessening of bile, although benzoate of sodium given afterwards stimulated its secretion. Rutherford concludes that the drug is a powerful intestinal, but not a hepatic stimulant, acting very like sulphate of magnesium, so that this particular salt can hardly be regarded as presenting the action of the manganese-ions.

The following observations may serve to throw some light on moot points connected with the pharmacology of manganese :—

The close chemical alliance of manganese to iron has led many investigators to administer it to the animal economy with the view of ascertaining if it may not be possible to replace the latter metal in the blood by the former. But the results obtained are more or less contradictory, and it is therefore desirable, not only from the mere theoretical, but also from a practical standpoint, to establish the fact whether, when every imaginable consumption of iron is avoided, the manganese given in an iron-free diet to a living animal, could be made to act as a substitute for it. Since the artificial producing a manganese hæmoglobin is impossible in the present state of chemical knowledge, a preliminary research had to be made with the view of selecting from the different groups of

manganese compounds one which would have a neutral effect on the entire organism except upon the blood itself.[1] The experiments performed were the following:—

THE EFFECT UPON THE COAGULATION OF EGG ALBUMIN OF MANGANESE PREPARATIONS.

Preparation.	At 15° C.	At 100° C.
Permanganate of Potassium	No precipitate	No precipitate.
,, of Sodium	No precipitate	No precipitate.
,, of Calcium	No precipitate	No precipitate.
,, of Barium	Abundant	Coagulation.
,, of Zinc	Flocculent	Coagulation.
, of Silver	Precipitate	Coagulation.
Manganese—Chloride	No precipitate	Coagulation.
,, Bromide	No precipitate	Coagulation.
,, Iodide	No precipitate	Coagulation.
,, Acetate	No precipitate	Coagulation.
,, Citrate	No precipitate	Coagulation.
,, Lactate	Trace of precipitate	Coagulation.

THE PRECIPITATION OF PROTEIDS BY MANGANESE CHLORIDE, BROMIDE AND IODIDE.

None of these substances were found to precipitate egg albumin.

Fibrin is dissolved only to a very small extent by saturated solutions of manganese chloride.

[1] Turner (1861), Vulpian (1881), Lacerda (1882) worked out permanganate of potash and proved its action due to its oxidising power. Gmelin (1824) worked fully the sulphate of manganese. Couper (1837) worked out manganic acid (MnO). Laschkowitz (1866) worked out the action of the lactate and citrate upon frogs, rabbits and dogs. Hoppe-Seyler (1853) worked out fully the sulphate. Wibmer (1831) found the carbonate of manganese perfectly inert.

THE ACTION UPON THE BLOOD OF SOME OF THE MANGANESE COMPOUNDS.

The effect on the red blood corpuscles of man:—

5 per cent. Watery Solution of	Reaction.	Observations under the Microscope.
Permanganate of Potassium	Strongly acid .	First, crenates corpuscles slightly and some plasma exudes. No formation of rouleaux. Secondly, discs become brown spheres.
Permanganate of Zinc	Acid . .	The discs become oval. A bulb can be seen at one end of a single disc.
Manganese—		
Chloride . .	Feebly acid .	Retain their shape, but after twenty-four hours become crenated.
Sulphate . .	Feebly acid .	Discs at once become shrunken and like stramonium nuts. After twenty-four hours discs appear normal again.
Citrate . .	Neutral . .	Decolorises the discs, the stroma may be seen. No crenation.
Lactate . .	Acid . .	No alterations observed.

NOTE.—The acidity was tested by litmus paper.

THE ACTION ON THE SPECTROSCOPICAL APPEARANCE OF THE BLOOD OF SOME OF THE MANGANESE COMPOUNDS.

The blood of frogs was used. The permanganates of potassium, sodium, calcium, barium, zinc and silver turn the spectrum of oxyhæmoglobin into that of methæmoglobin, which was afterwards confirmed by changing it back again into hæmoglobin by the addition of ammonium sulphide, or better still, by Stokes' reagent. Under similar circumstances the permanganate of potassium exerts the strongest action, so that two drops of a 5 per cent. solution will produce the characteristic

line of methæmoglobin in blood diluted forty times, provided that about fifteen c.c. be taken, whereas permanganate of zinc requires double that amount to produce it, although on the left side of Frauenhofer's Line D a shadow is very quickly perceptible.

The manganese salts of the organic acids, acetic, citric and lactic, leave the oxyhæmoglobin for a long time unaltered; upon the first addition the bromide and chloride do not seem to produce any pronounced change, but if strong concentrations of oxyhæmoglobin were employed there could be demonstrated a change going on in the colour of the solution, which alteration could also be recognised by the spectroscopical appearance.

For example, the following experiment may be described:—

Take the blood of a frog, shake it up well with air, divide it into two parts in two test tubes of the same calibre.

The results are tabulated on next page.

Blood.—In regard to the action of manganese compounds on the blood and its constituents, it may be stated that the permanganate compounds, from their oxidising power, dissolve the whole mass of the blood into a clear brown solution, and at the same time they distinctly arrest the coagulation of the blood. It must always be remembered that permanganate salts act in virtue of their being so highly oxidised, and not owing to the manganese they contain.

A.	B.
1st Action— Dilute with water.	1st Action— Dilute with saturated watery solution of manganese chloride (Columbers).
Observation— No alteration in colour, only in depth.	Observation— Distinct alteration in colour, the blood assuming a brighter tint.
Spectroscopically— All absorbed except orange and red rays, which are quite bright.	Spectroscopically— Absorption of violet end to D, of red to B, half shadow to C.
2nd Action— Dilute till green rays between F $\frac{1}{2}$b is visible.	2nd Action— Dilute of manganese chloride gives no appearance of same part of green. Absorption of red rays scarcely weakened.
3rd Action— Dilute till oxyhæmoglobin lines are distinctly visible.	3rd Action— Dilute with same amount of Mn Cl_2 absorption of red rays as above half shadow between F and G.

The two test tubes closed and put aside, and after months one appears to contain hæmoglobin and the other acid hematin.

Fibrin.—If fibrin be taken, which has been either preserved by hardening in alcohol or freshly prepared, and exposed to a solution of permanganate of potassium, it will be found readily to be dissolved by the permanganate of potassium, yielding a brown solution. From this solution it may be precipitated by the addition of sodium chloride, the solution formerly brown becoming quite colourless or a little flesh pink. A similar reaction may be effected by means of sodium-bicarbonate in place of the chloride.

The manganese acetate, citrate and lactate hinder the coagulation of blood, and similarly

manganese bromide and chloride arrest the clotting of it also.

Blood.—In regard to the manganese chloride, a further observation was conducted. An equal amount of frog's blood was placed in two dishes; one was treated with distilled water, the other with manganese chloride (five per cent. of aqueous solution).

After one hour the aqueous solution of the blood consisted of one large clot; the manganese chloride preparation in the same length of time, however, was still liquid, the red plasma mixing in beams with the serum and manganese chloride if the dish was turned to one side, *i.e.*, the corpuscles had been allowed to gravitate to the bottom of vessel.

After twelve hours the same condition was maintained, both preparations still being red in colour, but after twelve hours more the manganese compound became brown, owing to the formation of acid hematin.

Fibrin.—Fibrin becomes, to a very small amount, dissolved by saturated solutions of manganese chloride.

If the filtered solution of fibrin in permanganate of potassium is left to stand two days, then a brown flocculent precipitate is thrown down.

If this solution now is subjected to heat and treated with sodium chloride, there is neither an increase in the quantity of precipitate nor the pro-

duction of a violet colour in the solution, as might be expected, and would be due to the formation of permanganic acid or to manganese sulphide, which would be of a flesh-pink colour.

Blood Serum.—In respect of the proteids of the serum of the blood, the scheme (Table I.) for egg albumin holds equally good for them also. Manganese chloride does not precipitate serum albumin, even if the solution be saturated with it.

This may be considered under the following headings :—

1. The effect upon the capillaries of the frog.

2. The action of *permanganate of potassium* upon the *capillaries*.

Of a saturated solution 2·5 c.c. of permanganate of potassium was added to 22·5 c.c. of a 0·6 per cent. solution of chloride of sodium. The vena hypogastrica of a large frog was prepared, and ten minims of the above solution were injected.

The frog having been made reflexless by destroying the nervous communication between the Occiput and Atlas vertebra, the circulation, which was observed by the microscope in the web of the frog's foot, was seen to stop, but commenced to go on again almost immediately. After a quarter of an hour capillaries formerly not seen could be observed by the appearance of a red colour in them. In about three-quarters of an hour the circulation was stopped in one of the larger vessels, though in the smaller

ones it still went on; and the blood corpuscles continued to present their normal appearance.

The stoppage of circulation having spread, the heart was exposed, but still found beating.

This experiment shows the difference between the action on the heart of manganese chloride and permanganate of potassium.

EXPERIMENTS CONCERNING THE DEPOSITION OF DISSOLVED FIBRIN IN PERMANGANATE OF POTASSIUM IN THE BODY.

Fresh purified fibrin was dissolved in permanganate of potassium, to complete saturation, and the solution filtered, and in the filtrate the presence of the fibrin, or that of the body which replaces it, was shown by means of sodium chloride test.

Under the skin of the neck of a medium-sized guinea-pig ten c.c. of this filtrate were injected. Protracted pains were observed after the injection, lasting for about two hours; after nine days the animal was found dead, though in the meantime no symptoms had been observed which could be ascribed to the injection.

Post-mortem Examination.—General appearance of the parts at site of injection was perfectly normal; subcutaneous connective tissue of the neck was of a brown colour, the point of the wound light red, and around it a small deposit adherent to the skin had formed. This deposit was of a

hard consistency, was perfectly white, and showed, when cut, a fibrillar structure.

The brown red connective tissue, with some fat, was then cut out and placed in a vessel and treated with distilled water. This watery extract showed with the spectroscope oxyhæmoglobin, but no methæmoglobin, and the absorption bands of the permanganate of potassium could *not* be detected in it. There was *no* manganese reaction with ammonium sulphide, nor by fusing with saltpetre and soda.

Another guinea-pig was similarly treated. It was killed after two days, and during that time lost one-twentieth of its weight. The general results were the same as in the foregoing instance.

EXPERIMENTS WITH REGARD TO THE ELIMINATION OF MANGANESE FROM THE BLOOD.

A rabbit weighing five pounds was injected subcutaneously with two c.c. of five per cent. solution of manganese chloride solution. During the following twenty minutes no effect was observed; during the next four or five hours three more injections were given of the same solution, making a quantity of fifteen c.c.

The pulse was counted fifteen minutes after each injection—the animal being at the time under no narcotic—and a diminution in rapidity was observed, *viz.*, two hundred, one hundred and sixty, one hundred and four per minute respectively. Three hours afterwards no abnormal symptoms

could be observed, but sixteen hours after the first injection it was found dead.

Post-mortem Examination.—Rigor mortis was not pronounced one hour after death. Much injection of the vessels was observed around the puncture produced by the cannula of injecting needle. The blood was brown and clotted. The kidneys hyperæmic. The blood in the vena cava was fluid, ecchymoses were found on the surface of the lungs. Chemical examination showed manganese present in the kidney, urine, brain, and especially in the liver, but none in the blood.

EXPERIMENTS CONCERNING THE TOXIC ACTION OF MANGANESE BROMIDE AND CHLORIDE ON FROGS.

Frogs.—The effect of bromide and chloride of manganese when exhibited subcutaneously.

(*a*) A frog weighing twenty-seven grammes was injected with two c.c. of an aqueous solution of manganese bromide under the skin of the back. The frog, previously very lively, showed the first symptoms of poisoning in ninety seconds. Adduction of the four limbs, and complete inactivity. Thirty seconds later eyelids drooped and respiration was slower and deeper, and four minutes after the injection no respiratory movement could be observed. The thorax was then opened, and the heart had ceased to beat, and was of a deep venous colour; it responded to pinching by single contractions only.

At site of injection there was marked venous hyperæmia. The blood in the vessels appeared black, only in certain lights brown, the arteries of the skin were much distended.

(*b*) A frog weighing thirty-four grammes was similarly injected with two c.c. of an aqueous solution of manganese chloride.

There was no difference recognisable between the result of this treatment and that of (*a*), either in a general or particular sense.

Rabbits.—The effects of manganese chloride when introduced by the mouth.

The hydrochloric acid in the stomach does not form a new compound. A rabbit weighing five pounds received five c.c. of five per cent. solution of manganese chloride as an injection into the stomach. No effect being observed after ten minutes, the dose was repeated. During the next three days the rabbit appeared to be in excellent condition. On the third day another four c.c. of the same solution were thrown into the stomach. It was found dead the following morning.

Post-mortem Examination. — No abnormal anatomical appearances were found. The lungs were full of air. The reaction of the liquid in the stomach was acid. Urine contained albumin and also gave the green violet rings with nitric acid. (Gmelin's test for bile pigments.)

The contents of the stomach gave a similar reaction when filtered and treated with nitric acid.

In two other instances in which manganese chloride was similarly introduced into the stomach, the urine of the animals after death gave the reactions of albumin and bile, no manganese could be detected in the blood. The mucous membrane of the stomach in both cases was partially necrotic.

Gmelin has shown that sulphate of manganese in large doses in dogs and rabbits, given either by the stomach or subcutaneously, causes general icterus, and bile may be detected in the urine.

He also specially alludes to the gastro-enteritis and to the peculiar form of nephritis, which partakes of a parenchymatous or interstitial character.

INJECTION OF MANGANESE CHLORIDE INTO A DOG BY THE MOUTH—GASTRO-ENTERITIS.

Male dog weighing fourteen pounds received a subcutaneous injection of ten c.c. of seven per cent. solution of chloride hydrate, and ether was administered.

When narcosis was established, an injection of five grammes of manganese chloride in twenty c.c. of water was given by means of a catheter into the stomach, and narcosis stopped. The dog immediately tried to walk about, but had no co-ordination of his limbs. Four minutes after the injections he vomited matter containing an abundance of manganese. In twenty minutes he vomited for a second time, and again in two min-

utes after that. Manganese could readily be detected in each instance. He then fell asleep. The following morning he was greatly depressed, refused food, and ultimately died thirty-six hours after the administration of the drug.

Post-mortem Examination.—The stomach contained only blood and mucus. The surface of the viscera was pale, and hæmorrhages were discovered throughout the whole of the mucous lining of the intestinal tract, some being the size of a shilling, others smaller. The intestine was filled with a dark coloured fluid, consisting of mucus blood.

Manganese could not be detected in the urine nor in the blood of the limbs, but it was found in the brain.

EXPERIMENT TO ESTABLISH WHAT DOSE OF MANGANESE CHLORIDE A DOG COULD BEAR.

A dog weighing fourteen pounds was injected subcutaneously with ten c.c. of ten per cent. solution of chloral hydrate, and twenty minutes later ether and chloroform were given. Respiration sixty-nine and pulse two hundred per minute.

After the reflexes were abolished 0·25 grammes of manganese chloride was injected under the skin, the fatty tissue being avoided. One minute after the injection, respiration forty and pulse one hundred and eighty per minute.

During the next ten minutes no further symptoms developed and the chloroform was

stopped, and in eight minutes more the animal walked about without any symptoms which could not be directly referred to the chloroform.

The animal was somewhat depressed and sleepy during the following week, but after that completely recovered.

Six weeks after the injection it was killed, and the *post-mortem* examination revealed nothing abnormal. No gastro-enteritis could be recognised.

The anæsthetic to a certain extent vitiates this experiment.

EXPERIMENTS UPON THE ACTION OF MANGANESE CHLORIDE ON THE HEART OF THE FROG.

A frog's heart was excised, and a drop of five per cent. solution of manganese chloride placed upon it. Instantly, contraction ceased and it was not possible to excite even a single contraction again.

When one-tenth per cent. solution was employed the heart's contraction ceased, and could not again be made to continue to contract, though single contractions could be produced on mechanical initiation.

ANTAGONISM BETWEEN MANGANESE CHLORIDE AND PERMANGANATE OF POTASSIUM.

If a solution of manganese chloride of a strength sufficiently weak for the animal to bear be injected under the skin of a frog, and under similar circum-

stances permanganate of potassium be employed, the following is the result observed :—

Action.	$Mn Cl_2$.	$K Mn O_4$.
On the heart . .	Destructive . .	Indifferent or increased.
Excitability of reflex action . . .	Diminished . .	Increased.
Blood . . .	Reduction (Hematin)	Oxydisis.

EXPERIMENTS CONCERNING THE SUPPOSED ASTRINGENT POWER OF MANGANESE CHLORIDE.

A dog suffering from a severe conjunctivitis was experimented on.

The palpable conjunctiva was painted every other day with five per cent. solution of manganese chloride.

No astringent effect was noticed locally, even after five days, but some brown spots were visible in the region of the insertion of the inferior oblique muscle. The pupils were dilated.

On the sixth day the animal was killed.

Post-mortem Examination.—Acute gastroenteritis was present, as also hæmorrhagic nephritis with albumin and bile present in the urine. There was no manganese detected in the urine.

From its behaviour towards the heart it would hardly be expected that this drug would produce any vaso-constricting influence on the vessels, but as some authors[1] speak of it as possessing such an

[1] Nothnagel and Rossbach, Hoppe-Seyler, find that sulphate of manganese produces very marked constriction of the vessels, and also paralysis of the heart and intestines.

action it may be well specially to mention it here.

This experiment shows that manganese is absorbed from the conjunctiva, and that it has an action on the blood in the organism as seen in the formation of the brown spots.

The chloride of manganese and iron has been used by Pétrequin in preference to the simple perchloride of iron, as a local hæmostatic; in Italy it has been applied to necrosed bone, and injected into fistulous tracts and hydroceles, but it has no advantage over other remedies.

The same remark applies to the use of an ointment made with the oxide of manganese (two drachms to one ounce of lard), which has been recommended in scabies and ringworm, and combined with sulphur in prurigo. The potassium permanganate treatment for chronic local patches of eczema is sometimes indicated; after removal of crusts the reddened surface is dried and painted with one in ten solution in water, once or twice daily, until a black adherent covering forms, and this is left on for six to seven days before separating. The application is painful at the time, but I have found it effective; it is suitable only for covered parts. A weaker solution is used as a lotion for ulcerations and suppurating wounds and as an injection in leucorrhœa, ozæna, empyema, gonorrhœa, etc., for which the zinc permanganate is specially good, while the calcium compound is best as a wash or spray in stomatitis or diphtheria.

The pink or green colour rapidly changes to brown on contact with discharges, which may be considered disinfected when the injections return unchanged. Brown stains may be removed by sulphates or oxalic acid in solution.

In snake poisoning the admixture of potassium permanganate with venom rendered it inert, and Lacerda reported that intravenous injection of a one per cent. solution soon after one of snake poison, proved antidotal in dogs. Vincent Richards found that if the salt were injected into the puncture sufficiently soon, ill-effects were prevented. Twenty minutes of a two per cent. solution freshly prepared should be injected under the skin in two or more places, and especially into the orifice made by the fangs, for it is essential that it should come into actual contact with the poison. It must be remembered that this is a chemical, not a physiological antidote. It by no means precludes the use of antivenine.

The value of permanganates in opium poisoning, suggested by B. Smith in 1884, has been amply demonstrated by W. Moore and others. The former took five grains of morphine sulphate in one ounce of water, and a few seconds afterwards eight grains of potassium permanganate in eight ounces of water, and found no narcotic effects whatever. A case where sixteen grains was taken recovered after three doses of five grains each of the antidote. Analysis of vomit mixed with known quantities of

both drugs proved the morphine was no longer detectable. The proper proportion is six grains of the antidote for each ounce of laudanum taken if known, or if unknown eight to ten grains in four to eight ounces of water. The stomach should be washed out with a weaker solution two or three times at intervals of half an hour. When swallowing is difficult the remedy may be given by nasal tube or by hypodermic injection.

Free chlorine is readily and cheaply generated by acting on peroxide of manganese with hydrochloric acid, or by heating a mixture of common salt and peroxide with sulphuric acid and water in equal parts. The former process is recommended in the Swedish Pharmacœpeia, one part of peroxide and four of acid being ordered; the latter process is known by the name of Guyton Morveau. A mixture of manganese oxide, seven and a half grammes, and ten grammes of salt, with sulphuric acid and water, of each twenty parts, will disinfect a space of thirty cubic metres. A saturated solution is five per cent., and when diluted five hundred times is suitable for lotions, disinfection of hands and of stools in typhoid, and for the disinfection of drains. It disintegrates fœtid and decomposing organic substances, and destroys bacteria, but it is now less frequently used than carbolic acid.

I have mentioned that Ure found one to two drachms of the sulphate act as a cholagogue purgative, and Goolden gave it in cases of enlarged

liver with dark or pale stools and jaundice, when no abscess or acute symptoms were present. Most of the patients (at the Dreadnought Hospital) were in a weak condition, having returned from India, and he sought for a non-mercurial remedy to stimulate the liver, and found that ten or twenty grains of sulphate of manganese, though at first it excited nausea or vomiting, soon acted on the bowels to the marked relief of the patient, and with rapid clearing away of the jaundice. This favourable result has not been corroborated by others, but Goolden has written further, stating that he has used the remedy with success in hepatic dropsy, hæmorrhoids and bronchial congestion.

Leared found that oxide of manganese had decided power in relieving gastrodynia and pyrosis. In the cases in which he describes benefit, epigastric pain, severe and radiating, coming on not immediately, but soon after food, especially after albuminous food, were the prominent symptoms. Pyrosis and vomiting were sometimes present. The tongue was generally red and patchy, and there was a rapid shedding of the epithelium, and exposure of the hypersensitive mucous surface. Bismuth is an excellent remedy for such a condition, but Leared found manganese relieve it more quickly, and without causing constipation. He reports two cases of gastralgia, "severe pain with occasional vomiting," one case

of derangement of the stomach, sympathetic with that of the uterus, and one of pyrosis, with "irritable mucous membrane"; all these got well quickly with ten grain doses of the oxide.

The real therapeutical use of manganese is in the treatment of amenorrhœa. For this purpose it was originally recommended by Ringer and Murrell, and their observations have been amply confirmed. By amenorrhœa is meant the functional condition, not suppression of the menses due to organic uterine disease or to pregnancy. It proves most efficacious in cases in which the flow has ceased from exposure to cold. It will not succeed when anæmia is the cause of the trouble. In these instances a preliminary course of iron is necessary to ensure success. The permanganate is not easy of administration. Dissolved in water it forms a solution which is nauseous, and the taste of which is not readily covered by any of the ordinary flavouring agents. It may be given in two-grain tablets, but caution is necessary in their administration, for if they adhere to the mucous membrane of the œsophagus or stomach they act as an escharotic, and may inflict a considerable amount of injury. They should be given only after food, and should be followed by a copious draught of water or other fluid. The permanganate may be made into pills with kaolin, but the same precautions as to administration will have to be observed.

At a later period, Murrell advocated the use of the binoxide in this condition, and it certainly has many advantages over the permanganate. It is not caustic, and may be given either in powder or in the form of a tablet. Its administration should be commenced some four or five days before the expected period. Murrell has also published cases in which the citrate of manganese has yielded good results. When the amenorrhœa is due to anæmia the citrate of manganese and iron may be prescribed, but as the amount of iron in this combination is small, it would be better to give the sulphate or the perchloride of iron first, reserving the manganese until the condition of the blood is improved.

Speaking generally, it may be said that although the sphere of action of manganese is limited, it is deserving of more attention as a therapeutical agent than it commonly receives.

THE PHYSIOLOGICAL ACTIONS AND THERAPEUTICAL USES OF PHOSPHORUS AND SOME OF ITS COMPOUNDS.

Phosphorus occurs in the bodies of animals, especially in the bones and in nervous tissue; it occurs in bone chiefly as calcium phosphate, which constituent is most abundant in the bones of young animals. Animals obtain the phosphates necessary for the formation of their tissues from plants, especially from their seeds. Plants again draw their supply from the soil, whilst soils derive their phosphates from manure, also from small quantities existing in the oldest granite rocks, by the disintegration of which the fertile soils have been produced.

Phosphorus taken by the mouth, and especially when finely divided or dissolved, is absorbed into the blood under the influence of the alkaline, albuminous or oleaginous materials it meets in the stomach and intestines; the amount and the rapidity of its absorption are proportionate to the amount of such materials, and especially of fats, which are its best solvents. It circulates in the blood as free phosphorus. When oxidised into

hypophosphoric or phosphoric acid it loses its characteristic toxic influence. A certain amount of phosphuretted hydrogen is probably formed in the bowel, but if so it is relatively unimportant.

Portions of unabsorbed phosphorus pass sometimes with the fæces, rendering them phosphorescent, and the urine may present a similar appearance; it has also been found in a free state in the liver after death. It is eliminated by this, and other glandular organs, by the skin, and by the lungs.

When applied locally in the solid form phosphorus is liable to cause sores and even gangrene, and the same results may follow its use in ointment. In certain experiments on dogs, however, when pieces were placed in the cellular tissue they remain unaltered, and no inflammation was excited, yet the animals died after a few weeks from phosphorus poisoning. On the other hand, rabbits and some other animals treated in the same way showed neither local nor general symptoms. When a dog swallowed a stick of phosphorus, it was afterwards found in an abscess, without other symptoms of local irritation. Hence it is clear that pure phosphorus does not necessarily act as a local irritant.

The fumes cause irritation, catarrh, and even inflammation of mucous membranes, especially those of the conjunctivæ and bronchi; they have also a special effect on the vitality of the periosteum

and bone, causing necrosis of exposed parts, such as the maxilla and decayed teeth. It is only when the phosphorus fumes directly reach the periosteum or some raw vascular surface having immediate connection with the nutrition of bone, and when their application is prolonged under particular circumstances of temperature, and probably of oxidation, that injurious effects are witnessed. The necrosis was formerly thought to be entirely due to the local action of the phosphorous fumes when there were carious teeth in the jaw, but Stockman finds staphylococci, streptococci and tubercle bacilli in the pus from cases of cario-necrosis of the jaw in workers with phosphorus, and having noticed the frequent association of the disease in tuberculous subjects, believes that the condition is due to the action of the tubercle bacilli on the exposed bone, resistance of which had been lowered by the influence of phosphorous fumes. By taking precautions to maintain good hygienic conditions in rabbits exposed to the fumes of phosphorus after the bone of the jaw had been laid bare, he was able to protect them against cario-necrosis. The substitution of the amorphous for the yellow variety of phosphorus in match factories prevents the occurrence of such cases.

After taking, in ethereal solution, one-fiftieth grain each morning for ten days, and then one one-hundredth grain for nearly four weeks, I ex-

perienced increased thirst and dryness of mouth, with coated tongue, flatulent distension and eructations, and an uneasy feeling in the region of the gall-bladder, without nausea or vomiting; the motions were dark, but healthy, the urine was natural. There was slight headache and sense of fullness at the vertex and over the left temple, with some restlessness and sleeplessness. On discontinuing the medicine, these symptoms disappeared in about three days, and on resuming it at the end of a month I felt them return in about ten days' time. Other persons may take the quantity just mentioned without so much inconvenience, but larger doses (one-thirtieth to one-fiftieth grain and upwards) are very liable to disorder the stomach, causing nausea and a sensation of warmth or irritation. The appetite may be at first increased, but in many patients dyspepsia quickly occurs, and nausea, flatulence, colic, or diarrhœa hinders the employment of at least the ordinary preparations of phosphorus. A silvery-white condition of the tongue may be caused, and the gums may become inflamed.

Zinc phosphide, in any quantity above one-quarter grain, readily induces vomiting. Gubler, examining the effects of this phosphide upon artificial digestion, found that the phosphuretted hydrogen which was developed arrested the process, and he concluded that the same thing occurred with other preparations of phosphorus

taken by the stomach. Thompson attributes gastric irritation to the formation of hypophosphorous acid, and states that he has only seen these symptoms occur after the use of mixtures prepared with a vegetable oil.

Whatever the precise explanation may be, the limit of medicinal and the commencement of toxic doses is marked by more evident irritation of the digestive organs, the mouth becomes tender and sore, the nausea is accompanied with retching, vomiting, and diarrhœa; tenderness and enlargement of the liver may be detected, and there is an icteric tint of the skin and conjunctivæ, with irritation of the same.

There is but little evidence of any stimulation to the generative functions, or organs, exerted by phosphorus in healthy subjects, whatever may be its power in certain forms of disease. The stimulation that has been noted in some cases, both in men and animals, was not special, but merely the result of the general stimulus to the whole nervous system. Leroy and other French authors have reported some temporary genital stimulation from large doses, and in a few cases of poisoning, irritation and excitement of the genitalia have been recorded, but they are to be explained as above. Thompson gave to two healthy adults one to one and one-half grains of zinc phosphide daily for eight or nine days, and to another one-eighth to one-sixth grain of free

phosphorus until symptoms of incipient poisoning arose, but without any trace of aphrodisiac effect. Eames has reported similar negative results from observations with phosphorated oil, and Bradley's experience is to the same effect.

With reference to this point, I have experimented upon twenty healthy men. Ten of them took one-tenth grain daily for a fortnight, five took one-third grain each day for a similar period, and the other five took one-half grain every third day for five successive doses. Slight toxic symptoms occurred in some of the subjects, but, except possibly in one of the last set, no sign of increased sexual excitement was observed. I have, however, seen men from forty to sixty years of age, apparently in good health, but suffering from complete loss of generative power (in consequence either of previous sexual abuse, or of overtaxed brain and nervous system), in whom very small doses, one two-hundredth of a grain, thrice daily, caused weak erections and involuntary emissions, but mental depression was developed to such an extent as to compel the suspension of the drug; this implies a state of irritation of the generative organs, but certainly not one of increased tone or strength.

With regard to its influence upon the uterus, we have evidence that long-suppressed menstruation may reappear under its continued use in small doses, but this may reasonably be supposed to be

connected with improvement in the condition of the blood, rather than with specific stimulation; in cases of poisoning, however, uterine hæmorrhage and abortion occur. It is said that if pregnant animals be poisoned with phosphorus there is fatty degeneration of the tissues of the fœtus.

The urine, under the influence of phosphorus, becomes high-coloured; it may be phosphorescent, and have a smell of violets or sulphur and urea is present in excess. The albumin, which is often present in the urine in cases of poisoning with phosphorus, is probably due to the fatty changes produced in the epithelial cells lining the tubules. Husemann reports the nitrogenous constituents increased in amount, and in dogs poisoned by phosphorus, Bauer found the excretion of urea twenty to ninety per cent. above normal; the phosphates are unaltered in quantity. Leucin, tyrosin and sarcolactic acid have been found in cases of poisoning; lecithin is said to be diminished.

Wegner has furnished definite proof that phosphorus stimulates the growth of bone, for after giving minute doses continuously to animals, he found the epiphyseal cartilages ossified more quickly and more completely than usual, and the cancellous and compact bone became more dense, even to the extent of obliterating the medullary canal. He also found that if lime salts were withheld from the food the growth of bone continued, but it was soft in consistence. Kissel could not

find any effect of phosphorus on bone structure, though toxic effects were readily produced, together with fibrosis. Maas and Kassowitz support Wegner's observations, and the effect on the jaw shows a special proclivity of phosphorus for bone.

The fact just recorded of phosphorus stimulating the growth of bone, a tissue of which it forms a component part, has led to the inference that it can stimulate the nutrition of nerve tissue, of which, also, it forms a normal constituent; but the evidence on this subject is not very definite. Gubler describes the effect of one-thirtieth to one-fiftieth grain to be a general sense of stimulation more complete than that caused by coffee, more active than that produced by opium. Thompson speaks of it as producing exhilaration and increased capacity for exertion, both mental and physical, and an effect like that of alcohol, without the subsequent depression. He states also that if one-half to one grain be taken in the course of twenty-four hours the feelings described are more sustained, and transient giddiness or quasi-intoxication occurs. There seems to me some exaggeration in these accounts, but it is within my own experience that a general tonic effect may be obtained from these and smaller quantities of the drug. In cases where poisonous symptoms are developed, marked excitement, tremor, and spasmodic muscular twitching occur, and, in severe

cases, cramp or partial paralysis, delirium, convulsions, collapse or coma.

In accordance with the general excitation already described, the pulse and temperature are slightly raised about an hour after taking doses of one-thirtieth grain; and after such doses, given daily for some weeks, the circulation has been found more equable and more steady than before. Large doses of phosphorus appear to directly weaken the heart; indeed rapid poisoning is said to cause death by this means; on the other hand, small and repeated doses cause weakness of the heart by producing fatty degeneration of its muscle. Thompson has noted dilation of the small vessels of the skin, and Pal has described a lowering of blood pressure, due to the same cause, *i.e.*, vascular dilation. In toxic cases the pulse rises to one hundred and twenty or more per minute, and the temperature to 102° to 103° F., though this condition is only temporary.

Sir W. R. Gowers has proved that under the influence of small continued doses the proportion of red blood corpuscles is increased, at least in lymphoma, and this observation may throw light on the tonic power of the drug. On the other hand, toxic doses markedly diminish the number of red corpuscles, as shown in fowls. The blood in several cases of poisoning has been found deficient in coagulability. This has been ascribed to an indirect effect through the liver and intestines,

leading to a reduction in the amount of fibrogen. According to von Jaksch, it diminishes the alkalinity of the blood.

The poisonous symptoms produced are essentially of an irritant and destructive character, but vary in degree, and are often obscure and insidious, probably in proportion to the varying amount absorbed, or the chemical changes which the drug undergoes under different circumstances. Lecorché describes three forms of "acute phosphorismus": (1) That produced by phosphorated hydrogen, (2) that by phosphoric acid, (3) a mixed form, but the clinical varieties described by Trousseau are of more practical importance; he calls them (1) the irritant, (2) the nervous, and (3) the hæmorrhagic forms.

The irritant form is the most common; it is induced by swallowing match heads, or rat-poison paste, and is accompanied by pain, vomiting, and purging, sometimes with blood and phosphorescence. In the early stages there is pyrexia, with nervous excitement, delirium and delusion sometimes erotic, though priapism is rare. Twitchings, cramps, and convulsions may occur, but later on follow prostration and collapse, loss of sensation, retention of urine, and partial paralysis, affecting mostly the extensor muscles.

In the nervous form these latter symptoms become more marked, but there is little pyrexia, erythematous spots occur in the skin, which is dry

and yellow, and later becomes cold; dilation of the pupil and strabismus are described, and the fatal termination comes on with somnolence and coma.

The hæmorrhagic form is less quickly fatal than the others, in it the ejecta are almost wholly sanguineous; bleeding occurs in and from the skin and mucous membranes, and many parts of the body. It is due partly to the altered state of the blood, and partly to general softening of the tissues, including fatty degeneration of vessels. In women there is uterine hæmorrhage, miscarriage or abortion, but these may be due to the irritant effects on the intestinal canal.

In cases of phosphorous poisoning the liver becomes enlarged, and about the third or fourth day pain is felt over the hepatic region, followed shortly afterwards by jaundice, headache, and sleeplessness; the urine is found to contain bile, and generally albumin, leucin, tyrosin, and sarcolactic acid. The presence of bile is an argument that the jaundice depends not on suppression, but on occlusion of the biliary passages, which is probably catarrhal in character. In exceptional cases (in which only a small amount of the poison has been absorbed) there has been neither gastro-enteritis, nervous excitement, nor quick pulse, but the prominent symptoms have been jaundice and hepatic congestion. The time that elapses from the taking of the phosphorus to the appearance of symptoms varies from a few minutes to two days. Death, when it occurs,

is usually from asthenia, but the course of the illness is not always steadily progressive ; sometimes the severe symptoms subside for a few hours or days, and death takes place suddenly from failure of the cardiac muscle. The fatal dose is one to two grains for adults, but much less for children, in whom vomiting and convulsions are usually the prominent symptoms.

The system becomes habituated to the use of phosphorus, to some extent, and a gradual increase of dose may be borne up to an amount which would not at first be tolerated. Any cumulative action may be explained by the mechanical accumulation of the drug in the stomach and intestines.

Ecchymoses and gangrenous spots have been found in the intestinal tract, together with swelling and softening of the mucous membrane and mesenteric glands, rarely perforation. The viscera are hyperæmic and odæma and hæmorrhagic infiltration affect the skin, serous membranes and other tissues, especially those of the mediastinum ; hæmorrhage has also occurred between the spinal membranes, thus accounting for paralysis. In some cases of phosphorus poisoning, there are deposits of pigment of hæmatic origin in the central nervous system, while the cord shows evidence of either inflammatory irritation or diffused or central myelitis, according to the amount taken. The blood itself is black and viscid, and in many cases,

even during life, the corpuscles are destroyed and the hæmoglobin is altered, so that it will not show the usual spectrum; in others, the corpuscles have been found normal after death, and the blood pigment unchanged; in all cases the blood and the solid organs contain an increased proportion of waste products, such as urea, creatin, sarcolactic acid, leucin and tyrosin, whilst fatty degeneration affects every tissue. The muscles, including the cardiac, are discoloured, soft and fatty; the vascular walls are degenerated in a similar manner, the gastric glands and renal tubules are choked with fatty epithelium, and the liver especially is enlarged, yellow in colour, and its cells filled with fat globules; for, in protracted cases, degeneration of the cells occurs. That this is a true degeneration and not simply a deposit of fat, is corroborated by finding, in sections of the liver and kidney, that the structure is entirely obliterated by ether. It is possible, as a consequence of this degeneration, that the glycogenic function of the liver is abolished.

The condition described resembles that found in acute yellow atrophy of the liver, and the question of diagnosis has been raised in medico-legal cases. An illustration of this is recorded by Surgeon-Major Martin, in a man admitted to Netley Hospital without any history of poisoning, whose case was diagnosed as acute yellow atrophy, and it was only after death that the real fact was disclosed by examination. A frequent, if not in-

variable, result of chronic phosphorous poisoning is to establish cirrhosis of the liver, kidney and stomach. This cirrhosis is probably due to a direct effect on the fibrous tissue.

Fatty degeneration was found in the tissues of frogs and rabbits within two or three days after giving phosphorus, and its occurrence in phosphorous poisoning has been amply demonstrated. In Tamassia's experiments it was very rapidly produced. He injected three, four, five, six grains, respectively, into the rectum of four animals (dogs and rabbits); toxic symptoms occurred in about fifteen minutes, death in eight hours (the temperature falling 8° F.). In all four of the animals the kidneys, and in two of them the liver also, were in a state of fatty degeneration.

The best antidotes for phosphorus are sulphate of copper and ozonised oil of turpentine. With any soluble salt of copper, phosphorus forms a black phosphide, which is not poisonous; and as copper sulphate is also a good emetic, it is especially available for cases when the poison has been taken by the stomach, and when the remedy can be given soon afterwards. Five grains should be given every two or three minutes until free vomiting is induced, and then either continued in small doses with opium, or turpentine substituted.

When oil of turpentine is brought in contact with phosphorus at a suitable temperature, a crystalline white solid is formed—terebinthino-

phosphoric acid—which is not poisonous. To produce this result, the oil must come into direct contact with phosphorus in the stomach, in the proportion of about one hundred parts to one of the latter. It should be given in forty minim doses in mucilage, every fifteen minutes for an hour. Eleven hours is the longest time that has elapsed before the administration of the remedy in successful cases. It is not every kind that acts well; the pure rectified oil, and much of that sold as German and American, do not form the crystalline acid, and hence a difference in the results of observers. It is the crude acid, French oil, or that which has been ozonised by long exposure, which gives reliable results. Milk lessens its good effects, and other fats and oils must be withheld, as they dissolve any phosphorus which may be in the alimentary canal and facilitate its absorption.

A case illustrating the value of both the antidotes recommended occurred in my practice some years ago. A young man swallowed some pieces of solid phosphorus, and, whilst his friends were gone for assistance, gashed his throat and body with a razor. When I saw him the most pressing need was to stay hæmorrhage, and while copper sulphate and turpentine were being procured, mustard and water was administered. This and the copper produced free emesis, with rejection of a piece of phosphorus two inches long. I then

gave turpentine in milk and water, and still encouraged vomiting, because from the small pieces left in the patient's bottle of phosphorus more was thought to have been taken. Eventually, two other pieces, one and one-half inches and one-half inch long, were rejected, after having been in the stomach at least three hours; after several more doses of turpentine the patient made a good recovery.

A case is reported of a man who swallowed one hundred and twenty match heads, and then took turpentine to increase the effect; he did not vomit, but recovered. The subject has been investigated by Bush, who gave to various animals, poisoned by phosphorus, emulsion of turpentine an hour afterwards, and with good result.

The value of phosphorus and its compounds as therapeutic agents to a large extent lies to their power of stimulating nerve centres when their activity is impaired. It must be remembered that debility of the nervous system is associated with other than purely nervous diseases. A tonic of this kind has a wide field of usefulness, and is applicable, not only in nervous exhaustion and pain, but in many conditions of adynamia. Rabuteau, however, expresses an opposite view when he says: "I do not hesitate to assert that this poison has never cured anything up to the present time, and I would never prescribe it; it has always been useless". Oliver also remarks that "clinical

experience lends little weight to its recommendation for nervous affections"; whilst Dujardin-Beaumetz, Thompson and others have recorded wonderful results from it. The truth probably lies between the two extremes, and we must not forget that some failures may be accounted for by inactive preparations of a drug always difficult to dispense.

Many years ago, Von Lobel, a physician, related his cure by an ethereal solution of the drug from an inveterate cranial neuralgia, which was accompanied with debility and failure of mental and sensory power. He took one-quarter grain every two hours, and was restored to health in a short time, and after only a few doses. This experience was corroborated, and the remedy came into great repute, but was soon found to be dangerous and difficult to manage, and it gradually fell into disuse, no doubt owing to the largeness of the doses. Bradley published a case of neuralgia of the chest-walls, rapidly cured by phosphorus, after failure of all recognised remedies, and later he recorded other successful results. Slade King added testimony to its value in doses of one-thirtieth to one-twentieth grain, and Ashburton Thompson recorded forty consecutive cases either cured or relieved.

Radcliffe employed it with good results in cardiac neuralgia. It was found useful in cases connected with extreme general debility, whether

from over-lactation, hæmorrhage, or simple asthenia, in cases due to pregnancy, to cold, and to local irritation, such as carious teeth, and even to rectal cancer. Anstie's experience was not so favourable. I have seen much benefit from it in many of the above cases, also in uterine neuralgia, occurring in sensitive patients, and induced either by protracted lactation, sexual excess or by mental or local causes. The severe pain is apt to come on just before or during the monthly period, and then one-hundredth to one-fiftieth grain should be given three or four times daily ; during the interval the smaller dose should be given, and less frequently. For upwards of twenty years I have been accustomed to use phosphorus in intercostal neuralgia, and can speak favourably of its power. I have notes of fifty-six cases wherein the pain quickly subsided under this treatment, and did not, so far as I know, subsequently return. In some instances phosphorus succeeded where arsenic had failed ; the dose was one-hundredth to one-fiftieth grain three times daily. In herpes zoster, also, phosphorus has, in some instances, relieved the severe pain. Twitching of the facial muscles, especially about the orbit, often occurs in cases of neuralgia, and I have known it improved by phosphorus.

With regard to the dose in neuralgia and nervous disorders generally, I may say that in my experience the comparatively large doses recom-

mended by Thompson cannot be tolerated for any length of time. They may seem at first to stimulate, or rather over-stimulate, the nerve-centres, but after a short time they depress in a disastrous manner; whilst the small doses of one three-hundredth to one-fiftieth grain, continued for a length of time, nourish and strengthen nervous tissue, without any evidence of undue excitement. A gradual alterative action is what is desired.

Gubler found phosphide of zinc removed the sensation of fatigue after hard work, improved the appetite and digestion, and conduced to sleep. He gave one-half grain with an ordinary digestive pill at dinner-time; but this dose is too large, and is liable to nauseate. When the nervous system is below par, so that slight impressions are too deeply felt and the nerve-controlling power is impaired, phosphorus has been found to supply what is wanting for a time; it has been said to improve intellectual tone in those subjected to either monotonous brain-work, or to an unusual mental effort. In the convalescence from many acute diseases the hypophosphites are valuable, and the same may be said of conditions of general debility, whether arising from defective hygienic conditions, or from prolonged anxiety or overstrain.

In cases of chronic exhaustion of brain power, or of general nervous exhaustion consequent on chronic functional diseases, small doses continued for some months are advisable, and have been

plausibly held to supply to the nerve-tissue a vital element in which it is deficient, and to improve its nutrition, just as Wegner showed that the drug improved the nutrition of bone. Certainly its supply in some form to nerve tissue is as necessary as that of iron to blood corpuscles.

The value of phosphorus in conditions of extreme exhaustion in advanced disease, is one of the earliest recorded experiences of Kramar, Mentz, Leroy and others. They used it in the muttering delirium and incipient coma of typhus fever, and the profound depression of extensive pneumonia. In every disease where death is imminent from failure of vital force without much structural alteration, phosphorus is indicated. We see this in severe continuous fevers during their last stage and in typhoid fever. It is indicated in the acute exanthemata when the eruption has disappeared suddenly with aggravation of the symptoms. It is recommended in intermittent fevers as often superior to arsenic, and as a good substitute for quinine.

Powers so extensive as these have not been accorded to phosphorus by all writers, but Clay has illustrated its value in collapse, and John Brunton in the adynamia of typhoid fever; rapid improvement taking place under drachm doses of the following solution: Tinct. phosph. æth. (one third grain to the drachm) three drachms, spt. rectif. half an ounce, glycerin to one and one-half

ounces. About two grains were taken in the course of two days.

I have frequently prescribed phosphorus in the exhaustion of typhoid, and have seen remarkably good results from it; but, on the other hand, have been often disappointed, and cannot but consider it an uncertain remedy. In such cases I place more dependence upon ammonia, camphor and other stimulants of that class, but if they failed, should have recourse to phosphorus.

In exhaustion of the generative system and impotence phosphorus has long had a reputation, and was much valued by early authorities, but modern experience has shown its power to be more limited than was supposed. If the special exhaustion be only part of a generally enfeebled state, it will improve as the general tone and vigour improves, but this system is not stimulated apart from the others; indeed, if it were so, this might be a serious drawback to its ordinary use. I may say, however, that in some of my own cases an irritable, weakly condition of the sexual organs, traceable to previous early abuses or subsequent excesses, has been much benefited by continued doses of one two-hundredth to one one-hundredth grain thrice daily.

Patients with scanty, watery and irregular catemenia, sometimes suffer, about the time of the periods, from sick headache, and when this is the case a continued course of phosphorus increases the quantity and improves the quality and

regularity of the menses, while the headaches frequently disappear. When the discharge is not only watery, but too profuse in character, and somewhat delayed beyond the natural time, phosphorus is of considerable use, as it checks the overflow, relieves the backache, improves the mental depression, removes the nausea and vomiting so frequently attendant, and strengthens the general condition. It is also useful in profuse menstruation attended with excessive sexual excitement. The dose should rarely exceed one one-hundredth of a grain every two to four hours during the menstrual period, and morning and night during the interval. Bromides usually act better.

In hysteria nervous power is impaired, the emotions not being under control; neuralgia is often concomitant. It is a condition in which we should expect phosphorus to be useful, and instances of its value are on record. The cases benefited by it have been acute or chronic, dependent on sudden shock, or gradually coming on with increasing weakness and despondency; in either form a period of debility is liable to be followed by convulsive attacks. I do not undervalue moral and hygienic treatment, but amongst medicines, phosphorus in doses of one one-hundredth to one-twentieth grain has proved efficient in my hands. When hysterical attacks are connected with delayed or suppressed menses, pain in the iliac and lumbar regions, neurotic vomiting,

palpitation and general excitement alternating with depression, I have found this remedy help to regulate the periods and cure the hysterical symptoms.

In cases of fracture, resection and transplanting of periosteum, Wegner found that small continued doses of phosphorus stimulated the growth of new bone, especially in young animals; also that ossification in the fœtus was promoted by giving phosphorus to the mother.

I have seen good results from phosphorus in other cases; in caries of bone and in cases of abscess connected with necrosed bone it lessens suppuration and hastens the separation of the sequestrum; given during pregnancy it relieves the dental caries and neuralgia often incidental to that state, and I have given the hypophosphites successfully in such cases. It may be presumed that phosphorus and preparations of it, would also improve the nutrition of the fœtus in weakly subjects, and I think they might often be used with advantage in chronic rachitis. Kassowitz has reported an exceptionally favourable experience in rickets, founded on the treatment of five hundred cases. Observations on hens and rabbits taking phosphorus, have shown normal spongy bone replaced by hard tissue. It may be a remedy for osteoporosis, but as the lesions in rachitis are different, it can not be considered equally a direct adjuvant in that disorder. In osteomalacia phosphorus has seemed

of service. It is usually given with cod-liver oil, and the good effect both in this disease and in rickets has been attributed to the oil. A case, however, has been recorded in which a relapse occurred when the oil was given without the phosphorus. Its administration should be begun early, and be continued for months.

In leucocythæmia, pernicious anæmia and lymphadenoma, phosphorus was advised some years ago, and has been used with success. A boy with essential anæmia, prostration, diarrhœa, yellow, waxy face, etc., recovered under phosphorus, and remained well for some time. In a case of leucocythæmia, treated in the same manner, inflammation of the spleen was said to be produced. In a woman with lymphadenoma, having symmetrical enlargement of cervical glands, anæmia and dyspnœa, who had been steadily getting worse for some time, recovery took place after taking phosphorus. Some support was given to these observations by a case, under Wilson Fox, of leukæmia splenica in a man, aged thirty-seven, for when extremely enfeebled he began to take one-fiftieth to one-thirtieth grain doses, and after three months' treatment greatly improved ; he died, however, in the following year. Verrall reported a marked case of subsidence of splenic enlargement and improvement in blood-condition.

The action of phosphorus in phthisis can only

be considered palliative, but it moderates some troublesome symptoms. I have used it in various doses in upwards of eight hundred cases, of which I have a record, and am satisfied that it does not cure advanced tuberculosis, although it appears in many cases to arrest its progress, at least for a time; also to improve the condition of the throat and voice, and to relieve the dry, harassing cough, the pain after food, and even the wasting diarrhœa and night-sweats. It has also removed pleuritic stitches, and seemed to strengthen the general condition; on the other hand, its use is not free from danger, and requires caution, since it may induce obstinate hæmoptysis. These remarks apply also to the hypophosphites.

It may be convenient in this place to discuss the modes of administration of phosphorus and the relative value of its salts and compounds, especially as much valuable work has been published on the subject. In the first place, it may be well to note that although phosphorus occurs both in the yellow and red varieties, the latter is less volatile and less soluble than the former. Red phosphorus, owing to the difficulty of absorption, is practically non-toxic when taken by the mouth. The two forms are, however, equally toxic when injected under the skin. It must also be remembered that phosphorus exists in forms which may be termed inorganic and organic. Respecting the difference to their mode

of action, Tunnicliffe, in a well-considered article, says:—

"The inorganic phosphorus compounds of which the official calcium phosphate may serve as a type, contain their phosphorus directly attached to a metallic ion. The phosphoric acid in these compounds can be demonstrated chemically by means of molybdic acid. Substances of this class have long been given as medicinal agents, and have earned upon clinical grounds a reputation of exerting a nervine tonic action and of acting as adjuvants to growth, especially bone, which latter substance consists largely of calcium phosphate.

"The other form in which we meet with phosphorus dietetically and therapeutically is in so-called organic combination. These organic compounds of phosphorus are, from a chemical standpoint, in many instances very complex, and may be regarded as being built up on the type of phosphoric acid, by the replacement of its hydrogen atoms by complex organic radicles, which latter have also in certain instances their hydrogen atoms likewise replaced by other organic radicles. The most notable instance of such a substance is lecithin, which may be regarded as derived from phosphoric acid and glycerin, first of all by the esterification of one of the hydroxyl groups of the latter and the subsequent replacement of the two remaining hydroxyls of the glycerin by two stearyl radicles, and the combination of the resulting di-

stearo-glycero-phosphoric acid with the base cholin. This substance lecithin and its congeners cephaline and protagon form essential constituents of the nervous system, and are so immediately concerned in its functional activity as to give rise to the dictum that without phosphorus there can be no thought.

"To pass from the nervous system to the other tissue cells, we find organic phosphorus compounds present as nucleins and nucleo-albumins, especially in such organs as the muscles, the thymus gland, the thyroid gland, the liver, the kidneys, and the spleen. The phosphoric acid test as it exists in these organic combinations cannot be demonstrated by the molybdic acid reaction, and must, moreover, be regarded as being directly attached not to a metallic ion but to an organic radicle."

The hypophosphites are and have been for many years extensively employed, and are frequently prescribed in the treatment of phthisis and other forms of tuberculous disease. Much difference of opinion exists as to their value. Some authorities regard them almost as a specific, whilst others maintain that they are simply tonics and have no power of arresting the progress of the disease. The question has never been worked out from the point of view of modern bacteriology. The probability is that they improve the resistive power of the tissues, and render them a less suitable nidus for the growth of the bacillus. They

have been recommended in the treatment of pneumonia, but there is no evidence to show that they shorten the progress of the disease or hasten the crisis of the acute lobar form. Such a result would be phenomenal, and could not be reasonably anticipated.

In the convalescence from many acute diseases they are undoubtedly valuable, and the same may be said of many conditions of general debility whether arising from defective hygienic surroundings, or from prolonged anxiety or overstrain.

The probability is that the hypophosphites represent an easily assimilable form of phosphorus and nothing more. On theoretical grounds it might reasonably be supposed that the calcium was the better salt, and that it had certain advantages over the sodium compound, for lime belongs to the digitalis group, and has many of the actions of that valuable drug, improving the tone of the heart and indirectly the general nutrition of the tissues. Children fed on the hypophosphites do well, and often gain rapidly in flesh.

The glycerophosphates are now extensively employed as therapeutic agents, and appear to have a distinct sphere of usefulness. The glycerophosphoric acid itself is a colourless, odourless fluid, having an acid taste, and a specific gravity of 1·3. It forms salts of which the glycerophosphate of lime is probably the most useful and the most frequently prescribed. It is a white crystalline

powder, freely soluble in cold water, and soluble with difficulty in hot water. The ordinary dose for administration by mouth is from three to ten grains, or from two to four grains hypodermically. Amongst other salts may be mentioned the glycerophosphate of iron, which is met with either as a whitish powder or in scales, the glycerophosphate of sodium, which is a translucent, straw-coloured pasty mass, and the glycerophosphates of potassium, lithium, magnesium, manganese and quinine. A useful preparation of the glycerophosphates is made by dissolving two parts each of glycerophosphate of sodium and lime, and one part of glycerophosphate of iron in two hundred and fifty parts of aromatic syrup. The dose is from two to four drachms.

Discovered in the yolk of egg in 1846, glycerophosphates were but little known before 1893, when Robin drew attention to the large amount of partly oxidised phosphorus in the form of glycerophosphoric acid eliminated in the urine of some neurasthenic patients; having obtained and administered compounds of this acid, he concluded that they increased the general metabolism of both organic and inorganic matter, principally the latter, as shown by augmented excretion of urea, chlorides and sulphates, though not of uric acid nor of phosphates; at the same time they favoured the current assimilation of the albuminoid matters, and moderated denutrition of the nervous system

and aided its reconstitution by remaining in the system. He indicated a wide range for their curative power, *e.g.*, in chronic gout, diabetes, phthisis, Bright's disease, and even Addison's disease with nutritive decay, meaning rather the improvement of vital power than direct antagonism of such maladies; similarly in any breakdown of the nervous system, as in the aged, or after acute illness or lowering treatment; in chlorosis and rachitis; in chronic dyspepsia, especially with lessened acidity (after appropriate treatment); in neuralgia, ataxy, sciatica, spermatorrhœa and neurasthenia, generally when marked by depression, headache and impaired power for mental and muscular work; whilst he notes that insomnia, palpitation and phenomena of excitement may be aggravated (this is not my experience), and that the medication is not suitable in conditions of azoturia, or when organic oxidations are above the normal, or in mental disease or general paralysis. He speaks also of improvement in cases of muscular atrophy of various causation and of benefit in diphtheritic paralysis.

Harris, in a communication to the Manchester Therapeutical Society, points out that there seems a probability on *a priori* grounds that the glycerophosphates act as foods to the nervous system. They favour assimilation and metabolism, and are especially useful in neurasthenia and Addison's disease. In many cases of the former condition

they fail, but some cases are benefited by them. Very few cases of true hysteria are favourably influenced. The best results are obtained in the treatment of nervous exhaustion from overwork, in which the glycerophosphates have really a good effect. Harris used only the sodium salt, and not the other compounds. He gave from fifteen to forty minims three times a day of a fifty per cent. solution.

Prof. R. B. Wild, of Manchester, uses the glycerophosphate of sodium for weakness following influenza and for nervous exhaustion from overwork, and the late Dr. Dreschfield found it useful in many functional diseases.

CHRONIC LEAD POISONING.

CHRONIC lead poisoning is so common a complaint, is the bane of so many trades and occupations, is so widespread, and produces such disastrous effects on almost every organ of the body, that no apology need be offered for dealing with the subject from the point of view of the pharmacologist.

Workers in lead, such as compositors, plumbers and painters, absorb the metal in part by the skin, in part by the lungs, and sometimes from eating with unwashed hands directly after food. Injurious effects are not uncommon from the application of cosmetics and dyes containing lead to the skin and hair.

Once introduced into the system lead remains for a long time, in small quantities at least, and may be deposited in almost every organ of the body. It passes through the placenta to the fœtus, and has been found, not only in the blood and the liver, spleen and kidney, but also in the muscles, bones, and nervous system. In two cases of lead poisoning which occurred at a lead factory in the east of London, the brain contained large quantities of lead, in one of them as much as 117·1 milligrammes of the sulphate. This may account

for the serious nervous effects absorption of the metal produces. Ebstein records the case of a man, aged forty-three, a lacquerer, who had had lead colic for eight years; there was no blue line on the gums, lead was not found in the muscles, but it was in the brain.

Lead is eliminated chiefly in the form of chloride through the liver, skin and mucous membranes, especially those of the urinary tract. This process is markedly promoted by iodide of potassium, iodide of lead, which is excreted with comparative ease, being formed.

The subject of chronic lead poisoning is exceedingly interesting both to the pharmacologist and the practical physician. Some of its symptoms have occurred from the medicinal use of the acetate, and from the continued use of minute quantities rather than from massive doses. Thus Sir R. Christison gave eighteen grains in two days without injurious effect, whilst one-fifteenth of a grain given two or three times daily for two months caused in a child fatal poisoning. As a rule, the worst effects of the medicinal use of lead limit themselves to an attack of colic, and the severe symptoms about to be described need not be feared from it.

The ordinary "lead colic," or plumbism, is traceable most frequently either to the mechanical use of metallic lead, its oxides or carbonates, or to the ingestion of these salts dissolved in drinking

water. After some general malaise, disordered taste, dryness of the mouth, fœtid breath, anorexia and constipation, abdominal pain is usually the most marked symptom, but not invariably, for Garrod found it absent in two or three per cent. of his cases. When fully developed it is much more intense than ordinary colic; it is referred mainly to the region of the naval (the colon), but severe cramp-like or neuralgic pains dart in many directions, towards the loins, the scrotum, the chest, and the thighs; it has a twisting, tearing character, so that German miners name it commonly "Hutten Katze" ("cat of mines"). It comes on in paroxysms, remaining constant but dull in the intervals, the whole attack lasting from a few minutes to several hours. It is worse at night, but its recurrence is irregular. Relief is found from firm pressure and altered position, and the sufferer either lies flat on his face, pressing the abdomen or is doubled up, bending his legs, or rises suddenly, still pressing the painful part with his hands, till a violent paroxysm again sends him to bed. Restlessness is extreme, and the whole attention is concentrated on the pain. The abdominal walls are rigid, knotty, and drawn in, there is commonly tenesmus, and the rectum has been felt to contract and relax spasmodically. The liver is retracted, or actually lessened in size; the intestines are drawn into less space from contraction of their muscular coat, and in prolonged cases,

after the abdominal fat has been absorbed, the retraction of the belly becomes very striking.

Tanquerel and Burton were the first to describe, as common in plumbism, a dark blue or grey line along the free edge of the gum, together with a brownish coloration of the teeth. Though a valuable sign, and often present, it is not always so, nor does it necessarily imply saturation of the system; it varies in its time of appearance according to the dose, but has been seen within twenty-four hours of administration of one large quantity; twenty to thirty grains, in divided doses, may develop it, and when once seen it is persistent, lasting twelve months at least after its cause has ceased. Similar coloured patches may be found on the buccal mucous membrane. The colouring depends on the formation and deposition of lead sulphide from the sulphuretted hydrogen evolved from particles of food left about the teeth, and it may be prevented by cleanliness. It is usually distributed in rounded loops corresponding with the vascular papillæ of the mucous membrane, and depends on small pigmented granules, some of which are external to, and others within, the vessels. It is probable that the gas from the decomposition of food particles diffuses into the textures of the gum, and then combines with lead circulating in the blood or lymph, so that particles of lead sulphide are precipitated. A similar condition may be present in the intestinal membrane. The

administration of iodide of potassium induces its rapid development.

I cannot so readily explain the pathology of the colic. It is in part dependent on constipation, for it is relieved when purgation is secured; yet Briquet claims to have relieved it more quickly by Faradism of the abdominal wall without any aperient effect. It is dependent partly on irregular muscular contraction of the intestinal tube, and is partly an enteric neuralgia. Harnack, using the triethylate of lead, which can be injected directly into the blood, found that the nervous ganglia in the intestinal wall were stimulated, in consequence of which sometimes diarrhœa resulted from increase of peristalsis, but more usually there was firm contraction of the intestine leading to severe constipation ; the former was more often seen in animals, the latter in man. The contraction of the bowel, he held, explained the colic. I think, however, that the irregular muscular contraction of the intestinal wall, which is the physical basis of the colic, is due not to a direct action of the lead on the muscular fibre, but to an indirect action through the nervous system.

Ordinary medicinal doses of lead do not usually produce definite effects on the nerves or muscles. It is in chronic plumbism that affections of the nerves and muscles become marked and significant, various forms of neuritis and paralysis almost always appearing. The most common is a paralysis

of the extensor muscles of the wrist and fingers, leading to a condition known as "wrist-drop," from the peculiar manner in which the hand hangs down when the limb is extended. This occurs more often, or earlier, on the right side than the left—the fingers and wrists are flexed, and the hand pronated, the elbow stands out from the side, and the forearm bends on the arm—wasting of the affected muscles quickly follows, especially of the muscles of the thumb. A special plastic, or fungoid, form of synovitis in the sheath of the extensor tendons has been described.

Sometimes other muscles are affected—thus, strabismus has been noted from paralysis of the ocular recti, and aphonia from laryngeal palsy. Death has resulted from paralysis of the respiratory muscles ; in a case where this was imminent, recovery occurred under atropine, which was presumed to stimulate the respiratory centre. Although the paralysis is generally of the forearm type, giving the double drop-wrist, yet it is not infrequently of the upper-arm type (in which the deltoid, biceps and supinator longus are implicated) ; sometimes it has the characters of an ordinary progressive muscular atrophy (Aran-Duchenne), attacking first the small hand muscles, and in about thirteen per cent. of the cases it attacks the legs first (peroneal type). Of the special senses, sight is the most often affected, amblyopia occurring sometimes without the presence of any

changes in the fundus, though double papillitis or neuro-retinitis are not unfrequently seen. Oliver has recorded cases of primary papillitis, and Gibson has described cases in children where there was much swelling of the disc. In these cases there was no albuminuria, but lead was found in the urine. Impairment of vision often persists, and in some cases ends in absolute blindness. Permanent loss of sight may occur also from a chronic atrophy of the optic nerves independent of papillitis.

It is not uncommon for the hearing to suffer, and common sensibility is sometimes altered. There are occasionally patches of anæsthesia, and sometimes hyperæsthesia is developed. From experiments on animals Curci concludes that lead irritates the vagus, and he thus explains the slowing of the heart action.

During an attack of lead colic the intellect is, as a rule, clear, but in long-continued cases the moral courage and the spirits give way, and sometimes in the course of the illness distinct delirium occurs, generally of the form "delirium of dread," not unlike delirium tremens. The patient is afraid of being alone, especially at night, and has visions of black and creeping things. The encephalopathic, or fulminant, cases may result in death in a few hours. In the cases where recovery occurs, there may persist blindness, or epilepsy, or insanity.

The fits, which are due to the presence of lead in the blood, resemble those of uræmia and alcoholism, indeed are indistinguishable from true epileptic attacks. Other cerebral symptoms, such as headache, delirium and coma, have been recorded; insomnia is usual. A comparison may be drawn between the effects of alcohol and of lead, both on the nervous system and on the kidneys. Of one thousand three hundred and ninety cases of lead poisoning, there was colic in eighty-eight per cent., paralysis in seven per cent., and encephalopathy in five per cent.

Whether the muscles or nerves are primarily affected, and in the latter case whether the peripheral branches or the centres are most at fault, has been much debated. Giacomini attributed the colic to direct muscular irritation from deposition of the metal in the abdominal muscles and the diaphragm, pointing out that superficial pressure often gives pain, even over the iliac crests, whilst firm supporting pressure relieves.

Tanquerel maintained that the colic was due to irritation of the great ganglionic centres, though signs of this could only be found in one out of forty *post-mortem* examinations.

Heubel argues that the peripheral intramuscular extremities of nerves are at fault rather than the main trunks. On the other hand, Bernhardt asserts that the real lesion is in the grey matter of the cord, and most modern observations

point to the same conclusion, at least in chronic conditions; lead has been found in its substance in some cases, and a granular partly atrophic state of spinal cells has been verified in one instance. Popow finds that lead, like arsenic and mercury, produces a central myelitis of the spinal cord. The affected muscles and corresponding nerve-trunks are much atrophied, so that sometimes scarcely one normal fibre can be found. The view that the nerve centres are the seats of the lesion is supported by the fact that large quantities of lead are found in both cerebrum and cerebellum. In animals choreic movements occur, and even convulsions, without impairment of sensation or consciousness. It would seem that the motor areas of the central nervous system are more affected than the sensory.

Recent research has shown that it is more than likely that the whole neuron is affected by the lead poison. The peripheral nerves are undoubtedly degenerated, but the fact that the supinator longus escapes in the ordinary wrist-drop indicates an affection of the centres in the cord as well.

Of the cerebral phenomena, to which the term saturnine encephalopathies has been applied, epileptiform convulsions are the most common; they may occur early, and come on suddenly without warning, and are usually accompanied by headache, vertigo, and dimness of vision. The convulsions

which ensue later are usually associated with an albuminous condition of the urine.

Full medicinal doses of the acetate slightly lower the force and frequency of the pulse. In chronic conditions of lead poisoning the pulse is small, hard and usually slow, and the sallow, bloodless skin has an icteric tint, anæmia is marked, and there is more than the normal amount of liquor sanguinis, with fewer red corpuscles. Malassez states that these are increased in size. Cardiac murmurs are common in lead workers, and the heart and great vessels have been found smaller than usual after death. Henle considers that the vessels are contracted (during life) by direct irritation of their muscular coat by lead circulating with the blood; certainly vascular tension is much increased in plumbism, as clearly shown by the sphygmograms.

Chronic lead poisoning often leads to abortion, and if this does not occur, the children born are delicate. Of one hundred and twenty-three conceptions amongst lead workers, fifty children only were born alive, and of those but fourteen survived infancy. It would seem that the influence of one parent only affected by lead is enough to produce these results. Amenorrhœa and menorrhagia have been traced to working in lead, and pills of diachylon are largely used to procure abortion, especially in factory towns.

The influence exerted by this drug upon

the kidney is of great practical importance. Albuminuria is not uncommon in acute plumbism, and is then connected probably with an altered condition of the blood, but in chronic cases a directly injurious action is exerted on the kidney structure, leading to chronic interstitial nephritis. This is said to be due to the deposition of earthy matter in the looped tubules, causing their blocking, and consequent cirrhosis. Shearman has recorded two remarkable instances of albuminuria in one family, traceable to the use of drinking water impregnated with lead; characteristic palsy was also present. The cases recovered for a time after removing the cause, but later one died of apoplexy, the other of Bright's disease. In a clinical lecture on the subject, Oliver concluded lead to be a "special poison to the renal cells," but all metals, if absorbed, affect the kidneys more or less severely.

During a paroxysm of colic the amount of urine is diminished, and it is passed with difficulty. It is proved also that the excretion of urates, urea and uric acid from the blood in its passage through the kidneys is lessened under the influence of lead, hence a larger than normal amount remains in the blood, and the patient becomes exposed to gouty attacks. Indeed, acute gout may be developed in susceptible subjects by the administration of lead salts, and it is calculated that thirty-three per cent. of gouty patients had been exposed in some manner to the action of lead. Pains about the joints

and deposits of urates are not uncommon in saturnine cachexia.

Of the different workers in lead, oxide of lead, or "white lead" (carbonate), those who grind it in factories are most liable to suffer, though less so now that the powder is ground with water, but house painters and coach painters, plumbers, pewterers and compositors, makers of certain white glazed cards, hat pressers, bleachers of Brussels lace and glazers of pottery are often affected. Severe symptoms have arisen from sleeping in a newly painted room, or from breathing the smoke of burning painted wood. Amongst exceptional and little suspected causes of plumbism, are the handling of vulcanised rubber and black horse-hair coloured by lead sulphide, the use of hair washes, dyes and cosmetics containing lead salts, breathing dust from "American cloth" whitened with lead salts, and in the process of making yellow cord fusees (chromate of lead). The case is recorded of an infant one and three-quarter years of age, who developed lead poisoning from the treatment of a general eczema with diachylon ointment. Poisonous symptoms have followed in an infant after the application of strong lead lotions, or "metallic shields," to the mother's nipples, and in children from yellow confectionery (chromate). Chewing "tea lead" (in which tea is wrapped), using snuff that had been wrapped in similar "foil," the use of soda water from lead syphons (free tar-

taric acid is said to help in this case), bathing in water impregnated from a leaden pipe, drinking wine from bottles which had been cleansed with shot, have all caused plumbism. Cases of lead poisoning have been recorded in a shoemaker from putting nails in his mouth; in a cigar roller from cutting cigars on a lead plate and putting the knife in his mouth; in a diamond worker who fixed small diamonds in masses of lead before proceeding to cut them; and from the manufacture of artificial flowers.

Two epidemics have occurred—one at Taunton, another in France—from flour ground between millstones that had been mended with lead, and even the handling of lead machines, as in ice-cream making, or cameo polishing, or cleaning "beer engines," or brass handles, has induced colic. Cases of lead palsy occurring in children in Australia were traced to the drinking of ginger beer which was found to contain one milligram of lead in twenty-four ounces.

There is reason to think that "dry colic," or enteric neuralgia, of tropical countries is connected with lead. Gubler gives instructive instances of its development from the use of lead cosmetics in creoles. Mialhe and other French physicians speak of lead colic being frequent on shipboard, and connect it with the action of a saline atmosphere on lead. It is especially frequent in Newcastle, "the home of the lead trade".

Excepting in the trades mentioned, the most frequent source of lead poisoning is the use of drinking water impregnated with the metal or some of its compounds. Bad symptoms have resulted from as small an amount as one-fortieth of a grain per gallon, and one grain per gallon is a dangerous dose. It is to be noted that the freer the water from saline ingredients, the more readily it takes up a soluble carbonate formed on the metal pipe or cistern. The formation and solubility of this are also favoured by much organic impurity, free access of oxygen, a little nitric or other acid, or the presence of a second metal (iron as well as lead). Carbonic acid in pure water also favours solubility, although in certain circumstances it may act differently. Lime and other saline constituents will, on the other hand, if present in the water, lessen the liability to contamination by forming insoluble coatings on the metal; otherwise, no doubt, plumbism would be more common than it is.

Epidemics have occurred at Huddersfield, Bradford, Sheffield and Keighley. In several of these the public water supply from moorland was found acid, and the acidity on which the plumbosolvency of the water depends has been shown to be due to the effect of peat.

There is a great difference in the susceptibility of different individuals to the poisonous action of lead—as may be verified in any large factory—

and it is comparable to what is noticed with arsenical wall papers. One attack of colic predisposes to another, which may follow after a long interval from a comparatively slight cause—thus a man who had suffered as a house painter turned gamekeeper, and got an attack long afterwards from stirring shot in water with his hands; and a house painter, who, on account of wrist-drop, became a college porter, had a relapse a long time after complete recovery, from sitting in a newly painted porter's box. Women, especially girls, are more susceptible than men. The most susceptible of all are underfed girls who have been living in bad hygienic surroundings before commencing to work with lead.

In chronic cases of lead poisoning an alkaline iodide should be given internally, and sulphur baths should be used containing seven ounces of sulphuret of potassium, or its equivalent. During half an hour of bathing, friction should be employed, and soap should be freely used afterwards. Electricity should be applied to the affected muscles—Faradism if it causes contraction; if not, the continuous current three or four times weekly for a quarter of an hour, whether it induces contraction or not; in curable cases it will ultimately do so.

Purgatives should be freely given. Castor oil will remove the lead excreted into the intestine. The best results are obtained, however, from

magnesium sulphate given with potassium iodide. Under the influence of the latter drug the lead is excreted by the bile and intestinal secretions, and is then immediately removed by the Epsom salts, so that re-absorption of the poison is prevented.

Fatty food is said to antagonise the development of plumbism in lead workers, and a long prevalent colic in large lead works in Birmingham was stopped by the free use of a "treacle beer" containing sulphuric acid. Washing the hands before eating is important, and washing with petroleum is prophylactic.

Dr. Murrell recommends the following prescription in cases of chronic lead poisoning:—

℞ Magnesiæ Sulphatis	2 drachms
Ferri Sulphatis	3 grains
Acidi Sulphurici Dil.	15 minims
Spiritus Chloroformi	15 minims
Tinct. Belladonn.	10 minims
Tinct. Capsici	2 minims
Aq. Menth. Pip. ad.	1 ounce

The sulphuric acid converts the lead into an insoluble sulphate which the magnesium salt expels from the intestine. The iron acts as a hæmatinic, whilst the belladonna relieves the colic. The other ingredients are carminatives.

THE IODIDES.

In this article it will be my endeavour to give an account, the result of many years' practical experience, of the medicinal uses of the various salts of iodine, including a brief sketch of their pharmacological actions.

Iodine and the iodides have a similar action ; the former is better adapted for modifying the general constitutional state as in tuberculosis, whilst the alkaline iodides being more quickly passed out of the system, act better where some morbid material needs elimination, *e.g.*, in syphilis, lead poisoning, or rheumatism. The potassium iodide is the salt most commonly employed, but the depressing effects of the potassium, especially when taken for long periods, have led many to employ the iodides of sodium or ammonium, in preference.

Melsens found that mercurial compounds were soluble in alkaline or neutral solutions of iodide of potassium, and that corrosive sublimate, if fixed in a muscle or tendon, could be dissolved out of the organic tissue by soaking it in such a solution. He found that even metallic lead was, to some extent, soluble in the same medium, with the formation of a double iodide of lead and potassium.

He argued that in cases of mercurial or lead poisoning, with salivation, tremor, colic and paralysis of groups of muscles, iodides introduced into the blood formed soluble compounds with the metal deposited in the tissues, and enabled it to be taken up by the absorbents and passed out by the kidneys, salivary glands, the mucous membranes, and skin. Support has been given to this argument by the fact that an insoluble salt of mercury or lead may be administered to animals without evident effect until after the administration of an iodide, when symptoms of poisoning appear. We know, clinically, that in metallic cachexia, when active symptoms are no longer present, and the poison cannot be detected in the secretions, if an iodide is given symptoms of acute mercurial or lead poisoning may be developed, and that foreign substances may be found in the urine. Chronic conditions of illness, such as palsy or cachexia, localised paralyses, may be present when the use of the iodide is commenced, but in the course of a few days acute symptoms such as colic or salivation, may be reproduced until elimination is complete.

The case of M. Faure, recorded by himself, is a good illustration of the value of iodides in cases of lead poisoning. Engaged in white lead manufacture, he suffered severely from symptoms of plumbism, and cured himself with iodide of potassium. He remarks that he could tolerate

the drug better when he took it before than with food, which he attributed to the "fasting stomach being coated with mucus".

I have had very good results with iodides in cases of plumbism, the best being obtained in conjunction with purgative treatment. The metallic iodide is excreted by the mucous membrane of the alimentary canal, and should be immediately removed to prevent its re-absorption; hence the necessity for counteracting the constipation which so frequently accompanies this condition. A good formula is:—

℞ Magnesii Sulphatis . . . . 30 grains
Potassii Iodidi . . . . . 5 grains
Aquæ Chloroformi . . . . 1 ounce
M. To be taken every four to six hours.

Iodide of iron is valuable in later stages.

It is probable that iodine acts in syphilis much as it does in metallic poisoning, by assisting the elimination of a morbid material. It has been maintained that its influence is best seen in cases which have been previously treated by mercury; but there can be no question that the drug has curative powers of its own, independent of mercurial action; they are evidenced in the later, or tertiary stages of constitutional syphilis, when either the mucous membranes are affected, as in deep ulceration of the fauces, or the bones are attacked with periostitis or nodes, or the skin is affected with rupial or lupoid eruption, or the meninges are thickened, or gummatous deposits

are formed in the viscera. In such conditions it acts better than mercury, although the latter is preferable in iritis. In a certain proportion of undefined syphilitic cases, an iodide and mercury together will give better results than either medicine alone.

By causing the absorption of deposits and thickenings in various parts of the body, iodides relieve many resulting symptoms, such as those due to the pressure on different portions of the nervous system, nocturnal pains, neuralgia, paralysis, dulness of intellect, and convulsive paroxysms. The dose of iodide of potassium is a matter of much importance, and need be limited only by the susceptibility or idiosyncrasy of the patient, and the progress of the disease; it may vary from one to two grains up to sixty grains two or three times daily, and the best results have sometimes been obtained from heroic doses, one-half to two ounces daily, when ordinary ones have failed. Personally, I am not in favour of the administration of very large doses.

Graves was one of the first to point out the value of iodide of potassium in rheumatism, and it is now well established. I connect its efficient anti-rheumatic action mainly with an eliminant action through the kidneys, and to promote this, recommend it to be largely diluted and combined with bicarbonate of potassium. To lessen irritation of the stomach, the medicine may be given in

an effervescent form. Sometimes if the patient is feeble, and the urine abundant and of low specific gravity, the iodide may be combined with hydrochloric acid and quinine. In cases of chronic rheumatism, small doses of iodide, continued for a long time, act exceedingly well, but some patients are very sensitive to its action, and need special care to secure its toleration. The use of iodide of potassium is now mostly limited to chronic cases, or to those acute cases where sodium salicylate cannot be tolerated.

I have had several cases of meningitis which derived much benefit from iodides, given alone or in combination. A child, aged six years, who had been ill for eight days, and was insensible, with dilated pupils, dysphagia, paralysis of one side, and convulsive twitching, and who had been getting worse under previous treatment began to improve soon after commencing potassium iodide, given in ten-grain doses every six hours, with five minims of tincture of belladonna in the intervals. Recovery ultimately ensued, and the boy has now reached adult age.

In another case, aged eight years, there was pain, vomiting, delirium, unconsciousness, convulsion, dilated pupils, tetanic stiffness of the neck muscles, grinding of teeth, difficult respiration, slow, weak pulse, and every sign of fully developed meningitis, yet recovery took place under potassium iodide and belladonna.

Leared recorded a case of recovery under five-grain doses of iodide of potassium when other remedies had been used without relief. He was satisfied as to the diagnosis of tuberculous meningitis. Trousseau and many physicians of experience deny that the tuberculous form is curable under any circumstances, and certainly a large majority of such cases end fatally.

In the subacute and chronic stages of bronchitis the iodides relieve by an alterative action on the bronchial mucous membrane, thinning and ultimately diminishing the muco-purulent tough secretion, and so rendering expectoration easier. They may with advantage be combined with antispasmodics. Potassium iodide should be given for this purpose in doses of three grains; but in weakly subjects, the iodide of ammonium, in doses of from five grains every four hours, acts better. When there is an increase of temperature, aconite should be given in doses of five minims every two to four hours. If an expectorant be required, tartar emetic should be chosen; the dose should be small and frequent, and care should be taken to avoid emesis or undue depression.

I have known iodide of potassium to relieve many asthmatic patients, and it is the main ingredient in a secret and successful remedy for asthma. Trousseau and Jaccoud speak of its value, and Sée has recorded valuable observations upon

twenty-four cases watched for a long time. Four of these were children, four old people, the others adults; the daily dose varied from twenty-two to forty-five grains, being reduced as improvement progressed. If given some hours before the usual attack this was often prevented; if given during it, respiration was rendered free in one to two hours. Chronic asthma with emphysema was also benefited by the remedy; inhalations of iodide of ethyl, ten drops several times daily, and the occasional use of opium or chloral were, with advantage, conjoined with the treatment. Hyde Salter observed benefit from iodide of potassium in full doses, fifteen to thirty grains every two to four hours, in very diverse cases of asthma. I think that such attacks as are connected with catarrh, and are relieved by free secretion, and in which the nerve symptoms are reflex rather than primary, show the best results from this remedy. I have known it to be efficacious in asthma connected with amenorrhœa and uterine congestion, and also in the asthma of rheumatic and gouty subjects. In an interesting case in a rheumatic patient, the asthmatic attack was relieved by four-grain doses of iodide, but severe pain in the region of the kidney followed, with secretion of scanty acid urine; this occurred more than once, and was only relieved by producing free excretion of alkaline urine by appropriate remedies. In this case the drug was supposed

to cause renal congestion by increasing the absorption of waste nitrogenous material.

In cases of thoracic and abdominal aneurism, in which surgical treatment is impossible, the clinical results obtained by potassium iodide should not be ignored. Nélaton recorded marked relief of the signs and symptoms of an innominate aneurism under the use of this remedy, which he gave empirically at the request of the patient, and Bouillaud, following up this clue, obtained good results in aneurisms of the carotid and thoracic vessels. Chuckerbutty, in Calcutta, published an account of three cases which were relieved; in one of these the aneurism was already projecting through the sternum when the drug was commenced.

It is to Dr. G. W. Balfour that we are most indebted for drawing attention to this subject. He summarises fifteen cases, all of which, save one, were relieved, and in twelve the external tumour was actually lessened, and the sac partly consolidated. In one of his earliest patients, the bulging, which was evident between the second and third ribs, disappeared after a few weeks' treatment with thirty-grain doses thrice daily, and this dose was continued for nine months "without any unpleasant symptoms," but with complete subsidence of aneurismal suffering. The same man had not improved under previous doses of twenty grains, and Balfour points out the impor-

tance of pressing the drug to saturation before considering it inert. It is quickly eliminated—large doses within two or three days ; and many of his patients took thirty grains several times daily. In a few, coryza and headache were produced, but as a rule, no worse symptoms were caused by large than by small doses. Suckling has contributed an additional series of twenty cases treated by potassium iodide in doses of ten grains, increasing to sixty grains, combined with Tufnell's diet ; of these twelve were benefited, but he notes that in several the pulse-rate increased, and the drug then disagreed. Referring to these cases, Balfour points out the necessity of regulating the dose by the effect on the circulation. After some days in bed the patient's normal pulse should be ascertained, and doses of ten grains commenced, and then later increased to fifteen grains if the pulse rate remain unaltered, the object being to lower blood pressure within certain limits. Although in his early writings on the subjects already quoted, Balfour was inclined to attribute to a sedative action on the nervous system the good effects of the drug, he has, for some time past, traced them rather to lowering of blood pressure, consequent on dilation of the arterioles, and some depression of heart action ; following this more resisting power develops in the sac, the coats of which tend to hypertrophy, and so to cure ; whilst if the nutrition be unduly

lowered by starvation diet, or by excessive doses of iodide removing albuminates from the system, the hypertrophy is hindered; if the pulse quickens under iodide, he concludes that tension is unduly lowered, and the dose too large.

In contrast with these observations must be noticed a very careful series of experiments on the blood pressure in rabbits after intravenous injection of potassium iodide; also of records of pulse rate and tension on patient's taking full and large doses of the sodium and potassium salts by Drs. Stockman and Charteris, which lead them to the conclusion that "these salts when given to man by the stomach in ordinary doses have no direct depressing effect on the action of the heart, or on the blood pressure in the arteries". If sometimes weakening and quickening of the pulse follow their use, it is an indirect effect due to increase of, or change in, the iodine containing thyroid secretion. With regard to their clinical value in aneurism, whilst quoting Rosenbach (of Berlin) against it, they acknowledged that almost universal experience is in their favour: certainly mine is.

In cases of chronic endocarditis and arteriosclerosis, hypertrophy, and even fatty degeneration, relief may often be given, especially to the anginal attacks and dyspnœa, by a steady course of various iodides. Of course, as Charteris remarks, in long-standing cases dependent on factors continuous in action, their cure cannot be reasonably

expected, and adjuvants of rest, diet, etc., must be secured, but under favourable conditions the drugs may be very valuable. Germain Sée, Laborde, and others, have recorded illustrations. Dr. J. B. Nichols (Washington) concludes that they arrest or retard the earlier symptoms, and ameliorate later by an alterative action, not only anti-syphilitic. Biering again recommends them in the sclerosis of gastric and intestinal vessels. Powell mentions it as valuable in angina pectoris "to reduce arterial pressure". Mott advises it as most useful when arterio-sclerosis is well marked. Sansom combines it with heart tonics, "to unlock the arterioles," *i.e.*, to lessen tension, and wherever there is thickening of arterial walls, gives a long course of iodides.

In a paper published in conjunction with Dr. Charteris, Professor Ralph Stockman shows that the action of the iodides on the circulation is not direct, but is due to increased formation of the iodine containing thyroid secretion, which exerts a powerful effect, both on the circulation and on metabolism.

The iodides are readily and rapidly eliminated by the different secretions, and may be detected in the saliva, the buccal and bronchial mucus, the tears, the milk, the perspiration, the urine, and even the serum of joints. R. W. Taylor has reported evidence of elimination of iodine by the skin in the case of a man with pityriasis, who took

large doses of the potassium salt whilst wearing a starched shirt; he had profuse perspirations, and a dark coloration, due to the formation of iodide of starch, appeared on his back. In another case of a man taking ten-grain doses for syphilis, not only the linen, but the hair became coloured brown.

It is probable that almost all the iodine taken is excreted in the urine, for Scharlau recovered from that excretion three hundred and forty-five centigrammes out of three hundred and fifty, and, according to Melsens, very little can be traced in the fæces, the iodine excreted into the intestine being absorbed by the lining membrane before it reaches the rectum. Rabuteau found a small quantity in the fæces, so long as it was present in the secretion; if diarrhœa occurred the quantity was notably increased. Ehlers concluded that doses above twenty grains are not completely absorbed; of that quantity he found seventy-five per cent. eliminated.

The rapidity of elimination varies with the quantity taken, a large dose giving evidence of its passage very quickly. Ranke found traces in the urine three and a half minutes after administration, and even sooner in the saliva. Nothnagel also found it early, in ten minutes in the latter secretion. Richardson found it in the urine within one minute of injecting tincture of iodine into an enlarged bursa, and three minutes after breathing iodide of

ethyl, iodine could be detected in the urine. It is an important practical point that the elimination of this drug is completed sooner than that of many others. Balfour noted that even if large doses of potassium iodide had been taken for many weeks, their elimination was complete within three or four days after ceasing to take them. Rabuteau, after fifteen grains, found traces in the urine for three days; after one hundred and fifty grains, for ten days, not afterwards. The greater part was eliminated during the first day, little passed on the second, and scarcely a trace on the third; and the elimination was somewhat slower. Speck states that in Bright's disease the kidneys do not eliminate iodine. Desprez gave potassium iodide subcutaneously, and succeeded in recovering two-thirds of it subsequently from the urine, its earliest appearance in that secretion occurring twenty minutes after the injection. He found that febrile conditions and disease of the kidney delayed the appearance of salt in the urine, prolonged the period during which elimination occurred, and in the case of Bright's disease, instead of finding two-thirds of the drug in the urine, he found only a quarter, a sixth, and even an eighth.

The earliest and most marked evidence of the constitutional action of the iodides is furnished by irritation and catarrh of the mucous membranes. It is shown mostly in the throat and bronchi, the nose and eyes, parts that are exposed to contact

with carbonic-acid gas, which it is supposed decomposes the iodide as it is eliminated, so that free iodine exerts its local irritant effect. The irritation shows itself by pain and sense of pressure over the frontal sinuses, œdema, prickling, and heat about the nose and eyes, with sense of stuffiness and discharge like that of ordinary coryza. The dose that will produce these symptoms varies a good deal with different persons, some being acutely affected by one or two grains of potassium iodide, others not by ten or even twenty grains, continued daily for a long time; in fact raising the dose will often stop the symptoms. Ammonium iodide, it is stated, is more liable to cause iodism than the other salts, because it is more easily decomposed in the body.

The phenomena described, as well as the skin eruptions caused by iodides, are included by Dr. David Walsh in the term "excretory irritation," *i.e.*, "disturbance set up by the eliminatory passage of the internal irritant through the essential cells of the excretory organs". He states that any drug or internal irritant that inflames the skin may be suspected of inflaming other excretory outlets, and such drugs must be administered with great caution.

Much disturbance of the nervous system sometimes follows the full action of the iodides. It is marked at first by excitement with restlessness, tremor, anxiety, and insomnia, but this state is lia-

ble to be succeeded by feebleness and depression ; these symptoms are possibly due to increased thyroid secretion. Toxic doses have caused violent headache and sometimes convulsion. Rilliet described neuralgia, tinnitus, disturbed intellect, and convulsions, as prominent symptoms in some cases of iodism, but these are of exceptional occurrence. Trigeminal neuralgia has also been reported, but I have rarely met with such cases. Altered vision and paralysis were noted by Brodie. "Occasional hyperæsthesia and temporary palsy of lower extremities" occurred in a man who was taking very large doses (ninety grains thrice daily) of potassium iodide. Such symptoms, however, must be considered rare, for H. Wood states that he has seen the nervous system affected only once, even with "enormous doses," and then the patient, who had been taking two hundred and seventy grains daily, became intensely sleepy and stupid, as if under the influence of bromide. Extreme depression is not an uncommon effect of even small doses in sensitive subjects, and sometimes compels the disuse of the drug.

Binz experimented with the sodium iodate and found that in large doses this salt caused narcosis in animals. It proved especially poisonous to the respiratory and cardiac centres, and he suggests that both this salt and iodoform are decomposed, and liberate iodine in the brain and cord. Many years ago Ringer and Murrell, experimenting on

the frog's heart, demonstrated by a series of tracings that potassium iodide exercised a much more depressing effect on the cardiac centres than either the ammonium or sodium iodide.

THE PHARMACOLOGICAL ACTION OF MERCURY AND OF SOME OF ITS COMPOUNDS.

In this paper an attempt will be made to discuss some moot points connected with the pharmacological action of mercury and its compounds.

Nutrition is so closely connected with hæmatosis that it is not surprising that it may be improved by small doses of mercury. Keyes found this to be the case—the weight increased and the remedy acted as a tonic. Hufeland had previously made a similar observation, and Basset, Liégeois and others corroborated it; the last named considers corrosive sublimate in minute doses *comme un réconstituant des plus puissants.*

On the important question of urinary excretion the evidence is negative. We need more research in this direction, but so far the evidence does not favour the theory of mercury (in small doses) curing disease by increase of tissue-change. It lowers the temperature in animals (except when "mercurial fever" occurs), and it does the same in specific fevers. I take this as evidence of its lessening change, rather than the contrary. Mercury, as a rule, in ordinary doses produces no

effect on the temperature of the body, but five-grain doses of calomel sometimes lower the temperature; exceptional cases have been recorded in which the administration of the drug produced pyrexia. Altogether, at least in the doses under consideration, mercury merits the name of "moderator of nutrition," rather than of alterative, and in this *rôle* we can see its analogy with small doses of arsenic, and antimony, under which weight may be gained, and nutrition improved. With full or poisonous doses, when the blood corpuscles are destroyed, the secretions rendered profuse, and digestion impossible, nutrition is profoundly impaired, and waste of tissue progresses rapidly.

Small (therapeutical) doses of all mercurial preparations are well borne by the stomach. Rebuteau cites cases where many hundred pilules of the proto-iodide were taken in the course of one to three years without gastric disturbance; yet we must allow for some idiosyncrasy in this respect, and practically we find that those who have resided long in the tropics, and fair, delicate women and chronic dyspeptics are very sensitive. It is not possible to say beforehand what amount of mercury will produce the characteristic effects in any given case—a single friction or a few grains may produce in one patient what many weeks of treatment will not do in another.

Single doses of calomel—from one to five, ten,

or even more grains—produce thin and "bilious" stools without much griping. If the intestine of an animal be examined after such action, it will be found reddened, especially in the upper part, and its glands stimulated. Symptoms of constitutional action may be early detected in the mouth, such as a sense of heat, metallic taste, sticky coating of the tongue, increased flow of saliva, and perhaps slight tenderness of the gums. On continuance of the medicine, these symptoms increase and diarrhœa occurs, with some nausea. The stools at first semi-solid, become thin and sometimes papescent with mucus, sometimes yellow, or dark or grass-green (the latter especially in children: they have been compared to "chopped spinach"): sometimes blood appears in the motions, and severe colic and tenesmus occur. The tongue is said to show a greenish coating with two long longitudinal red stripes. In severe cases when the poisonous action of mercury has been induced, intense stomatitis appears, with swelling of the tongue and gums, a membranous deposit, fœtor, and loosening of the teeth, with severe pain and difficulty in mastication. The salivary glands become enlarged and tender, and a vast amount of secretion pours from the mouth—ten pounds of saliva have been secreted in twenty-four hours; at first viscid as usual, it soon becomes thin and watery, containing albumin, mucus, and alkaline chlorides. Children and the aged are seldom

salivated—Graves suggests because their salivary glands are "inapt"—diarrhœa or prostration is with them the earliest symptom. Salivation is dependent partly on local causes: it occurs more quickly when the mouth is unclean, and may be almost wholly prevented by great care with the teeth; dental caries will determine it; it is said to commence near the last molar on the side on which the patient mostly sleeps. The irritation of a wisdom tooth or of a pipe will influence it.

Such facts have led to the supposition that salivation is only secondary to buccal soreness, but this is incorrect. It may be induced by rubbing mercury over the parotid, and before any irritation is produced. Ricord detected the drug in saliva drawn from Steno's duct by a catheter, in animals when calomel had been injected beneath the skin, and salivation occurs, as we know, independently of irritation of the mouth from the action of gold, iodine, various acids, etc., as well as during pregnancy and certain diseases. The test of a mercurial salivation is detection of the metal in the secretion. Women seem to be more readily affected in this way than men, and the subjects of granular kidney, and of tuberculosis, are peculiarly susceptible. It occurs more frequently under fractional non-purgative doses of calomel, or inunction of blue ointment, than from fumigation, suppositories, or injections. It is markedly less under the use of sublimate, iodide,

or cyanide, than of insoluble preparations either on account of the smaller doses of the former employed, or of some peculiarity in their elimination. Ulceration or sloughing of the gums, hæmorrhage, periostitis, and prostration of even fatal character have occasionally followed a profuse salivation, and necrosis, scars and contractions have accompanied recovery.

Local action, irritant in character, is exerted by most compounds of mercury on the alimentary tract; but H. Wood speaks of calomel as "free from all irritant properties," and Lente argues that large doses (one teaspoonful) act as a sedative—this was the argument of Annesley, but it is not a safe one on which to act. The irritation excited by corrosive sublimate in toxic doses is severe. There is an acrid taste, and a sense of burning and constriction in the mouth and fauces, with whitening and shrivelling of the mucous membrane if the dose be concentrated. Vomiting and purging, with tenesmus, usually occur, with passage of blood, suppression of urine, and general symptoms of gastro-enteritis. After death, signs of inflammation, contraction or ulceration have been found, especially in the stomach and upper part of the intestine, and that this is not merely a local effect is proved by its occurrence when the drug has been administered by the skin. Profound depression is usually a symptom of sublimate poisoning, and is sometimes more marked than pain, vomiting, or

purging; salivation is by no means constant in acute cases.

The iodides of mercury act much like corrosive sublimate, the red iodide being more actively irritant than the green. The red oxide produces similar lesions of the intestinal canal; it is not given internally in medical practice, nor is the ammoniochloride (white precipitate), but in a case where a large quantity of the latter compound caused death, the stomach was found contracted, and its lining membrane ecchymosed. A single dose of twenty grains, dispensed by mistake for sal-ammoniac, caused severe vomiting, purging and salivation, some albuminuria, with illness for six weeks. The liquor hydrargyri nitratis acidus has produced intensely severe effects on the intestinal tract, and irritant poisoning has followed the accidental use of the sulphides and the cyanide of mercury.

Most of the glandular organs become congested and stimulated under the influence of mercury. This has been noted not only in the case of the salivary glands, as already described, but also of the pancreas and intestinal glands, the kidneys, the liver, and the testicles. As illustrating the effect on the pancreas, Copland recorded a case where, in addition to salivation, deep-seated epigastric pain set in, with nausea and diarrhœa of thin fluid resembling saliva; after death the gland was found large and congested.

Radziejewski found, on analyses of the stools

after giving calomel, a large proportion of leucin, tyrosin and indol (the result of the action of the pancreatic ferment), which he did not find after other purgatives. That calomel also stimulates the intestinal glands was demonstrated by the late Prof. Rutherford: the lymphatic glands are simultaneously affected.

The mode of action on the liver is still a subject of discussion, and the conclusions of some physiologists on this subject are opposed to those of many practical physicians. Up to a recent period, mercury was universally regarded as a typical "cholagogue," in the sense of its stimulating both the secretion and the excretion of bile, and hence was commonly employed both in cases of deficient secretion to stimulate, and in cases of excessive secretion to "carry off" the excess.

The early experiments of Murray were taken to corroborate the theory of "cholagogue" action, for after giving purgative doses of calomel to dogs, he found the discharge of bile increased, and the stools contained excess of mucus, and of serous effusion. Buchheim also reported an increase in the amount of bile discharged by dogs with biliary fistulæ. Still more important evidence was furnished by the analyses of Michéa, which were made first upon the normal stools of six healthy subjects without detecting bile; then, with nearly like result, upon the green stools of persons suffering from diarrhœa; then upon the greenish motions

which occurred in eight healthy persons after taking calomel, and in all of which bile was clearly detected ; and, lastly, upon discharges produced by different saline and resinous purgatives, and in which no bile was found. Although these observations show an increased discharge of bile under calomel, it is clear that they do not necessarily prove an increased secretion by the liver cells, and, therefore, experiments on animals as to this point were undertaken.

Kölliker and Müller, after giving calomel to dogs with biliary fistula, and collecting the bile discharged, reported contradictory results—the secretion being in one instance increased, whilst in two others it was diminished. Scott, experimenting with large doses of calomel on four dogs with fistulæ, recorded diminution of both fluid and solid biliary constituents in all the animals. Mosler, with two dogs, obtained a similar result, and the late Prof. Hughes Bennett, reasoning from the experiments of the Edinburgh committee, announced as a positive fact that mercury really lessened the biliary secretion in man as well as in animals. The experiments on which this physician founded his important conclusions require a brief consideration. They were made upon forty-one animals, and on account of difficulties in the operations, results considered satisfactory were obtained only in nine instances—on four of these, calomel was used ; a permanent fistulous opening into the

gall-bladder was very carefully effected, and fourteen days afterwards the bile was collected on a sponge. The first dog, before taking any drug, secreted a daily average of eighty-seven grains of bile, which contained five grains of solid constituents; after taking four to twelve grains calomel daily, it secreted only a daily total average of sixty grains; but it must be noted that the animal's condition was much impaired, it took little food, and soon afterwards died. Smaller doses (one-sixteenth grain) were given to the second dog; the general health became affected, and it soon died; the average bile secretion was about the same, before and after giving the drug. The third dog received some blue pill in addition to the small doses of calomel, and the average amount of bile secreted was diminished one-half. The fourth dog was given purgative doses, with an average diminution of bile whilst under their influence; on one day, however, when blue pill was given, the average was increased. Such results scarcely warranted Bennett's conclusions, which were controverted by Christison, Fraser and other members of the same committee. Röhrig (of Kreuznach) reported that large doses of calomel slightly increased the biliary secretion, but we may take the experiments of Rutherford and Vignal as showing, so far as experimental research can show, that the drug does not really do so.

They proved (1) that doses of ten grains, five

grains, or two grains, several times repeated, placed (without bile) in the duodenum of a fasting dog, produced a purgative effect varying with the dose, but so far from increasing the amount of bile secreted, usually diminished it; (2) that there is no difference in the result if the calomel be given in one-grain dose, several times repeated, mixed with bile, and introduced into the duodenum.

On the other hand, the same observers found that corrosive sublimate in doses of one-eighth and one-sixteenth grain, powerfully stimulated the secretion of bile, whilst it did not stimulate the intestinal glands.

Rutherford himself notes that the experiments referred to above do not prove anything as to the action of mercury on the bile-expelling apparatus, and we may grant that they are correct without any denial of the clinical fact that a purgative dose of calomel will increase the amount of bile discharged by the bowel; it may do this, not necessarily by a previous stimulation of the liver, but either by irritating to unusual contraction the gall-bladder and bile-ducts, or by lessening a congested condition of these parts, through the discharge induced from intestinal glands.

Sir Lauder Brunton has pointed out that the clinical fact of calomel relieving "bilious" conditions, receives from the experiment of Schiff and Lusana an explanation not inconsistent with Rutherford's conclusions; these experiments go

to prove that the liver not only secretes bile, but also excretes it, separating from the blood a part of that which normally circulates in it; for after effecting biliary fistulæ in animals, bile flowed at first freely—afterwards in much diminished amount, independently of any drugs. This diminution was accounted for by the passing away of bile so soon as formed, and the consequent impossibility of its being reabsorbed from the duodenum into the circulation to be again excreted, for if fresh bile were passed into the blood by intravenous or subcutaneous injection, then the amount of excreted bile was again increased.

Schiff further showed not only that bile can thus circulate without giving rise to jaundice, but that it probably always does so, passing from the liver to the duodenum, thence into the blood, and so to the liver again, a portion only in a changed condition passing out by the fæces.

This tallies with the observation of Murchison, that "by increasing the elimination of bile, and lessening the amount circulating in the portal blood, mercury is a true cholalogue, relieving the liver thus, more than by merely stimulating it to increased secretion". The green, liquid, spinach-like stools produced by calomel have been variously attributed to intestinal irritation, to altered hæmatin, and to subsulphate of mercury; it is possible that they may contain sometimes mercurial compounds, but they certainly often con-

tain bile. Hoppe-Seyler showed this, and according to Simon's analysis of the fifth stool passed after a large dose of calomel, it was fluid, green, without fæcal odour, of acid reaction, and contained mucus and epithelial cells, fat, cholesterin, bilin and bile-pigments—no mercury whatever.

Wasilieff asserts, as a result of experiments on animals, that the special action of calomel is to prevent certain processes of retrogressive metamorphosis and putrefaction in the alimentary canal; also that it prevents normal change in the colouring matter of the bile, which remains, therefore giving to the fæces the characteristic colour referred to. It prevents, too, changes in the pancreatic secretion, so that no indol is formed in the intestine whilst under the influence of a few grain-doses of calomel.

Therapeutical doses exert a stimulating effect on the kidneys, and we have seen that the drug is largely eliminated by those organs. Overbeck, indeed, found leucin and evidence of disintegrated albumin in the urine of animals; but Harvey, experimenting on dogs, found the quantity of urine unaffected, the phosphates always diminished, the urea not increased beyond a normal variation. Von Böck could find no definite change in the excretion of nitrogen or uric acid, and Conty, after observation on twelve syphilitics taking therapeutic doses of proto-iodide, could verify no definite alteration. Some careful experiments of Noel

Paton on dogs seem conclusive as to the real increase in water, urea, and uric acid excreted under moderate doses of perchloride and iodide. Boecke showed a similar result in man, but his patient was syphilitic. It has been plausibly said that the increase of urinary water is dependent on the increased amount of urea formed under mercurial liver action. Fractional doses (one-sixth grain) of calomel at intervals of three to four hours have been found markedly diuretic, but more so in disease than health.

During pronounced mercurialism, albuminuria may occur with or without hæmaturia. After death congestion and fatty degeneration of the kidneys have been found; and Ollivier has pointed out the analogy between such conditions and those produced by lead. The albuminuria does not necessarily imply altered renal structure, it may be dependent only upon general dyscrasia and loading of the blood with organic debris. Bouchard has recorded two important illustrations; in one case of acute mercurialism five days after salivation had commenced, suppression of urine occurred, and on the ninth day the patient died comatose, and a very large amount of urea was found in the blood, implying that anæmia was the cause of death. We have no details of the second case, but in both the Malpighian bodies were found to contain mineral matter, proved to be carbonate of lime. This condition is interest-

ing when compared with Salkowski's results in rabbits; he injected fractional doses of sublimate, of iodide, and of calomel, and after death found constantly lime and soda deposits in the Malpighian bodies; the urine became pale and contained sugar, whilst the bones became decalcified. More recent observations also report congestion, hæmorrhage, cloudy swelling and deposits of chalk in the kidneys of rabbits—less deposit and more fatty degeneration in those of dogs. Under some conditions, it is said to produce subacute inflammation and cirrhosis of the kidney, like lead. Cornil found calcareous deposits, and Kletzinski reported glycosuria.

From the medicinal use of mercury we seldom see definite effects on the nervous system, beyond a temporary malaise, chilliness, depression, or hyper-sensitiveness; the severe symptoms of neuralgia, tremor, convulsion or paralysis are met with only in persons who have been for a prolonged period or in great degree exposed to its action, such as those who work with it and indeed suffer from a "chronic mercurial poisoning". A grain of calomel or blue pill has been taken every night for more than forty years without other than good effects apparently, for one cannot argue much from fatty degeneration at the age of seventy-four. On the other hand, tremor has developed in one night under the influence of strong mercurial fumes (Christison), but as a rule the

slow and continued absorption by the skin and the lungs of metallic quicksilver or its vapour is the cause of symptoms such as those we are now considering. Ainstie pointed out that sensory nerves were sometimes affected by it, "a selective affinity" being shown for the fifth, whence an attack of severe and persistent facial neuralgia; but severe pain may also affect the head generally, or all the limbs, or the spine; the pains are usually made worse by warmth; tingling or other alterations of sensibility may be experienced; there may be partial anæsthesia or analgesia, which either varies as in hysterical subjects, or may be permanent; abnormal sensations of cold are also described. Tremor is the most constant symptom of chronic mercurialism; all the workmen in mercurial mines suffer from it, and sometimes it is the only symptom apparent, there being neither salivation nor erethism; it commences usually in the lips and the tongue, and soon affects the upper extremities; it is most marked, like the tremor of disseminated sclerosis, under the influence of voluntary movements or of fatigue; it may exist in all degrees up to severe convulsive movement affecting the whole body; slight cases of tremor are curable in a few weeks; more serious ones last for months or years, and yet the subjects continue to walk and to work. The tremors cease during sleep, and also, it is said, during intoxication; this is an interesting fact, as

also is the transmission of the malady by inheritance, so that children are born in the state of tremor.

Chronic mercurial poisoning sometimes produces a paralysis which resembles that due to lead and is characterised by dropped wrist, but it may be more general; occasionally, as from lead, the laryngeal muscles are implicated, or hemiplegic weakness occurs. The paralysed muscles may show some wasting, but their electrical excitability is preserved. The sphincters are not affected.

It remains to note the mental condition in chronic mercurialism: emotional sensibility is generally heightened, the patient is timid and easily excited, intelligence is weakened, and a delirious condition may occur in paroxysms; sleeplessness is marked. Convulsions resembling both the major and minor forms of epilepsy may be induced from mercury, as in lead poisoning.

With regard to the pathology of the nervous symptoms described, Ainstie suggested that the cortical grey matter was mainly affected. Ross, in his able paper, seems to think that an effect on the connective tissue of the nerves would explain it. Mercury has been found by analysis in the brain, but we can scarcely consider its effects to be directly and locally poisonous to the nerve-cells; we may gain some light from the changes discovered in cases of alcoholic or saturnine saturation of the nervous centres, and those we find to be

mainly chronic inflammation and fatty degeneration. Popow has found that in animals mercury produces hyperæmia of the meninges and of the cord, followed by hæmorrhages and inflammatory exudation, similar to those produced by arsenic and lead. He found but few peripheral changes, and considers it proved that the nervous symptoms in mercurial poisoning are of central origin. Examination of the nerves in animals after poisoning by mercury shows, it is said, no affection of the axis cylinders but degenerative changes in their medullary sheaths.

I have spoken of the local irritation that may be excited by mercurial frictions. There may be merely erythema with much itching, or an eczematous rash, or even erysipelas and gangrene. The internal use of mercury may also, exceptionally, give rise to eruptions, of which Bazin has distinguished three forms, "hydrargyria mitis, febrilis, and maligna," showing either a simple efflorescence about the thighs, scrotum, abdomen and axillæ, or a more intense form with vesicles, or one still more severe with œdema and purpuric rash. The general symptoms in such cases may be serious; desquamation occurs in the milder forms about the eighth or tenth day; malignant forms (which I have never seen) may give rise to adenitis, abscess or ulceration. Occasionally owing to idiosyncrasy, a scarlatinoid rash may be excited by a single dose, as by three-fourths grain

of protoiodide in a case recorded by Fournier; one application of acid nitrate produced the same effect, as also did a few Dupuytren's pills (one-sixth grain sublimate). If cachectic ulceration be present, the action of mercury is likely to increase it, especially in the mouth; such ulcers are more irregular, and less indurated than those of syphilis.

In exceptional cases the secretion of sweat has been increased, becoming of a clammy character and fœtid odour; a general brown colour of the skin or the occurrence of rupia and ecthyma has been sometimes noted, but it is not true that eruptions really equivalent to syphilitic eruptions are produced by mercury.

The hair and nails have fallen off under its use. The teeth show the effect of the drug, especially when administered in infancy, by a deficiency in the enamel, most marked in the first molars; but I believe such deficiency may occur from rickets independently of mercury.

With regard to the tissues of the eye, we have evidence that iritis and retinitis may be produced by the continued employment of mercury, but a more usual condition is conjunctivitis, which occurs with the ordinary symptoms, such as suffused redness and injection, smarting, burning and some excoriation and purulent secretion.

A form of periostitis occurs sometimes during a course of mercury, and it has been a question whether this is due to the remedy, or to the syphi-

lis for which it is commonly prescribed. Pereira thinks the latter supposition correct, but Graves states that he has seen periostitis occur in patients mercurialised for other illness and who had never contracted syphilis, and to this I can add my own testimony, having witnessed such an occurrence several times. The tibia, the bones of the forearm, the clavicle, sternum and frontal bones are those more commonly affected, and the pains, intermittent at first, are increased by warmth, or by changes of temperature, though sometimes relieved by a low temperature. The articular ends of the bones are liable to be affected, and even caries may be produced.

Women are, as a rule, more susceptible to the general action of mercury than men, while children are less so. There is also marked difference in its effects on different individuals, among men, women and children. Subjects of Bright's disease are especially prone to serious symptoms of poisoning from even small doses of the drug.

THE THERAPEUTICAL USES OF MERCURY.

I WILL attempt to give an account of some of the chief therapeutical uses of mercury. First and foremost comes syphilis. In 1497, Gilinus employed mercury in the treatment of syphilis, then epidemic, borrowing his practice from that of the Arabians, and using only external applications by friction, bath, or fumigation. Several accidents that occurred from the remedy, as used by empirics, contributed to discredit it, and in 1517 it was almost entirely superseded by guaiacum.

Not long afterwards, however, the internal administration of corrosive sublimate, red precipitate and calomel became general, and by the time of Boerhaave was carried to such excess that mercurial treatment was not considered thorough and satisfactory till it secured the ejection of three or four pounds of saliva in twenty-four hours. Protest against such abuse was not wanting, and between mercurialists and anti-mercurialists sprung up a controversy which has lasted to our own time.

In the early part of the last century a reaction against the extravagant use of the drug in syphilis became general—thanks mainly to Rose, Guthrie,

Thomson, and Abernethy; and it was proved that syphilis sometimes tended to spontaneous cure, and yielded to non-mercurial treatment. Later on, an important distinction was made between the soft or non-infective, and the hard infective sore, and professional opinion pronounced strongly in favour of mercury for the latter, whilst allowing it unnecessary in the former, and in gonorrhœa. This was clearly evidenced in the report of the Admiralty Commission on the subject, which records the opinions of forty eminent practitioners (1864).

Amongst others, Sir James Paget called mercury "a specific—if the patient could take it well; in favourable cases it would prevent secondary symptoms, and at least it would shorten their duration".

Hutchinson speaks of it as a "true vital antidote," and, if given early, as really stopping the development of symptoms, and absolutely curing the disease.

Syphilis is commonly divided into three stages, fairly well distinguished as primary, secondary and tertiary, and the best period for giving the remedy has been much discussed. Some have maintained that its early exhibition only defers the appearance of secondaries, and it is better for these to appear, and then to give mercury till they disappear; but the best authorities favour early commencement. Sir Alfred Cooper objects to

too early use as liable to obscure the diagnosis. Ricord, who gave mercury as soon as the hard chancre was distinctly diagnosed, and insisting on a year's continuance of treatment, was satisfied that he prevented secondary symptoms. Barallier supported the same conclusion after much experience amongst sailors. The majority of British surgeons follow this practice, and it seems to me the right one.

On the other hand, most are agreed that in tertiary syphilis, mercury is not a desirable remedy, and a reason for this is found in the different processes which occur at different periods of the malady.

In the primary and secondary periods, plastic lymph is being effused, but in late stages degeneration is going on; mercury causes absorption of the effused products, but its further action can only assist degeneration, induce cachexia, and be injurious.

As clinical evidence of this, if any were needed, reference might be made to the cases recorded by Hutchinson, where phagedenic ulceration in delicate subjects distinctly increased under the influence of mercury. If a syphilitic sore be much inflamed, or if aggravated dyspepsia, anæmia, phthisis, or albuminuria be present, treatment for these conditions must be instituted independently of mercury. Pregnancy has been considered a bar to mercurial treatment, but in my opinion the

danger of miscarriage in the mother and of injury to the infant are greater from syphilis than from mercury.

In any case, a moderate use of the drug must be the rule. It is true that Trousseau and Pidoux blame a relaxation of the old methods for what they consider the present gravity of the disorder, but the large majority of the best authorities, including Ricord, Sigmund and Hutchinson, deprecate full mercurialisation, and find the best effects from small doses continued for a long time. Hutchinson uses grey powder in one-grain doses from three to six times a day, with enough opium to prevent diarrhœa, and seldom for a shorter time than six months. Attention to the teeth is necessary, and soups, green vegetables, fruit and malt liquors are avoided. Cooper recommends the tannate of mercury, one to two grains, in pill, thrice daily. It is quickly absorbed and eliminated, and is little likely to cause stomatitis. Sigmund stated that of nearly nine thousand patients treated in the Vienna Hospital, eight thousand five hundred showed no sign of salivation, but were cured as permanently as those salivated. Slight tenderness of the gums may be safely and properly produced as evidence of systemic influence, and a method sometimes successful is to give fractional doses (one-twelfth grain) of calomel every hour; given in this manner, three grains may suffice for the purpose.

In hereditary syphilis, mercury is still to be preferred, but in all forms of tertiary syphilis, in rupia, and deep ulcerations, especially of the mucous membranes, tongue and fauces, in cases of gummata, visceral syphilis, and most syphilitic nervous affections, the great remedy is not mercury, but iodide of potassium. For late secondary and early tertiary symptoms, a favourite combination is that of small doses of corrosive sublimate with iodide of potassium. Bartholow, however, considers the administration of the two drugs in the same mixture a mistake, and gives them separately and alternately, so allowing the iodide to be diffused through the system before the mercury is given.

Some writers speak highly of the bicyanide of mercury, in doses of one-twelfth grain, combined with quinine and arsenic in the form of a pill, for delicate patients, especially women, and the same salt, the cyanide (twenty minims of a one per cent. solution), has been injected into the veins of a syphilitic patient when it was desired to produce the constitutional effects of the drug as expeditiously as possible. Berkeley Hill is quoted for the statement that iodides are not curative in some cases of tertiary syphilis, and that in these mercurial inunction is preferable.

After a hot bath, one drachm of a lanolin preparation is rubbed in thoroughly over the whole body for six days in the week, till forty-two baths

are taken (unless special symptoms require modification), then after a rest, a second similar course may be required. Care is prescribed as to clothing, and astringents are used to the gums.

Cases of serpiginous ulceration, necrosis, and gummata, are said to yield to this, after failure of other treatment.

In syphilitic iritis and retinitis, the early and sufficient use of mercury is more clearly indicated than in any other inflammation, and they are the only conditions in which Ricord held salivation justified. Watson has graphically described how effused lymph in the anterior chamber may be seen to "melt away" under the influence of the drug. I often combine, with its internal use, collyria of corrosive sublimate, one to two grains in six ounces of water with opium, or an ointment of ammonio-chloride with belladonna for frictions round the orbit, with good success, but the same treatment cannot be depended upon in rheumatic or traumatic cases. In serious iritis, Carter objects to the rapid administration of mercury, but gives one-sixteenth grain of perchloride thrice daily, with local application of discs containing one two-thousand five hundredth of a grain, which may be placed on the conjunctiva night and morning, ten minutes after a cocaine disc.

In syphilitic laryngitis, mercury must be promptly and freely used, for in acute cases life is rapidly endangered by the disease. Syphilitic

infants, as a rule, develop only a subacute form of this disease, which may be treated less actively by moderate frictions with satisfactory result. A good general treatment for congenital syphilis is to rub a piece of blue ointment, about the size of a pea, into the abdomen or chest every day.

A germ theory to account for the action of mercury in syphilis has been advanced, and the benefit of mercurials, whether applied locally or given internally, is supposed to be due to their germicidal action. The general likeness of syphilis to the acute exanthemata would suggest a similar bacterial origin.

Mercury is useful in many inflammatory diseases. From the time when Robert Hamilton described his successful treatment of inflammation by calomel and opium (Duncan's *Commentaries*, 1764), down to perhaps forty years ago, mercury, in some form, was, in English practice at least, the almost universal remedy, both for acute inflammations and for their results, such as effusions, adhesions and indurations. Trousseau described mercurials as "*les antiphlogistiques les plus puissants*"—more active, perhaps, than blood-letting; and Nothnagel remarks that at one time the name of any malady ending in "itis" seemed sufficient to indicate their use.

Sir Thomas Watson, in the later editions of his classic lectures, quotes his own earlier opinion that "mercury is a very powerful agent in control-

ling inflammation, especially when acute and adhesive" in character, also in preventing exudation, but owns that this can be said no longer—"it requires much qualification" (fifth edition, 1871).

This is, perhaps, the most important point in which modern experience and opinion would discredit the therapeutical power of mercury. It is not denied that full doses can act destructively on the blood and the tissues, though we have given some evidence against its aplastic energy, but modern clinical experience affirms that it has not great, but comparatively little power over acute inflammatory disorders; that these often run a natural course towards recovery, independent of mercurial or other medicinal treatment, and that when it is pressed to a full effect, convalescence is protracted by greater anæmia and debility. The unquestioned good results recorded from the treatment of Hamilton, which led to its general adoption, have been attributed to the opium rather than to the mercury. Sufficient account of the evils that followed was not made by our predecessors, who, knowing too little of the natural history of disease, attributed all bad sequelæ to it rather than to the medicines, and considered themselves successful if, when "the disease was subdued," life, at least, was saved.

On the other hand, we cannot agree with the assertion that mercury is never useful, but always injurious in inflammation. There is evidence of

its advantage in certain conditions, though this evidence is not so consistent nor so general as of its value in syphilis.

It will certainly remedy some of the results of inflammation, as chronic effusions in joints or lungs, and no number of instances in which the medicine has been abused, or even has failed, can contradict the cases in which it has conferred evident benefit. For my part, I still hold it useful in many chronic inflammations, whether syphilitic or not, affecting mucous membranes and parenchymatous tissues, and having a general tendency to suppuration and ulceration, but I am satisfied that it should never be pushed to salivation.

Many preparations of mercury are antiseptic in action. The power of corrosive sublimate to destroy bacteria has led to its general use as an antiseptic in surgical and gynæcological practice. Over carbolic acid it has the advantage of being odourless, of not numbing the hands, and of being effective in much weaker solution, one in ten thousand, though the strength usually ordered is one in one thousand. This is prepared according to the formula of Lister, by making first a glycerin solution containing one part of mercuric chloride in one and one-half (by weight), and then adding one fluid drachm of this to four pints of water.

In surgical operations, the hands of the operator, the instruments, the skin of the affected part, and all tissues exposed to the action of atmo-

spheric germs, are washed with such a solution, just as with carbolic preparations. There is a large amount of evidence in favour of sublimate dressings preventing suppuration and septicæmia, and promoting union by the first intention. Sublimate lotions are used also for wounds, sinuses, and inflammatory and septic conditions of skin, mucous membrane, and internal viscera, such as the bladder and uterus.

Kehrer advocated such injections for the vagina and uterus after delivery, especially when metritis occurred, and a number of cases having been thus treated with success, injections of sublimate became matters of routine in lying-in hospitals. Still such applications are by no means free from risks.

One of the earliest illustrations was reported by Stadfelt in a healthy primipara irrigated with solution of one in one thousand five hundred, and dying a few days afterwards with exhaustion, diarrhœa, sore mouth, etc. The case was considered to be doubtful, but since then further evidence of toxic enteritis has accumulated. Lucien Butte noted diarrhœa a few hours after dressing the wound—at first watery, afterwards sanguineous and with pain. Salivation was rare, but albuminuria and headache occurred, and sometimes death followed from exhaustion; the principal lesions being found in the digestive tract and kidneys.

A fatal case by Keller is reported, and a case of Murray's with severe diarrhœa, and there are observations on animals to the same effect. The cases of Richet and of Prévost show a large amount of success, with some drawbacks, and one serious case from the surgical use of one in one thousand solution. Müllen reports a death after sublimate dressing of an operation for cancer uteri. Szalios reports serious results short of death, and Braun states as to vaginal injections that absorption is rapid, especially if the exit of fluid be delayed, and that mercury is found in the fæces; an injection should be used only for one minute, and followed at once by one of clean water. He thinks that a strength of four in a thousand may be used in septic endometritis, but not when there is an open wound. Toxic symptoms followed a rectal injection of one pint of a one in two thousand solution, though previously used per vaginum without any ill result.

At the Obstetrical Society of London, Dakin reported two serious cases, one fatal, but the general opinion was favourable—with the qualification that sublimate should be reserved for occasional use, and a less dangerous drug, *e.g.*, carbolic or permanganate, employed for ordinary daily injection. Good authorities hold that not even a dilution of one in five thousand is safe for an intra-uterine injection. On the other hand, Godson gives remarkable testimony to the value

of sublimate injections—one in two thousand—after delivery. With the routine use of these, not one septic case occurred in five years at the London Lying-in Hospital.

The perchloride has been used successfully in the disinfection of rooms, in much the same manner as sulphur—fifty to sixty grains being placed on a shovel over a firepan in a room with doors and windows closed.

The biniodide has been commended by some observers as a more effective and convenient antiseptic. Miguel states that a strength of one in forty thousand is fatal to micro-organisms, and a vaginal injection of one in four thousand four hundred is reported as safe and satisfactory.

Cheifetz supports the favourable account as regards surgical practice in sixty cases, including ovariotomy, lithotomy, herniotomy, resection of joint and removal of breast, all dressed with solution of biniodide.

Napier recommends soloids of the biniodide, and Boxall testifies to the value of the salt for *post partem* injections. This also, used as a continuous bath to the open wound, was serviceable in a case of tetanus, but a strength of one in five hundred caused salivation.

When pediculi infest the head or the clothing, ointments containing the red oxide or the ammonio-chloride often suffice to cure, and have the advantage of being free from unpleasant colour or odour;

mercurial fumigations may sometimes be required for the body. For the pediculus pubis, blue ointment is commonly prescribed, but it is not a pleasant application, and I have seen it produce much irritation. As in all cases when the hair is affected, destruction of the eggs or "nits," which are closely attached to the hair, is important for cure, and for this purpose weak lotions of sublimate are good (two to three grains to one pint of water), or strong lotions of vinegar, or one in forty carbolic, followed by the use of a dusting powder or ointment containing calomel, or white precipitate, or oleate of mercury, six drachms, with ether, two drachms.

Vigier recommends that a mixture of perchloride of mercury and glycerin (one and one-half drachms of perchloride in eight ounces) should be employed as a parasiticide in these cases, the admixture with glycerin hindering absorption through the skin, and preventing the general effect of mercury from taking place. I think sublimate soap, five to ten per cent., better and safer.

Mercury is useful in many skin affections. The parasitic growths of tinea tonsurans may be destroyed by lotions containing one or two grains of corrosive sublimate in the ounce, which should be applied twice daily after cleansing. Ointments containing the same, or the ammonio-chloride, are also useful. Their curative effect, like that of all similar remedies, is often somewhat slow in ringworm of the scalp, and especially in favus, but in

ordinary ringworm of the body, and in pityriasis versicolor, a few applications will suffice for cure.

Aldersmith has recommended the oleates of mercury as having more penetrating power, and records their curing chronic and obstinate cases not amenable to lotions and blisters. For children under eight, he uses a strength of five per cent., and for others who can bear it, ten per cent., mixed with acetic ether, one part to seven. After cutting the hair close, thorough washing and drying, this is rubbed into the whole scalp regularly night and morning, a cap or turban being worn to keep any of the preparation off the face. It is important that the head should not be washed more often than once a fortnight.

Mercurial remedies should not be used too concentrated, or over too large a surface, for fear of producing constitutional effects, and it is well to remember that blistering increases the absorptive power of the skin. Cases have been mentioned in which death followed inunction of the scalp for ringworm, and one in which a single painting with a vesicating solution of sublimate (ten grains to the drachm) caused salivation and death from mercurial poisoning. I have seen a case in which death resulted from the local use of a strong sublimate ointment, and more than one case with serious symptoms.

In many non-parasitic forms of skin disease, mercurials are useful locally; sometimes by an ab-

sorbent action or quickening of the functions of the lymphatics, sometimes by stimulating the epithelial and other tissues also, sometimes by exciting irritation of "substitutive character," and in some cases by a powerful caustic effect. In syphilitic affections they exert a "specific" power, and in many cases their local effect is supplemented by a varying amount of general action consequent on absorption.

Gubler has drawn attention to the cure sometimes obtained by general mercurial treatment in very chronic inflammations of the skin, such as psoriasis and eczema.

In the acute inflammatory stages of eczema, mercurials are usually unsuitable as being irritant, but Spender speaks highly of the use of lotio hydrarg. nigra in eczema rubrum. He adds glycerin, and applies it fresh three times in twenty-four hours, without oiled silk. Salivation from the local use of such a lotion has, however, occurred. In subacute and chronic stages with thickening from infiltration of the cellular tissue, moderate crusting, scaling and dryness of the skin, mercurial ointments are serviceable; that of the red oxide often irritates even at this stage, and that of the ammonio-chloride, diluted one in four or eight, is more generally suitable. Niemeyer commends it for chronic eczematous patches on the face. When there is more than average secretion or irritation, better results are obtained by a combina-

tion with equal parts of lead or zinc ointment, and a formula much used for eczema capitis is the following :—

℞ Plumbi Acet. . . . . 10 grains
Zinci Oxidi . . . . . 20 grains
Hydrarg. Subchlor. . . . . 20 grains
Ung. Hydrarg. Nitrat. . . . . 20 grains
Olei Palm. Purif. . . . . ½ ounce
Adipis Recentis . . . . . ½ ounce
M.

Such ointments are useful in the chronic general eczema of childhood especially.

For eczema mammae, which is often obstinate, Hebra uses sublimate lotions (one in one hundred and twenty), but they require care if lactation is continued. For eczema of the genitals, Devergie recommended a much weaker solution of the same ; Guénau de Mussey prefers calomel (fifteen grains to half an ounce of lard). For eczema about the hands, and especially for "cracks" about the fingers and nails, an oleate of five per cent. strength is efficacious. Calomel ointment of the strength of one drachm to one ounce is serviceable for small patches of eczema, on the hands or elsewhere. I have found hydrarg. ammoniatum, ten grains to one ounce, with tar, useful for the same and eczema capitis et aurium after thorough removal of the crusts, and for most cases of chronic eczema. In sycosis, parasitic or not, mercurial ointments combined with sulphur often give good results. In herpes preputialis, calomel is a useful dusting powder.

The ointment of the white precipitate diluted to

an equal amount acts almost as a specific in this affection. As in eczema, the crusts must first be removed thoroughly; this may be painlessly done by softening them with a little carbolised olive oil. In obstinate pemphigus, frictions with the oleate of mercury—five per cent. and upwards—may be useful.

Many cosmetic waters owe their efficacy to a minute proportion of sublimate or to an albuminate of mercury. Hardy's formula for the treatment of freckles contains lead acetate and zinc sulphate of each forty grains, sublimate eight grains, alcohol two ounces, and distilled water four ounces; it acts by slightly irritating the epidermis, so that this exfoliates quickly. For a more decided effect Hebra uses a stronger solution (four grains of sublimate to the ounce), applying it for four hours until the skin grows red, or even is blistered, and then under soothing applications it peels off, leaving a new surface. For ordinary erythema of the face, a lotion containing one to two grains in four ounces of almond mixture, with bismuth or zinc oxide, and spirits of wine, is useful.

The last formula is suitable for many cases of acne when sulphur would not be well borne, but the pustules of this disorder may be aborted with still more satisfactory results by means of the acid nitrate of mercury. The apex of the pustules should be lightly touched with this, on a glass brush or a match point, and the drop of liquid

should be soon removed by blotting paper or sponge; some temporary irritation may be expected, and strong carbolic paint has almost superseded this, as being less liable to scar.

The application just described (of acid nitrate) has been recommended for chronic patches of psoriasis, especially for such as occur along the forehead at the roots of the hair, but it should be used with great caution. The ointments of white and red precipitate have a certain value for psoriasis of the face, or scalp, or hands, because they have no unpleasant colour or smell, but they are seldom so efficacious as tarry or chrysophanic preparations. The iodides, with iodide of potassium, are also recommended. Mapother uses not only ammoniated mercury ointment locally, but the iodide or blue pill internally, and John V. Shoemaker of Philadelphia uses injections of perchloride.

The carbolate of mercury is useful in macular and tubercular syphilides and in syphilitic psoriasis of the palms and soles of the feet, also in syphilitic rash and specific affections of the mucous membranes, and in papular and pustular eruptions, in doses of one-sixteenth to one-fourth grain three or four times daily; it is also used hypodermically with success in the form of a mucilage containing two per cent.

In all itching papular eruptions, hot dilute solutions of the perchloride are likely to give

relief. Trousseau recommends a strength of twelve grains to the pint, and justly lays stress upon the importance of its being used hot.

In prurigo the ointment of ammoniated mercury, either alone or combined with hydrocyanic acid, or with lead compounds, often gives relief, and calomel ointment is a good remedy for pruritus ani, and for pruritus of the scalp connected with chronic eczema or pityriasis.

It is in syphilitic ulcerations and eruptions that the efficacy of mercurial lotions and ointments is the most marked. For condylomata, calomel with astringents is a good dusting powder, but the acid nitrate lightly applied is more effective; one application will sometimes destroy the growths when nitric acid alone and other caustics have failed. The injection of fifteen minims of a one per cent. solution of formamide of mercury, at intervals of three to four days, is very successful. The acid nitrate is the best agent to employ in the rare cases when it is desired to destroy a chancre by caustic in its early stages. As a dressing for hard chancre and for squamous and ulcerative forms of cutaneous syphilide the "emplastrum mercuriale" (Prussian form) is recommended by Dr. Liveing; it contains metallic mercury (three ounces), turpentine (one and one-half ounces), and lead plaster (twelve ounces).

For generalised syphilitic eruptions, especially those of papular or scaly character, baths of

corrosive sublimate have been recommended by Baumé, Trousseau and others; but their proportion of one-half ounce to each bath I think too large; headache, drowsiness, and sometimes colic and diarrhœa, were produced, and the skin was irritated by them. Baths containing only ten to fifteen grains have been found useful for syphilitic infants.

In ulcerative conditions of the mouth and throat, due to syphilis, gargles of "black-wash," or applications of calomel in substance, are useful; more active effects are, however, to be obtained from painting with dilute acid nitrate—one part in eight or in sixteen, one minim to one ounce of water, is sufficient for a spray. A solution of the cyanide (five or ten grains to the ounce) is also useful to paint on syphilitic sores in the mouth. Trousseau used cigarettes for these and for laryngeal affections. A gargle of bicyanide of mercury (a half to one ounce) is useful when black-wash and other preparations fail.

For syphilitic and other ulcerations of the Schneiderian membrane, an ointment of the grey oxide is preferred (half a drachm or even half an ounce). A powder containing cyanide of mercury and camphor may be cautiously used.

THE ACTION OF THE LIME SALTS.

The various salts of calcium differ somewhat, not only in the powers of absorption but also in their pharmacological action. The tribasic and neutral phosphates, in small doses (less than five or six grains), when administered with but little water, are wholly absorbed by the acid gastric secretion; but if given with much water, the acid is so far diluted that it does not act upon the insoluble drug, which then passes off mainly by the fæces. Raudnitz concluded that absorption occurred chiefly in the intestines, especially the duodenum, but when large doses are given the greater part passes unchanged.

Gourlet has suggested that the solubility necessary for securing the absorption of calcium phosphate is effected partly by means of the sodium phosphate contained in the saliva, partly by the ammonium phosphate and the acids in the stomach, and when it has passed into the veins solubility is still further assisted by the carbonic acid present in venous blood. During respiration, when carbonic acid is given off and lactic and other acids are altered, the phosphate that has been taken is retained in solution only by the help

of normal alkaline phosphates of the blood; if these are in small proportion the calcium salts are soon deposited (more in bone than in other tissues) and little passes in the urine. If, however, the alkaline phosphates are in excess, most of the calcium salt is retained in solution in the blood until it is excreted through the kidneys. This explanation is too essentially chemical, and must be compared with the observations made more recently by Paquelin and Jolly. They conclude that the tribasic phosphate of calcium is not acted upon in the stomach unless it be by part becoming superphosphate, and this again is precipitated in the intestine under the influence of alkaline biliary and pancreatic secretions; as an insoluble phosphate, it is not capable of absorption, except in small quantities the circulation conveys but little, and the tissues, except bones, contain only traces, the bile rather more. A certain amount of lime must enter the system from the food, and does so mostly as carbonate which becomes changed and prepared for absorption by contact with alkaline phosphates and gastric acids, but phosphates given experimentally are eliminated almost entirely unchanged, only some of the acid being absorbed. They conclude that the addition of such compounds to the food is an obstacle to nutrition, and that even the soluble acid preparations act only as acid principles, and pass out of the system as phosphates of another base. The calcium phos-

phate contained in urine and phosphatic calculus, even when primary, is almost entirely formed within the bladder. These views, as they are not in accord with commonly received clinical evidence, require confirmation, but they suggest moderate expectation of cure by calcium salts.

The bicarbonate is soluble by virtue of the excess of carbonic acid and is readily absorbed. The neutral carbonate in small doses (five or six grains) is soluble in the gastric juice, and is absorbed as chloride. The chloride itself in similar dose, and even up to fifteen or twenty grains, diluted sufficiently to disguise its caustic taste (as with three ounces of sugared water), is absorbed without gastric disturbance, and is rapidly excreted by the kidneys; larger doses cause a sense of oppression, with nausea and diarrhœa. According to Perl, the chlorine passes in the urine, the lime mostly in the fæces. Unduly large doses of lime-water, or of phosphates or carbonates, may cause gastro-intestinal irritation.

Of that which is absorbed an equivalent quantity is eliminated, except during the period of growth, and especially of bone development. There seems to be a power of laying by some of the substance for this purpose, *e.g.*, during the early months of pregnancy when bony growths (osteophytes) sometimes form in the bone of the parent, which diminish with the growth of the fœtus. The excreted calcium is found in the

urine as acid phosphate and in many other secretions such as pancreatic juice; some may be detected in plastic exudations; sometimes it forms calculi. It is often deposited in tumours, fatty, fibrous, and sarcomatous, and in old inflammatory exudations, as in tubercle of the lung and strumous glands.

Researches by Hoppe-Seyler show that the elimination of lime salts is augmented during prolonged rest in bed, although after a time it becomes again of average normal amount. It is increased also under mercurial treatment and diminished during febrile maladies. About forty-five grains are daily eliminated by an adult.

Lime-water and calcium carbonate, when taken internally in moderate doses, act as absorbents and antacids. The phosphate is astringent to some extent, but the sulphate may alternately confine and relax the bowels, according as astringent or irritant effects are produced. Ringer points out that calcium salts play an important part in the circulation and in most of the other functions of the body; the heart, or any other muscle deprived of calcium, will no longer contract. Fishes immersed in distilled water soon die; in tap water they live a long time, but they live almost equally well in distilled water to which a trace of calcium chloride is added.

The most interesting point in the physiological action of calcium salts is their influence on

nutrition—the necessity of phosphate for healthy growth, whether vegetable or animal, being especially evident. Experiments with plants have shown that the phosphates are in close relation with the nitrogenous elements. If, for instance, the nitrogenous husk or coating of a seed is removed, the phosphates are removed with it, and in the starchy parts of the grain none are found. In the leaves they occur in the parenchyma, not in the nervules, and generally are most abundant in the cellular parts of vegetables wherein nutrition and reproduction are most active. Wheat planted in earth containing phosphate germinates and thrives, but if all phosphate of calcium be removed, it germinates, but soon dies. Peas (which contain a larger proportion of azotised matter), when similarly treated, germinate and even bear a crop, but if this crop be sown in a soil without phosphates it does not flower. That the improvement in nutrition is not due to the presence or absence of phosphorus as such, but to phosphate of lime, is shown by experiments on birds. Wheat contains a large quantity of phosphate of potassium, and when pigeons are fed upon this alone and are prevented from getting any carbonate or other salts of calcium, they waste away, and their bones become weak and brittle. If, on the other hand, they can obtain lime in any form, it becomes changed into a chloride during digestion, and combining with the alkaline phosphates of wheat, provides them with

calcium phosphates and secures or favours their nutrition.

There is good evidence that calcium phosphates serve especially to nourish cartilage, bone, tendon and muscle, so that they have been called "restorative or analeptic tonics" to the locomotor organs, just as iron is to the blood, or phosphorus to the nerve tissue. As the result of observations on the reproduction of the shell in crabs, Schmidt found that a combination of phosphate of calcium and albuminous material was most favourable to the formation of osteoid cells; phosphate was required for the first growth, though carbonate was formed later. Bridgman noted the formation of "artificial cartilage" by the passage of an electrical current through a viscous solution of carbonate of calcium. Beneke found that phosphate of calcium was specially abundant in plastic exudations and wherever new growth was going on. He adopted the microscope as a ready means of its detection—and found that if a drop of sulphuric acid were added to the liquid, crystals of calcium sulphate were quickly formed. The organism can assimilate phosphate of calcium either in the soluble acid form (for the liquids and soft tissues) or in the basic insoluble form (for the skeleton); but its effects are produced slowly, and without the evident stimulation which we associate with the action of wine, iron or quinine, so that we describe such calcium compounds rather as restoratives than as

general tonics, and as modifying rather than stimulating nutrition.

Besides their effect on ossification, Mouriès has described a special effect of calcium salts upon "irritability" or vital organic changes, so that if these salts are absent, assimilation and nutrition do not go on, and emaciation and death ensue, while if they are deficient, various degrees of lymphatic and osseous disease are produced. He has calculated that the food of those who live in towns is deficient in these principles, and that while every one ought to have at least ninety grains daily, women especially receive only about half that quantity—hence a secretion of poor milk and consequent weakly children; and he claims that by the use of food containing calcium phosphate with albumin, the proportion of still-born and rachitic children in many families has been reduced.

Lime-water was formerly much esteemed as an internal medicine, and was given not only as an antacid and astringent, but also as an antiseptic and especially as a lithontriptic or solvent of calculi. It was not unfrequently given in excess and produced irritant effects, but its use now is restricted, and the doses given are smaller and more diluted.

When digestion is accompanied with discomfort and oppression or with acidity, pyrosis and flatulence, especially if there is a tendency to diarrhœa and to acidity of urine, lime-water and the carbon-

ate of calcium are more serviceable than alkalies, because they are not only antacid but astringent. I have found them especially useful in the dyspepsia of chlorotic women marked by the above symptoms, and generally by craving for acids and dislike to animal food. For cases of acid dyspepsia, when flatulent distension is not so prominent a symptom, but when there is heartburn and pain with evidence of gastric congestion, the bicarbonate of calcium dissolved with an excess of carbonic acid in an effervescent form is useful, for it is less nauseous to some patients, and more easily tolerated than lime-water, so that more may be given at a time. It may be mixed with an equal part of milk, whilst of lime-water not more than one-eighth part should be used.

For the special symptom of nausea and vomiting from irritative gastric conditions, milk and lime-water is a simple and effective treatment; given frequently in small quantities, iced, it provides digestible nourishment which is better retained than any other form. It is valuable in the vomiting of pregnancy, and even in that of gastric ulcer, in which latter malady only a dessertspoonful in a wineglassful of milk should be tried at a time. The lime acts partly as a sedative to the mucous membrane, partly as an antacid, and partly mechanically by breaking up the curd of milk; it is useful as an addition to cow's milk for children brought up by hand, but in cases where constipa-

tion is marked, barley-water or soda-water may be substituted. It is not to be looked upon as supplying additional lime, since the small amount contained in lime-water is really less than that in an equal bulk of milk.

In chronic diarrhœa dependent upon a relaxed condition of the alimentary canal, and when kept up by ulceration of the bowel, I have used lime preparations with the best possible effect. Bretonneau recommended them in enema for these cases.

In the diarrhœa of enteric fever, and of tuberculosis, milk and lime-water may prove of great, if only temporary service, but should not be used in large quantities when hæmorrhage or symptoms of acute inflammation are present. The alkaline earth is plausibly supposed to combine with the secretions of the ulcerations, and to form a layer which protects the terminations of sensitive nerves against contact with the contents of the bowels.

Mialhe applied this explanation to the phosphate of calcium, which salt has been much used in the treatment of diarrhœa and of acidity, and owing partly to its phosphoric element is considered to exert a special restorative power; according to him, if given with bread and sugar, it becomes changed by the slight acid of the former, and by the gastric acids into a soluble acid salt, which does not itself coagulate albuminous material, but when brought into contact with a small

proportion of alkali becomes converted into an insoluble basic phosphate of gelatinous character, which protects the mucous membrane, and checks diarrhœa; the nitro-phosphate in this connection is said to be especially good.

Piorry furnishes evidence of the value of phosphates in osteomalacia, or softening of the bones generally, also in spinal caries or Pott's disease, and I have certainly seen them beneficial in cases of caries and joint disease. Reasoning from the observation that birds with a broken limb lay eggs without shell during the process of repair, Fletcher was led to administer a mixture of calcined bone, prepared chalk and lime-water in cases of fracture (in man), and reported several cases of early union of long bones.

Milne-Edwards made similar observations on dogs and rabbits, producing fractures as nearly as possible alike, and then finding that the animals which were given calcium phosphate recovered more rapidly than the others; and Gosselin found the same results in men; on the other hand, it has been held that in fractures of old persons in whom the bones are brittle, calcium salts are better avoided. They have been strongly recommended during pregnancy and lactation in enfeebled mothers, both to relieve their neuralgia, debility, and dyspepsia, and also to favour the development of healthy non-rachitic children; and I have for years recommended their use in back-

ward dentition, delayed power of walking and retarded closure of the fontanelles. These are usual signs of a rachitic tendency, and in the fully developed malady of rachitis saccharated lime is strongly recommended. It is true that although parts of the bones become softened in this disease, and are deficient in lime, calcium phosphates are largely excreted in the urine, so that the fault is one of mal-assimilation rather than of actual deficiency, yet I agree with Ringer that the administration of lime, and especially of calcium phosphate, "appears to control this defective and perverse nutrition, and to induce healthy growth, so as to favour consolidation of the skeleton and improve the condition of soft parts," and that practically they are valuable, though not always alone curative. He compares this use of it to that of iron in anæmia, where the fault is equally one of want of assimilation rather than of quantity.

Some have thought that natural salts of calcium, such as have recently passed through organic structures, were preferable to such as have been deposited as mineral. Piorry recommended in softening of the bones and spinal curvature fine filings of fresh bone, one ounce to be taken in milk or rice-milk, and found it succeed when light, warmth and food had failed. Others have derived medicinal phosphates from the vegetable kingdom. Tilbury Fox recommended a strong

decoction of bran to be made and evaporated, and the residue mixed with sugar, and a preparation of this kind is largely used for malnutrition, rickets, etc. The advantage of calcium salts in bone disease is traced not simply to chemical and physical processes, but to direct improvement of digestion, absorption and nutrition, and such substances as cod-liver oil often produce greater benefit in rickets.

Lime-water was long since commended for the treatment of suppurating glands, and of ulcerations, as well internally as locally. The phosphate was especially found serviceable, though not always curative, in the different manifestations of struma by Beneke and by Stone, whilst Beddoes collected upwards of one hundred cases, including many of so-called "tabes mesenterica," benefited by the chloride, and Begbie has corroborated the good results to be obtained from doses of ten to twenty grains daily.

In anæmia and debility, the consequence of overwork and close confinement, or when affecting the young or suckling or menorrhagic women, Ringer speaks highly of the phosphate of calcium, especially when combined with the carbonate and with iron.

In nervous disorders with sleeplessness, and in infantile convulsions, Hammond found bromide of calcium more readily taken and more effective than the potassium salt, and I can confirm his

observations. It is richer in bromine than many other bromides.

In the early stages of phthisical anæmia and debility, especially in excitable and florid persons with a tendency to headache and dyspepsia, and when in later stages profuse sweating, or expectoration, or diarrhœa is present, or when menses are frequent or profuse, the carbonate or phosphates of calcium exert a good influence in lessening such discharges and in improving strength. Even when actual softening has occurred and cavities formed, I have given these salts with the object of assisting cretaceous deposits, and often with benefit. Dr. Murrell, at the Westminster Hospital, has employed chloride of calcium in forty-grain doses, given in a tumbler of milk, with much success in the treatment of phthisis. It facilitates the deposit of calcareous matter at the apex of the lung and in other parts affected, and promotes those fibroid changes which are so beneficial from the pathological point of view when the activity of the tubercle bacilli has been reduced by the inhalation of formic aldehyde, pure terebene and other antiseptics. Lime well supplements cod-liver oil, and the two remedies may be suitably combined, since they form an emulsion readily taken by children ; one and one-half parts of lime-water to one of cod-liver oil is perhaps the best proportion. Van den Corput, though praising this combination, recommends rather the chloride

flavoured with anise and such proportions of lime-water as will make a solid jelly, which is even better taken.

If the taking of calcium salts has any power in inducing the calcification of tubercle—and there is good clinical evidence to that effect—and if they diminish the blood supply of the fibroid tumour and hasten calcareous degeneration in it, it is not unreasonable to expect advantage from them in cases of cancerous degeneration.

Wright, in accordance with his proofs of the chloride increasing coagulability of the blood, has advocated its use in all forms of hæmorrhage, epistaxis, hæmoptysis, and hæmophilia, and has published good instances of its power.

There is a consensus of opinion as to the power of calcium salts to relieve uterine hæmorrhage. Dr. Rigby published a marked case dependent on "fibrous tumour" treated by the chloride, and others have recorded similar experiences; they give doses of ten minims of the liquor calcii chloridi, increasing by degrees to thirty or forty minims, and continued for some months.

From the power of calcium salts to dissolve organic membranes, they have been recommended in chronic Bright's disease, and in post-scarlatinal albuminuria "to dissolve proteinous infiltrations of the kidney". Kushenmeister reports cases treated by large doses of lime-water and soluble calcium salts, with immediate and marked increase

in the quantity of urine passed, and with corresponding subsidence of the dropsy. The amount of albumin was lessened, but sometimes slight hæmorrhage occurred.

From our knowledge of the styptic properties of calcium salts, we should expect them to restrain renal hæmorrhage rather than to cause it, and Stromeyer and Caspari report the value of the phosphate for this purpose.

BARIUM AND ITS COMPOUNDS.

It is a curious circumstance that although the salts of barium have a very characteristic pharmacological action, they are but rarely prescribed, and their very existence is ignored by many writers on therapeutics.

The barium compounds belong to the same group as lime, digitalis and strophanthus, and have every claim, as will be presently shown, to be regarded as cardiac tonics.

The most convenient salt of barium for internal administration is the barium chloride. It is mentioned in the British Pharmacopœia of 1898, but only as a test, and is described as follows:—

Colourless crystals, $BaCl_2 2H_2O$. Its solution should not give a precipitate with solution of ammonia hydro-sulphide, and no residue should remain after adding excess of diluted sulphuric acid, filtering and evaporating the filtrate to dryness in a platinum dish. Barium nitrate, $Ba2NO_3$, or barium acetate $(CH_3COO)_2Ba$, may be used in place of barium chloride, but each must respond to the foregoing tests.

The dose is usually said to be from one-half to two grains, but this I regard as too high, at all

events to begin with, and I am satisfied that from one-sixteenth to one-twelfth of a grain three or four times a day is safer and more suitable. As it is soluble in water, there is no difficulty in prescribing it either in the form of a pilule or in a mixture.

The carbonate of barium is a white insoluble powder. The sulphide of barium is also a white powder, but is soluble in water; it is luminous in the dark.

The chloride is sometimes found in natural waters; for example, there is a spring near Shrewsbury which contains sixteen grains in the gallon, and in the waters at various collieries amounts varying from nine to ninety-six grains per gallon have been met with.

Llangammarch, in Breconshire, has a spring which contains chloride of barium. Its composition is, per litre: sodium chloride, 2·6 grammes; calcium chloride, 1·2; magnesium chloride, 0·3; barium chloride, 0·096. The water is said to have a marked influence in the excretion of uric acid. Cases of cardiac dilatation are treated there with gaseous saline baths.

There is abundant evidence to show that some, at all events, of the salts of barium are absorbed, and are capable of producing marked physiological effects.

The chloride has been taken by mistake for Epsoms salts, and the nitrate for sulphur. Murrell

sums up the symptoms of a toxic or lethal dose as follows: "Pain in the stomach and bowels, purging, vomiting, face anxious, pulse feeble, breathing short and laboured. There may be giddiness, cramp, paralysis and convulsions, collapse ensues, and may be followed by death."

Orfila detected the chloride of barium in the liver, spleen, and kidneys of animals poisoned by it. Neumann made numerous observations on this subject, and after injecting sulphate of barium into the veins of animals, searched for it in the urine, and also in the blood some hours afterwards, but without detecting it. It was, however, found deposited in the liver, spleen, kidney, and bone. When the chloride of barium was given in the same manner, the greater part passed by the bowel, but some was found in the urine and saliva, as well as deposited in bone. He concluded that the drug was not easily eliminated.

The following is a summary of the pharmacological action of salts of barium:—

Small doses (one-twelfth to one-eighth of a grain) of the chloride exert a stimulant effect on the stomach, increase the appetite, and produce loose stools. Larger doses prove irritant or caustic; three grains taken several times daily induce a sense of pressure at the epigastrium, nausea, vomiting and purging, with faintness. John V. Shoemaker refers to a death from two and one-half grains taken in daily doses of one-

fourth grain, but this must be exceptional. The minimum fatal dose is commonly put at one drachm, which, in one case, caused much vomiting and purging, and death in convulsions in seventeen hours. Two and a half drachms were given to a girl by mistake for Carlsbad salts, exciting vomiting in twenty minutes and causing death in four and a half hours. Half an ounce produced similar irritant symptoms, and death in two hours; evidence of severe gastro-intestinal inflammation was found. The nitrate and acetate of barium have also caused death, and the carbonate is commonly used as a poison for rats and mice. Although one teaspoonful of this salt has destroyed life, larger doses have been taken without fatal results.

Since strontium salts have been used in medicine, the amount of barium contained in them has become an important consideration. It has been estimated as not more than one in one thousand, which would be well under an injurious dose.

The nervous symptoms caused by toxic doses of barium compounds are clonic convulsions and motor paralysis, with impairment of reflex excitability, fibrillary contraction and muscular cramps. From the slow respiration observed in cases of poisoning, it has been concluded that the vagi are paralysed. According to Cyon, the lesion is central, for even in advanced poisoning the muscular irritability and the sensibility of the peripheral nerves remain intact. Severe pains in the head,

throbbing in the temples, giddiness, dimness of sight, double vision, deafness and tinnitus have been experienced; also muscular cramp, especially in the legs.

The chief and most characteristic action of barium is on the heart and blood-vessels.

The heart's action is at first stimulated, afterwards quickly and powerfully depressed by full doses of barium compounds, then, after some palpitation, the pulse becomes irregular, feeble, or imperceptible, and the surface cold and pale. Small doses raise blood pressure, while large doses cause a transient rise, succeeded by a fall, or from the first a sudden fall, according to the dose given. Voluntary muscles in frogs were apparently stimulated, and twitched for a long time after death. Boehm concludes that the action is very similar to that of digitalis. I can confirm this statement, for I have many tracings showing its action, in most of which its striking similarity to calcium and digitalis is distinctly demonstrated.

In some experiments with Roy's tonometer, it was found that one hundred c.c. of saline solution, containing two c.c. of a one per cent. solution of chloride of barium, produced in the ventricle of the frog's heart tonic contraction, the ventricle speedily passing into a condition of tetanus. In its action on the heart, barium is very like calcium and strontium, but it accelerates the beats much more than do either of these drugs.

Onsum suggests that barium compounds cause embolism by precipitation of the sulphates of the blood, but this I cannot accept.

Ringer and Murrell have also pointed out the great similarity of the effect of barium compounds and of digitalis on the frog's heart: the pulse is slowed, and the heart finally stops in systole; the blood-pressure is raised, probably from the direct action of the metal on the muscular tissues of the vessels; these actions take place independently of the nervous system. This is quite in accord with my own observations.

We have no clear evidence of the effect of barium on the lymphatic system, but it is presumed to exert some absorptive power on inflamed or thickened lymphatic glands. Small doses increase the secretion of urine and of sweat.

The therapeutical uses of the barium salts, although not numerous, are well marked, the chief sphere of action being as a cardiac tonic.

The late Sir Thomas McCall Anderson recommended sulphide of barium for removing surplus hair, one part being made into a paste, with four parts of zinc oxide and a little water; this should be left on the part for about three minutes, and then washed off. It should be prepared only as required for use. It may be made stronger (one to three parts) with a little starch added, and left on from five to ten minutes.

Barium chloride was introduced many years

ago as effective in tuberculous and syphilitic dyscrasiæ, and in white swelling. Lisfranc and Torget used it in such cases, and in glandular tumours, and reported much advantage from it; the former began with one-eighth of a grain every hour, and increased the dose to much larger quantities than I should consider safe (forty grains). In a child, many glandular tumours subsided under a month's treatment, but frictions with potassium iodide were used at the same time. Some have recommended barium chloride as superior to iodine in cases marked by pallor, languid circulation, and irritable mucous membranes. Mr. Balman used it in chlorotic and cachetic states generally.

Many cases of successful treatment of scrofulous joint disease, of ophthalmia and of enlarged glands by barium chloride (one-twelfth grain doses) were recorded some years ago. Thorne records cases of glandular disease, of anæmia, and of cardiac dilatation benefited by Llangammarch water, and George remarks on the constant association of barium with calcium chloride.

I have for many years used barium chloride as a substitute for digitalis in cardiac disease, and like it; it has acted especially well in cases of dilatation with mitral disease and cardiac dropsy. I only prescribed one-fortieth grain, three times daily.

Da Costa praises it highly in restoring compensation and lessening cardiac pain; he gives one-

tenth grain in pill three or four times daily for three weeks.

Larger doses may be given but tend to cause diarrhœa.

Hare finds that it slows and steadies the heart, that it acts as rapidly as digitalis, and does not disorder the stomach. Small doses, one-half grain to one drachm of a one per cent. solution, do good in mitral incompetence and acute dilatation. Carpenter agrees as to its value, but advises caution, for a patient, aged thirty-one, having taken one and one-half grains three times, was attacked with symptoms of gastro-enteritis and collapse. He recommends as a dose, a half drachm of a one per cent. solution, gradually increased to two drachms.

Flint, considering that it gives tone to the vascular wall, used it in a case of fusiform aneurism of the abdominal aorta in doses of one-fifth of a grain thrice daily; within a fortnight improvement ensued, and in five months cure was complete. Prolonged rest and rigid dietetic treatment were used at the same time.

It will be seen that although barium has a limited range of action, the indications for its employment are clear and precise, and it is probable that with increased experience and the record of clinical cases, its sphere of usefulness will become more accurately defined.

THE PHYSIOLOGICAL ACTIONS AND THERAPEUTICAL USES OF OXYGEN, OZONE AND COMPRESSED AIR.

I. OXYGEN.

The chief characteristic of oxygen is its energetic power of combining with organic principles, and with minerals, to form oxides, acids, and bases—for instance, with hydrogen to form water. It is a gas, devoid of colour, odour, or taste, of specific gravity 1·1057 (atmospheric air being taken as one). Under a pressure of three hundred and twenty atmospheres, and at a temperature of 220°F., it was liquefied by Pictet (1877), and in this form is colourless and transparent.

Professor Dewar (1892) produced liquid oxygen in large quantities and showed it boiling in air at 182°C. below zero; its chemical reactions disappear in the liquid form; for instance, phosphorus may be added to it without change, but its magnetic properties are intensified; it leaps up to the poles of a magnet, and remains there till it disappears as gas; it is almost a non-conductor of electricity.

The mode of absorption of oxygen in the lung is still under discussion. Whilst Pflüger and others

hold that the tension of the oxygen in the air of the alveoli is greater than in the lung blood, and, consequently, that the gas passes inwards, in accordance with the law of diffusion, Bohr, Lorrain Smith, and others, maintain an opposite view as to the tension, and hold that the epithelial cells of the lungs remove oxygen from the air, and abstract carbon dioxide from the blood. Dr. Charles concludes that the entrance of oxygen into the lung blood depends, first, on diffusion, modified by the chemical affinity of hæmoglobin in the corpuscles, and, secondly, on the vital activity of the endothelium of the alveoli and capillary walls. The amount of oxygen removed from the air probably depends not on the partial pressure of the gas, but on the affinity of reduced hæmoglobin for it.

To describe fully the physiological action of oxygen would involve a description of the processes of respiration, blood-formation, nutrition, and tissue-change, for to all these, as to life itself, it is essential. If it be deficient in the respired air, or if it be insufficiently absorbed, all the functions become disordered, assimilation is impeded, circulation diminished, and the body temperature lowered, and if its access to the lungs be prevented for a few minutes, life ceases. But we are concerned, at present, only with the results of certain experiments in which animals and men have been made to respire either pure

oxygen, or an atmosphere artificially charged with a definite proportion of the gas, and the first question which arises is whether more than a normal amount of oxygen can be taken into the blood under such circumstances.

It was early concluded that animals kept under a bell-jar filled with oxygen lived longer than in ordinary air, and that animals made to breathe oxygen could resist asphyxia longer than similar animals that had breathed only air, but Regnault and Reiset maintained from a series of experiments that breathing an atmosphere rich in oxygen, or even one of the pure gas, did not make the blood take up more oxygen than it would from ordinary air, nor was more carbonic acid excreted in consequence.

Preyer showed that a greater saturation from oxygen inhalation was, *a priori*, probable, and that ordinary arterial blood was not fully saturated with oxygen—that it could take up more by being shaken with the gas. Demarquay thought he proved it by showing that suppurating, indolent or unhealthy wounds on the extremities of animals became quickly florid and hyperæmic when pure oxygen was inhaled, arguing that an extra amount of the stimulating gas must have been carried by the circulation to the wound. Allen and Pepys, and, later, Limousin, by inhaling an equal quantity of atmospheric air at one time, and of oxygen at another, found that after the latter, double the

amount of carbonic acid was expired, and this increase continued fifteen minutes after the inhalation had ceased. Other observers reported that the elimination of uric acid during a course of oxygen inhalation was markedly lessened, *i.e.*, that more complete combustion occurred within the system; thus Kollmann found that whilst three hundred grammes of the ordinary secretion of urine contained two hundred and thirty-six milligrammes of acid, the same quantity of urine contained only one hundred and twenty-two milligrammes after inhalation of twelve litres of oxygen. On another occasion, the amount of acid came down from one hundred and thirty-four to twenty-five milligrammes.

A clinical illustration, pointing in the same direction, was given by Gubler. After several copious draughts of the pure gas in an active nascent condition, the respiratory movements and the pulse became slower, a general sense of comfort was felt, and without any dyspnœa the pause between expiration and inspiration could be much prolonged. Thus, taking thirty seconds as a maximum time during which the breath may be "held" after breathing atmospheric air, it rises to ninety or one hundred seconds after breathing oxygen. Rosenthal proved the same in animals. From these and other observations, Gubler concluded that the blood received the gas in proportion to its physical capacity for it, rather than in proportion

merely to the vital necessity of hæmatosis; the corpuscles absorbed what they needed, whilst any excess circulated free, and entered into combination only as the hæmoglobin lost oxygen in passing through the capillaries. Hence the amount of oxygen absorbed by an individual was proportionate to the number of his corpuscles (we should now say to the amount of his hæmoglobin), and a plethoric man using up quickly his reserve air, breathed faster than a healthy one.

On the other hand, an anæmic patient also breathed more rapidly than normal, since his corpuscles were either too few in number or poor in hæmoglobin, so that they could not take up enough oxygen. Buchheim, however, advocated an opposite view, *viz.*, that oxygen was not absorbed proportionally to the amount of it brought to the lungs, but to the requirements for tissue change; yet even he admitted that the amount taken in would be increased to some extent by continued deep inspirations, and by breathing air rich in oxygen or under high pressure. He only denied that such adventitious oxygen affected the tissue change. He admitted that improvement in symptoms might result from breathing compressed air or pure oxygen, but thought it impossible to influence the course of any illness by increasing the amount of oxygen contained in the blood.

The appeal for therapeutical purposes must always be to clinical results, and Hayem, after

many observations, concludes that it stimulates energetically the nutritive function, the appetite, temperature, circulation, etc., and increases the formation of corpuscles and their amount of hæmoglobin.

Granting, then, the possibility of taking into the blood slightly more than the normal amount of gas, yet it remains true that in many healthy persons no marked effect is to be noted from inhalations of fifteen to thirty litres of oxygen, unless it be a sense of warmth in the mouth and at the epigastrium.

Gilman Thompson, of New York, in an able paper based on many experiments, concludes that very little additional oxygen can be made to enter the blood under conditions of healthy circulation, by any degree of pressure short of that which mechanically interferes with functions; still he found that pure oxygen under slightly increased pressure often proves beneficial, mixing readily with carbonic acid already in the lungs, a little more than usual being taken up by the plasma; in a case of acute lung congestion (traumatic) marked relief was given. The metabolism of the body is regulated by the activity of the tissues, and not by the supply of oxygen.

In the healthy animal, breathing ordinary air, the blood without doubt contains as much oxygen as the tissues need. But in many diseases the condition is different; owing to diminished absorp-

tion of oxygen in the lungs, the blood is often abnormally venous, and too little oxygen is taken to the tissues. In these cases the breathing of pure oxygen is of service, for the percentage of oxygen in the alveolar air is thus increased, and the pure oxygen diffusing more rapidly through the respiratory passages than the atmospheric oxygen, the blood in the lungs takes up more of it.

In some persons, inhalation of the gas causes temporary nervous symptoms, such as exhilaration, sense of vigour, heat of skin, tingling of fingers, and even pain referred to the fifth nerve. I have observed all these symptoms, except the last, immediately after the inhalation; also some giddiness, and some rise of pulse, probably from extra effort in breathing; in the delicate, improved appetite, improved motor power and sleep have followed. Carter of Liverpool says that if inhaled suddenly in large quantities, "it is very stimulating, and may produce a tetanic condition of muscles".

It was held, not many years ago, that animals could not live in pure oxygen, because of greatly increased metabolism leading to convulsions and death. Bert found that excess of oxygen, under a pressure of three atmospheres, produced tetanic symptoms and death, not due to simple increase of pressure, as air at a similar pressure had no such effect. Richardson and Demarquay, who reported a similar conclusion (although they endeavoured to purify the re-breathed gas), described the blood,

post mortem, as in a condition of "hyperinosis"; but Seegen concluded that death in such cases was due to poisoning by products of tissue waste. These give an unpleasant odour, and may be removed by passing the gas through a red-hot tube, and then on reintroducing it at the other end of the chamber, the animal can be kept in it almost any length of time without injury. A. H. Smith, of New York, has clearly proved that, as long as exhaled waste products are removed, animals live many hours in the pure gas under ordinary pressure, without special symptoms or change. Lorrain Smith has more recently found that oxygen at high tension will produce pneumonia, and, later, tetanic spasms in mice in about sixty hours: effects which are attributable to the tension of the gas, and not to the amount of oxygen in the blood.

Some observations by Cyon on the direct influence of oxygen on the heart deserve notice. Separating the heart of a frog, he connected it with a system of glass tubes and a manometer, and then passed through its cavities first serum saturated with carbonic acid gas, and afterwards serum saturated with oxygen. The former caused sudden arrest in diastole, whilst the latter restored the movements of the heart. Sir John Erichsen found, in experiments on asphyxiated animals, that ventricular contraction could be re-excited by oxygen when ordinary air had no effect. According to Hermann, oxygen is not indispensable for

the cardiac contractions—they may occur without it, but irregularly: if the gas be absent, or supplied in insufficient quantities, regular and synchronous contractions are impossible.

The necessity of oxygen for the proper activity of the nervous and muscular systems is shown by the increased absorption of the gas during muscular work. Absence of sufficient oxygen diminishes the activity of the nerve cells, so that unconsciousness may result.

Gangrene has been attributed by Raynaud to deficient oxygenation of tissues, and Langier and other French surgeons have recorded good results from its local treatment by oxygen. The destruction of tissue has been checked and limited, the swelling subdued, and the neighbouring threatened livid tissue restored to its natural colour.

Tuberculous peritonitis frequently gets better after laparotomy, apparently from exposure to air and light; it has been presumed that oxygen might act even better, and one to two litres have been injected in such cases, and in ascites due to cirrhosis of the liver, it is alleged with benefit.

Remedially, oxygen may be considered as it exists diluted in the atmosphere, or as prepared artificially for inhalation with or without a definite proportion of air.

Pure, fresh air of the elevated country or the coast is of well-known efficacy in all conditions of debility, of chronic catarrh, and chronic dyspepsia.

Sea air especially contains more ozone than inland air, and is of value to those who live in towns and follow sedentary occupations. On the other hand, patients with weak chests and readily congested lungs are better in a less rare and less ozonised atmosphere, since a large proportion of ozone may excite in them irritation of mucous membrane. The choice of a climate for any given case is, however, generally influenced by other considerations than the mere amount of oxygen to be obtained; the subject need not, therefore, be fully considered in this place. The chief cases in which theory indicates, and experience justifies, the use of oxygen inhalation, are those of asphyxia and of venous congestion occurring in the course of phthisis, pneumonia, asthma, emphysema, and other forms of lung or heart disease, and in these its use has of late become much more frequent.

When asphyxia is induced by breathing noxious gases, the best results are obtained from oxygen. Sometimes a free current of fresh air is sufficient to restore persons rendered unconscious by an escape of gas, or by the products of combustion retained within a room; but in extreme cases, pure oxygen would seem the only means of saving life. Limousin has reported a case of asphyxia from carbonic acid inhalation, with intense cyanosis, which recovered under the use of oxygen, and in which he was able to verify a steadily increased

elimination of carbonic acid by the lung in proportion to the oxygen taken.

Constantin Paul has recorded many cases, including cyanosis, from obstructed respiration, coma from opium poisoning (when the respirations were only seven per minute), and asphyxia from carbonic oxide all quickly and markedly relieved by oxygen. Rabuteau refers to an instance of its good effect in asphyxia from sewer gas, when ordinary means had failed to relieve, and a striking case has been reported by Dr. Charles B. Ball. A man, wife and daughter were found unconscious in a small room, where there had been through the night a large fire though the chimney was blocked. The two adults recovered with fresh air and ordinary means, but the daughter, aged sixteen, a phthisical girl, remained unconscious and convulsed. After many hours of stimulating treatment, she seemed to be dying—respiration was feeble and slow, the pulse imperceptible ; then she was made to inhale pure oxygen, afterwards oxygen and air. The effects were rapid and marked, respiration, colour and pulse improved, and though at first convulsed, she ultimately recovered.

In various forms of poisoning, whenever death threatens from asphyxia, as under prussic acid, chloroform, morphine, etc., artificial respiration, *i.e.*, supplying more oxygen, offers the best means of saving life. Colonel Esdaile published a sensational case of oxygen inhalation in coal-gas poison-

ing, and others are recorded, but the results are not always so favourable. Dr. G. Thompson could trace no satisfactory result in blood-poisoning from diphtheria, or coal-gas, or in endocarditis, but much in bronchitis, pneumonia, and wherever there was lessened surface for äeration of blood, especially in neurotic and uræmic dyspnœa.

Dr. Catlin points out that if, with a limited lung capacity, we can secure absorption of the same quantity of oxygen as in health, the result must be good, and describes it as a sure and satisfactory stimulant in cases of shock, also in phosphorus poisoning. The combination of oxygen with nitrous oxide has been found to make its action both safer and pleasanter, cyanosis being often altogether absent during the anæsthesia, and Neudörfer, Kreutzman and others have spoken well of a mixture of oxygen with chloroform as an anæsthetic. It is claimed that it prevents vomiting, excitement and after-headache; that vomiting does not occur even if the patient has food in his stomach, and that consciousness is at once regained when the administration of the mixture is discontinued.

The main suffering, the *besoin de respirer*, common to asthma, emphysema and many other conditions, is clearly traceable to deficient access of oxygen to the blood in the lung capillaries, and I am satisfied that in the majority of instances relief to this suffering may be given by supplying a

larger proportion of the gas. If it be objected that permanent good results are not obtained from it, the same objection may be made to many other remedies; it is still something to have a means at hand for temporary relief.

Dr. John Hooper thus describes its effects in a man of fifty-five, for many years a martyr to asthma. "During a very severe paroxysm, he was thought to be dying; it seemed impossible that he could rally. As a *dernier ressort*, oxygen was tried, the end of a glass retort containing it being applied to his mouth, though he had not power to enclose it with his lips. The effect was wonderful and quickly manifest in increased mobility of the ribs, fuller inspiration, disappearance of lividity, and lastly in his seizing the end of the retort, and in the avidity with which he inhaled when possessing the voluntary power."

Details of diagnosis are not given in this instance, but paroxysms of true nervous asthma may sometimes (not always) be shortened by similar inhalations. Beddoes related twenty-two cases, of which he claimed to have cured ten and relieved nine; and it seems worth while to refer to his case of "Mr. Hare, of Conduit Street, who in 1796, after having been subject for eleven years to asthmatic attacks accompanied by indescribable suffering, and only relieved after many hours by blisters and expectorants," recovered average health under use of the gas, continued for some

months. M. Demarquay also witnessed excellent results, *e.g.*, in a man aged nineteen, subject from childhood to asthmatic attacks, "they ceased, as if by magic, as soon as he began to inhale oxygen". Several cases of uræmic dyspnœa and coma are recorded in which the inhalation of oxygen gave great relief.

Dr. Mackey has reported the case of a lady, aged fifty-five, subject to constant dyspnœa, increased by movement, and amounting at times to partial asphyxia. She had advanced ephysema with dilated weak heart, embarrassed circulation, and œdema of the face and extremities; she was subject to attacks of bronchitis, but at the time of treatment the main complaint was the difficulty of breathing. She inhaled a mixture of from three to twelve pints of oxygen, with sixty of air, at intervals of three or four days for a period of six weeks. After each dose, "Marked relief was experienced, which she expressed as being able to take a deep breath and get sufficient air (a feeling not known for years), as being able to move with comparative ease, feeling more buoyant and more like healthy persons should feel than she ever remembered". Expectoration was rendered more copious and easy for a day or two after the inhalation; there was no other definite effect on secretions, nor any on circulation unless it were some palpitation during the night after a large dose. The nervous, irritable states to which such patients

are liable are also soothed under the treatment, which certainly effects more than ordinary medicinal agents. These illustrations seem sufficient to prove that oxygen might be used more often than it commonly is in such cases; on the other hand, later experience, both in asthma and ephysema, has given varying results, showing that benefit is not always to be depended upon.

I have used oxygen in several cases of pleuritic effusion and empyema, with good results. During inhalation, relief to breathing was experienced, which lasted for some time afterwards; compressed air has also been employed for these disorders. Biedert reports two cases of pleuritic adhesion in which vital capacity was much increased by it, and Kelemen one of empyema, in which the effusion disappeared as diuresis set in. Williams' results in pleuritic cases are not so favourable. It is a method that might be employed with advantage until operation can be performed.

The value of oxygen inhalations in phthisis has been the subject of much discussion. As early as 1783 it was tried with good results, and Fourcroy was appointed by the French Government to report on the subject. After examining twenty cases, he concluded that almost all benefited, for a time at least, by the treatment, but relapsed and got worse more rapidly, and with more inflammatory complication than if oxygen had not been used. It is evident that to establish such a con-

clusion, very careful observation is required, more precision than the then art of diagnosis could attain; but the opinion exercised considerable influence at the time, was adopted by Dr. Beddoes, and some other observers, and was one reason why this method of treatment fell into a disuse which was not altogether deserved. Albrecht has reported good effects in cases of phthisis, the patients gaining weight under oxygen inhalation; inoculated animals, also, subjected to inhalations, continued to live long after those not inhaling it had died. Thorowgood, Neumann and others have also reported relief to the dyspnœa of advanced phthisis, and Ransome administered ozonised oxygen "to fifteen patients in all stages of the complaint, and results were very marked in procuring improvement in general health, better appetite, sounder sleep, freedom from fever, and consequent gain in weight". It had no germicidal action, though the amount of expectoration was lessened, partly due, without doubt, to the supply of an abundance of oxygen.

The experience of recent years during the numerous epidemics of influenza has shown that the inhalation of oxygen is of service in the relief of the dyspnœa of pneumonia. It enables more oxygen to reach the blood in the portions of the lung still available for respiration; it diminishes the frequency of respiration, and relieves the strain on a heart already overtaxed and weakened by the

supply of impure blood. There is evidence that resolution sometimes takes place more rapidly after the use of oxygen, but such good results can by no means be depended upon.

In broncho-pneumonia, of which an unusual amount has followed the late epidemics of influenza, oxygen has again been largely used. A paper by Sir Lauder Brunton and Dr. Prichett described a severe case with cyanosis, in which, after failure of venesection and strychnine, improvement followed the use of this gas, which did not, however, prevent a fatal issue. Similar cases were reported by Allen, Gilchrist, and Langston, and with more fortunate terminations by Beverley Robinson, Maughan, and Collier.

My own experience has not been so favourable —no effect was produced in one case by a free stream for fifteen or twenty minutes, and the greatest objection was shown by the half-conscious patient to the oro-nasal inhaler, and in another case to the gas current from an open rubber tube. If this remedy is adopted, it should be given a fair trial, and the use continued for several hours, or even days.

In cardiac dyspnœa, due to mitral disease, especially when recurrent in the early morning, I have known oxygen inhalation give relief. Blair and others have reported similar benefit in the cyanosis of such conditions. A large number of cases are recorded by A. H. Smith, and his

general results are favourable, and have been corroborated.

I would except from its use cases of acute character, and of hæmoptysis, in which, indeed, the mere exertion of inhaling would contra-indicate it. In other cases, benefit may be hoped for, not so much through any local action on the lung tissue as by an improvement of the blood condition, the appetite, and the power of assimilation; nor speaking from experience, do I believe that oxygen, used with ordinary care, and in such dilution as has been mentioned, can irritate or inflame the lung tissue. In anginal cases it may give relief.

Beddoes relates instances of chlorosis benefited by inhalations, but other observers have not met with equal success from its use in this malady. I have, however, known it relieve chlorotic headache.

Pettenkofer and Voit concluded that diabetics absorbed less oxygen than healthy persons, and hence they hoped, by introducing more into their system, to obviate some conditions of their malady. Bouchardat, and also Demarquay, have recorded cases relieved by this treatment, but no extensive trial of it has been made. Peroxide of hydrogen has been given internally with the same object. I have tried oxygen inhalation in several cases of diabetes in which prostration, dyspnœa, and a tendency to cyanosis were prominent symptoms—one case was at the very unusual age of seventeen

months, another at thirteen years, and three others at adult age. The gas relieved for a time the symptoms, although it did not in any instance reduce the sugar in the urine. It was especially useful during the coma.

In a few cases of Bright's disease narrated by Dr. C. Paul, albumin disappeared from the urine during treatment by oxygen. This occurred also in the often-quoted case observed by Kollmann and Eckart. Dujardin-Beaumetz reported a case "in the last stage," in which every diuretic had proved useless, and yet twenty-four hours after inhaling oxygen the albumin disappeared, and was still absent twelve days afterwards. Other physicians whilst recording similar cases in their own experience, have stated that the good result was not of long duration. Jaccoud observes that if albuminuric cases do not show marked improvement under his ordinary treatment of milk diet and cold douches, his next resource is always inhalation of oxygen—thirty litres daily, at three or four sittings.

Richardson refers to some cases of tetanus, under Sir J. Paget, relieved by oxygen inhalation. The patients became bathed in perspiration, and the muscles relaxed. He insists also on its importance in strychnine poisoning in conjunction with amyl nitrite; as unless elimination be promoted by oxygen, the spasm, even if relieved, soon returns.

The argument for the use of oxygen in these cases is that the muscular contractions involve a large consumption of it, and this together with the defective respiration, renders the supply of oxygen to the nervous and other tissues insufficient; at the same time an anæsthetic should be given to diminish the abnormal activity of the nerve cells.

When divers are submerged at a considerable depth, the high pressure causes both the nitrogen and oxygen of the air to be absorbed into the blood. On coming to the surface, the nitrogen being set free, gaseous emboli may be formed. Bert found in animals with this condition that the normal state of the blood was restored by the inhalation of oxygen as into a vacuum; he, therefore, strongly recommends it in this form of paralysis.

I have not met with any case in which oxygen, more or less diluted, could not be safely used. If organic heart disease be present, care should be taken to regulate the force and the effort of inhaling, which sometimes gives rise to giddiness or palpitation independent of the remedy. Soreness of the throat and temporary discomfort about the mouth may occur if the apparatus be not quite free from dust, but from the gas I have seen no bad results.

II. OZONE.

Ozone is an allotropic form of oxygen. Its discoverer, Schönbein, of Basle, failed to arrive at a

knowledge of its real nature, but Odling (in 1860), by a "splendid hypothesis," concluded it to be a condensed condition of oxygen, and this was afterwards verified, amongst other observers, by Brodie, who adopted the symbol O_3, implying that three atoms of oxygen are condensed in each molecule of ozone. A minute proportion is found in the atmosphere—more in that of the open country and of the sea than of towns, but its precise distribution and variation are not yet ascertained. Richardson calculated its amount as one in ten thousand of air.

Ozone is produced in small quantities during the slow oxidation of phosphorus, terpenes, and some other substances. Lender recommends for its evolution in sick chambers a mixture of peroxide of manganese, permanganate of potassium and oxalic acid, to be dissolved in water. In the laboratory it is prepared by passing a succession of electric shocks through a closed chamber filled with air, or by liberating a high tension current in a room, and sending through it a current of air. It develops under many out-door conditions of air-currents; thus damp linen exposed for some hours to a high wind, and brought indoors, brings ozone with it, as shown by starch paper.

Ozone is denser than oxygen, and in most chemical and physical though not in all vital effects, it is more active; it is further distinguished by a peculiar odour—hence the name; it is a power-

ful oxidising agent, and changes many protosalts into persalts; it displaces iodine from some of its combinations, hence iodised starch paper is used as a test for the gas—the paper turns bluish as iodine is set free and combines with the starch, but the test is not very reliable.

According to Paul Bert, it possesses marked antiseptic properties, and animal substances keep long unputrefied in an atmosphere to which a minute proportion of ozone has been added, but the necessary amount of ozone cannot in practice be maintained in the air, and in any case its antiseptic action is only exerted on the surface of substances liable to putrefy.

Professors Dewar and McKendrick pointed out the remarkable fact that, instead of the blood becoming more highly oxygenated under ozone inhalations, it assumes venous characters in all the vessels, a fact which is explained by the greater density of this gas interfering with the due excretion of carbonic acid from the blood; it causes also some local irritation of the lining of the air-passages, with slowing of the heart's action and respiration—probably reflex. After exposure to ozone, albumin undergoes a change, becoming uncoagulable by boiling and by acids (except in large quantities), and by the other reagents usually employed to precipitate it, with the exception of basic lead acetate, and of alcohol. This change probably occurs also in the mucous

membrane of the air-passages when the gas is breathed, and explains the irritation caused.

Dr. Ireland found that ozone quickened respiration and circulation, excited the nervous system, and promoted coagulation of blood, but it is probable that his animals respired mainly oxygen. Dr. Day also found that oxygen, "ozonised in proportion of one-twelfth caused rapid respiration and heart-action, and much local irritation"; and Dr. John Barlow has confirmed and added to the observations of Professors Dewar and McKendrick. He reports that ozonised air depresses the nervous system, probably by leading to accumulation of carbonic acid in the blood; it lessens the frequency of respiration, and hence also of the heart's action, together with the excretion of carbonic acid and the absorption of oxygen. Elimination of nitrogen and of urea is said to be increased under it. It irritates the pulmonary and nasal mucous membrane, and may cause inflammation of the latter. Any such irritant effects may however be obviated by dilution; thus Ransome reports that pure oxygen ozonised to nine or eleven per cent. may be freely inhaled without causing inflammation.

It is poisonous to bacteria, and is a powerful, if not a practicable, antiseptic. The latest experiments, however, show but little sterilising effect of currents of oxygen and ozone on bacteria—none at all on tubercle bacilli in sputum—but

some on other bacilli when suspended in milk. Any purifying action ozone may have in the economy of Nature, is due to the direct chemical oxidation of putrescible organic matter.

It decolorises the red corpuscles, and causes a granular appearance, probably from uniting with hæmoglobin; it stops the amœboid movements of the white corpuscles, and renders the nucleus apparent; but there is no evidence of its entering the circulation in a free state. It is a physiological impossibility to take ozone into the blood through the lungs, and even were it possible, its presence there is incompatible with the continuance of the circulation.

III. COMPRESSED AIR.

The physiological action of compressed air varies somewhat according as the patient is wholly immersed in air compressed one-half to one atmosphere in a closed chamber for one or two hours, or whether he simply breathes it from a reservoir through a tube with closely fitting mouthpiece for twenty to sixty inspirations.

The former and older method, caused oppression of the head, tinnitus, and acute pain in the ears, and other disagreeable sensations, but had a sedative and equalising effect on the circulation, slowing the heart's action, raising arterial tension, and altering the distribution of blood, lessening its amount in the veins, and increasing it in the

arteries. It increased also expectoration and excretion. The physiological effects are described by Von Vivenot as follows: Pallor of the skin and mucous membranes, sense of pressure in the eyes, more ease with less frequency of respiration, increase of "vital capacity" and volume of the lungs with depression of the cardiac force, and, consequently, of the strength of the pulse, rise of the body temperature with increase of muscular vigour, of secretion and nutrition, compression of the intestines, and probably some increased absorption of oxygen and excretion of carbonic acid. Under excessive pressure, dangerous, even fatal, effects may be caused. Frequent exposure, *i.e.*, for two hours daily during several weeks, afterwards less frequently, to an atmosphere compressed one-fifth to one-half above normal, can permanently increase the "vital capacity," and the other effects described are fairly persistent.

In the method employed by Waldenburg and Biedert, the extra compression amounts to only one one-hundredth to one forty-fifth atmosphere, and the good results obtained are more clearly traceable to the extra amount of oxygen. Nutrition and blood-formation are improved, the "lesser circulation" is rendered freer and less congested, and at the same time the vital capacity of the lungs is increased.

Inspiration of air condensed one-sixtieth to one-fortieth of an atmosphere causes a sensation of

extreme distention of the chest as well as a real expansion of it and of the lungs, and increased taking in of air, with relief of inspiratory dyspnœa, if present. The thoracic contents are naturally compressed, and become comparatively anæmic, whilst arterial pressure is increased; the jugular veins become distended and the systemic vessels full. The alternate use of rarefied air, which induces rather opposite conditions, is employed in this method. Expiration into air rarefied by one-sixtieth of an atmosphere causes a sense of compression of the thorax, and partial retraction of the lung occurs with increase in the amount of air expired, and relief to dyspnœa, if present; the ultimate result being to somewhat lessen the circumference of the chest, but to increase vital capacity and respiratory power. Certainly theory favours further trials of "pneumatic medicine," but we require more extensive experience before judging of its merits. Ducrocq, indeed, reports almost opposite conclusions to those of Burdon-Sanderson.

A third method of employing compressed air is an air bath, with arrangements by means of which the air upon the exterior of the body may be either compressed or rarefied, while the patient breathes at normal pressure air either saturated or not with medicinal vapours. It was Hawke who first applied this method to bring about increased thoracic movements in atelectasis, and other lung affections in children. Mosso describes various anoma-

lous results in the distribution of blood in the extremities under a pressure of two atmospheres and explains them by changes in the innervation of the heart, or with Paul Bert by chemical rather than by mechanical effects.

Divers who work under a pressure of two to three atmospheres suffer from pain, often very severe, in the extremities, and sometimes in the trunk; pain in the epigastrium which may or may not be associated with nausea and vomiting; paralysis more or less extensive and complete; headache, vertigo and coma. Sudden death may occur. The symptoms possibly depend on the too free liberation of air from the lungs leading to air embolism, and particularly of bubbles of nitrogen. A. H. Smith, of New York, has shown that they are more probably due to changes in the distribution of the blood, especially in closed cavities, and subsequent congestions of blood stases. Danger seems to lie in too sudden changes of pressure, and the symptoms do not occur if the change be made gradually, and if severe they are relieved by a return to the compressed air. This condition is known as Caisson disease.

THE PHARMACOLOGICAL ACTION OF STRYCHNINE AND ITS ALLIES.

STRYCHNINE crystallises out of alcoholic solution in colourless, four-sided, or octahedral right-rhombic prisms. They are slightly soluble in water (one in seven thousand), more so in alcohol of specific gravity 0·863, especially when heated nearly to boiling point. The solution is odourless, intensely bitter, and leaves a characteristic metallic after-taste. The proportion of this alkaloid in nux vomica varies from 0·9 to 1·9 per cent. Strychnine is soluble without change of colour in pure sulphuric acid. If a single crystal be thus dissolved on a white plate, and a drop of solution of some oxidising substance (*e.g.*, bichromate of potash) be made to mingle at its edge with the dissolved strychnine, there is presented a unique play of colours, including blue, purple, crimson, and red-brown; this change occurs in a few seconds, and then the red-brown gradually fades into a light red, which is persistent for some hours. It has been erroneously stated that other alkaloids answer to this test, but Dr. Guy has clearly proved that nothing but strychnine produces the particular sequence of colour-changes above described.

There is a physiological test based on the sensitiveness of frogs: One one-thousandth of a grain in a drop of water applied to the dried skin will cause spasm in ten minutes; of the acetate of strychnine one two-thousandth injected will do the same, or even one twenty-thousandth applied to the skin when thoroughly dried. The physiological is more delicate than the chemical test, but it is given also by brucine.

Strychnine is a powerful and very stable base, which neutralises the strongest acids, and precipitates metallic oxides from their solutions with formation of double salts; the nitrate, hydrochlorate and sulphate are crystalline, intensely bitter, and soluble in about fifty parts of water. Strychnine is about thirty times as active as brucine.

Brucine occurs in transparent four-sided prisms, or if the solution be quickly evaporated, in pearly scales resembling boracic acid, or they may form a cauliflower-like mass. They are soluble in one hundred and fifty parts of boiling, and in three hundred and twenty parts of cold water, the taste of the solution being strong and persistently bitter. Brucine and its salts are turned scarlet or blood-red by strong sulphuric acid. The proportion of brucine in nux vomica is variously stated to be 0·12 (Merck), 0·5 (Wittstein), and 1·01 (Mayer) per cent.

Igasurine was discovered by Desnoix in 1853. It is obtained in colourless, silky prisms, and is

more soluble than strychnine or brucine, *viz.*, in two hundred parts of cold and one hundred parts of hot water. Strong sulphuric acid turns it rose-red, the colour changing to yellow and yellowish-green. Nitric acid gives a deep-red colour. Igasurine has the bitter taste and poisonous properties of the other strychnous alkaloids; all its salts are crystallisable. Schutzenberger states that it is a compound body, yielding no fewer than nine bases, "all colourless, very bitter, and acting like strychnine".

Strychnine is absorbed comparatively slowly from the stomach, more quickly from the rectum, still more so from the bronchi and cellular tissue; it has been detected in the blood, the spinal cord, the pons Varolii, and especially in the medulla oblongata; also in a later case in the brain substance, though very little had been given. The salts, especially the hydrochlorate and the nitrate, are absorbed more rapidly than the alkaloid itself. Fatty or astringent substances taken at the same time delay absorption.

The amount found in the blood is so small as to suggest the hypothesis that the drug is partly decomposed in the circulation; but Kratter concludes that it is excreted unchanged in the urine. That enough circulates to produce all the characteristic symptoms is shown by a striking experiment of Vulpian's, in which the blood is conducted from one living dog to the vessels of another; soon

after strychnine is injected into dog number one and toxic symptoms appear in dog number two, which latter dies before the former, the life of this being prolonged by artificial respiration.

Elimination takes place mainly by the urine and the saliva, and with ordinary medicinal doses is completed in two or three days. Being so slow, it follows that continuous doses may lead to unpleasant symptoms suddenly—after, for instance, a customary dose that has not been previously felt; hence it is important to omit the drug occasionally during a course of treatment. Elimination is quicker in children than in old persons; it begins within one hour and continues for forty-eight hours, and this is even more rapid in the case of brucine. Meelzer and Salant have shown that if in animals whose kidneys have been removed, strychnine be injected, cumulative symptoms do not occur, and the minimum fatal dose is not smaller than in normal animals. By what channel elimination is effected is not clear. The fear of accumulation in chronic renal diseases, it is held, may be set aside on these results.

Small doses, one-seventieth of a grain, stimulate the muscular coat of the intestinal tract to more active contraction, increase appetite and regulate peristalsis. Larger doses may even cause diarrhœa.

The primary action of strychnine on the digestive system in increasing appetite and improving digestion is in virtue of its being a bitter

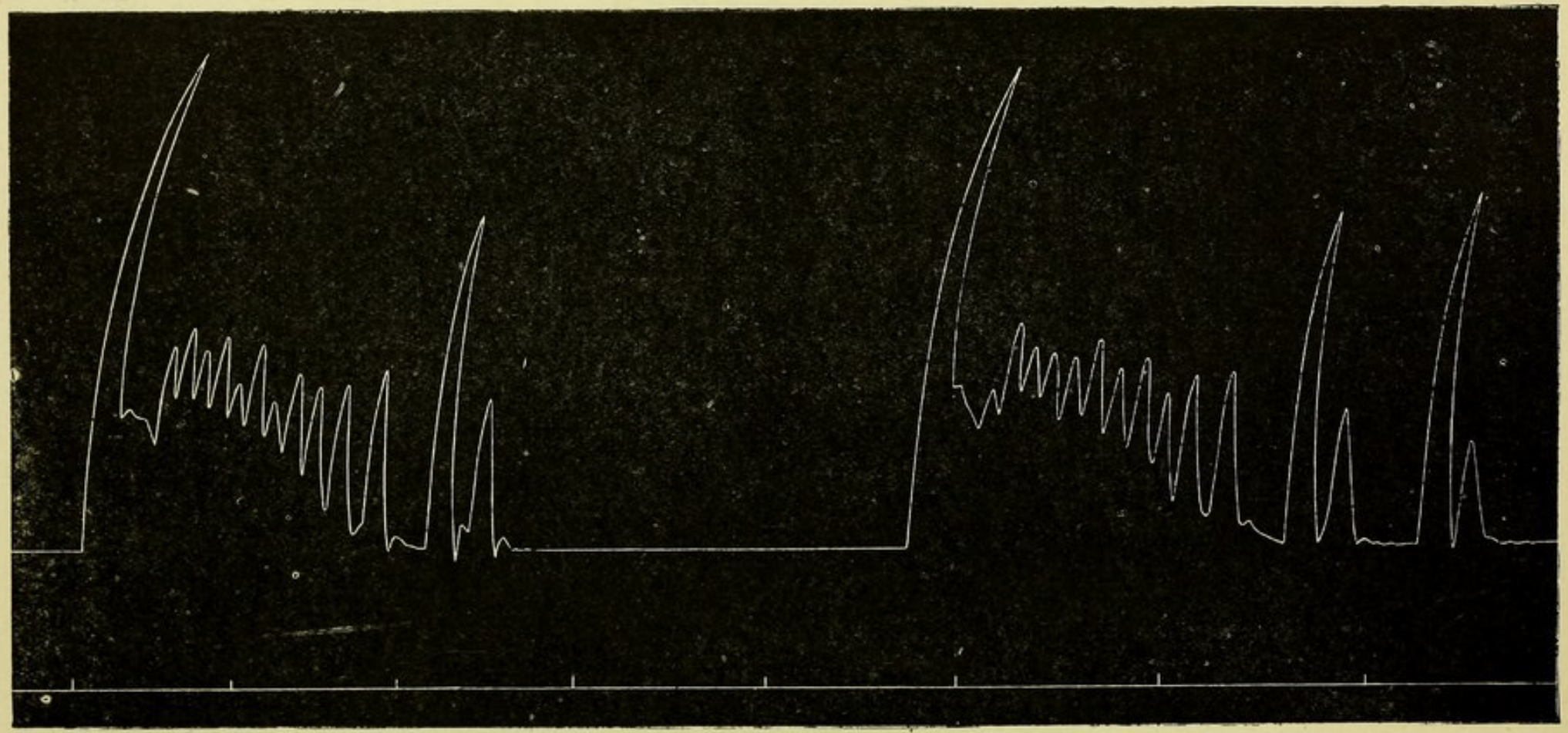

CHART I.—Incomplete tetanus of the gastrocnemius produced by action of strychnine on the brainless frog. Time marked in seconds.

principle. The after-effects on the muscular wall of the alimentary tract, in preventing constipation, are exerted through the nervous system after the drug has been absorbed into the blood. The tonic effects of strychnine are best obtained by small, repeated doses.

Experiments appear to show that large doses of strychnine paralyse the secretion of the pancreas.

Full medicinal doses, if continued, induce a state of heightened reflex irritability with general discomfort, restlessness and twitching of the muscles. The special senses are affected, so that bright light and loud sounds become painful, and in exceptional cases a simulation of alcoholic intoxication is produced. Such effects were formerly not uncommon when unwisely large doses were administered in the hope of curing paralysis.

Strychnine is a powerful tetaniser, especially in frogs. In conjunction with Dr. M. S. Pembrey of Guy's Hospital, I have made a series of observations illustrating the fact. Many of these experiments are given in detail in our book on *The Physiological Action of Drugs*, a work intended as an introduction to practical pharmacology. The following is a typical experiment :—

Under the skin of a brainless frog are injected ten to fifteen minims of a saturated solution of strychnine in normal tap-water saline. In two or three minutes it will be observed that the frog can-

not readily draw up its hind legs after a jump, and soon the reflex excitability of the spinal cord is so much increased that a slight touch or puff of wind upon the skin brings about a general spasm of the muscles. Convulsions quickly follow, and the body becomes rigid and rests on the mouth and toes in the position known as *emprosthotonus*. This attitude is due to the different strength of the various muscles; all are thrown into contraction, but the stronger overcome the weaker. The muscles are somewhat relaxed after the convulsions, but are again sent into tetanus by the slightest stimulus applied to the skin. These *tonic* contractions are followed by prolonged twitches or *clonus*. The spinal cord soon loses its excitability and the frog lies in this condition for several hours; if, however, it be kept in shallow water and covered by a bell-jar, the excitability will return and recovery from the action of the drug occurs in less than twelve hours. This is due to the excretion of the strychnine by the kidneys. The urine of a frog poisoned by strychnine will produce the characteristic convulsions when injected into another frog. If, during the stage of convulsion, a probe be pushed down the vertebral canal, so as to destroy the spinal cord, the convulsions cease at once, showing that the drug acts upon the ganglion cells and their dendrites. The death of a frog from a larger dose is quickly followed by a well-marked *rigor mortis*.

The following experiment serves to demonstrate that the action of the drug is on the spinal cord :—

The cerebral hemispheres of a frog are destroyed and then the gastrocnemius muscle is prepared. A strong ligature is placed under the gastrocnemius and tightly tied round the upper portion of the tibio-fibula and the remaining muscles ; the leg is then removed below the ligature ; this method of precaution prevents hæmorrhage. A pin is placed through the lower extremity of the femur and is pushed firmly into the cork of the myograph ; a piece of moist flannel is then pinned down over the trunk to prevent the contractions of the muscles of the trunk from disturbing the lever connected with the gastrocnemius muscle.

A dose of strychnine similar to that used in the last experiment is injected under the skin of the back. Twitches and convulsions soon begin, and if a signal marking seconds be simultaneously recorded the twitches of the tetanus can be observed to number about eight a second. This is a measure of the rate of discharge of impulses from the nerve cells of the spinal cord. The stage of incomplete *tetanus* is followed by one of *clonus*. The curves in Chart I. illustrate the tetanus, the time is marked in seconds.

It will be noted that the curves in Chart II. of clonus is similar to that produced by hydrastine,

one of the alkaloids obtained from *Hydrastis canadensis*, the golden seal.

In man in toxic doses of half a grain, sometimes less, strychnine produces powerful and characteristic tetanic convulsions. The first symptoms are developed in from a few minutes to an hour after the administration, with a sudden sense of suffocation and dyspnœa. The head and limbs begin to

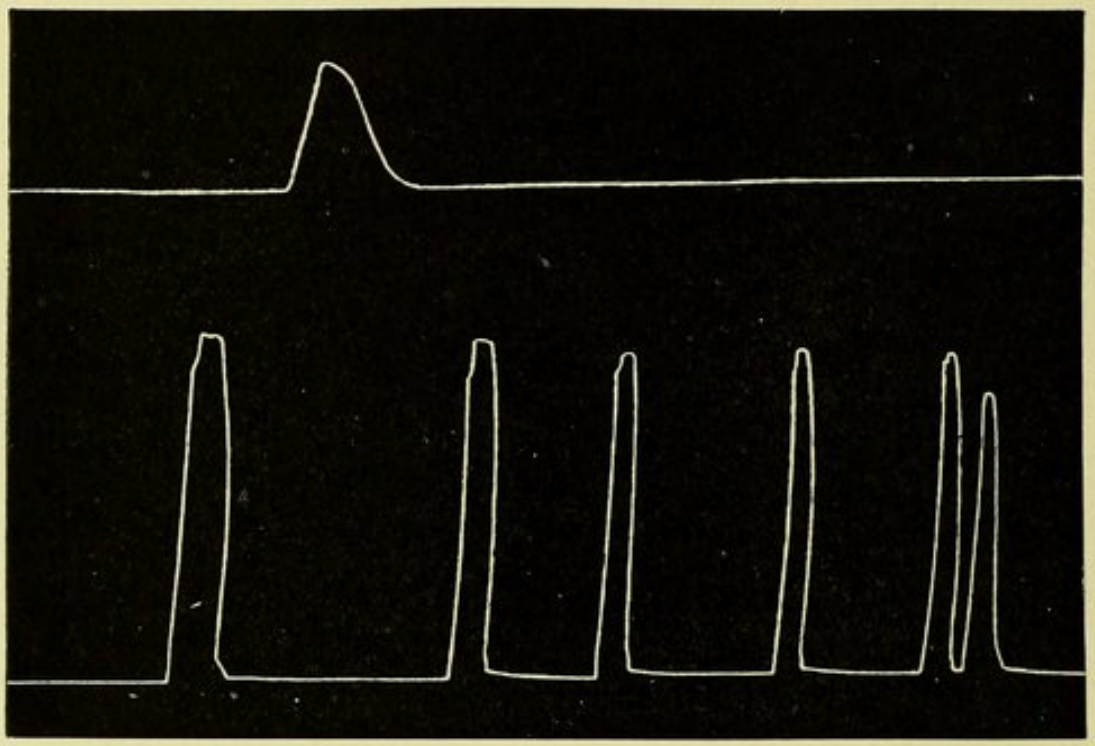

CHART II.—Clonic contractions of the gastrocnemius produced in a brainless frog by the action of hydrastine hydrochlorate. The contractions are few but prolonged. Duration ten seconds.

jerk in a shuddering manner, and the latter are suddenly stretched out rigidly, the hands clenched, the head is bent backwards, and at last the whole body is stiffly arched, so as to rest upon the head and the heels. The soles of the feet are arched, the belly is hard and tense, the chest is fixed, and the breathing nearly arrested. In the height of

the spasm, the face looks dusky and congested, and the eyeballs stand out strongly; the jaw-muscles are also affected with spasm, and the throat is dry, with a sense of choking. It is worthy of notice that the jaw-muscles are never so soon or so powerfully affected as in tetanus. The patient often expresses a fear of impending death, but the intellect remains unclouded. After the paroxysm has lasted a minute or two, there is usually a relaxation, during which the patient suffers only from soreness of the muscles, but before long he experiences sensations which warn him that the fit is returning, and cries out for some one to hold him or rub his limbs. After one or two, or a succession of paroxysms, respiration stops in the middle of a fit, and the heart soon after ceases to beat. Death may occur within five minutes, and is seldom delayed more than five hours. The smallest dose which has produced a fatal result is of nux vomica extract three grains, of strychnine one-half grain, but several persons have recovered after swallowing even larger quantities, the paroxysms gradually becoming less violent, and the intervals longer. On the other hand, one-third of a grain of the alkaloid may imperil life. Chronic poisoning from continued medicinal doses has cumulated in a sudden attack like apoplexy.

Tamassia records a rise of temperature in strychnine poisoning as contrasted with a fall under arsenic, corrosive sublimate and phosphorus.

After death there are no characteristic lesions generally recognised, but the occurrence of rigor mortis is usually rapid, almost immediate.

The action of strychnine on different animals varies in degree, man apparently being one of the most sensitive to it. The monkey is very little so, and birds less than rabbits. Puppies newly born are said to be less susceptible to its action than those a little older, the explanation given being that their nervous system is not so fully developed. Wintzenreid found with brucine that different species of frogs were differently affected; on the *Rana esculenta* it acted like curare, on the *Rana temporaria*, and on warm-blooded animals, it acted much like strychnine. It is worth noticing that in this latter alkaloid the substitution of a molecule of ethyl for one of hydrogen converts it into a paralyser allied to curare.

We must next consider the mode of action of strychnine. Magendie taught that it acted on the nerve centres as a direct irritant, like galvanism or other mechanical stimulus, and that ultimately paralysis followed over-stimulation; but the view advocated by M. Hall, Brown-Sequard, Vulpian and others, supported as it is by many experiments on the lower animals, is the one now generally adopted, *viz.*, that strychnine acts only on the grey substance of the spinal cord, exalting its reflex power to such a degree that comparatively slight stimuli, intrinsic or extrinsic, provoke con-

vulsive spasm; if anæsthesia (general or local) be induced, the spasm is arrested, though on direct touching of the cord it recurs, showing that the anæsthetic only abolishes reflex action. Its main effect is on the spinal cord, the vital nerve centres of the medulla have their reflex excitability increased; the only purely cerebral effect is that increases the activity of the special senses, but it is not yet certain whether this is due to stimulation of the higher centres of the brain or the peripheral nerve mechanism in the organs of special sense. It does not increase capacity for intellectual work, nor relieve fatigue induced by the same.

Rosbach and Nothnagel agree in stating that the drug acts on the whole spinal cord, especially the cells of the grey substance and of the vasomotor and respiratory centres, as well as those concerned with reflex action.

Spitza, in a prize essay of the American Neurological Association, thus sums up his knowledge on this subject: (1) Strychnine acts on the whole of the grey substance in the same manner, and affects both its sensory and motor elements. (2) The white substance and the peripheral nerves act only as conductors. (3) Strychnine has no local action on nerves or muscles, except on the peripheral extremity of organs of special sense. (4) It causes tonic spasm in all vertebrate animals —in the higher classes clonic spasm also. (5) Its

maximum influence is intracranial (medulla), and becomes less, progressively, in the lower portions of the cord. (6) It augments reflex excitability, or as put by Cushny, "removes resistance to the passage of impressions along the reflex arc"; but all the spasms are not due to this only, some depend upon a direct irritation of motor cells. (7) The lower animals it kills by nerve exhaustion, the higher by asphyxia, with venous congestion of the nervous system. (8) After administration it is found in all organs and tissues of the body—more is found in the grey than in the white substance; post-mortem lesions in toxic cases are due to secondary effects of the drug.

Continuing our investigation of the pharmacological action of strychnine, we note that the proof of its stimulative action on the sympathetic is to be found in the ocular phenomena—the protrusion of the globe, and the dilatation of the pupil, but especially in the contraction of the small arteries by vaso-motor influence, and the consequent increase of arterial pressure. Strychnine has little or no direct effect on muscular tissue, and little or none on peripheral sensory nerves. Magendie early established the facts that if the nerve to a muscle be divided strychnine produces no spasm, but if the artery alone be ligatured it does. If the brain be separated from the cord convulsions still occur, but if the sensory nerves are paralysed, *e.g.*, by section of the posterior roots, or by the

application of cocaine to the skin, they cease. The effect of strychnine upon muscle and nerves can be demonstrated experimentally as follows:—

Two muscle and nerve preparations are made, and the minimal stimuli for both nerve and muscle are determined. The muscle of one preparation A is placed in a watch-glass filled with normal tap-water saline solution, saturated with strychnine (one in six thousand seven hundred); the nerve is left outside upon a piece of wet filter paper. The nerve preparation B is placed in the solution, but its muscle is placed outside upon the filter paper. The minimal stimuli are determined from time to time, and it will be found that the endings of the nerve in the muscle exposed to the strychnine are paralysed. Stimulation of nerve A produces no contraction, but direct stimulation of the muscle readily evokes a response. In this respect strychnine resembles curare.

The effect on the heart will now be considered. Of the increase in arterial pressure there can be no doubt, and Richter and Mayer have demonstrated it in animals previously curarised, and lying immovable, *i.e.*, free from the convulsions of strychnine. The pressure may be seen to rise as the drug begins to act, and is not due to any influence on the heart; for it occurs even after section of the vagi, and it fails to occur after transverse section of the cord in the upper cervical region. This may be taken to prove that

the narrowing of the vessels depends upon the poison acting on the vaso-motor centres, and especially those in the medulla oblongata; the pressure may arise to twice its normal amount. The pulse is naturally rendered slower at the same time. The primary stimulation and rise in pressure described are followed by opposite conditions —a fall in pressure and vaso-motor paresis; very large doses produce these latter symptoms directly.

Recent experiments by G. W. Crile on the action of strychnine in dogs confirm and amplify these findings. In the majority of animals when sufficient strychnine was given to raise the excitability of the cord, as shown by increased reflexes and muscle tonus, a rise in blood pressure occurred. After doses less than this nothing noteworthy occurred.

When more was given after this stage of increased excitability, convulsions occurred, and the blood pressure rose enormously, sometimes to even more than double the normal, and if the convulsions were prevented by curare, the blood pressure rose equally high.

After frequent repetition of the dose the blood pressure not only failed to rise, but sank to a level even below the normal, with irregularity of the curve, the result of exhaustion of the vaso-motor centre, as in shock.

The systole of the heart is increased in force,

and the diastole prolonged; the organ may cease to beat and become fixed in a state of spasm at any period of poisoning; the action on it is exerted partly through the cardiac ganglia, partly through the pneumogastrics.

In the vertebrata, the heart sometimes does not quite stop when apparent death takes place, and its activity may be restored by artificial respiration, if this be quickly commenced.

The blood pressure rises from stimulation of the vaso-motor constriction centre presiding over the internal organs, but the superficial vessels of the skin and mucous membranes seem to be dilated, a condition to be explained by stimulation of their vaso-dilator centre; hence the distribution of the blood may be altered by it, more in the surface, less internally. Certain experiments I have made on frogs with Dr. Pembrey may, I think, be regarded as conclusive as showing the effect of strychnine on the heart. I quote only one example:—

The vago-sympathetic nerve is exposed, and a record is taken of the contraction of the heart. A few drops of normal tap-water saline solution are applied to the heart, the record is continued, and then the vago-sympathetic nerve is stimulated by a strong faradising current. The inhibitory action of the vagus and after-effect are observed (Chart III., Curve I.). A few drops of a saturated solution of strychnine in normal tap-water saline

(one in six thousand seven hundred) are allowed to flow over the heart. In a few seconds the heart-beat becomes slower, but larger; the vago-sympathetic is again stimulated. Inhibition is not so marked; there is an after effect, but the contractions are slow (Chart III., Curve II.). Further doses of strychnine are given, and the stimulation is repeated. The inhibitory effect of the vagus is removed (Chart III., Curve III.). The period of stimulation of the vago-sympathetic is shown by the white line. The time is marked in seconds.

The prolonged action of the drug is to produce a slow and feeble beat.

Under the influence of strychnine the respiration is first increased in frequency by raising the reflex excitability of the respiratory centre; it is later decreased, and ultimately arrested, by the respiratory muscles being thrown into tetanic spasm. A gradual respiratory failure may, however, occur from paralysis when death has not occurred suddenly.

Strychnine is said to act to some extent as an expectorant by stimulating the respiratory centre. The action of strychnine on the respiratory centre is evidently a portion of its wide influence on the whole motor tract.

The passage of strychnine by the urine, doubtless, determines vesical symptoms, such as frequency of micturition with some spasm, which occur especially in women; the ultimate effect of

toxic doses is loss of controlling power of the sphincters, the urine, as well as fæces, passing involuntarily. The uterus is stimulated to contraction, and menstruation is promoted; the drug increases the sexual appetite, and there is evidence that it induces erections.

Professor Cushny remarks that strychnine, in increasing the movements of the body, augments oxidation, and the consequent excretion of carbonic acid. The continuance of the spasms exhausts the supplies of energy—thus it lessens the glycogen of the liver and muscle. Glycosuria is often found during experiments on animals, but has been traced to partial asphyxia, rather than to any specific action.

Strychnine does not interfere with the heat-regulating mechanism of the body, for while the body heat tends to rise, owing to the muscular spasm, it is kept at a normal level by the increased heat-loss through the skin.

Electricity favours the effect of strychnine, according to an experiment of Vulpian, in which he galvanised the cut end of a sciatic nerve in a frog subjected to strychnine, and found that characteristic spasm occurred in it more violently than in the opposite one, and it lost its proper powers sooner from exhaustion. Ignatia, brucine, picrotoxin, thebaine, to some extent ergot, and, according to Rabuteau, belladonna, are also synergic.

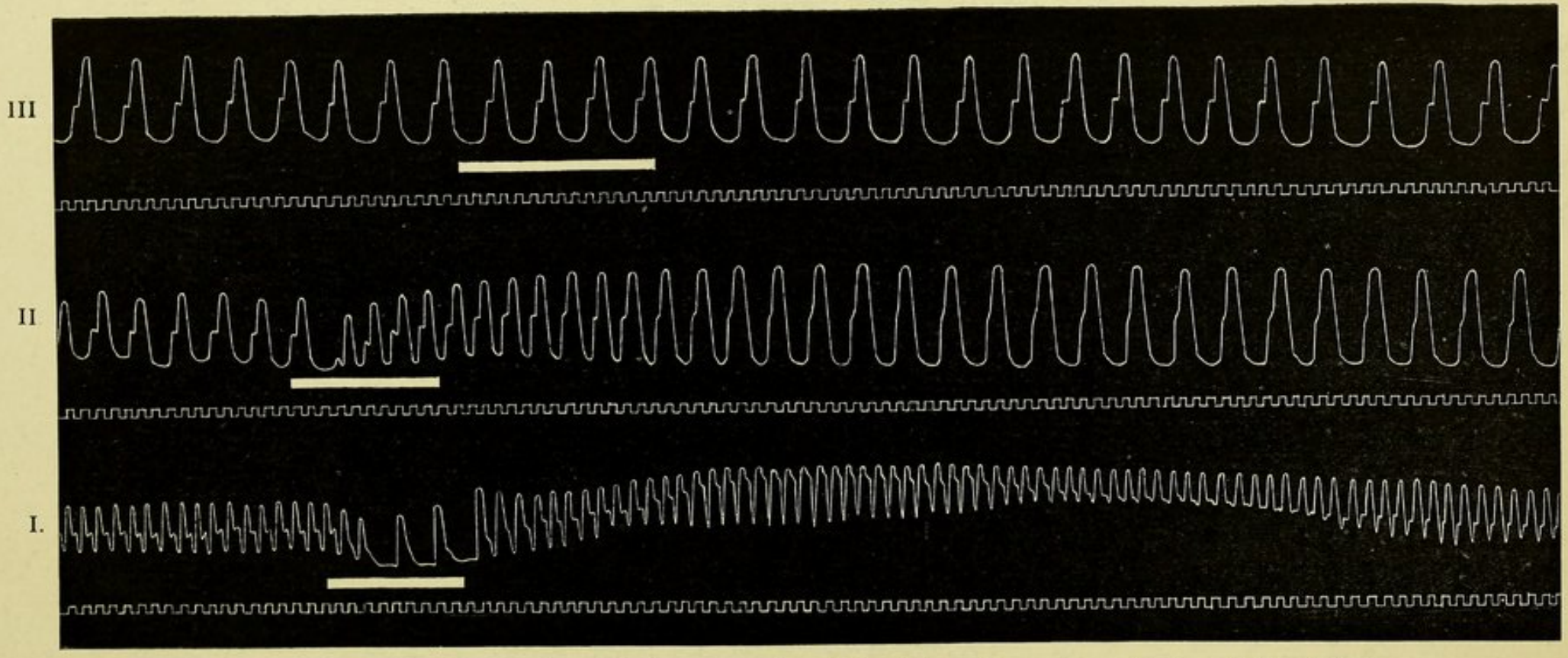

CHART III.—Contraction of the heart of a frog. Stimulation of vago-sympathetic with faradising current. I. before, II. after application of strychnine in tap-water saline solution, and III. after further doses of strychnine. Period of stimulation shown by white line. Time in seconds.

There is much evidence as to the definite antagonism exerted within certain limits by this drug, between chloral hydrate and strychnine. Hughes Bennett showed that a recognised fatal amount of strychnine was counteracted in its effect by a certain dose of chloral—though, of course, a very large dose of the former may kill before any antidote has time to act; and, on the other hand, the dose of the latter may be such as to destroy by its own power. The antagonism extends to the soothing, or stimulating, respectively, of the reflex activity of the cord. Strychnine will not antagonise the coma of chloral. The proofs offered by Liebreich of the antidotal power of chloral are weakened by the results of Orr, who showed that the dose considered fatal by the former did not always prove so. Bennett put the minimum fatal dose of strychnine for rabbits at one two-hundred and eighty-eighth grain per pound of body weight, and out of twenty rabbits poisoned by more than this proportion fifteen recovered under chloral; these died quickly a few days afterwards from a similar dose of the poison, given without the antidote. In man, cases in which four grains and upwards have been taken have recovered under chloral.

Gray quotes a case where twenty-two grains of strychnine were taken, and, after an emetic, one drachm of chloral was given, and followed by a second drachm, recovery ensuing.

Vulpian has demonstrated the antidotal power of intravenous injection of chloral in dogs with much exactness.

Relief of the spasms has been recorded after the administration of oxygen and amyl nitrite, chloroform, ether, and also, though more slowly, bromide of potassium.

A case of recovery after three grains of strychnine, when one-half ounce of the bromide was quickly given, is quoted by H. C. Wood. There was no vomiting, but relaxation of the spasm occurred half an hour after the bromide was given; small doses of it were continued for an hour or two afterwards. Alcohol pushed to narcosis acts in a similar manner to chloroform, as shown on animals.

Other drugs that might seem indicated from physiological experiment, such as aconitine, prussic acid, nicotine, are unsafe, and have not proved useful in practice. Opium has markedly delayed the onset of strychnine symptoms, *e.g.*, when one and one-half and two drachms, respectively, of laudanum were taken at the same time as a packet of "vermin killer". In a case where one and one-eighth grains of strychnine, and at the same time one or two ounces of tinctura opii were taken, symptoms from the former drug did not set in for eight hours. Chloral was given four hours afterwards, and recovery occurred. Artificial respiration, practised forcibly with a tube in the

larynx, prolonged life, and contributed to recovery in poisoned animals, but it is doubtful whether any possible method of employing it in man can be efficacious.

Charcoal acts as a mechanical, and tannin and preparations of iodine as chemical antidotes, precipitating and decomposing part of the alkaloid; but if they are first administered in cases of poisoning they should be followed by emetics, such as apomorphine, or the stomach-pump, since the compounds formed are still poisonous. Practically, as Murrell has shown, the best pharmacological antidotes for strychnine are chloral and bromide of potassium.

THE THERAPEUTICAL USES OF STRYCHNINE AND ITS ALLIES.

In the previous article I dealt with the pharmacological action of strychnine. In the present contribution I propose dealing with the practical application of the facts so ascertained to the treatment of disease. Incidentally, I may remark that all rational therapeutics, modes of treatment that is apart from epiricism, must of necessity be founded on pharmacological evidence. It is the custom of the hour to decry the work of the pure pharmacologist, but without him and his methods no real advance can ever be made in the rational treatment of disease.

The action of nux vomica and of its alkaloids is practically the same, so that either may be prescribed, according to considerations of convenience and safety.

In dyspepsia, of the simple atonic form, strychnine, or tincture of nux vomica, is often of the highest value; it is best given alone, but an excellent combination is the tincture, with dilute nitrohydrochloric acid—five-minim doses of the former, and ten or fifteen of the latter. It has also good influence upon the gastric irritation of

alcoholism; it may be added that heartburn, hiccough, regurgitation, and even pyrosis, when chiefly due to atonic dyspepsia, may frequently be cured by a short course of this medicine. It is useful in the morning sickness of pregnant women, also in abdominal cramps and spasms. In cases of anachlorhydria, or "anadenia gastrica," as Ewald calls them, cases characterised by failure of gastric secretion of unknown origin, but probably dependent on some functional derangement of the nervous system, strychnine injections are useful, not only by restoring the normal hydrochloric acid to the secretion, but by increasing the mobility of the stomach.

On the other hand, cramp and pain in the bowels may be caused by ordinary (five minims) doses of the tincture of nux vomica in some patients, especially, as I have noticed, in nervous, delicate women; it is well, therefore, to begin with one to two minims.

Brunton, in an interesting paper, describes strychnine as "at once a gastric, vascular, and nervous tonic," aiding appetite and digestion, preventing putrefaction, and exciting the sensibility of the vasomotor centre.

In atonic conditions of the intestine strychnine is of service, especially in that apparently almost hopeless form of constipation in which the large bowel does not contract properly, and becomes passively loaded with more and more fæces, day

after day. In prolapsus ani, arising from such a state of rectum and sphincter, nux vomica is strongly recommended, and I can speak with equal emphasis of its benefit in hæmorrhoidal tumours of the anus. Five drops of the tincture of nux vomica, taken in a tumbler of cold water before breakfast and dinner, act as a laxative, and often overcome obstinate constipation. In some forms of diarrhœa, *i.e.*, when there is debility without irritation, and when it is readily excited by nerve causes, and the muscular coat of the bowels is wanting in "tone," small doses of the drug are well combined with other remedies, such as acids. In subinvolution of the uterus in weakly subjects, strychnine is of service.

In dysentery, with much depression and tympanites, it may be useful. Even in cholera, combined with sedatives, it is said to have acted well.

The earliest applications of strychnine in medicine were directed to the cure of paralytic affections, and for many years it was employed indiscriminately, and often in too large doses. It was thought that the drug should be pushed to the production of actual symptoms of poisoning, and doses as high as one-eighth and one-quarter grains, twice or three times a day, were often reached, with the frequent result of throwing the patient's nervous system into great disorder, manifested by twitching of the limbs, hyperæsthesia of the retina

and the auditory nerve, and a state of perpetual restlessness. It was discovered, after a time, that such effects were injurious, rather than useful, and although it has been stated that tinnitus must be caused before any benefit can be expected, violent strychnine action is specially hurtful, while the drug in any dose is valueless in certain forms and stages of paralysis. In paralysis of cerebral origin it is seldom beneficial; on the contrary, its early use in these affections, especially such as proceed from hæmorrhage, has often proven mischievous. It would be natural to expect better results from its employment in spinal paralysis, yet even in such cases there is frequent disappointment, and in the early stages of organic lesions it may do harm, if given in large doses. Its chief value in cord diseases seems to be in chronic affections of the anterior horn cells, particularly in progressive muscular atrophy, where it has seemed in some cases to lead to arrest of the morbid process.

In functional paralysis, such as that connected with hysteria, with sexual excess, or concussion of the cord; in paralysis due to lead, alcoholic or diphtherial neuritis, strychnine is often of use, decidedly promoting recovery of power in the muscles. Some cases of facial palsy and of aphonia have been improved by it. The local injection of a solution of strychnine has been employed in the treatment of prolapse of the rectum

and of various occupation neuroses, but it is probable that any effect it may have is not exerted locally.

Cases of "craft-palsy," *e.g.*, of fingers from flute-playing, and of "writer's cramp" have been cured by hypodermic injections of strychnine, after failure of other measures.

Barwell treated effectively cases of infantile palsy (chronic) by strong solutions, using as much as one-sixth of a grain at a time, which excited sufficient local inflammation to limit absorption. A sixth of a grain is a large dose, and it would be better to give not more than one-twelfth, using a two per cent. solution. Even then the injection should not be repeated more than twice a week. It must be remembered that children are very susceptible to the action of strychnine.

In anæsthesia of functional character, the good effects of the drug are often marked; a circumstance which illustrates the difference between its poisonous and therapeutical actions, since among the former we scarcely find any direct and evident effects upon common sensation.

In tremors and ataxic movements of certain kinds strychnine has proved useful; for instance, in the tremor of chronic alcoholism, part of its beneficial action being due to its removing the usual catarrhal condition of the stomach. In some cases of hysteric tremor, where the hysteria is merely the product of great bodily weakness, in-

duced by illness or exhausting fatigue, it is similarly beneficial. In the later stages of chorea, particularly in those cases where fright, or the disturbing effect of commencing puberty, rather than rheumatism, is the principal cause, strychnine in minute doses (one-eightieth of a grain *ter die* for a child of ten years, one-sixtieth to one-fortieth of a grain after puberty) has often been found of use.

This, however, is not the best treatment for chorea, nor the one most commonly employed. I should place much more reliance on (1) arsenic, (2) sulphate of zinc, or (3) ergot, all in fairly large doses.

In epilepsy, when bromides depress too much, strychnine acts beneficially in certain cases, in combination with them. Notably in the nocturnal attacks of anæmic weakly subjects.

Although the combination of potassium bromide with strychnine is often prescribed, it must be remembered that these drugs are physiologically antagonistic.

In cases of impairment of the nervous apparatus of sight and hearing, strychnine is useful. As regards vision, no one, of course, expects it to do good in those diseases in which the tissue of the retina is destroyed by inflammatory or degenerative processes, but there is reason to think that cases of simple atrophy may be really improved by it. Nagel especially brought forward cases of amaur-

osis, and of white atrophy, in which improvement occurred, and similar results may be verified in the amaurosis from tobacco, also amblyopia from debility, or remaining after operation for strabismus; but in other cases not much must be expected.

Rampoldi of Pavia in a well-considered essay on strychnine in atrophy of the optic nerve, points out that the improvement observed after the first few days of treatment is only transient, and that the administration of the remedy should be continued until toxic symptoms are perceptible. He prescribes powders containing 0·03 gramme of St. Ignatius' bean, with injections subcutaneously of 0·001 gramme of strychnine, dissolved in two grammes of water.

Wyatt Wingrove (*Medical Press*, 1903) calls attention to the effect of smoking strong tobacco in producing deafness, and finds strychnine in full doses successful. Three cases were completely cured, in eight, nine, and twelve months, respectively, and nine showed marked improvement. It is necessary in these cases to abstain entirely from smoking, as there is always a relapse on resuming the habit.

In neuralgias, of various kinds, strychnine has often proved most useful, and especially where the pain is visceral, rather than superficial; in hepatalgia, for instance, and in the milder forms of angina pectoris, and in gastralgia. In the latter disease, with flatulence, and eructations, tincture

of nux vomica has long been a favourite and fairly successful remedy, and may be well combined with antacids and carminatives, though there are intractable cases, where this, like every other medicine, will fail.

In true angina pectoris it is of little value, and is much inferior to nitroglycerin and nitrite of amyl.

In all forms of neuralgia the dose of nux vomica, or of strychnine, should be small; of the latter there is seldom occasion to use more than one one-hundredth, or, at most, one thirty-second of a grain twice or three times a day. In pruritus it is said to be serviceable, and may fairly be tried in purely "nervous" cases.

In weak heart strychnine proves an excellent tonic, and is sometimes the first remedy which begins to do good in cases of fatty heart, when many others have been tried. One caution must, however, be added, namely, that any undue pushing of the remedy will produce, even more seriously than in other subjects, a state of nervous worry and restlessness, in which sleep is broken, or even destroyed by a tendency to perpetual muscular movement. To the subjects of fatty heart this condition is not merely fatiguing and annoying, but dangerous, and we are, therefore, bound to inquire for the first symptoms of its appearance when administering strychnine to such persons. It is of the utmost value in the failing heart of

acute diseases, more especially, perhaps, in heart failure ensuing in the cases of lobar and broncho-pneumonia. Its utility in these cases is due to its power of (1) vasomotor stimulation, with accompanying rise of blood pressure, (2) of stimulating the heart muscle directly, and probably its peripheral inhibitory apparatus. To tide over heart failure, such as so often occurs in acute specific diseases, it is of the utmost value as a temporary measure, but as a continuous stimulant, except in the very smaller doses, it may defeat the object for which it was employed. In the treatment of cardiac dilatation nothing is more efficacious than complete rest in bed, but strychnine is useful, and it must be remembered that it is often more important to lessen the work of the heart than to increase it. In the failure of compensation in cardiac valvular disease the combination of strychnine and tincture of digitalis often gives better results than either separately. Strychnine is probably one of the most powerful respiratory stimulants we possess, and to this, no doubt, the good effect of its administration in pneumonic conditions is largely due.

In pneumonia strychnine is useful as a respiratory and vasomotor, as well as a cardiac stimulant. It is quicker in its action than digitalis, but the action is not so prolonged; the combination of the two is often most valuable.

In dyspnœa dependent on heart disease, or on

chronic bronchitis, or emphysema, strychnine has been praised, and is sometimes useful.

It is to be recommended as facilitating expectoration in cases of chronic bronchitis.

In spasmodic asthma and in coryza nux vomica and strychnine have been used with much benefit. It is useful in bronchitis, where there is blocking of the respiratory passages with mucus, chiefly in the way of maintaining the coughing reflex. It is one of the most useful drugs to administer in emphysema. It has been recommended for the night sweats of phthisis, on the supposition that they are due to the imperfect æration of the blood during sleep.

In atony of the bladder, with incontinence or retention of urine, such as occurs in old people with enlarged prostate, strychnine is sometimes employed with much benefit, and the same treatment is applicable to the spermatorrhœa of debility; when, however, the latter disorder, or incontinence, depends on irritability and excitation of the parts, the more usual treatment by bromides or belladonna is indicated; hence, this succeeds better if the disorders are nocturnal only, whilst strychnine is likely to suit if they occur in the day also, *i.e.*, are more persistent, and less spasmodic. In impotence, connected with relaxation of the genitals, it is effective.

As a general tonic in convalescence from acute diseases it is of much value, and in the maladies

associated with mental depression it is of use, probably through a general influence, and not a special effect, of the brain.

There is no better medicinal means of combating conditions of collapse and shock than the hypodermic injection of strychnine, and it is given with good effect in full doses as a preventive of shock before surgical operations.

In the recent experiment of Crile on animals, in which varying degrees of shock were produced, strychnine caused a rise of blood pressure proportionate to the degree of shock. On repeating the injections, if the shock were deep, frequently no rise occurred. In the cases in which the shock was nearly to the fatal degree, only a slight rise occurred, and lasted but a few minutes, after which no amount of strychnine produced a rise.

In cases of collapse, in which, unlike those of shock, the vasomotor centre was not exhausted, as from excessive hæmorrhage, or asphyxia, in which the blood pressure had fallen to the level of the final breakdown from excessive doses of strychnine, therapeutic doses caused a marked rise in blood pressure.

The preparations of nux vomica may be prescribed without any special pharmaceutical precautions, but, in prescribing the salts of strychnine in solution, great care is required that nothing should be added that will precipitate the alkaloid, and thus cause a danger of a poisonous quantity

being taken in one of the later doses of the mixture. Alkalies and carbonates must not be used for this reason; tannic acid precipitates an insoluble tannate, and bromides, iodides and chlorides form insoluble salts. Potassium bromide and strychnine are both pharmacologically and chemically antagonistic.

The bromides form with strychnine a bromide of strychnine, which is insoluble, and if given in a mixture gradually sinks to the bottom of the bottle in the form of fine crystals; the last dose, for the most part, contains the whole of the strychnine, and many cases of poisoning have occurred from want of knowledge of this fact.

THE PHARMACOLOGICAL ACTION OF BERBERINE.

BERBERINE was first obtained from the bark of the *Xanthoxylum clava Herculis*, by Chevallier and Pelletan in 1826, and named by them "xantho-picrit". Büchner, in 1835, isolated from the root of the berberis vulgaris an alkaloid, to which he gave the name berberine, and Perrins, in 1862, showed that these two substances were identical. Since then it has been found in calumba root, in the rhizome of podophyllum peltatum, in hydrastis canadensis, and in a number of other plants belonging to different natural orders.

When pure, it occurs in yellow acicular or prismatic crystals, having a bitter taste and neutral reaction, readily soluble in boiling water, very slightly so in cold water. Its salts are also yellow in colour, and very insoluble in cold water.

Previous researches have shown that one-half to one grain, administered hypodermically to rabbits caused death after some hours, with muscular tremors, paresis, especially marked in the hind limbs, and great embarrassment of respiration.

The alimentary canal was not affected when the substance was given subcutaneously.

In dogs, berberine, by mouth, produced symptoms of severe gastro-intestinal irritation, abundant watery and mucous diarrhœa, marked salivation, general muscular tremors and paresis. The respiration was not markedly affected.

After death, the spleen was found to be much contracted, as was also the whole intestine; the abdominal organs generally were much congested, and the heart was contracted. Cursi pointed out in an elaborate series of observations that locally its action was irritating, and that it readily causes chronic inflammatory thickening.

According to my observations, berberine exerts a very decided action on the alimentary tract when given by the mouth, but when given hypodermically, so much irritation is caused locally and such large quantities of fluid are required to dissolve it, that the slowness of its absorption renders its action uncertain. In rabbits and dogs, the first manifestations after medium doses are profuse salivation with loose motions, followed by severe watery diarrhœa and colic; great thirst and muscular tremors also occur.

After death from an overdose the intestines are found much contracted, generally empty, or containing an abundance of mucus and watery fluid, the mucous membrane being much inflamed.

There does not appear to be any direct action on the liver, as there is no increase in the quantity

of bile produced, but the gall-bladder is usually found contracted.

When applied to the heart of a pithed frog *in situ*, the effect is not very marked. A solution of one in four hundred produces a slight slowing, the systole being prolonged, and the diastole apparently less complete; with stronger solutions arrest occurs in systole.

Observations made on the detached heart with Williams' apparatus show that one part of berberine in five thousand parts of circulating fluid slows the heart and strengthens its contractions, the rhythm remaining regular, and the general character of the beat being unaltered. The blood pressure is a little increased, or may be unaltered.

Larger doses (one in two thousand five hundred) slow the beat very considerably, the systole becoming more prolonged and the diastole less complete. The pressure may be increased at first, but symptoms of cardiac failure soon begin to appear, with irregularity of action and a rapidly falling pressure until death occurs with the heart in systole.

The action of the heart of warm-blooded animals appears to be similar to that just described in the case of the frog. Intravenous injection of 0·025 to 0·03 grammes in cats, dogs and rabbits causes an immediate and rapid fall in blood pressure, with great slowing and more or less irregularity of action. These effects, however,

are transient, and the pressure soon returns to normal, and then rises to somewhat above it.

During the period when the blood pressure is rising, irregularity of the heart's action, if it has not previously occurred, is more or less pronounced, and though lasting only a few seconds at a time, recurs at intervals. This effect, however, seems to be due rather to stimulation of the cardio-inhibitory centre in the medulla than to any direct action on the heart itself, since the irregularity never occurs if both vagi be divided. The rise of blood pressure which succeeds the primary fall is apparently due to the vaso-motor centre being thrown into action and causing a constriction of the peripheral arterioles throughout the body. It does not occur if the spinal cord be divided high up in the neck, the scarcely appreciable rise which then takes place being explained by the contraction of those vessels of the head and neck, the connection of which with the centre in the medulla are still left unsevered. In this series of experiments the heart was found to have stopped in systole, although Guenste and Falck state that in rabbits they generally found it dilated and engorged. The left ventricle is always contracted and empty, but a small amount of blood may be found in the right side of the heart.

These conclusions are founded on a considerable number of experiments, spread over a long period, illustrated by many hundreds of tracings.

This evidence in full it is impossible to adduce in the course of this short paper, but I will mention one or two observations which may be regarded as typical.

Experiment XXVI.—The subject was a dog, weighing twelve pounds. Morphine and ether were used as anæsthetics, and the experiment was painless. The injections of the drug were thrown into the external jugular vein. The blood pressure was recorded in the left carotid. Cannulæ were placed in both ureters and the urine was measured as collected in c.c. measures. Sugar was found to be present in the urine, probably due to the morphine. The following table gives an abstract of these observations :—

Time.	Blood Pressure. m.m.	Urine.	Remarks.
		c.c.	
1.15-1.30	148-150	9·95	Cannulæ in each ureter.
1.30-1.45	146-148	7·95	Trace No. 1.
1.45-2.00	146-148	6·5	No. 2.
2.00-2.15	160-170	5·0	Trace No. 3.
2.15-2.30	145-155	3·6	No. 4.
2.30-2.45	128-140	2·95	No. 5.
2·50 intravenous injection of 30 m. of ¼ per cent. solution of berberine.			
2.45-3.00	95-150	1·8	Nos. 6 and 7.
3.5 injection of 30 m. of berberine.			
3.00-3.15	105-158	4·75	Nos. 8 and 9.
3.15-3.30	120-145	5·4	No. 10.
3.35 injection of 30 m. of berberine.			
3.30-3.45	88-152	3·4	Nos. 11 and 12.
3.50 injection of 30 m. of berberine.			
3.45-4.00	80-150	3·45	Nos. 13 and 14.
4.00-4.15	130-136	3·55	No. 15.
4.25 injection of 30 m. of berberine.			
4·15-4.45	90-144	4·35 in half an hour.	Nos. 16 and 17.
4.50 injection of 30 m. of berberine.			
4.45-5.00	90-135	2·7	Nos. 18 and 19.
5.00-5.15	110-125	2·0	No. 20.
5·15-5.30	125-138	2·3	Nos. 21 and 22.
5.35 experiment stopped.			

The experiment is illustrated by the following tracing, which shows the influence on blood-pressure of an injection of thirty minims of a one-fourth per cent. solution of berberine. For convenience of reproduction the chart has been divided; but A and B are continuous.

This chart is perfectly easy to understand, and is a portion of trace No. 9, referred to in the table.

The top line shows the blood-pressure. The second line is the dose or injection line, the rise showing when the drug was administered. The third line is the time line. The bottom line is the abscissa. The effect of the drug is apparent, for there is a well-marked fall in the blood-pressure.

Experiment XXIX. was made to test the influence of the drug on respiration. The following table gives the details:—

Time.	Blood Pressure. m.m.	Heart.	Resp.	Remarks.
3.49′ 30″-40″	112-118	15	4	
49′ 50″	110-118	15	4	
3·50′ 00″	110-118	15	4	Injection of 10 m. of berberine ¼ per cent. sol. into vein. Lasted over 27 seconds.
50′ 10″	110-116	15	4	
50′ 20″	104-110	16	4	
50′ 30″	90-104	17	4·5	
50′ 40″	90-96	17	5	
50′ 50″	90-100	19	4·5	
3.51′ 00″	92-106	18	4·5	
51′ 10″	92-110	17	4	
51′ 20″	96-114	16	4	
51′ 30″	98-116	17	4	
51′ 40″	108-112	16	4	
51′ 50″	106-110	15	4	
3.52′ 00″	110-116	16	3·5	
52′ 10″	108-114	15	4	
52′ 20″	110-116	15	3·5	
52′ 30″	98-118	16	4	
52′ 40″	110-118	16	4	
52′ 50″	110-118	16	4	
3.53′ 00″	110-118	16	4	

Berberine does not exert any marked effect upon the respiratory system, excepting in the case of rabbits, which appear to be especially susceptible. In them, small doses injected into a vein cause a gentle excitement of the centre in the medulla, and this increase in its activity manifests itself by the respiratory movements becoming quickened. Large doses cause respiratory embarrassment to a very considerable extent, great irregularity, occurring not only in the frequency, but also in the fulness, of the inspiratory efforts. The serious cardiac and vaso-motor disturbances, already alluded to as being produced by the exhibition of this drug in large doses, render it impossible to recognise how much of the respiratory embarrassment may be due to a direct action on the centre in the brain alone, or to the vascular disturbance.

That the action is directed rather upon the medulla than upon the terminations of the vagi in the lungs is readily recognised, since the influence upon the respiratory functions is still well marked, even after both vagi have been divided.

The methods employed to appreciate any special action that this drug might exert upon the function of the kidneys were the following :—

I. To collect and measure the quantity of urine secreted by the kidneys for several hours previous to the exhibition of the drug, and then to observe the alterations in the quantity of urine eliminated

during and after the intravenous injection of different solutions of berberine. This was readily ascertained by placing a cannula in both of the ureters and collecting the urine as it was secreted, this method being much more reliable than that of emptying the bladder at stated times, as it is always difficult to insure complete evacuation of its contents in living animals.

II. To record by means of the oncometer any alterations in the volume of the organ, collecting and measuring the urine at the same time.

The influence berberine exerts upon the urinary flow does not appear to be a very pronounced one. It does, however, cause a slight increase in the quantity of urine eliminated, even after the injection of small quantities of solutions into the venous circulation, quantities not sufficiently large in themselves to cause any increase in the urinary flow apart from the action of the drug. By studying the condition of the organ by means of the oncometer, and at the same time collecting the urine secreted, the conclusion was come to that the increased diuresis is dependent rather upon the elevation of the blood pressure brought about by the drug than by any direct stimulation of the renal cells themselves.

The volume of the organ as registered by the oncograph is found to follow closely the variations in the blood pressure. After intravenous injection, when the blood pressure falls, the kidney

contracts and becomes smaller; at the same time there is diminution in the urinary flow, and when the pressure gradually again returns to and rises above the normal, the volume of the kidney increases to a greater size than previously.

Although the diminution in bulk is synchronous with the lowering of the blood pressure, the subsequent increase does not precisely correspond in point of time with the rising pressure, but rather is a little delayed, and is prolonged over a longer period.

The period of greatest activity of the kidney is during the state of full distention; the urine may then flow sometimes twice as fast as prior to the injection. By repeating small doses with sufficient frequency, a state of almost constant contraction of the organ may be brought about, and thus a diminution in the urinary flow.

Berberine cannot, therefore, be said to have any marked action upon the kidneys themselves, as a diuretic, though it undoubtedly does cause, under ordinary conditions, an increase of the urinary eliminative processes.

As has already been stated, after death the spleen is found to be contracted, but if the organ be studied during life with the oncometer, it is seen that this organ follows much the same course as the kidney, diminishing in size with the fall in pressure and again expanding when the pressure has risen. This latter effect—expansion

—however, does not occur at the same time as the rise in pressure, but comes on gradually a little later, and, after a short duration, the organ again contracts to a little less in size than the volume previously occupied, and thus the spleen is a little smaller after each dose, until finally it becomes markedly contracted and will no longer respond except by a further contraction to the subsequent administration of the drug.

THUJA.

For many years I have employed thuja in the treatment of warts. By the term thuja I wish to indicate the fresh tops of *Thuja occidentalis*, the white cedar growing in the Northern United States of America. It contains pinicripin, a bitter, active principle, probably not an alkaloid, and thujin, a yellow colouring agent. Its most important constituent is a volatile oil allied in pharmacological action to savin, and known as thujetin.

Thuja is useful in all papillomatous conditions, and a wart is a papilloma of the skin, whether it be single or multiple, simple or branched, acuminated or flattened. My experience, lasting now over a considerable number of years, induces me to recommend it in the highest terms for the cure of warts with a narrow base and a pendulous body. They may occur upon any part, and have often a history which is hereditary. Many of them are removed by cleanliness, and the external application of nitrate of silver, glacial acetic acid, or the acid solution of nitrate of mercury, or by cutting off the growth with a pair of scissors, and dressing the part with an astringent lotion, but these remedies are far inferior to a strong tincture of

Thuja occidentalis, applied three times a day for a week or a fortnight.

Warty growths about the penis or the vagina are undoubtedly contagious, and are often syphilitic or gonorrhœal in origin. It is in this variety that the efficacy of mercurial lotions and ointments is the most marked.

For condylomata, calomel with astringents is a good dusting powder, but the acid nitrate lightly applied is still more effective; one application will sometimes destroy the growths where nitric acid alone and other caustics have failed.

For generalised syphilitic eruptions, especially those of papular character, baths of corrosive sublimate have been recommended by Baume, Trousseau and others, but the proportion of half an ounce to each bath I think too large; headache, drowsiness, and sometimes colic and diarrhœa are produced, and the skin is irritated by them.

The peculiar form of wart which is apt to appear on the hands of pathologists and others engaged in making post-mortem examinations is of quite a different character, and is due to cadaveric infection. I have a suspicion that they are often tuberculous in origin; they are best treated by a strong tincture of thuja.

In addition to warts about the genitals, only some of which are gonorrhœal in origin, crops of filiform warts sometimes appear on the scalp, about the skin of the neck, in the axilla, and even

on the eyelids. In these cases a wash or lotion of thuja is most useful, and often the warts fall off in two or three days after this application, leaving the base perfectly healed, although the strong tincture should be applied locally to such as are intractable.

Condylomata about the arms or pudenda of either sex—whether of a syphilitic character or otherwise—are rapidly cured by the application of the same tincture.

In addition to the local application, five drops of the tincture should be taken in a wineglass of water internally every night and morning.

Although the great and most useful sphere of action of thuja is in the treatment of warts and papillomatous growths, it is also valuable in rheumatic and arthritic pains, and in ulcerated surfaces, especially about the corona glandulis.

CURARE AND ITS ACTIONS.

CURARE or curara (woorara, wourali) is a poisonous compound prepared by certain savage tribes in South America. It was first brought into Europe from Guiana by Sir W. Raleigh, in 1595. There seem to be two kinds of it, one in calabashes, the other in clay vases, the latter being the stronger. Its exact constituents are not certain; but according to the researches of Planchon, they are different species of strychnos, mixed sometimes with cocculus, and, according to Claude Bernard, with Paullinia curara (Sapindaceæ). Preyer identified the last-named in one specimen. In the preparation described by Waterton, poisonous ants and serpent-venom were contained; but in that now imported there is probably no animal poison.

Curare, as seen in England, is a blackish-brown substance, of consistency varying from that of an extract to a resin: the taste is very bitter.

It is incompletely soluble in water, *i.e.*, the solution is brown and turbid, and when heated gives out an odour resembling that of chocolate. Concentrated sulphuric acid produces a red coloration, gradually becoming deeper, and with chromate of

potassium the same colour reactions as strychnine.

The physiological action is characteristic, and serves at once for the identification of this curious drug. If a drop of the solution be injected beneath the skin of a frog, the animal quickly becomes paralysed in all its voluntary muscles. The extract retains power for an indefinite period, but is weakened by moisture.

The activity of curare has been proved to depend upon the presence of the alkaloid curarine $C_{18}H_{35}N$, discovered by Roulin and Boussingault in 1830, and procured in well-defined crystals by Preyer in 1865. These crystals are four-sided, colourless prisms, of very bitter taste, and weak alkaline reaction. They readily attract moisture, are soluble in water and alcohol, but not in pure ether, sulphide of carbon, benzol, or turpentine.

There is also a crystalline alkaloid curine, $C_{18}H_{19}NO_3$.

As with serpent venom and some other poisons, absorption does not readily occur from the stomach, if the mucous membrane be sound; and hence a comparatively large dose may be given, and but little effect observed, since elimination by the kidneys is rapid, and almost as soon as the drug is taken up by the stomach it passes into the urine, and does not accumulate in the system. It is said that the South American Indians take it internally as a medicine if there be no abrasion of

the lips or mouth and that they habitually eat the flesh of animals killed by arrows poisoned with

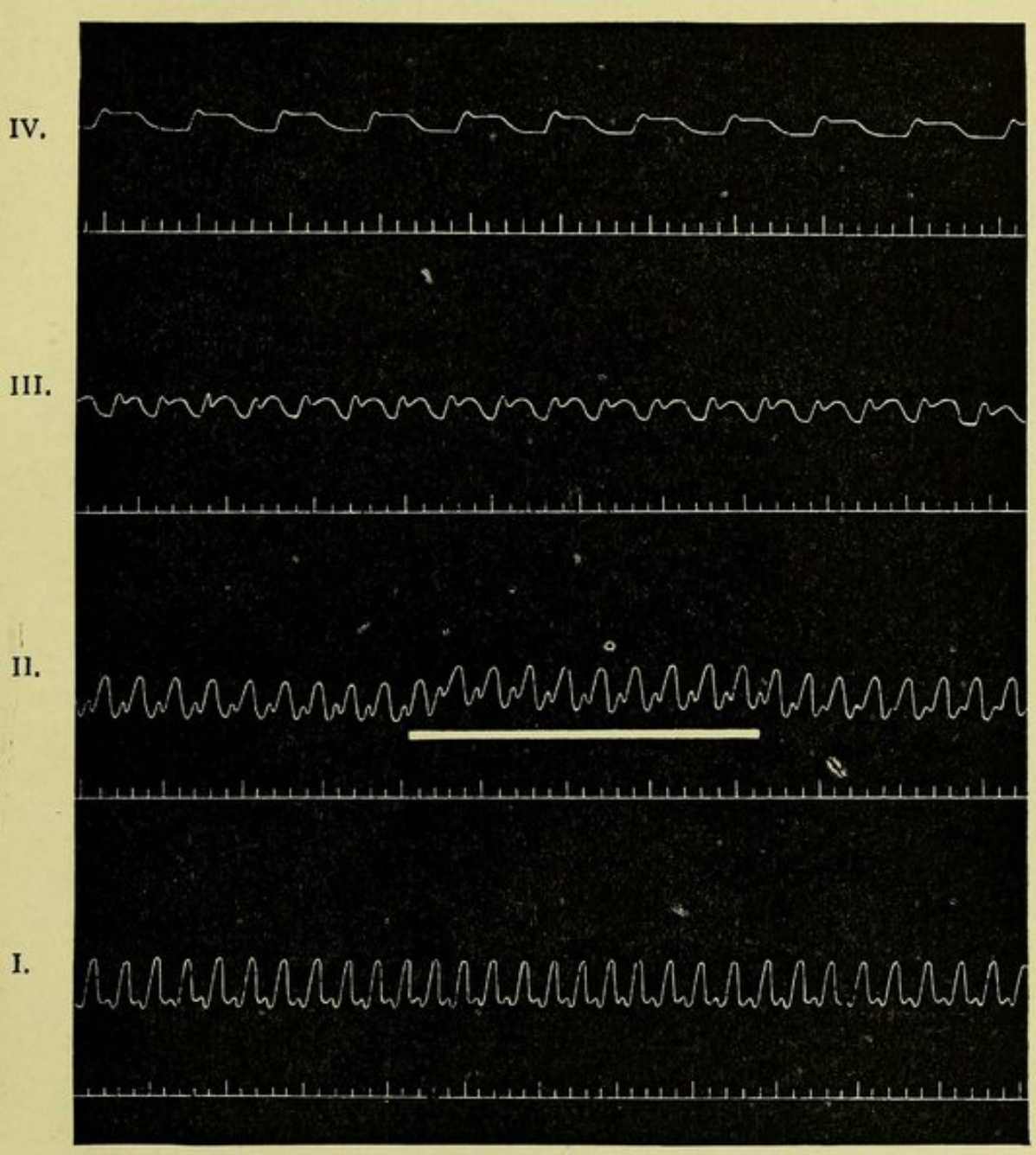

FIG. A.—Action of curare on frog's heart. I. Before the application of the drug. II. Stimulation of the vago-sympathetic after application of drug. III. and IV. Later effect of curare.

the drug. Bernard and Pelikan, however, have observed slow poisoning in animals after its administration by the mouth. Absorption per rectum

is also slow, and by the bladder it is almost *nil*; by the subcutaneous cellular tissue, or by the muscles, as in a wound, it is more rapid; by the lungs still more so, whilst by intravenous injection a smaller quantity develops its effect most quickly. That elimination takes place mainly by the kidneys, and that its rapidity prevents, to a great extent, poisoning by way of the stomach, is shown by the experiments of Bernard and of Hermann on rabbits and other animals; when they ligatured the renal arteries and then injected the poison into the stomach, toxic effects soon developed.

The same remarks apply to the alkaloid curarine. The fact of its elimination by the urine was distinctly shown by Voisin and Liouville, who injected the urine of curarised frogs into healthy frogs, producing the characteristic curarl effects; and the matter was carried still further by Bidder, who paralysed a third frog with urine taken from one that had itself been poisoned by the urine of the animal to which the original dose of curarine had been given. There is no reason, however, to think that the whole of the curarine is eliminated without change: for it is known to be easily acted on by ozone, which destroys its poisonous properties; and probably a certain amount of it always gets oxidised and destroyed in the body.

The special action of this drug is to paralyse the voluntary or striped muscular tissue, slight convulsive action sometimes preceding the paralysis.

Couty has reported, from small doses of some native preparations, more marked excitation—jumping, hyperæsthesia, choreic movements and spasms, distinguishable from those of strychnine and of asphyxia ; and concludes that curare is not destitute of convulsant action, and also that it has some effect on the central nervous system. The muscles of the limbs are first affected, and then the respiratory muscles, so that death threatens by asphyxia, and may be averted for some time at least by artificial respiration, the paralysis of the muscles continuing.

Hence it has become frequent in physiological experiment to "curarise" animals, and then keep them alive by artificial respiration, the limbs and trunk remaining motionless without forcible restraint ; one-thousandth grain is sufficient to place a frog *hors-de-combat* in about twenty minutes. Animals pierced with arrows poisoned by curare show no symptoms for two or three minutes, and then, if the quantity absorbed be sufficiently large, they soon die, without struggle or apparent pain, in a state of stupor or paralysis. The paralysis does not depend upon a lesion in the central nervous system whether of the brain or cord, neither is it in the nerve-trunks, for they are found to retain their function ; for instance, if a muscle—*e.g.*, a gastrocnemius in a frog—be isolated from its connections and left attached to the body only by its nerve (being thus prevented from any

direct contact with the poison injected into the body), galvanisation of the sciatic nerve will cause the usual contraction of this muscle—not of any other in the body, though, of course, the same nerve supplies many others. Again, if the two gastrocnemii, with their connected nerves, be detached from a frog's body, and the nerves of one specimen, but not the muscle, be immersed in a curare solution, these nerves will be found, on galvanic stimulation, to retain their conducting power; whilst, if the muscle of the other specimen be steeped in a solution (the central ends of the nerves being kept from contact with it), this specimen quickly loses all contractile power, the poison having directly affected the peripheral ends of the motor nerve or the muscular fibre or the cement substance at the junction of the nerve endings and the muscular fibres.

From many experiments it is concluded that the peripheral nerve ending and the muscular fibre are not directly affected, for it retains its irritability after the action of the poison; there are, in fact, various difficulties in precisely explaining the effect of the drug, but it is most probably exerted on the place of connection between the ultimate nerve-fibril and the muscular fasciculus, causing a kind of "functional solution of continuity" between the conductor and the tissue in relation with it.

The researches of Rouget point to a distinct

affection of the "plaque motrice terminale," some modified condition of tissue where the nerve and muscle join each other. It is not that the nerve-fibre becoming then destitute of "myeline," is more exposed to the poison than at other points of its course, because it is equally devoid of myeline at its origin in the brain, and yet is not there affected. The intellectual functions of the brain do not seem affected, but there is ground for believing that the stimulus of the will is less actively conducted than normally, though the mechanical stimulus of galvanism works as usual and the lethargic condition into which a frog falls almost immediately after the injection of curara and before reflex action is abolished has been held to indicate a cerebral effect.

Certain parts of the encephalon or of the nervous system are stimulated for a brief period—the pupils are moderately dilated, the secretions somewhat increased, and reflex power persists.

Sensory nerves retain their function almost unimpaired, and it is suggested by Vulpian, not that they are essentially different in structure from the motor nerves, but that their mode of connection with other organs may be different. Brunton and Binz have considered that a slight sensory impairment has resulted from the injection of curara.

The sympathetic system of nerves, though not paralysed, is impaired in power, for dilatation of

small vessels occurs, with lowering of arterial pressure and rise of surface-temperature: still, after section in the neck, the usual symptoms develop, *viz.*, narrowed pupil, retraction of the globe, lessened palpebral aperture, and congestion of conjunctiva; whilst on galvanising the upper end these conditions are reversed.

In explanation of the comparatively slight action on the sympathetic, it may be said that they do not join on to the smooth muscular fibre in precisely the same way as motor fibres join muscle.

The sympathetic fibres, the inhibitory nerves, the vaso-dilators, and the nerves of secretion preserve their functions, until at least the motor nerves are completely paralysed, *i.e.*, the full influence of the drug is exerted; but the resistance of all the nerves is only a question of degree, for direct injection of the drug into a neighbouring artery will overcome the normal action of any nerves.

Rhythmic movements—those of vegetative life, such as of the heart, the intestines, etc.—also continue under all but the fullest influence of curare, provided that sufficient aeration of the blood be kept up: the intestines, in fact, are more than usually sensitive to stimuli. Similarly the vasomotor centre becomes very sensitive to stimuli, so that slight stimulation of the skin may induce a great rise in blood pressure. It has recently

been stated that one variety of curare acts only on the smooth muscular fibres, and kills by lowering of arterial tension (Couty and De Superdat). The inhibitory nerves of the heart are notably more quickly paralysed in frogs than in mammalia.

The action on the heart, just referred to, is exerted through the nervous system. It is known, from experiments of Bernard and of Waller, that the motor fibres of the vagus, both to the heart and to the laryngeal muscles, are derived from the spinal accessory, and we know that galvanising the vagi will arrest the heart's action, *i.e.*, by stimulating the "inhibitory nerves". Now, under the moderate action of curare in the frog, and under its full toxic influence in mammalia, this arrest-action under galvanism does not take place —*i.e.*, the inhibitory nerves are paralysed (though inhibition may still be produced by stimulating the junction of the auricle and sinus in frogs—a point of difference from atropine). Similarly the arrest-action of digitalis does not occur, but the slowing-action of muscarin or jaborandi is not interfered with. Curare itself does not, as a rule, arrest the heart, but somewhat weakens its pulsations; under certain conditions, however, of physiological experiment it can be shown, in full doses, to have a paralysing action upon it.

The weakening is partly dependent on dilatation of peripheral vessels, which is very marked, and is the cause of less blood reaching the heart-

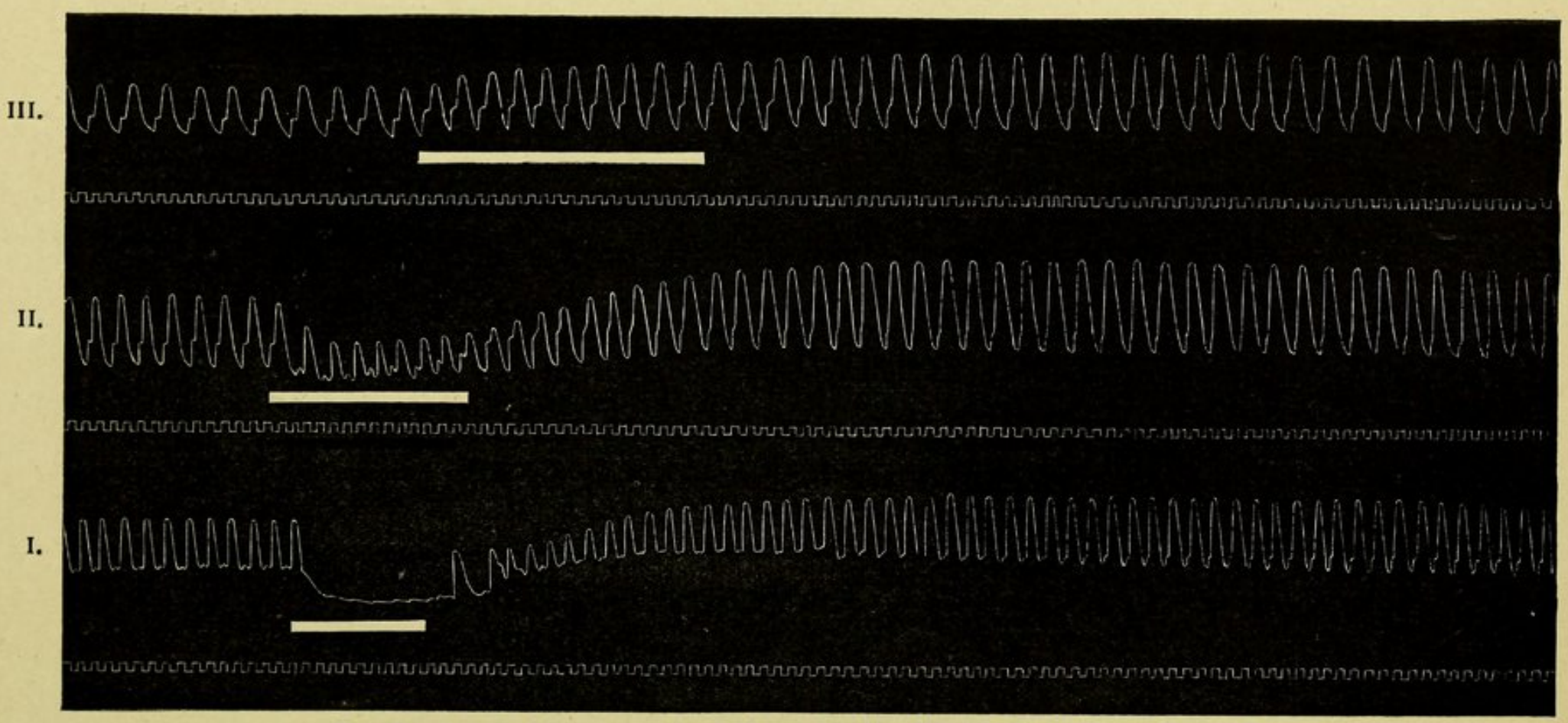

FIG. B.—Action of curare on frog's heart. I. Heart treated with curare ninety seconds before stimulation of vago-sympathetic. II. Stimulation after further application of the drug. III. After prolonged action.

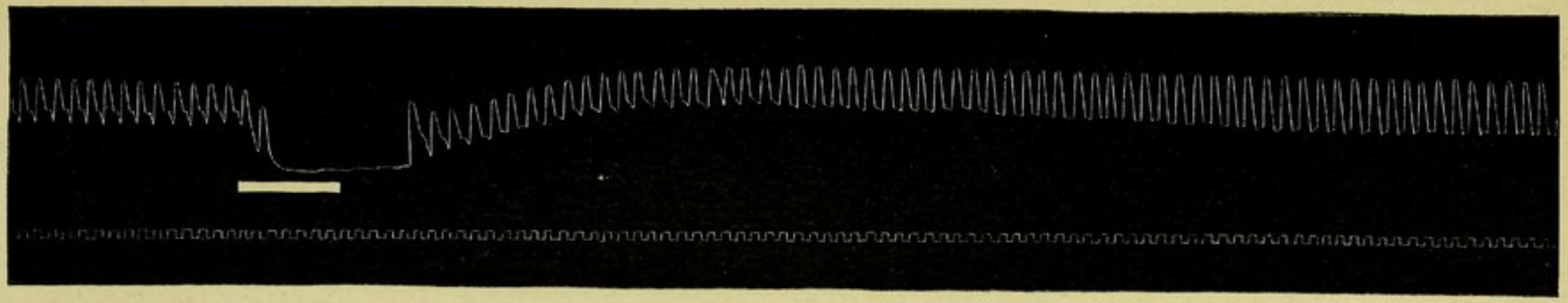

FIG. C.—Frog's heart. Showing result of stimulation of vago-sympathetic without application of any drug. Time marked in seconds.

cavities for them to contract upon: reddening of the extremities, the face, the eyes, and ears is evident, and is accompanied with marked increase of temperature there. The pulse, though weakened, is quickened, and so also is respiration. Distinct pyrexial phenomena, with chills, were developed in some epileptics under full doses of the drug; and it generally raised the temperature three or four degrees. According to Vulpian's observations on animals, the rise is temporary and superficial, and the internal temperature is soon markedly lowered, probably, as he suggests, from rapid loss of caloric by the surface.

It has already been stated that secretion is not arrested by less than fatal doses of curare; but a remarkable change occurs in the composition of the urine, an artificial glycosuria being set up. This occurred both in animals under experiment and in the epileptic patients referred to, *i.e.*, under full medicinal doses. It is presumably connected with alterations of the capillary circulation through the liver—from vaso-motor paralysis. In frogs, when the bladder became enormously distended with urine under curare (due to paralysis), Vulpian noted the occurrence of much oxalate of lime. Sometimes an excess of secretion, especially of the salivary glands, is set up by the administration of curare.

Conium exerts a similar effect in destroying the conduction of efferent impulses to muscles, their

physiological functions proper remaining intact. Vulpian finds, in the frog at least, the same condition produced in certain stages of poisoning by strychnine, brucine, atropine, hyoscyamine, nicotine, aconitine, Calabar bean, thebaine, even by bromide of potassium, sulphate of magnesium, and other salts, as well as by the ethyl and methyl derivatives of most of the toxic alkaloids: this does not, of course, mean that the totality of symptoms produced is the same as with curare. Schulz, however, finds a close parallelism in the action of hydrobromate of coniine.

Salt, the halogens, and carbolic acid have been named, and have some influence in lessening or preventing toxic effects without being truly antidotal. More value has been ascribed to strychnine; or, rather, curare has been held to be directly opposed in action to that drug. From one point of view it might seem truly so, since the latter often kills by tetanic spasm of respiratory muscles which the former can paralyse, but practically it is extremely difficult to gauge the suitable dose; if a little too much be given, the curare itself arrests the breathing, especially in the human subject when artificial respiration cannot well be set up: small doses only mask the symptoms of strychnine, which cease for a time,—to recur when the curare is eliminated. There is no true antagonism, since curare affects the motor nerve-ends, and strychnine the central nuclei. It has been said that bromine

and chlorine mixed with curara *in vitro* antagonise its effect.

Although extremely interesting to, and closely studied by, the physiologist, curare has not yet proved itself very serviceable to practical physicians.

In tetanus much was at first expected, and a certain amount of success was obtained from it: thus, of four Italian cases, three treated by hypodermic doses of one-sixth to one-half grain recovered after about five to twelve grains had been given, and another after sixty-four injections. Chassaignac treated a case, which set in severely a fortnight after a wound of the foot, with doses of one-half grain by the mouth, and a lotion of one-thousandth to one-five-hundredth; recovery took place, after one relapse, in sixteen days. Busch has recorded his experience of twenty-one cases treated in field hospitals during the war in Bohemia: fourteen were fatal; of the whole number eleven were treated by curare, and six recovered, hypodermic-morphine being also used freely in some. Demine, in the Italian war of 1859, saved eight out of twenty-two cases treated by curare: his total average mortality was over 90 per cent., so that the malady is essentially very fatal. Isolated successful cases have been reported by Vella and others, but, according to Vulpian, "success has been extremely rare, and in the majority of cases this remedy has neither prevented nor retarded

the fatal issue". Still, if it be argued that tetanus does sometimes recover untreated, and that many of the cases just referred to were instances of this, it must also be conceded that in very severe cases every remedy is futile, and to expect this to always succeed is unreasonable. Certain cases of tetanus will, it may be feared, always remain on the list of necessarily fatal maladies; the personal or inherited nervous constitution of the patients rendering them peculiarly easy victims to the kind of influence which sets up this disorder. It need be no serious discouragement to the use of curare that it has failed in such exceptionally severe and rapid cases as those recorded by Vulpian. Some other instances that have been cited against curare in tetanus are equally inconclusive: thus, a case in Professor Schuh's clinic was fatal, but it was one of extreme severity, as attested, not only by the rapid course, but by the unusual amount of structural lesion found in the cord; the curare, however, produced temporary amendment. Its effect on strychnine-tetanus has been already referred to. In epilepsy, Voisin and Liouville thought it exerted sometimes a favourable influence when pushed to physiological effects; they gave from one-seventh to two grains by injection, producing some palsy of the eye-muscles with ptosis and strabismus, pyrexia, and temporary glycosuria.

More general experience is, however, unfavour-

able to the drug, and Beigel especially has shown it to be ineffective.

In rabies it deserves further trial. It had already some reputation in this disorder when Waterton made a special expedition to Demerara in search of a larger and better supply. He watched its preparation, which he describes as from the "woorali vine, a bitter root, two bulbous plants, Indian pepper, two species of ants, and the fangs of two kinds of serpents". Professor Sewell strongly recommended its use, but the cases treated by it are not numerous enough for a definite judgment. In two that occurred at Milan, fifty-eight and a hundred and three days respectively after the bite, death was not prevented. Niemeyer was one of the first to use it, injecting five milligrammes (one-twenty-fifth grain), and then one centigramme (one-seventh grain), at intervals of three to four hours. Even these small quantities "seemed of temporary service, more so than large injections of morphine," and he strongly urged a trial of large doses.

In Watson's cases the bad symptoms subsided after the third injection; one-sixteenth, one-ninth, and one-sixth grain having been given. A girl bitten by the same dog, died of rabies; but the case recorded by Offenberg has attracted most attention: it was that of a woman aged twenty-four, cauterised with caustic soda three days after the bite, but developing hydrophobic symptoms

eighty days later. Morphine and chloroform failed to benefit, and one-third grain curare was injected three hours after the commencement of the attack. Fifteen minutes after, there being no evident effect, the dose was repeated; then the condition began to improve, the spasms becoming less and with longer intervals. Six injections followed at intervals of one or two hours, according to symptoms, the patient then being better, free from pain in the chest, and having ten minutes' rest between the spasms. After the seventh injection the spasms ceased, and some paralysis of voluntary muscles was evident—the eyelids could scarcely be raised, or the voice made audible; occasional slight arrest of respiration required some artificial movements: the dread of water and sensitiveness to light had now disappeared. Altogether nineteen centigrammes (nearly three grains) of the drug had been given in four and a half hours. One more injection was required in the next two days, and the patient gradually recovered by the eighth day.

In chorea, curare has been tried by many with different results; on the whole, nothing can be said to be definitely established in its favour.

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