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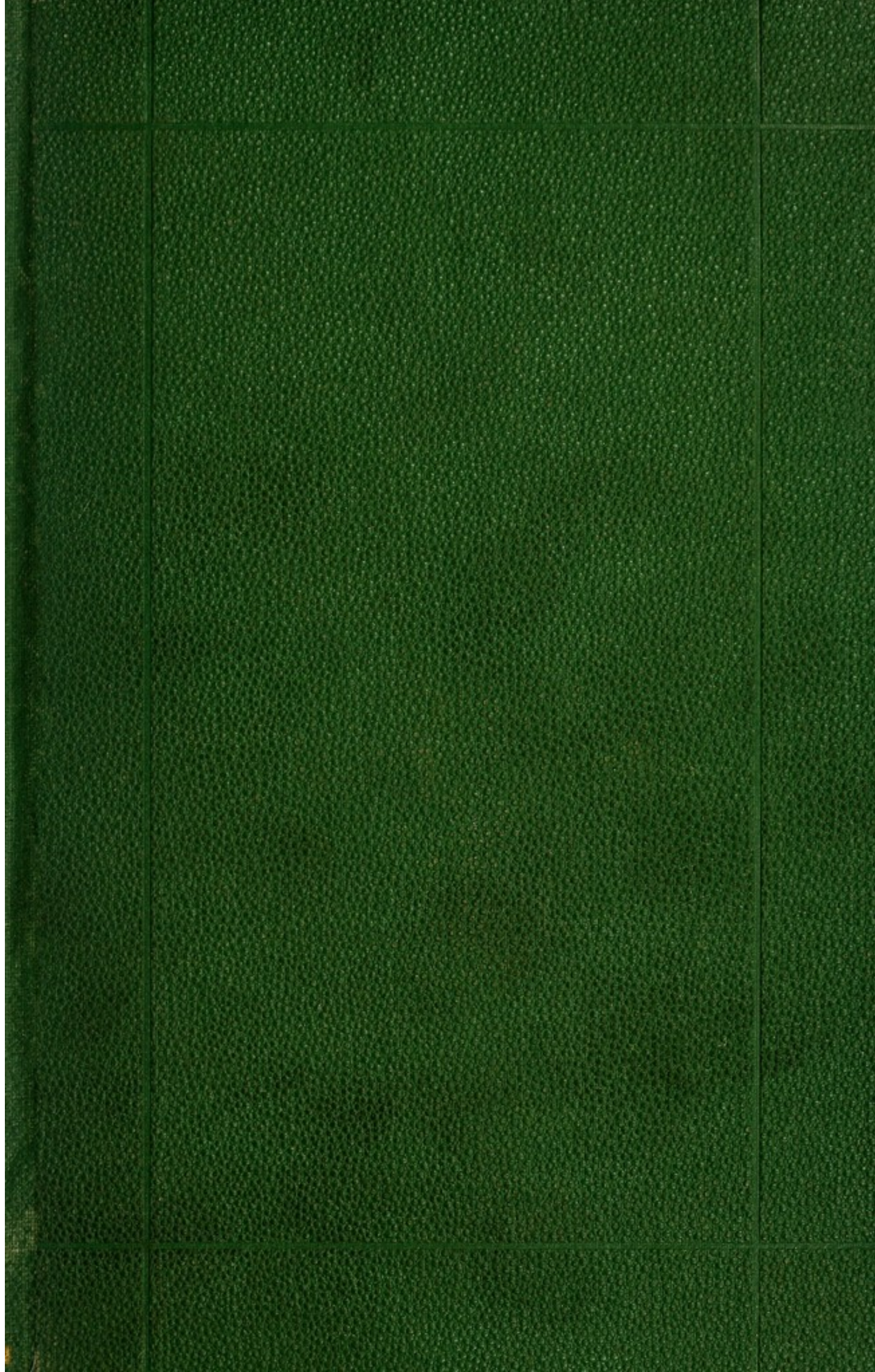
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PER AMPLIORA AD ALTIORA

Oliver Wendell Holmes.

My dear Doctor

Knowing that he who writes a book is in danger of killing himself, I have put into this little volume two or three of my lectures, so as to see what percentage of killing I shall get from it. Please accept a sample of the fatal shot - *lethalis arundo*. In me, *me ipsum arma fero*.

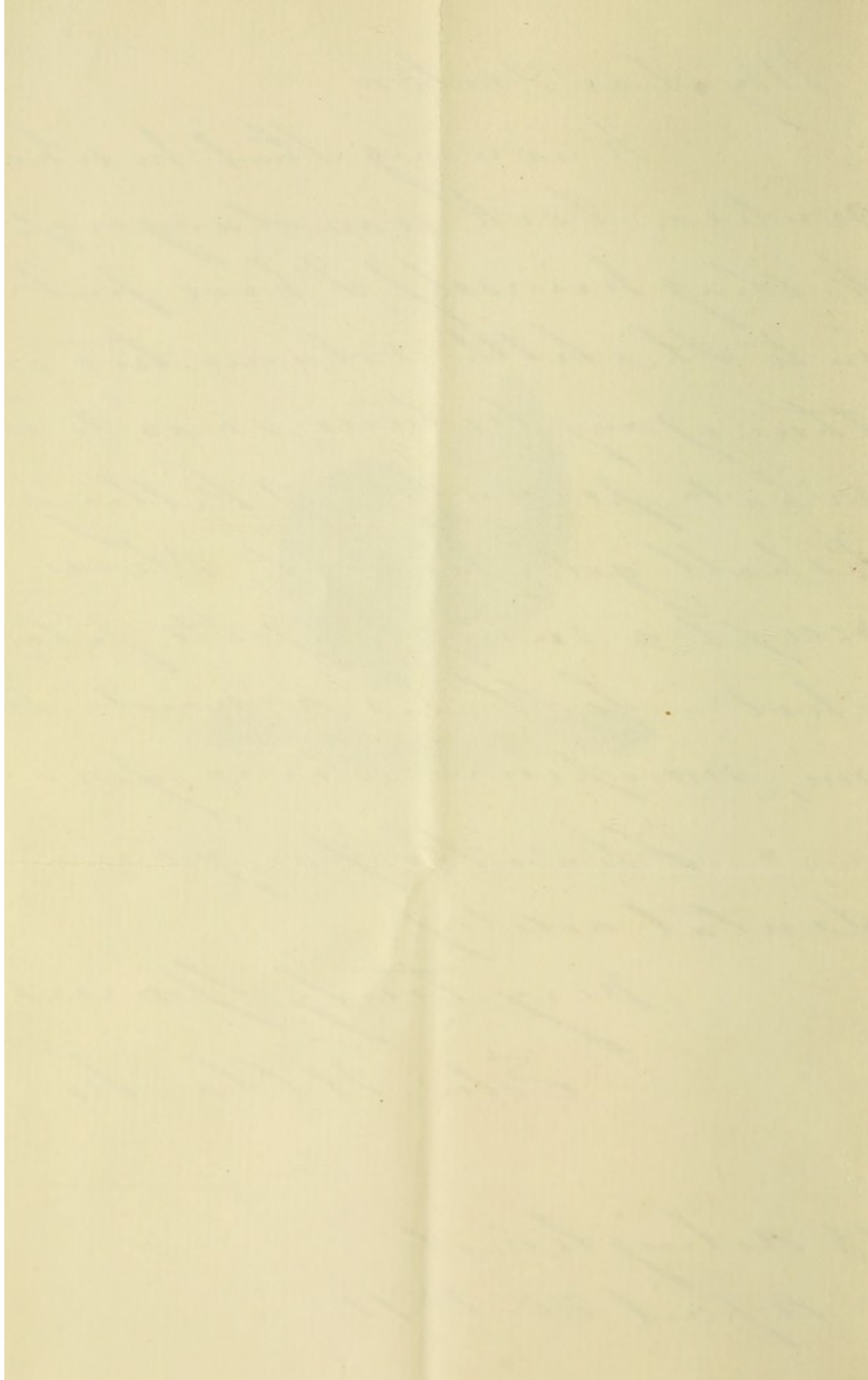
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Very truly Yours

Edw. H. Clarke

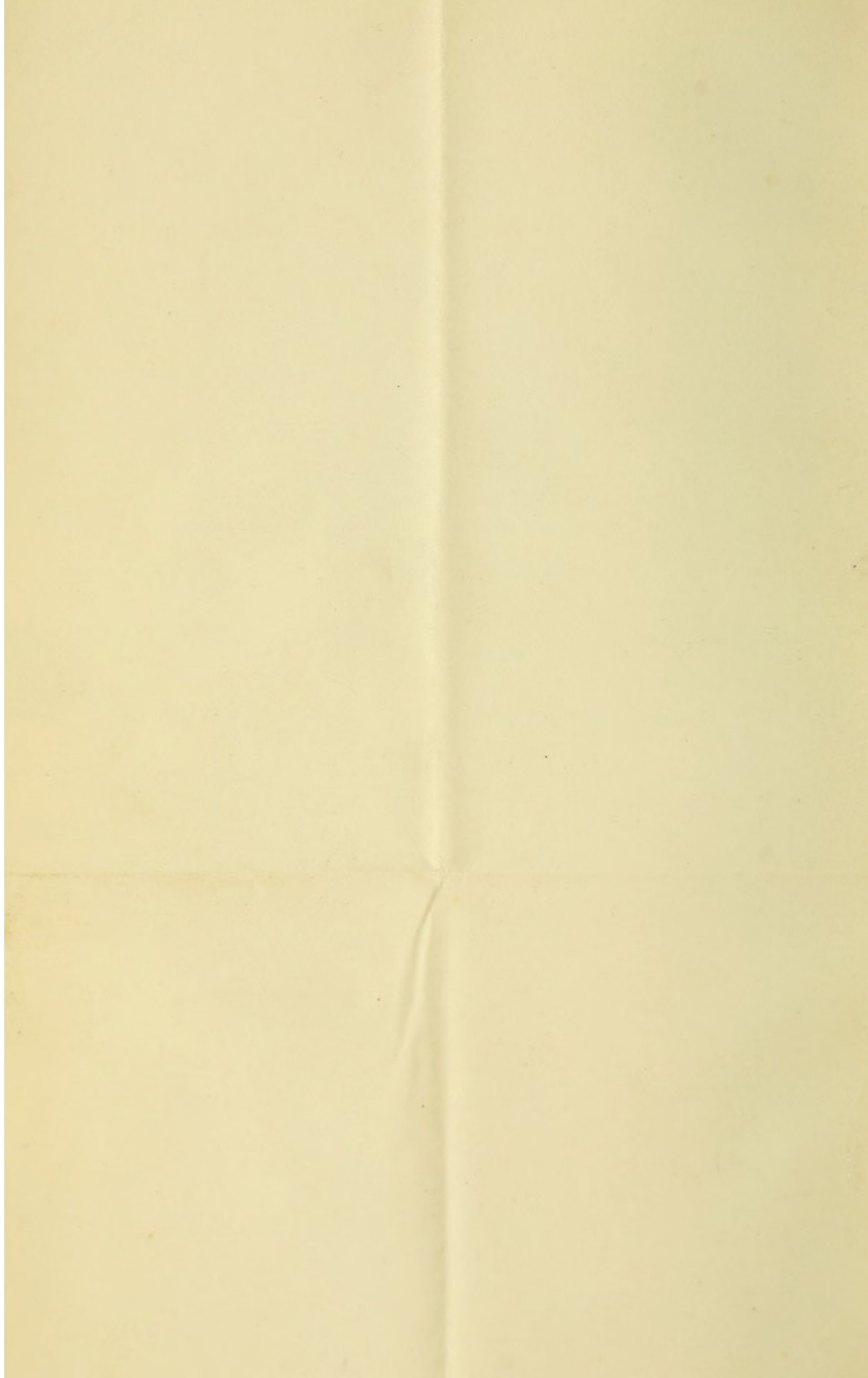
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Dr. O. W. Holmes

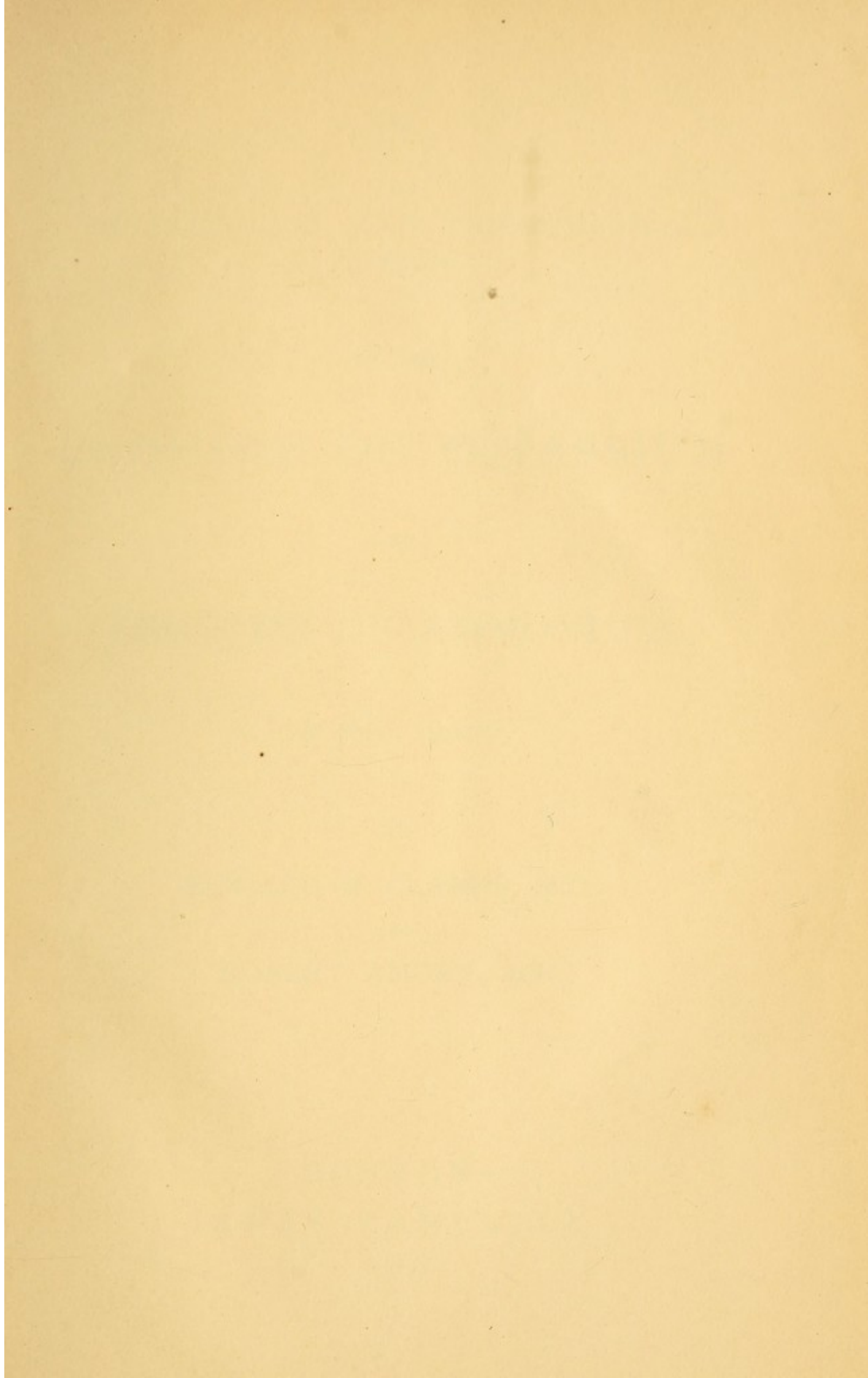
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regards of his friend
Edw. M. Clarke

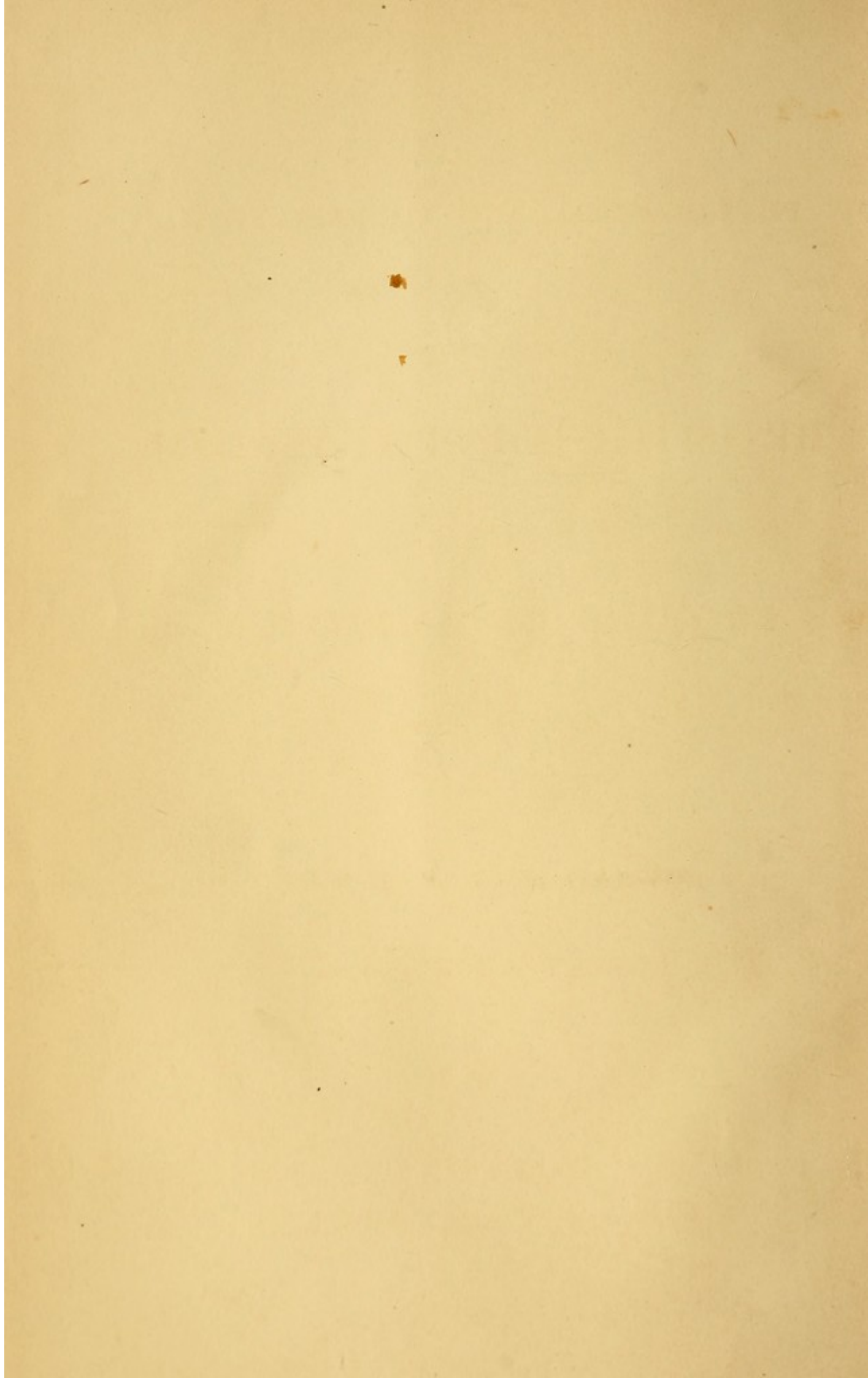
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THE
PHYSIOLOGICAL AND THERAPEUTICAL
ACTION
OF THE
BROMIDE OF POTASSIUM
AND
BROMIDE OF AMMONIUM.

IN TWO PARTS.

BY
EDWARD H. CLARKE, M.D.,
AND
ROBERT AMORY, M.D.

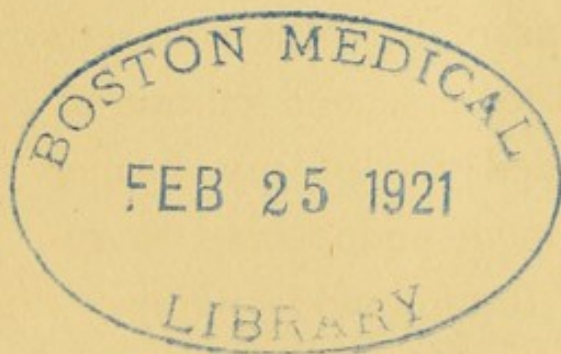
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P R E F A C E.

WHEN Dr. Amory, two or three years ago, commenced his study of the physiological action of the Bromide of Potassium, I promised to supplement his investigations by some account of its therapeutical use and value. Circumstances prevented the fulfilment of this promise at the time his paper appeared in the Transactions of the Massachusetts Medical Society. The call for a second edition of his monograph has reminded me of my former unavoidable neglect, and I have endeavored to repair it by the preparation of the following paper.

The number of essays that have latterly appeared, both in this country and Europe, from the pens of physiologists and practitioners, on the Bromide of Potassium and kindred salts, attests the important place which it holds in the present *Materia Medica*. This importance is my apology for burdening the medical public with an additional paper upon a

drug about which some may think too much has already been written. The honest observations of the humblest observer are not altogether valueless; and I am glad to contribute my mite towards an exact knowledge of the therapeutical applications and just value of so important an article as the Bromide of Potassium. The paper is not exhaustive. It is only a contribution.

BOSTON, 18 Arlington Street,
March, 1872.

CONTENTS.

Part I.

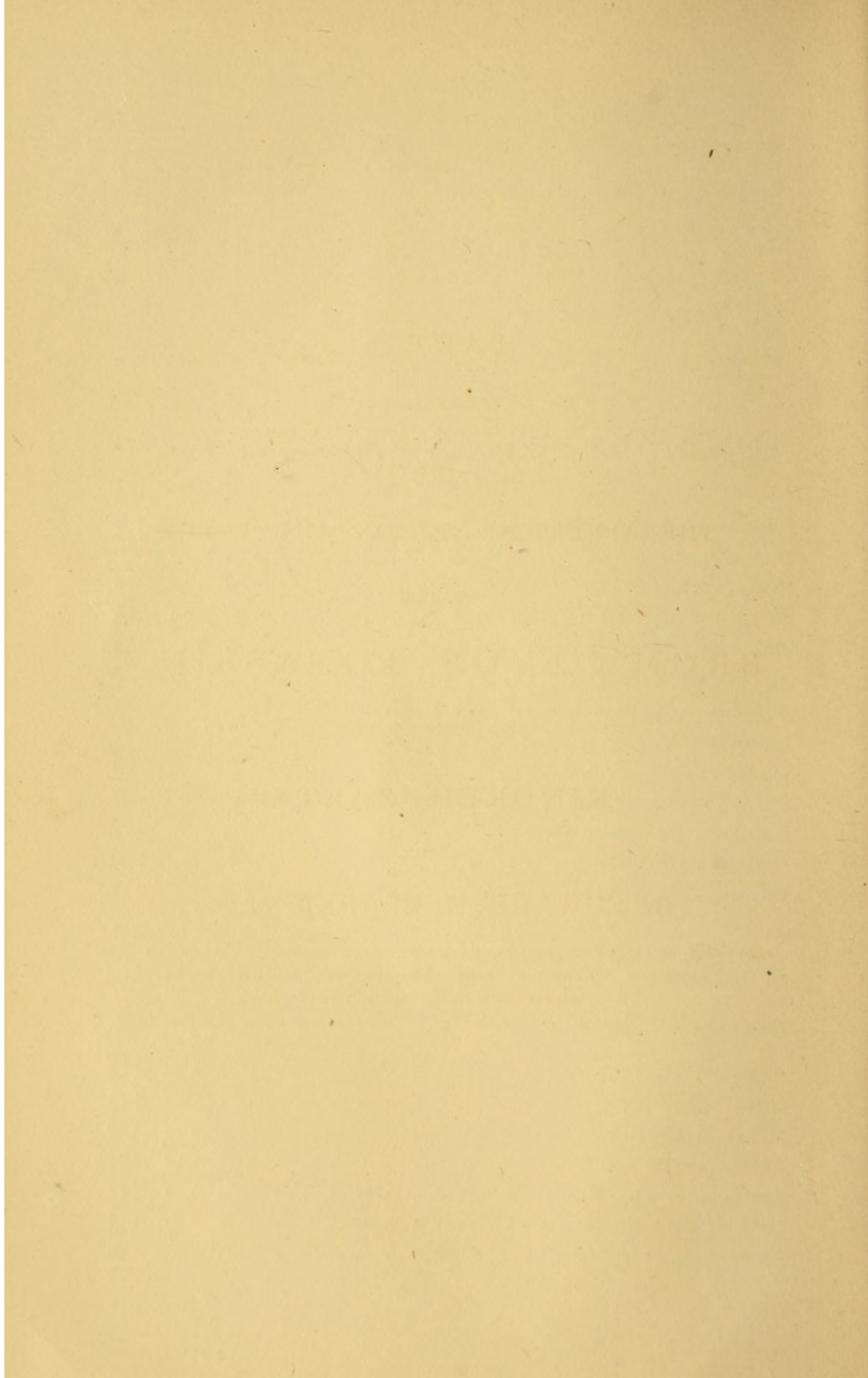
Therapeutical Action of Bromide of Potassium and Kindred Salts.

	PAGE
BROMIDE OF POTASSIUM	9
ABSORPTION	10
ELIMINATION	14
ACTION WHILE IN THE SYSTEM	17
THE CONTINUED DOSE	34
ACTION OF THE TOXIC DOSE	57
SPECIAL APPLICATIONS OF THE CONTINUED DOSE	64
EPILEPSY	82
HYSTERIA	92
ANTAGONISM OF BROMIDE OF POTASSIUM AND STRYCHNIA	97
BROMIDE OF AMMONIUM	102
BROMIDE OF LITHIUM	110
BROMIDE OF SODIUM	112

Part II.

Physiological Action of Bromides of Potassium and Ammonium.

ABSORPTION	115
CHEMICAL PROPERTIES	123
EFFECTS UPON THE SECRETIONS	130
ELIMINATION	134
EFFECT ON THE BLOOD-VESSELS	142
EFFECT ON THE NERVOUS SYSTEM	145
CONCLUSIONS	156



PART I.

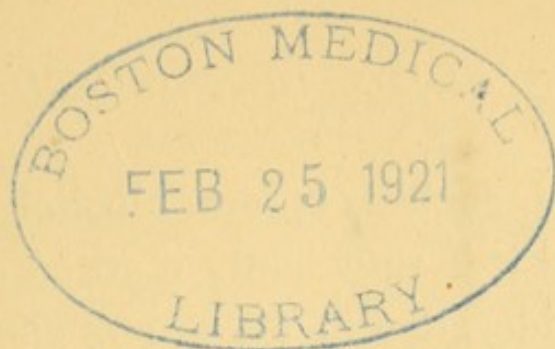
THE
THERAPEUTICAL ACTION AND VALUE
OF THE
BROMIDE OF POTASSIUM,
AND SOME OF ITS
KINDRED SALTS.

By EDWARD H. CLARKE, M.D.,

PROFESSOR OF MATERIA MEDICA IN HARVARD UNIVERSITY; FELLOW OF THE
AMERICAN ACADEMY OF ARTS AND SCIENCES; FELLOW OF THE
MASSACHUSETTS MEDICAL SOCIETY, ETC., ETC.

“EVEN at the present day, our Materia Medica is in a state of chaotic confusion; and its history is merely a summary of the fruitless efforts of thousands of gifted men, searching as it were in the dark for the curative power of drugs.”—JAMES ROGERS, M.D., *The Present State of Therapeutics*, p. 2.

“Our knowledge [of remedies], though augmented of late years by the wonderful advance of Organic Chemistry and Physiology, can scarcely yet be said to have passed the threshold of inquiry. We must avow that this whole department of medical knowledge, so important in all its bearings, is the one where most remains to be done to raise it to the character of a science. . . . Despite these difficulties, the scope and prospect of future attainment are ample and certain.”—SIR HENRY HOLLAND, *Medical Notes and Reflections*, pp. 21, 22.



BROMIDE OF POTASSIUM.

INTRODUCTION.

THE therapeutical value of the bromide of potassium rests solely upon clinical observation. The only safe guide to its administration as a therapeutic agent, however, is to be found in a correct knowledge of its physiological action. Hence the importance of studying and comprehending the latter, before endeavoring to ascertain the former. It is moreover important to recollect that the state or condition of the body in disease is not the same as its state or condition in health. Pathological states are different from physiological ones, and consequently modify, in a degree proportionate to this difference, the physiological action of all drugs. This pathological modification of physiological action is not so marked in the case of the bromide of potassium, bromide of ammonium, bromide of sodium, and bromide of lithium, as in that of many

other articles, such as opium, alcohol, digitalis, and the like; yet it is sufficiently marked to deserve the careful consideration of the practitioner.

Absorption.—It appears from the researches of Voisin, Laborde, Eulenberg, Damourette, and Pelvet, Saison, Zaepffel, Bowditch, and others, as well as from the experiments detailed in the second part of this monograph, that the bromide of potassium is easily and rapidly absorbed by any mucous surface, and especially by that of the stomach. When the stomach is healthy and empty, and when the bromide of potassium is largely diluted with water, the whole of a therapeutic dose passes into the circulation in a short time, probably in less than half an hour after it has been ingested.

If the above conditions do not exist or are modified, there is a corresponding interference with absorption. Thus if the mucous membrane of the stomach is irritated as in some dyspepsias, or inflamed as in gastritis, or degenerated as in organic disease, it absorbs the bromide with a certain degree of difficulty, and indeed under these circumstances may refuse to tolerate its presence at all, and so instead of absorbing it throw it off by vomiting. Hence these conditions generally contra-indicate the exhibition of the bromides. Mere vomiting, however, is no contra-indication. When vomiting is sympathetic, as in some diseases of the brain, or during pregnancy, or

after the inhalation of ether, or during sea-sickness and the like, the gastric mucous membrane appears to absorb the bromide of potassium as readily as in health.

When the stomach is empty and at rest, physiologists tell us that it is neutral ; and, when it contains food and is at work, that it is acid. Though the bromide of potassium is a fixed salt, it is disturbed by acids, and apt to be disturbed by the acids of the stomach. If such a disturbance takes place, free bromine is liberated, and gastric irritation and eructations are produced. In order to prevent this, in case there should happen to be acid in the stomach when the bromide is taken, some practitioners, imitating in this respect the bromidal prescriptions of the eminent Brown-Séguard, add an alkali, like carbonate of ammonia or carbonate of soda, to whatever solution of the bromide they prescribe. Whether this is done or not, it should not be forgotten that a stomach crowded with food may not only delay absorption, but decompose some of the bromide.

The bromide of potassium in powder, or in a concentrated solution, is a slight irritant. The mucous membrane does not like it in this shape ; and when the bromide is presented to the stomach in such a form, this organ is sometimes irritated by it, and sometimes throws it up, and at any rate delays the absorption of it for a time, in order to pour

out water with which to dissolve it or to dilute its solution.

These facts point out three obvious, practical, and important rules which should guide the exhibition of the bromide of potassium, bromide of sodium, bromide of ammonium, and the bromide of lithium, so far as their absorption by the stomach is concerned. 1. They should be freely diluted with water before they are swallowed. There should be at least a drachm of water to each grain of the salt. 2. They should be taken when the stomach is empty and practically free from acid. Their administration fifteen minutes before a meal, or three hours after one, secures this condition, and is therefore the best time for taking them. 3. They should be given with caution to the stomach, when there is gastric irritation or inflammation or degeneration.

Bromide of potassium is absorbed by the rectum less readily than by the stomach. Still it can be absorbed by the rectum; and consequently, in case of necessity, that organ may be used for the purpose of passing it into the blood. The rectal mucous membrane, unless inflamed or irritated, readily tolerates its presence, provided it is not injected in a warm or a concentrated solution. In the proportion of ten grains to an ounce of cool water, it is generally retained. A solution of greater strength than this is apt to be rejected. It is always well to put

the dose, which it is proposed to give per rectum, into as much cool water, or better still into cool water-gruel, as the rectum can comfortably hold. Two advantages are gained by this: first, more rapid absorption, because a dilute solution is more rapidly absorbed than a concentrated one; and, secondly, less danger of its rejection. The rectum does not fancy any more than the stomach an irritating solution.

The skin is practically useless as a surface for absorbing the bromide of potassium and similar salts. Unless the solution has a temperature below blood heat,—in fact, as appears from Dr. Amory's experiments, considerably below blood heat,—it refuses to absorb the salt from its solution at all. A general bath, of such a temperature, is sometimes employed as a therapeutic application, but could not be safely used for the purpose of introducing two or three times daily any drug into the blood.

The irritant qualities of a solution of the bromides also forbid their hypodermic use. A therapeutic dose of any of them, injected into the subcutaneous cellular tissue, is almost sure to produce inflammation, and sometimes suppuration.

Hence it appears that the stomach and the rectum are the only organs at the service of the physician for the absorption of the above salts. Fortunately these take them up, and pass them on so readily

that it is unnecessary to use the skin or the subcutaneous tissues for this purpose. Of these organs, the stomach is always to be preferred, when it is available. When it is not, the rectum should be resorted to.

Elimination. — The bromide of potassium and kindred bromides are eliminated moderately by the skin, chiefly by the kidneys, and scarcely at all by other organs. This bare statement, however, is of little value to the practitioner. Besides this, it is important for him to know how much of any given dose goes into the blood, how long it remains there, and how much of it and how rapidly it passes out. Without this knowledge, no correct notion can be formed of how constantly or how completely the blood and system of a patient can be kept charged with the drug.

The first point, or how much goes into the blood, depends, as we have already seen, only upon how much is given. Provided the conditions of absorption are observed, an indefinite quantity, more than should ever be given therapeutically, can be sent rapidly into the blood. I have known a person to drink a solution, containing several drachms of the salt, which the stomach evidently disposed of in a short time, without rejecting it.

Once in the blood, the bromide is of course carried throughout the organization by that fluid. But

it cannot get out as rapidly as it can enter. Elimination is not as rapid as absorption. Traces of it appear in the urine within ten minutes after it is swallowed;* and, although it is not wholly eliminated until several days after the last dose of it has been taken, yet the major part of any given dose is eliminated in less than twenty-four hours after its ingestion. Indeed, elimination is so active for the first eight or ten hours after ingestion, that the most of any dose leaves the blood during that time. Hence, any required amount may be kept in the blood by giving it so often and in such quantities as to make up for the loss occasioned by elimination.

This ratio of elimination to absorption should be kept constantly in mind by the practitioner. If it is desirable to keep the blood constantly charged with it, a dose should be administered three times during each twenty-four hours, and at nearly equidistant intervals. If the intervals are not equidistant, there is danger of having too small an amount in the blood during a portion of the day. This, in the treatment of certain diseases, — as we shall see by-and-by, and especially in the treatment of epilepsy, — deprives the patient of the continued therapeutic action of the remedy. A fit

* M. Rabuteau, Société de Biologie, July, 1868.

may occur just at the moment when a considerable portion of one dose has been eliminated and before another has been taken. Sometimes it is desirable that the system should be nearly free from the bromide during a portion of each day, and should be well charged with it during another portion. For this purpose, only one daily dose should be given. Sometimes a cumulative action is indicated. This is readily obtained by administering successive doses at short intervals, — an hour or so apart. In this way, it is made to enter more rapidly than it leaves the blood. The inflow is greater than the outgo: a constantly increasing charge is given.

ACTION WHILE IN THE SYSTEM.

The therapeutic action of the bromide of potassium varies so much with the dose, the manner of giving it, and the pathological state of the system, that it is well to consider each of these points separately.

The dose of it may be single or continued; and, whether single or continued, it may be excessive, and then its action ceases to be therapeutic and becomes toxic. Sometimes a dose, which in a physiological condition of the system would be toxic, becomes, in certain pathological states and owing to these states or conditions, only therapeutic. The reverse may occur. A dose that in the ordinary or physiological condition would be harmless or therapeutic becomes, in peculiar pathological conditions, harmful or toxic.

By the single dose is meant the giving of it only once in twenty-four hours, or two or three times in twenty-four hours, with short intervals between the doses. By the continued dose is meant the giving of it twice or oftener in the twenty-four hours, at equidistant intervals between the doses, and for several days, weeks, or months consecutively. The

excessive dose is either one that would be toxic in any condition of the system, or one that is ordinarily therapeutic, but in peculiar pathological conditions is toxic. These variations refer to the action of the bromide on adults. It is unnecessary to describe the influence of age upon the therapeutic action of the bromide of potassium, except to state in general terms that children and infants tolerate greater, and aged people less, proportionate doses than are usually given of most drugs.

Therapeutic Action of the Single (or Hypnotic) Dose. — A single dose of the bromide — that is, one given only once in the twenty-four hours — rarely exerts upon the adult a therapeutic action of any value, in a quantity less than twenty grains. Only those who are very susceptible to its influence — and there are some such persons — perceive any effect from a single dose of ten, or even from one of fifteen grains. The limits of the single therapeutic dose are from twenty to sixty grains, the average being thirty grains. Sometimes, though rarely, on account of the state of the stomach, as in the irritable stomach of pregnancy or of sea-sickness, it is wise to administer this dose in divided portions, giving a third or half of it, at intervals of ten or fifteen minutes.

Twenty or thirty grains produce, soon after they are ingested, a decided sedative action on the gen-

eral nervous system. There are mental and physical lassitude, indisposition to effort, and indifference to all slight causes of nervous irritation. The crying of children in the house, the rattling of carriages on the pavement, the irritation of worrying or anxious thoughts, all are disregarded. The sweet carelessness of doing nothing, the Neapolitan's *dolce far niente*, is almost realized after such a dose. This state is soon succeeded by drowsiness, and drowsiness by sleep.

"The hypnotic action," says Voisin,* referring to his patients in the Bicêtre, "was very remarkable upon them, both by day and night. Some were obliged to sleep for a few minutes at a time in the midst of their work. None, in spite of whatever efforts they made to the contrary, could resist sleep directly after their evening meal. During the night their sleep was calm, and in the morning it was difficult to arouse them."

In experimenting upon myself, I have found quite a difference both in the quantity and quality of the sleep following a single dose of the bromide of potassium, which evidently depended fully as much on the state of the system when the drug was taken as upon the dose. I have several times taken forty and fifty grains at night after a day of hard and

* Bulletin Général de Thérapeutique, Tome 71, p. 102, 1866.

exhausting work, and found that wakefulness, not sleep, was the result. But if sleep did not follow this dose, the general quietude and nervous sedation just described did. At other times, when simply wakeful in consequence of mental labor during the evening, but not exhausted, the same dose has produced quiet and profound sleep. At other times, when neither tired nor wakeful, a dose of thirty grains has only produced more profound slumber than usual. Whether the larger or the smaller dose was taken, and whether wakefulness or profound sleep followed, I could discern no disturbance during the morning or day after taking it, beyond a moderate increase of the urinary secretion.

The above results are the natural effect of the action of the bromide upon different conditions of the brain.

Dr. Hammond * has shown that "sleep is directly caused by the circulation of a less quantity of blood through the cerebral tissues than traverses them while we are awake." It is also true that the quantity of blood circulating through the brain may be diminished so much as to prevent sleep. Too much blood in the brain produces wakefulness; a proper diminution of that amount induces sleep. Too little

* Sleep and its Derangements, by William A. Hammond, M.D., p. 29.

blood in the brain, as in some anæmic conditions of that organ, or in excessive flowing, also produces wakefulness; and an increase of the circulation there is followed by sleep.

It appears, from the experiments of Brown-Sé-
quard * upon the effects of the bromide of potassium on the vasomotor nerves, that under its influence "the arterial vessels alike of the periphery and of the nervous centres undergo a manifest contraction; from whence there results a topical oligæmia of the encephalon and of the spinal cord, and a consequent diminution of the irritability of this organ." The experiments of Meuriot † upon the frog are to the same effect, as are also those of Dr. Amory described in another part of this monograph.

It is apparent, from these considerations, that the bromide of potassium, by contracting the arterioles of the brain and expelling temporarily a certain amount of blood from them, may produce wakefulness or sleep, according as the condition of the brain is one of hyperæmia or oligæmia. In the first experiment upon myself just detailed, the brain, like the rest of the system, was exhausted after work. It had become somewhat anæmic in consequence of the expenditure of force, by which nerve-tissue and

* Nouveau Dictionnaire de Médecine et de Chirurgie Pratique, art. Asthma, by G. Sée.

† L'Étude de la Belladonne, par le Dr. Meuriot, pp. 50, 51.

blood had been correlated into labor during the day. So much work had taken out of the organism so much blood and so many nerve-cells. A further oligæmia of the brain was produced by taking forty or fifty grains of the bromide of potassium. The cerebral circulation was reduced below the sleeping-point, and sleep did not come till the effect of the drug had passed off. As a matter of therapeutics rather than of physiological experiment, a cup of beef tea or a glass of wine, not fifty grains of the bromide, was the proper agent to have put the brain into the condition for sleep.

The second experiment on myself consisted in taking bromide of potassium at night when I was not physically exhausted, but only wakeful after mental labor. In order to understand the value of this experiment, it should be stated that two or three hours of hard study or engrossing mental labor in the evening will always, or nearly always, prevent my sleeping at all for the first few hours after retiring. This is so constantly the case that I am obliged to avoid such sort of work at that time. Forty grains of the bromide, taken on going to bed after this sort of work, will send me into the land of sleep directly. The fact is not difficult of explanation. The cerebral circulation having been increased by study, — *i.e.*, by intellection or cerebration, to use recent terms, — just as the vascular-

ity of the stomach is increased by digestion, the brain becomes temporarily incapable of sleep. By the physiological action of the bromide, the cerebral circulation is contracted and the brain made capable of sleep, sooner than it would become so without the aid of the drug. The third experiment, that of taking thirty grains of the bromide at night when neither the brain nor the system generally was unusually fatigued, simply shows (what has been so often observed) that such a dose, taken in the normal state of the system, does not interrupt sleep, but renders it more profound.

These apparently unimportant experiments illustrate some valuable points in the clinical administration of the bromide of potassium, especially when given in the single dose which we are now considering. Thirty to sixty grains exert a decided hypnotic action upon an adult in a physiological or normal condition, whether given by day or night, — an action consequent upon the diminished cerebral circulation which the drug induces. If the brain is already in an anæmic condition, it is not wise to deprive it still further of blood, by the exhibition of the bromide. If this is done, sleep may sometimes follow; but more commonly the result will be the opposite. Hence anæmic conditions of the brain contra-indicate, as a rule, the exhibition of the hypnotic dose. Clinically, I have found

this to be the case. The restless wakefulness which is so apt to follow excessive flooding is relieved by opium and alcohol, and aggravated by a full dose of the bromide. A combination of the latter, however, with a stimulant, such as a glass of wine or brandy, will sometimes in these cases produce a most satisfactory result. In the convalescence from typhoid fever, I have sometimes found the hypnotic dose to be followed by sleep, and about as often by the opposite. I suppose the difference may be explained by the varying vascularity of the brain in different patients, or in the same patient at different periods of convalescence.

The hypnotic action of the bromide of potassium, which is most apparent if given when the brain is not anæmic, — that is, when this organ is in a physiological condition, or when it is in a state of congestion or hyperæmia, — is of the highest value.

Dr. Hammond, in the work previously quoted, speaking of the treatment of wakefulness, says: *
"Among the more purely medicinal agents, bromide of potassium occupies the first place, and can almost always be used with advantage to diminish the amount of blood in the brain and to allay any excitement of the nervous system that may be present in the sthenic form of insomnia. That the first-

* *Op. cit.*, p. 283.

named of these effects follows its use, I have recently ascertained by experiments upon living animals, the details of which will be given at another time. Suffice it now to say, that I have administered it to dogs whose brains had been exposed to view by trephining the skull, and that I have invariably found it to lessen the quantity of blood circulating within the cranium, and to produce a shrinking of the brain from this cause. Moreover, we have only to observe its effects upon the human subject to be convinced that this is one of the most important results of its employment. The flushed face, the throbbing of the carotids and temporals, the suffusion of the eyes, the feeling of fulness in the head, all disappear as if by magic under its use."

Clinical observation confirms these teachings of physiological experiment. The bromide has been given as an hypnotic with excellent results in a large variety of complaints; or rather, I should say, in a large number of cases in which the condition just described has existed. In order to obtain satisfactory hypnotic results from the dose we are considering, the routine practice of prescribing for the name of a disease must be abandoned, and the condition of the brain, not the name of the malady, be kept in mind. For example, during the progress of an erysipelas, occurring in two indi-

viduals, it will often happen that a nightly dose of the bromide will be indicated in the case of one patient and contra-indicated in the other. In like manner it may be indicated or contra-indicated in the same individual at different stages of an illness, as in the instance of typhoid fever just referred to.

Insomnia, depending upon hyperæmia of the brain, which is what Dr. Hammond calls the sthenic form of insomnia, indicates the hypnotic dose of the bromide of potassium at any age, in either sex, and in any disease. It is perhaps needless to say that it will not *always* relieve the hyperæmic sleeplessness of every disease, in both sexes and at any age. Such unvarying action is not to be expected from this or any drug; but it will relieve this kind of insomnia so often and so satisfactorily, that it forms one of the most precious resources of the practitioner. When severe pain "murders sleep," a dose of thirty or forty grains will not often drive the assassin off, and procure the relief that opium gives.

So far as my own clinical observation extends, and I have used the bromide of potassium in quite a large number of cases for the past few years, I have found the cerebral — or, strictly speaking, the encephalic — condition that indicated the single hypnotic dose we are now considering, to occur most frequently as follows; viz., with the insomnia ac-

companied mental anxiety, excessive intellectual labor, hysteria, pregnancy, teething, the exanthemata, simple and typhoid fevers, erysipelas, rheumatism, and a sort of hyperæstheria which I know not how to describe by any other name than "general nervous irritability." These are not the only, or the most important affections in which the therapeutic action of the bromide of potassium and its congeners may be invoked. They are only those in which the single hypnotic dose has proved, in my experience, to be most frequently indicated and most efficacious. The frequent and the continued dose, which will be considered presently, meet a larger number of therapeutic indications than the single one.

Examples are better than abstract statements, and I will therefore venture to illustrate the above remarks by a few cases.

CASE I. *Insomnia following Mental Anxiety.*
—A merchant, just passing sixty years of age, was engaged, during the latter part of our late civil war, in important mercantile transactions, which placed and kept at risk large amounts of money. He lost and gained a great deal. At times, a large portion of his fortune was at risk. He naturally became uneasy and anxious. He always worked with friction. His temperament was nervous. He

could not leave his business at his counting-room, but carried it home with him. It followed him through the evening and into his bed-room, and little by little drove away his sleep. At first, he only lost an hour or so of his usual sleep; but gradually he slept less and less. He could not drive off at night the anxious speculations of the day. In other respects he was well. His color, flesh, appetite, strength, and general condition were excellent. After about three months of this sort of imperfect or half sleep, he asked my advice. It was useless to advise him not to be anxious: he knew and acknowledged the importance of this, and had tried to make his will keep his brain still at night, but unsuccessfully. He took thirty grains of the bromide of potassium on going to bed, with great but not complete relief at first. After a few nights, however, his sleep became natural. For a period of three or four months, he took either thirty or forty grains, nearly every night, on retiring. When he omitted it, he slept less well. At the end of this time, the causes of his anxiety ceased to operate, and he slept sufficiently without the drug. He experienced no disturbance from taking it; neither acne nor any apparent bromism. It is possible that, in this case, the bromide prevented serious trouble. There had been insanity in the patient's family, and the danger of the development of in-

sanity by prolonged sleeplessness is not a small one.

CASE II. *Insomnia following Mental Anxiety.* — A lady, past middle life, worn by nursing her husband, who was slowly wasting away with cirrhosis of the liver, and anxious with the knowledge of his inevitable fate, began first to sleep lightly, and then scarcely to sleep at all. Her appearance, while making my usual visits to her husband, at length attracted my notice. I found on inquiry, that, though well provided with hired nurses and night-watchers, she not only frequently left her bed at night, but slept very little while upon it at any time. In other respects, excepting an organic affection of the heart, of long standing, she was well. She took of the bromide of potassium a nightly dose varying from fifteen to thirty grains, according to circumstances which she soon learned to recognize, with the most satisfactory result. After taking it every night for two or three weeks, she re-acquired the habit of sleep, and then only took her hypnotic occasionally.

CASE III. *Insomnia accompanying Teething.* — A male child, of an irritable and nervous constitution, — which he came honestly by, for both his father and mother were of the neuralgic and fidgety sort, — was troubled through his whole first

dentition, from the cutting of the first incisor to that of the last molar tooth, by wakefulness to an extraordinary degree. He slept little himself, and permitted those who took charge of him to sleep less. Lancing his gums at appropriate times gave some relief, but not much. Various hypnotics — not including opium, however — were tried, none of which were of any service except the bromide of potassium and the hydrate of chloral. These were given alternately — that is, one of them for a week or two and then the other for a week or two — during the major part of his dentition, and with the desired result. It was found by experience that he required not less than ten, and generally as much as fifteen and sometimes twenty grains of the bromide to put him to sleep. His general health did not suffer from the treatment. On the contrary, when the anodynes were not given — and they were occasionally omitted — he not only did not sleep, but his general condition was unsatisfactory during the following day. At the close of dentition, he slept without artificial assistance.

When sleep is prevented by acute pain, the bromide of potassium is rarely of service as an hypnotic. It is not an anæsthetic, like opium. But when there has been acute pain, which has passed away and left the system racked, restless, and un-

able to sleep, the bromide is often an excellent sleep-compeller. In rheumatism, when the acute stage has passed and the muscles and joints are weary, partly from the disease and partly from protracted confinement in bed, the bromide is a better hypnotic than opium or narceine or hydrate of chloral. In the early stages of typhoid fever and erysipelas, I have frequently found the single hypnotic dose to be of great service.

As a preparation for the exhibition of opium, the bromide of potassium is sometimes of value. I have noticed that thirty grains of it, given an hour or two before the administration of a dose of opium, will enhance the anodyne influence of the latter. Individuals who do not tolerate opium well, who are excited and not soothed by legitimate doses of it, whose skins are made to itch or whose nervous systems are badly affected by it, can often be made not only to tolerate it, but to derive great benefit from it, provided the bromide of potassium is administered to them before they take the opiate. For this purpose, the dose should not be less than thirty grains; and sometimes forty or fifty grains are requisite. Dr. J. M. Da Costa, of Philadelphia, has noticed this corrective influence of the bromide of potassium over opium, and lately published several cases in illustration of it.* In order

* American Journal of the Medical Sciences, April, 1871, pp. 359-63.

to increase the hypnotic action of opium, the bromide should be given about an hour before opium is taken. In order to correct the unpleasant action of opium, it is better to follow Dr. Da Costa's method, and give the bromide some hours—three or four—before giving opium. The nausea, which so often annoys a patient perhaps for hours after the soporific effects of opium have passed off, may be relieved, or at least mitigated, by a dose of the bromide, taken as soon as nausea appears.

But it should be stated that bromide of potassium will not invariably prevent or correct the unpleasant action of opium. It is easy to conceive of conditions of the system in which the former, instead of correcting, would aggravate the disturbing action of the latter. In cerebral anæmia, for example, or after excessive loss of blood, it would be rational to expect that the soporific, though not the anæsthetic, action of opium would be lessened by the conjoint administration of bromide of potassium. Opium, in therapeutic doses and for a certain period after it is taken, produces hyperæmia of the brain, which gradually passes away into oligæmia, and sleep follows. Dr. Hammond* has demonstrated this by several ingenious experiments. The bromide, as we have previously seen, produces more or less cerebral oligæmia. If opium and the bromide of

* *Op. cit.*, p. 25 *et seq.*

potassium are simultaneously administered to a patient with an anæmic brain, it would naturally follow, after the primary stimulant action of opium has passed away, that the sedative action of the bromide would reinforce the secondary sedative action of the opium, and possibly lead to disagreeable results. At any rate, whatever may be the correct physiological explanation of the matter, we know from clinical observation that, while the bromide of potassium will often correct the unpleasant results of a dose of opium, it sometimes fails to do so; and sometimes, though rarely, leads to greater secondary depression after opium than if it had not been taken.

It appears from these observations that the single or hypnotic dose of the bromide of potassium, by which is meant one of not less than fifteen grains and not usually above forty, is indicated in any disease, when appropriate conditions of the nervous centres exist, to control insomnia, restlessness at night, general nervous irritability, or abnormal reflex excitability. The same dose is contra-indicated, whatever may be the disease, even when the same symptoms of insomnia, irritability, or hyperæstheria exist, provided the appropriate conditions of the nervous centres that have been referred to are not present. This is only another way of saying that, in prescribing the bromide of potassium, as

in the exhibition of all drugs, the condition of the patient, and not the name of a disease, must be prescribed for.

Depression, exhaustion, weakness, irritability, and the like, connected with or dependent upon oligæmia of the nervous centres, contra-indicate the single hypnotic dose. Increased depression and greater restlessness, instead of sleep and quiet, are apt to follow its administration when thus given.

THE CONTINUED DOSE.

Physiological Action. — It has already been stated that by the continued dose is meant the exhibition of the bromide of potassium two or more times in the twenty-four hours, with equidistant intervals between the doses. By this method of administration the blood is kept constantly charged with the drug. When only a single dose is given, or two or three doses are given so near together as to form substantially one dose, the major part of the salt is eliminated in the course of a few hours, and consequently the blood is practically free from it more than half the time. The difference between the single and the continued dose is the difference between keeping the blood constantly charged with bromide of potassium, and allowing the blood not only to free itself from one dose, before a second one is administered,

but making the interval between the doses so long, that the blood shall be practically a longer period uncharged than charged with the salt.

The observance of this difference is important physiologically and therapeutically. The neglect of it explains much of the confusion and discrepancy that may be found in the statements of different observers. Many of the phenomena, both physiological and toxicological, that follow the exhibition of the continued, do not follow that of the single dose. And, what is in fact a corollary from this, many therapeutical results may be obtained by the continued that cannot be got from the single dose. It is also to be remarked that, although few or no practitioners write as if they were aware of the important difference here referred to, yet the largest number of their observations evidently are founded on the action of the continued dose. Physiologists, on the contrary, seem to have experimented oftenest with the single dose. Their experiments with regard to the physiological action of the bromide upon the vasomotor nerves, the nerve centres, and the circulation, have been mostly made on animals to whom they have given a single dose, or at most two or three doses near together.

The daily amount of the continued dose varies from thirty to one hundred and twenty grains; and it should be given in divided portions, at equidistant

intervals during each twenty-four hours, and on an empty stomach. There is not any marked therapeutic action on the adult in a quantity less than ten grains three times a day, and it is rarely necessary to exceed three times that amount. There are cases in which forty grains three times a day, or twenty grains six times a day, are indicated. Sometimes it is wise to divide the doses unequally, and give, for example, ten grains in the morning and ten at noon, and thirty or forty grains at night. When more than one hundred grains are given continuously for any length of time, some of the toxic phenomena of the bromide are pretty sure to appear. I have repeatedly given thirty grains every four hours daily for several days consecutively, making one hundred and eighty grains in the course of each twenty-four hours, not only without harm, but with evident advantage to the patient. In a few instances I have exceeded this quantity. It is hardly necessary to say that in these cases there were abnormal conditions of the system, which antagonized the physiological action of the bromide, and rendered a toxic dose therapeutic.

The principal phenomena following the continued dose are: acne; salivation and salt taste in the mouth; irritation of the fauces generally, with œdema and redness,* and sometimes with pale-

* Voisin, Bulletin Général de Thérapeutique, ut supra.

ness* of those parts; moderate anæsthesia of the pharynx; laryngo-bronchial weakness, sometimes with cough and sometimes with a changed or whispering voice, rarely with aphonia; a fetid or bromized breath; occasional stammering; increase of renal secretion; diminution of mucous secretion generally; slight constipation, and in a few rare instances diarrhœa; sense of mental and physical languor or weakness; sometimes temporary impairment of the memory; general aspect of hebetude and indifference; more or less somnolence; repression and occasionally temporary abolition of sexual desire and power; impaired locomotion, which, when the dose is excessive, resembles the gait of locomotive ataxia; diminished nervous sensibility in general, and especially diminution of reflex sensibility; and, finally, an increase of destructive, without a corresponding increase of constructive metamorphosis, and consequent emaciation.

Hearing and vision are unaffected. The conjunctivæ, like the fauces, are often congested; but we have the authority of Laborde † for the statement that the optic nerve of a bromized person exhibits no alteration, discoverable by the ophthalmoscope. The pulse and heart are unaffected, except in doses so large or long continued as to be toxic: the same

* Gubler, *Bulletin Général de Thérapeutique*, 1864.

† J. V. Laborde, *Archives de Physiologie*, May, 1868.

is true of the temperature. When the dose is excessive, the heart acts slower and feebler, and the temperature is lower than normal. The capillary circulation is materially affected, not only of the nervous centres, as has been previously pointed out, but of the whole system. This, however, is independent of the heart and large arteries. There is sometimes slight nausea directly after a dose is swallowed, which soon disappears; but as a rule, and with very few exceptions, the appetite and digestion are unimpaired: the former is often increased. Tactile sensibility, the sense of temperature and of tickling, appear to be imperfectly conducted, but really are unimpaired. Intellection and emotion may seem to be sluggish, but when roused they act normally. A consciousness that the currents or sources of psychical force are hampered sometimes makes an intellectual patient, who is moderately bromized, reason himself into depression; but spontaneous depression is rare. When the bromide acts favorably, a sense of buoyancy, comfort, and relief rather than of depression accompanies its exhibition. It exerts no direct action on the globules of the blood, nor does it alter the chemical constitution of the secretions, however much it may check or increase them.

The importance of some of these phenomena demand a more detailed account of them.

Acne do not always appear after taking the bromide of potassium. I am aware of no data by which to determine the proportion of those who do to those who do not exhibit these phenomena. As a guess, founded only on my own observation, I should say that two-thirds of the persons to whom I have given bromides continuously suffered from acne. I do not recollect ever to have seen it follow the single dose previously described. The number and continuance of the eruption are variable. In some individuals it is sparse, and each pustule is small; in others it is abundant, and many of the pustules are large. It affects the face, scalp, and back rather than other parts of the cutaneous surface. The pustules appear in successive, but irregular crops. They vary in size from a millet-seed to a large pea. Generally they disappear without suppuration, each individual pustule lasting only a few days. In some cases, suppuration occurs: when this takes place, each pustule lives longer than it otherwise would; and as new pustules are constantly cropping out, the eruption may become unpleasantly copious. A moderate degree of heat with some itching usually attends the eruption, but this is not invariable. No permanent scar or mark remains after the disappearance of the pustules, though a red spot points out where they have been for some time after their departure. I recollect the

case of a young lady, twenty five or six years of age, whom I subjected to the continued influence of bromide of potassium for more than a year, and in whom the eruption was so copious and the pustules so large as to remind one of variola. Many of them suppurated, and smooth red spots remained to mark their existence for several months after she had ceased to take the drug. In her case, the acne were more troublesome than I have ever observed in others. The cause of the eruption has not been fully ascertained. Some attribute it to the local irritation attending its elimination by the skin. So little passes out from the system by this avenue, that this explanation cannot be considered satisfactory, until the truth of it has been demonstrated. I should think it more probable that deranged nutrition of the skin, resulting from the action of the bromide upon the peripheral nerves, might induce the eruption; that it might be a neurosis, like herpes. Beyond its disagreeableness, it is not important. It temporarily disturbs the vanity, and sometimes the physical comfort of many who take bromide of potassium, but does no other harm. Its appearance, therefore, should not lead to a discontinuance of bromidal medication, when this is continuously indicated. In former times, and not very long ago, such an eruption would have been regarded as evidence that the drug was driving pec-

cant humors from the body. I have met with persons who, entertaining some such notion, felicitated themselves upon the pushing out and continuance of the eruption, which they regarded as a blood-purifying process.

Few, who take the continued dose of bromide of potassium, escape the infliction of a disagreeable salt taste. The salivation, which frequently but not invariably attends this, is not copious, but merely disagreeable. Both result from the elimination of the salt by the faucial mucous membrane and salivary glands. They are commonly accompanied with a fetid or bromized breath. All of these phenomena — the taste, salivation, and bromized breath — are not disagreeably apparent, till after the bromide has been taken for a considerable period.

A good deal has been said about the anæsthesia of the pharynx, that may be produced by the bromide of potassium, and attempts have been made to utilize it for surgical manipulations or operations in the pharyngeal region. No great success, however, has attended such efforts. According to Voisin, this local anæsthesia does not appear after a less dose than thirty grains. It is not always produced by this dose; but, if two or three such doses are given several hours apart, there will be impaired sensibility of the pharynx for several hours after the administration of the last dose. Consequently, a con-

tinued daily dose of above half a drachm generally affects the sensibility of the pharynx, in proportion to the amount taken above that quantity. But only one part or kind of the sensibility of the pharyngeal mucous membrane is impaired or abolished. "We should distinguish," says a late writer, * "two kinds of sensibility in the region of the vail of the palate, — a functional sensibility and an ordinary sensibility. The ordinary sensibility varies with different individuals; but it is not the measure of the functional sensibility. The latter varies little. This functional sensibility is the same as the sensibility of the intestine; and like the latter, it depends, according to M. Claude Bernard, upon a ganglion, the sphenopalatine. It has its special mode of irritation, which is neither pricking nor burning, but the lightest contact. If the touching even [*chatouillement*] exceeds the physiological limit, vomiting is produced. Bromide causes this to disappear at once. Movements of deglutition remain intact in bromized individuals, and are not performed with less energy than previous to the treatment. When, by titillation of the uvula, no effort of deglutition or of vomiting is induced, it is apparent either that the pharynx and palate no longer conduct the tactile impression, or that this impression is not reflected.

* Emile Zaeffel, Thèse pour le Doctorat, &c. Paris, 1869.

As the reflex power of the cord has lost none of its energy, and there is no want of precision of movement, we must admit that the periphery alone is affected."

It is not so clear, as this writer would have us believe, that the reflex power of the cord is unaffected in bromized individuals; but the distinction which he draws between the ordinary and the specific—or, as he calls it, the functional—sensibility of the pharynx is a true and important one. The latter is the only one, which is impaired or abolished by bromide of potassium. Hence, in bromidal anæsthesia of the fauces, cutting, pricking, or any surgical operation near them, like excision of the uvula or tonsils, is felt as much as ever; but the contact of a finger, or an instrument like a laryngoscopic mirror or a sponge, is readily tolerated. The practical advantages resulting from a knowledge of this fact, in examinations of the throat and larynx, are obvious.

A changed or whispering voice, aphonia, slowing of the respiration, diminution of the force and frequency of the heart's action, and diminished animal temperature appear only when the bromism is so complete, as to exceed the limits of therapeutic action and become toxic. They are evidences of too long-continued or of excessive doses, and should warn the practitioner that he is on the limits of danger. In

some persons the elimination of the salt is so rapid that it is very difficult to excite any of these phenomena. I have one patient, who has repeatedly taken more than three drachms daily, for several days consecutively, without one of these symptoms of excessive bromism. Others exhibit some of them after comparatively small doses. Different rates of elimination in different individuals are probably sufficient to explain these differences of action.

The hypnotic action of the bromide of potassium has already been described when speaking of the single dose. It remains to be remarked upon this point, that the continued dose keeps up a sort of semi-somnolent state, whereby the system is predisposed to sleep, and slumber at night rendered more profound. When only the hypnotic action of the bromide at night is indicated, and it is found that an average or a tolerably large single dose, given at bed-time, is insufficient to produce sleep, a better result will be obtained, and less of the drug given, by administering two moderate doses through the day, and a somewhat larger one on retiring, than by crowding large doses near together at night. Thus I have often seen better and more sleep follow ten grains given in the morning, and ten at noon, and twenty at bed-time, than sixty grains would produce in the same individual, given in one

or two doses near together in the evening. The hypnotic action of hydrate of chloral, hyoscyamus, cannabis Indica, lactucarium, ether, chloroform, and sometimes of opium, at night, is reinforced and otherwise favorably modified by the continued dose of the bromide of potassium. The following case is an illustration of the above statement:—

CASE IV. — A gentleman, sixty-five or sixty-six years of age, who had suffered, while in London some years previously, from an acute and dangerous cerebral attack, and recovered from it there, was alarmed by sleeplessness and some other symptoms, reminding him of his illness in London, while at his country residence in the summer and autumn of 1870. By the advice of a neighboring physician, he took bromide of potassium, hydrate of chloral, and other anodynes, at night, unsuccessfully. When he returned to his city home, he came under my care. I proposed the same remedies. He objected to them on the ground that he had already tried them sufficiently, and without effect so far as sleep was concerned. It appeared on inquiry that he had repeatedly tried, on some nights, thirty and forty grains of the bromide, and on other nights as much of chloral hydrate. He was directed to take a combination of the bromide of potassium and bromide of ammonium, ten grains of the former and three of

the latter, before breakfast and before dinner, and double the amount at night. The experiment was successful. He slept well. After continuing this a few days, twenty grains of hydrate of chloral were substituted for the nightly dose of the bromides, and on the whole with a more satisfactory result.

It is needless to recite similar cases. They would add to the bulk, not to the value of this paper. I have so often observed the hypnotic effect at night of the continued daily dose, that I am sometimes at a loss which to select, in the treatment of insomnia, the single hypnotic dose at night, or the continued daily dose. When the former will produce the effect, it is preferable, because the organization is not subjected so continuously by it to the influence of the remedy, as by the continued dose. The former is discharged from the system during a part of each twenty-four hours, while the latter is not. One other practical point deserves to be stated in this connection; viz., when the continued daily dose is exhibited, there is not apt to be any noticeable somnolence by day, or profounder sleep at night for the first two or three days. This comes on later, as soon as the system has become impregnated with the drug, or is what might be called therapeutically bromized. Hence, if a hypnotic action is indicated at night, and the continued

dose is selected, the physician should not be discouraged, if the desired result is not immediately obtained.

The somnolence during the day of the continued dose is little more than a sense of quiet and comfort. It sends a person to sleep easily if there is nothing to prevent sleep, but does not interfere in the slightest degree with reading, writing, or the ordinary avocations of daily life.

The increase of the renal secretion, which accompanies the elimination of the bromides, is not so invariable nor so large as to render them serviceable as diuretics. In like manner, their influence over the peristaltic movements of the bowels, and upon the secretions of mucous membranes is not sufficient to make them of value in the treatment of ordinary diarrhœa, or for the purpose of checking the secretions from mucous surfaces generally.

Repression of sexual desire and power, like anæsthesia of the fauces, is not produced by a single dose of the bromide. This phenomenon does not usually occur till the salt has been taken for several days continuously. The extent of it is exceedingly variable. In some individuals it merely amounts to a moderate diminution of desire: in others there is a temporary impairment of power. In all cases there is return of the ordinary genital condition, as soon as the drug is eliminated. Referring to this

point, Zaepffel* remarks, that "the bromide of potassium seems to affect particularly the phenomena of reflex sensibility, whose seat, according to some authors, is in the orifice of the ejaculatory canals. The passage of the bromized urine over this orifice produces a local anæsthesia there, and so takes away the point of departure of the reflex action (the excito-motory point) of an erection." Advantage may be taken of this physiological action of the bromide in the treatment of certain emissions, and of some forms of genito-urinary irritation. The genital erethism, sometimes occurring in young girls at the commencement or establishment of menstruation, and which sometimes induces epileptiform attacks, is particularly amenable to bromidal medication. Certain irritable conditions of the bladder are likewise favorably modified by it. These matters, however, will be referred to more in detail, presently, when the application of bromide to the treatment of special diseases is considered. The point here emphasized is, that bromide of potassium produces local anæsthesia of the orifices of the ejaculatory canals, only when large and continued doses are given.

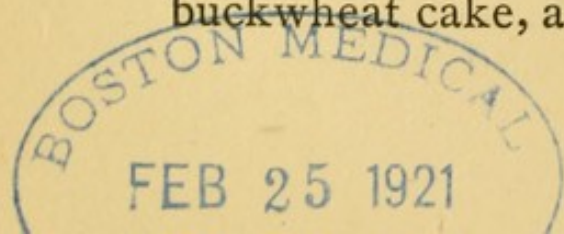
The most curious, interesting, and important phenomena of the continued dose are the sense of im-

* *Op. cit.*, p. 30.

paired mental force, loss of memory, depression, and diminution of general and of reflex sensibility, as well as the sense of physical weakness that is sooner or later complained of. Accompanying these, the face wears an expression of hebetude, the limbs move sluggishly, and the whole body becomes somewhat indifferent to subjective and objective impressions. When the quantity or continuance of the dose is so excessive as to become toxic, these symptoms are exaggerated into complete hebetude or idiocy, hallucinations and paralysis.

It is to be observed, however, that when the continued dose is restrained within therapeutic limits, — and it is of this we are now speaking, — the impairment of mental and physical force is more seeming than real. Of this I have been repeatedly assured by patients. A well-known clergyman and author, to whom I was obliged to give the continued dose, often spoke to me of this state of mimotic mental and physical weakness, which attracted his attention in his own case, and upon which he curiously speculated. He said that he was disinclined to talk, read or study, to walk or work; that he was quite indifferent to many objective annoyances that commonly irritated him; that in fact he was superlatively lazy, indifferent and sleepy. And yet, by a slight effort of the will, he found that he could converse, study, compose, walk, work, and fret as well

as ever. He entered his pulpit on Sunday with an indifferent step, and commenced his sacred exercises there without his usual buoyancy. But the necessity and excitement of the hour and place dispelled all this. He conducted the services as well as ever. One Sabbath he thought himself unusually depressed and weak, and, in spite of my previous assurances to the contrary, almost believed his mental force was dwindling. After the service, he asked a confidential parishioner about the matter that troubled him. The reply was reassuring: "Dr. —, you never preached with greater animation or better than to-day." In this case, as in all others that I have ever seen, the discontinuance of the treatment was directly followed by relief from the troublesome sense of weakness and depression. In some individuals, the memory is oddly affected. Single words are forgotten; or one syllable is constantly dropped out of a word, whenever that word is spoken by the patient; or two words are invariably interchanged. Thus a lady, twenty-eight or thirty years of age, suffering from chronic ovarian disease, to whom I gave about twelve grains three times a day, making a continued daily dose of nearly forty grains of the bromide of potassium, began, after she had taken it two or three weeks, to exchange two words for each other. She called a buckwheat cake, a comb; and a comb, a buckwheat



cake. At the hour of her morning toilet she would direct her maid to bring her a buckwheat cake, and arrange her hair. At breakfast, if there were buckwheat cakes on the table, she asked for a comb to eat. At first this was thought to be delirium, and naturally alarmed myself as well as the family. But, as it never went beyond this, our alarm on this point soon subsided. Moreover, as the mutual exchange of these two words was invariable, her family and attendants became accustomed to her acquired idiosyncrasy, and adapted themselves to her new nomenclature. Once, during the existence of this peculiarity, I undertook to convince her that she had transposed these words, and that a comb was the spoken sign of a comb and not of a cake. The effort was unsuccessful. She never transposed or confused the ideas of cake and comb, only the words or signs. Shortly after she discontinued the use of bromide of potassium, this peculiarity disappeared. She adopted the ordinary signification of buckwheat cake and comb with no consciousness of change in her language. This occurred five or six years ago. My patient is now well, and has never exhibited any other symptom of cerebral disturbance. I have talked with her since about this odd mental phenomenon, but she would never acknowledge any recollection of it. Voisin * men-

* Bulletin Général de Thérapeutique, 1866, vol. 71, p. 108.

tions a similar instance. It was that of a hospital patient, who, while subjected to the continued influence of bromide of potassium, forgot certain syllables or parts of certain words, and when writing or speaking did not write or utter these. Thus he called "quelques q—ques," and sometimes he duplicated one or two syllables of a word. Such instances are curious, and perhaps will some time be found instructive illustrations of aphasia. They are hints of a distinct organ of language. They suggest the notion that, inasmuch as the drug we are considering paralyzes reflex before it does ordinary sensibility, language may be the expression or correlation of a peculiar reflex power.

Intimately associated with the sense of impaired mental force and loss of memory is the diminution of excito-motory or reflex sensibility. This is produced by a smaller continued dose than that, which is followed by an interference with ordinary sensation. Anæsthesia is a toxic, not a therapeutic result of the administration of the bromides. Diminished reflex sensibility, however differently physiologists may explain the fact, is one of the most frequent phenomena of bromidal medication that has been clinically observed, and is therapeutically one of the most important. M. Gubler * has seen such medication "diminish the excito-motory action

* Bulletin Général de Thérapeutique, 1864.

of the spinal cord, and thereby resolve tetanic contractions and restrain reflex movements." A. Voisin * not only testifies himself to its action in diminishing reflex power, but quotes M. Claude Bernard to the same effect. Laborde, † relying upon experiments on animals, regards its primary action as one that impairs the control of the spinal cord over reflex phenomena, at the same time pointing out its great influence over the general nervous system, affecting both the central and peripheral nerve extremities. The clinical observations and physiological experiments of Brown-Séquard largely illustrate the same fact. Eulenberg and Guttman ‡ satisfied themselves of the paralyzing influence of it over the nervous system, including both reflex and general sensibility. The experiments, detailed in the second part of this Memoir, illustrate the manner in which it modifies reflex action by "producing oligæmia of the tissues and nerve substance." Martin Damourette § has corroborated the experiments and conclusions of Voisin as to its control over excito-motor action. Puche, || whose investigations upon its physiological action on man, nearly thirty years

* Bulletin Général de Thérapeutique, May, 1871; Ibid. 1866.

† Archives de Physiologie, May, 1868.

‡ Gazette des Hôpitaux, No. 77, 1867.

§ Gazette des Hôpitaux, Fév. 1868.

|| Stillé, *Materia Medica and Therapeutics*, article Bromide of Potassium.

ago, were strangely ignored by his contemporaries, pointed out the disturbed locomotion, muscular weakness, and anæsthesia, which physiologists refer to or connect with reflex power. Echeverria* found anæsthesia of the skin and mucous membranes, a tottering gait, inability for any sort of effort, and other indications of subdued reflex power, conspicuous among his epileptic patients. My own clinical observations are to the same effect. Inertia of look and movement, diminished susceptibility to physical and psychical irritants, disregard or forgetfulness of customary disturbants, and a general blunting rather than abolition of sensation, sometimes local in the fauces, sometimes in the genital apparatus, or upon the skin, and sometimes general throughout the whole organization, so that I could not ascertain that one part was more affected than another, have been among the most constant phenomena of the continued dose that I have witnessed. These occur, in varying degrees of course, but so constantly, that I have come to regard them as the invariable results of such medication.

Clinical observation has confirmed the teachings of physiological experiment. Different observers have given different explanations of the fact, but all agree as to the fact itself; viz., that, by means of

* M. Gonzalez Echeverria, M.D., on Epilepsy, p. 317.

the bromide of potassium, the practitioner can at will, and almost to any extent and for any length of time, diminish or blunt, not only the normal reflex sensibility, but also the frequent abnormal reflex hyperæsthesia of his patients. The advantage which an intelligent physician can derive from such agent, in ameliorating suffering, cannot be over-estimated. There is scarcely any disease in which the indication to diminish reflex sensibility may not sometimes exist. The particular diseases in which this indication is most likely to occur will be referred to farther on.

The disturbing influence of the continued dose over metamorphosis of tissue, which has hitherto only been referred to, deserves the careful attention of the practitioner. Dr. Roberts Bartholow* has been led, by his interesting experimental investigations upon the physiological action of the prolonged administration of the bromide of potassium, — the continued dose of this paper, — to regard its interference with secondary assimilation, and the consequent lessening of the retrograde assimilation of tissue, as one of its four predominating actions. The other three, which I have already sufficiently described, he considers to be diminution and ultimate neutralization of the sexual appetite, weakness

* Cincinnati Lancet and Observer, 1865.

of the muscular system, and irritation of the stomach when considerable doses are given. Dr. Z. C. McElroy,* of Zanesville, Ohio, in a recent ingenious essay, — which, however, is founded less on clinical observation and experimental investigation than on *a priori* reasoning, — arrives at the conclusion, “That, from the inherent relations of bromine and the bromides to the organic tissues and structures of the human body, their physiological and therapeutical effects must always be those of promoting destructive metamorphosis, or waste: first, of all matter below the normal dynamic condition; second, of tissue or structure of type or form foreign to the human body; and, lastly, of the normal tissues themselves.” Dr. Amory’s experiments † have led him to a similar result. Relying on clinical observation, not on precise experimentation, I am satisfied that the continued dose increases destructive without correspondingly increasing constructive metamorphosis; and that, consequently, it may gradually produce emaciation and pallor. Fortunately, however, if it does not increase, it does not check constructive metamorphosis. It does not prevent the normal repair of the body, even if it hastens the waste. Moreover, by a generous diet and other appropriate concomitants, constructive

* New York Medical Journal, July, 1870.

† Vide Second Part.

metamorphosis may be aided so as to neutralize the wasting action of the continued dose. In this way, the bromide may be given for years without producing emaciation or loss of color, or real diminution of strength. I have administered it to a considerable number of persons, of both sexes, — certainly not less than twenty, — for two and three years continuously. Combined with an appropriate regimen, — which included iron, wine, quinia, &c., — this was done not only without injury, but with manifest advantage. Their color, weight, and strength were as good at the close of the treatment as it was in the beginning, and with some of them better.

Action of the Toxic Dose. — It has already been stated that the quantity of a toxic dose of the bromide of potassium cannot be fixed precisely. What would be toxic in a physiological condition may and often will be only therapeutic in a pathological one. Moreover, individual idiosyncrasies largely modify the dose. Some persons tolerate easily an amount, that would produce decided bromidal intoxication in others. Echeverria* has seldom "seen forty grains repeated thrice daily for five or six days without determining bromism." My

* Op. cit., p. 315.

experience confirms this statement. In fact, I have generally noticed some of the symptoms of bromism, other than acne, after thirty grains have been taken thrice daily for a week or two. One hundred grains a day, given in divided doses at equidistant intervals, and continued for several days, may be regarded as the maximum therapeutic dose. More than that quantity is generally toxic. It is not to be forgotten in this connection, what has previously been insisted upon, that a given quantity — say one hundred grains — is less likely to prove toxic if given in one dose, or two doses near together, than if given in divided and equal doses, and at equidistant intervals throughout the twenty-four hours. By the latter mode of administration, the blood retains more of the salt, and for a longer time than by the former.

The symptoms of a toxic dose are only an increase, or an exaggeration of those of a therapeutic one. The fetid breath becomes nauseous; œdema supervenes on congestion of the uvula and fauces; the whispering voice sinks into aphonia; sexual weakness degenerates into impotence; muscular weakness becomes complete paralysis; reflex, general, and special sensations disappear; the ears do not hear, nor the eyes see, or the tongue taste; the expression of hebetude becomes first that of imbecility, and then that of idiocy; hallucinations of sight and sound, with or without mania, precede

general cerebral indifference, apathy, and paralysis; the respiration, without the stertor of opium or alcohol, is easy but slow; the temperature of the body is lowered; as the bromism becomes more profound, the patient lies quietly on his bed, unable to move or feel, or swallow or speak, with dilated and uncontractile pupils, and scarcely any change of the color of his skin or face; the extremities grow gradually colder and colder; the action of the heart becomes feebler and slower, till it ceases altogether.

This picture, drawn from a case that will be narrated presently, is admirably supplemented by Echeverria's description of bromism, as it was exhibited by his epileptic patients. He says: * "In those relieved by full doses of bromide of potassium, forty, fifty, sixty, or seventy-five grains have been administered every third or fourth hour, occasionally, until producing bromism. The symptoms then exhibited have been, — congestion with swelling of the fauces and of the tongue; redness of the conjunctivæ and cheeks; dilation of the pupils, dimness of sight, thickness of speech; slowness of pulse and respiration; increased secretion of the salivary glands and kidneys; in some instances hallucinations of sight and hearing, and mania, —

* *Op. cit.*, p. 317.

on three occasions of a suicidal nature. The swelling of the fauces, extending to the Eustachian tube, has determined deafness in some cases, but readily disappearing on discontinuance of the bromide. The anæsthesia of the skin and mucous membranes has been very conspicuous at this stage of intoxication, as also a tottering gait, with inability to steady exertion of any kind (writing, buttoning up the clothes, &c.), and an overwhelming drowsiness. In no case has the appetite to eat or to smoke been completely lost. I have long ago noticed that fetidity of the breath, usually an accompaniment of the exhibition of the bromide of potassium, occurs earlier and more remarkably in those who do not attend to regular cleanliness of the teeth."

When bromism occurs, even if it is excessive, the discontinuance of the drug is sufficient to relieve the patient. As soon as the salt is eliminated, the functions resume their ordinary action, and health returns. Death from the bromide of potassium is rare. The following cases, therefore, — one of excessive bromism and the other of probable death, — are interesting illustrations of the toxic dose.

CASE V. *Epilepsy — Bromism — Recovery.* — A lawyer, from a neighboring city, actively engaged in professional work, who added the excitements of politics and the pleasures of authorship to

the labor of the law, had an epileptic attack, directly after making a long and exhausting argument in court. In the course of the next few years, he had several other attacks. He consulted Professor Brown-Séguard, who prescribed a mixture, of which the principal ingredient was bromide of potassium. Not long after the treatment was instituted, that distinguished physiologist and physician left America for Europe, and the patient continued the treatment without any medical supervision. He took the drug four times daily, taking treble the amount at night that he took at any one of the other three doses. It was taken at nearly equidistant intervals through the day, and his total daily amount averaged about eighty grains. He took this quantity daily and uninterruptedly for nearly four years; and then, finding himself troubled with a group of uncomfortable symptoms, he put himself under my care. He was thoroughly bromized. He had the vacant expression, tottering gait, œdema and anæsthesia of the fauces, somnolent condition, whispering voice, slow and feeble pulse, and mental and physical weakness that have already been described. His hand trembled so much that his attempts at writing were illegible. His friends thought he was "breaking up," and his wife anxiously asked me if his brain was not softening, and he was not becoming

imbecile. His appetite and digestion were unaffected. He was pale and had moderately emaciated. Fortunately, he never had hallucinations or mania, or defective vision. The sequel of the case can be briefly told. A discontinuance of the bromidal medication and a tour in Europe dispelled all of these uncomfortable symptoms. As soon as the bromism disappeared, his health returned. This was several years ago. It should be added, for the credit of the treatment that Dr. Brown-Séquard instituted, that the epilepsy has not reappeared. So many years have now elapsed since a fit occurred, that the patient may be regarded as well; a most fortunate escape from a dire calamity.

CASE VI. *Cerebral Disease — Bromism — Death.* — A general officer in the regular army of the United States, about fifty years of age, was in active service through our whole late civil war. His duties were arduous and his labors incessant. He participated in the labors, dangers, and exposures of the last, long siege of Richmond, and also in the excitements and triumphs of the short and decisive campaign, that terminated at Appottamox Court House. Soon after the war was over, he showed symptoms of mental aberration. He was treated at Washington for a short time, and then sent to Boston. Before leaving Washington, his

physician prescribed bromide of potassium, and directed his attendant to give it to him freely enough and often enough to keep him quiet. He travelled slowly from Washington to Boston, stopping a few days at intervening places. His attendant, putting a literal interpretation on the physician's directions, gradually and steadily increased the dose. I saw him on the day of his arrival in Boston. He took in divided doses, during that day, at least four hundred and eighty grains. This dose was repeated the next day; for it was not till then, that I ascertained what and how much he was taking. As soon as this was known, the bromide was discontinued. The sort of mania he was in disappeared shortly after the discontinuance of the medicine; but a heavy, stupid, and paralyzed state remained. He died in about a week, without emerging from this condition. Unfortunately no autopsy was possible; and whether he died from cerebral disease, or from bromism, or from bromism superadded to cerebral disease, I could not determine. Probably, from the history of the case, he had fatal cerebral disease, upon which bromism was superinduced: at any rate, he was thoroughly bromized.

SPECIAL APPLICATIONS OF THE CONTINUED DOSE.

The preceding analysis of the action on man of the single, continued, and toxic dose of bromide of potassium exhibits two distinct groups of phenomena, — one therapeutic and the other disagreeable and toxic.

They may be arranged as follows: —

THERAPEUTIC GROUP.	DISAGREEABLE AND TOXIC GROUP.
Sleep.	Acne.
Anæsthesia of reflex power of fauces.	Salivation.
Reflex anæsthesia of genito-urinary organs.	Aphonia.
Diminished reflex sensibility of system generally.	Slow respiration.
Contraction of cerebro-spinal arterioles.	Slow and feeble pulse.
Repression of general nervous irritability.	Increase of destructive metamorphosis.
Control of reflex convulsion.	Tottering gait.
	Cerebro-spinal anæmia.
	General paralysis.
	Hallucinations.
	Mania.
	Diminished temperature.
	Cessation of heart's action.
	Death.

It is the duty of the practitioner, whenever he employs bromidal medication at all, to secure such of the phenomena of the first group as may be indicated, and to avoid as far as possible all of the second group. This may be accomplished by

careful attention to the physiological action of the bromide, which has already been pointed out; and especially by keeping in mind the ratio of elimination to absorption.

The special therapeutic applications, of which the continued dose of the bromide of potassium is capable, have been rendered obvious by the preceding investigation of its physiological action. It will not be inappropriate however, and it may be useful, to supplement this account by a brief statement of some of the special diseases or pathological conditions in which it has been found by experience to be serviceable.

As a preface to this, it is well to bear in mind two important observations of Echeverria, taken from the work previously referred to: one is, that strong coffee may be advantageously given with meals, or through the day, when large doses of the bromide are continuously administered. He says: "The operation of the remedy seems aided by this practice, and the supervention of bromism very materially delayed."* His other observation is, that the association of the bromide of potassium with the arseniate of potash avoids the disagreeable eruption that has been previously described. "From five to eight minims of Fowler's solution, added to each

*Op. cit., p. 318.

dose of the mixture of the bromide, will prevent the cutaneous eruption. . . . We, however, fall short of this result if alkaline baths are not employed in conjunction, or if the eruption be not previously arrested on discontinuance of the bromide." I have only recently met with these observations, and have not yet had any opportunity of verifying them, but shall improve the first occasion of doing so. The authority of Echeverria, however, renders them deserving of careful attention.

The continued dose of the bromide of potassium may be advantageously used in a large variety of pathological conditions, the most of which are embraced in the following classes. It may be used:—

1st, As a palliative or comforter of nervous symptoms in many diseases of dissimilar character; as pneumonia, bronchitis, rheumatism, gout, simple and continued fevers, conjunctivitis, ovarian disease, and the like.

2d, As a moderator of reflex action in certain local maladies: as irritation or inflammation of the fauces, bladder, and vagina; emissions; reflex nausea and vomiting; and nymphomania.

3d, As an anodyne or anæsthetic in various neuroses: as in some kinds of headache and neuralgia; angina pectoris, pertussis, asthma, and during the menopause.

4th, As a moderator or sedative of general reflex

power in spasmodic and convulsive diseases; as epilepsy, hysteria, and chorea.

5th, As a vascular sedative in hyperæmia of the brain and spinal cord.

This last indication underlies all the others; for the preceding analysis of the physiological action of the bromide of potassium has shown that to it all the other indications must be referred. There is, however, an obvious practical advantage in dividing them into separate groups. Let us look at each of the above groups of indications more carefully.

1st, *A Sedative in Dissimilar Diseases.* — The judicious employment of the continued dose, as a palliative or comforter of nervous symptoms in the management of disease, will depend largely on the intelligence, good sense, and ingenuity of the practitioner. Disagreeable or uncomfortable symptoms of a nervous character, — known by the vague terms of nervous irritability, nervous hyperæsthesia, nervous derangement, restlessness, flying pains, and the like, — without being pathognomonic of any disease, are very apt to accompany all sorts of maladies, and especially affections of the nervous system. Every physician recognizes them clinically, and has to combat or control them. Various means, not exclusively drugs, adapted to the idiosyncrasies of patients, and the varying conditions of disease, are employed in

the treatment of them. Of the drugs employed for this purpose, the bromide of potassium is perhaps the best. It may be given in any disease, where the above vague sort of symptoms exists, in whatever dose it is necessary to employ for the control of the nervous disturbance or hyperæsthesia, and for any length of time short of producing bromism. I have used it very largely for many years past, in this sort of way, and with most satisfactory results. It may be combined with other drugs, with which it is not chemically incompatible, or made an adjuvant to almost any treatment. It often renders a patient insensible to the discomforts of his position; and this is no small matter. I recollect a gentleman, who was convalescent from acute rheumatism, who took it for a while, and after a few days discontinued it. "Why did you leave that medicine off?" said his wife to me the day after its discontinuance: "my husband was *so* good-natured while he took it." If good-naturedness during sickness can be purchased by bromide, it is well to make the bargain.

When bronchitis assumes a spasmodic form, and the cough is out of proportion to the physical signs, bromide of potassium affords more relief than opium.

It palliates the pain of conjunctivitis only when it is given in doses large enough to subject the whole system to its influence.

It possesses no curative action over simple, continued, typhoid, or other fevers, but as a moderator of reflex excitability affords the comfort just spoken of; and by diminishing the congestion of the brain, that so often accompanies some forms of fever, may aid materially the resolution of the disease. If the brain, during any period of fever, by reason of impaired nutrition or other cause, becomes anæmic instead of congested, and is consequently irritable, the bromide is more likely to do harm than good. Ten grains, three times a day, is generally enough to afford sufficient palliation of these discomforts of fever or of convalescence. Double this amount may be given if necessary. Sometimes a single hypnotic dose at night is better than the continued dose. Generally, however, the latter is preferable.

2d, *An Anæsthetic in certain Local Maladies.* — As a moderator of local reflex action, in the treatment of local maladies, the continued dose of the bromide of potassium is often of service.

Ordinary sore throat is not benefited by it. But when there is frequent or constant irritation of the fauces, provoking useless and disagreeable efforts of hawking and spitting, which is unattended with redness or swelling, relief may generally be obtained from the continued dose of the bromide. It is of little use in these cases, unless it is exhibited in quantities large enough to destroy, or at least

diminish, the reflex sensibility of the parts. Twelve or fifteen grains, given three times a day, are commonly sufficient for this purpose.

Difficult deglutition of a spasmodic character, whether hysterical or otherwise, is sometimes completely relieved by the continued dose. The following case illustrates its fortunate action in this respect: —

CASE VII. *Difficult Deglutition — Cough — Recovery.* — A lady, sixty two or three years of age (residing in the country at some distance from Boston), took care of her grandchildren, through a scarlet fever, in January, 1870. During their sickness she had more or less sore throat, without being seriously ill. After their recovery, she became hoarse, and subject to violent paroxysms of coughing. In a few weeks she began to experience difficulty in swallowing, especially in the swallowing of liquids. A variety of measures were tried, by her attending physician, for her relief; but they were not successful. As one of her sisters had died of malignant disease of the throat, both her physician and herself were naturally apprehensive of a similar difficulty in her own case. I saw her in consultation three months or thereabouts after the commencement of the difficulty.

She was pale, emaciated, but able to sit up and

walk about. By a strong effort, and with evident physical difficulty, I saw her swallow a mouthful of solid food. Liquids were apparently swallowed with still greater difficulty. At any rate, she complained more of the swallowing of these; and when she made the effort, some of the liquid, whether it was water, milk, tea, or broth, regurgitated out of her nose. The cough occurred only in paroxysms, which were violent, and sometimes suddenly aroused her from sleep. Her appetite was good, but she could not get down as much food as she craved. There were no signs of disease of the lungs. The upper part of the fauces was pale, rather than red. Lower down, the mucous membrane appeared, in the laryngoscopic mirror, congested. No tumor or growth was discovered.

The continued dose of the bromide of potassium, in combination with the iodide of potassium, was advised. She took ten grains of the former and two of the latter three times a day for several weeks. There was a manifest improvement of her condition in about a week after the treatment was commenced, and in three months she was able to swallow with comparative ease. I saw her a year later, and the improvement continued. She then called herself well.

The anaphrodisiac and sedative action, upon the genito-urinary apparatus, of the continued dose of

the bromide of potassium may sometimes be rationally invoked in the treatment of seminal emissions and nymphomania. When the former are kept up or excited by local irritation or erethism, they may be controlled to a greater or less degree by giving enough of the bromide to diminish, or remove any excessive local excitability. If they have what may be called a central origin, and are the consequence, not the cause of sensual and erotic feelings, the continued dose of the bromide will materially aid the patient in his efforts to repress the desire that annoys him. In order to accomplish this object, at least twenty grains should be given during the day; and twenty or thirty more in a single dose on retiring.

It is important, however, to remember in this connection, that the most effectual treatment of these emissions is a moral one. The advertisements of charlatans, and the books of pseudo-physiological writers, who, under the guise of instructing the young, seek only to fleece them, have frightened a great many persons into the belief that emissions, which are often only natural and physiological discharges, always and necessarily lead to death, or to what is worse than death. In Niemeyer's *Practice* * a case is referred to, where a man had an

* German edition, vol. ii. p. 103.

abundant loss of semen with each dejection for at least ten years, without any injurious influence upon his health. A little physiological information upon this matter, judiciously imparted by the physician, will often do more good than the bromide of potassium or any other treatment.

The continued dose controls sexual excitement in the female as well as in the male. Stillé testifies* to its efficacy, in what he calls "those sad instances of hysteroidal excitement which verge on nymphomania;" and truly adds, "In all these affections, small doses of the medicine are unavailing. Not less than twenty grains, three times a day, will exert a decisive control over excessive sexual propensities, even in adolescents; nor can its effects be expected to be permanent, unless advantage is taken of the improvement it occasions to invigorate the system by the combined resources of food, exercise, and habits of living."

Reflex nausea and vomiting are sometimes, not always, admirably controlled by the continued dose. When the stomach will not retain the medicine long enough for it to be absorbed, it may be administered by the rectum, till the nervous centres are quieted by it, and then the stomach will generally retain it. In order to obtain the greatest benefit

* Therapeutics and Materia Medica, vol. ii. p. 800.

from it, in these cases, it should be exhibited in doses large enough, and near enough together, to bring the nervous system decidedly under its sedative influence. When this result is attained, the sedative action should be kept up continuously for several days or weeks, long enough, at least, for the irritation or congestion of the nervous centres to pass away, if this is possible.

Neither inflammation of the bladder, nor of the mucous membrane of the vagina, yields to the continued dose of the bromide of potassium; yet there is occasionally a sort of irritability, or hyperæsthesia of these parts, that is happily modified by it. Frequent micturition and incontinence of urine, connected with nervous disturbance, of a local or general character, are ameliorated and sometimes permanently relieved by it. In like manner, vaginismus occasionally yields to the sedative influence of the bromide of potassium. In the treatment of the latter malady, local injections of a solution of the salt, held in the vagina for ten minutes at a time, twice a day, may be advantageously employed in connection with the internal administration of the medicine. Small doses are of little value in these cases. Enough must be given to take away the reflex excitability of the palate, as in the treatment of epilepsy, before the difficulty is relieved.

3d, *An Anodyne or Anæsthetic in Various Neu-*

roses. — The bromide of potassium, either in the single or continued dose, possesses very little direct anæsthetic power. It will rarely stop pain directly; but indirectly, by removing some of the causes of pain or diminishing reflex or general sensibility, it sometimes renders an important service in a variety of painful and distressing maladies.

The functional derangements of the brain and nervous system, which so frequently accompany the menopause, have been more fortunately controlled, in my experience, by the continued dose of the bromide of potassium than by any other drug. The common symptoms at that period, of timidity, irritability of temper, inquietude, broken sleep, apprehension of serious evil, flushing of the face and head, numbness, deranged sensation, and the like, are commonly ameliorated and sometimes completely controlled by it. This is particularly true of the flushing of the face, — that wave of heat and redness, which many describe as rolling up to and through the brain, and which they dread as the precursor of paralysis. It is scarcely necessary to say, that it would not be judicious to administer the bromide, through the whole period, often three or four years, during which the constitutional change in the female system that attends the menopause is going on. It should be given only when the symptoms of nervous disturbance are excessive.

When it is exhibited, the largest relief will be obtained by giving it continuously, and in doses sufficient to bring the system fully under its influence. Its sedative action should be kept up for two or three weeks, and then the treatment should be discontinued. The same course may be resumed, whenever the condition of the patient warrants it. The importance of appropriate hygienic, moral, and tonic treatment, as supplementary to the use of the bromide of potassium, in these cases, need not be insisted on.

Among the numerous remedies that have been invoked for the relief of angina pectoris, the bromide of potassium should not be forgotten. Not much can be expected from it, in this intractable malady; yet the little it can do is sometimes of great value. At the time of this present writing, I have under my observation a great sufferer from this complaint, who has obtained more relief, after taking the bromide, than after taking any other drug that I have given him. Here, as in many other diseases that have been mentioned, small doses do very little good. Ten or twelve grains should be given three times a day, for a considerable period; and when a paroxysm occurs, thirty grains additional should be administered at once, and this dose repeated in half an hour, or an hour, if necessary.

Whooping cough and asthma, like angina pec-

toris, are only occasionally benefited by the continued dose of bromide of potassium. But it is this occasional benefit which it is well for the practitioner to bear in mind. I know of no methods or symptoms by which to discriminate a case of asthma or whooping cough, that can be favorably influenced by the bromide, from cases of these diseases that are utterly rebellious to it. My use of it, therefore, in these maladies is wholly empirical. But a good result is obtained often enough to induce me, in many severe cases of pertussis, to try the effect of putting the patient well under the sedative action of the bromide, and keeping him under it for a week or two at least. Trousseau* quotes with approbation, in his "Clinical Lectures," the following recipe for the treatment of asthma, which he says he derived from an American source:—

℞ Potassii Iodidi	32
Decoct. Polygalæ	33
Tinct. Lobeliæ	36
Tinct. Opii Camphor.	36

Of this mixture, the taste of which must be experienced to be appreciated, he advises a tablespoonful to be given two or three times a day. The addition of ten grains of the bromide of potassium, to each dose of the above mixture, will materially enhance

* Clinique Médicale, tom. ii. p. 409. French ed.

its control of asthma, without adding much to the disagreeableness of its taste.

Little can be expected, either from the single or continued dose of bromide of potassium, in the treatment of ordinary neuralgia or ordinary headache. But there are classes of both of these affections that are especially amenable to it.

Dr. Anstie has clearly pointed out the kind of neuralgia which is relieved by the bromide, and I am glad to reinforce my own observations by his statements. He says: * "Four very different types, at least, of narcotic-stimulant drugs, are useful in neuralgia." These he calls the opium type, the belladonna type, the chloral type, and the bromide of potassium type. Of the last, he has given the following admirable description: † "The use of bromide of potassium in neuralgia is a subject of great importance, and which requires much attention and discrimination. In common with, I dare say, many others, I made extensive trial of this agent when it first began to be much talked of; but was so much disappointed with its effects in neuralgias, that at one time I quite discarded it in the treatment of those affections. Renewed experience has taught me, however, that though its use is restricted, it is ex-

* Neuralgia and the Diseases that resemble it. By Francis E. Anstie, M.D. p. 185. English ed.

† Op. cit., p. 191.

tremely effective, if given in appropriate cases and in the right manner. For the great majority of neuralgias it is quite useless, and, what is more, proves often so depressing as indirectly to aggravate the susceptibility of the nervous system to pain. The conditions, *sine quis non*, of its effective employment seem to be the following: The general nervous power, as shown by activity of intelligence, and capacity of muscular exertion, and the effective performance of co-ordinated movements, must be fairly good, and the circulation must be of at least average vigor; the patient must not have entered on the period of tissue degeneration. Among neuralgics who answer to this description, those who will benefit by the bromide are chiefly subjects — especially women — in whom a certain restless hyperactivity of mind, and perhaps of body also, seems to be the expression of nature's unconscious resentment of the *neglect of sexual functions*. That unhappy class, the young men and young women of high principle and high mental culture to whom marriage is denied by fate till long after the natural period for it, are especial sufferers in this way; and for them the bromide appears to me a remedy of almost unique power. But I wish it to be clearly understood that it is not to the sufferers from the effects of masturbation that I think the remedy specially applicable: on the contrary, it is rather to those who have kept themselves free

from this vice, at the expense of a perpetual and almost fierce activity of mind and muscle. The effects of solitary vice are a trite and vulgar story: there is something far more difficult to understand, and at the same time far more worth understanding, in the *unconscious* struggles of the organism of a pure-minded person with the tyranny of a powerful and unsatisfied sexual system. It is in such cases, which it needs all the physician's tact to appreciate, that it is sometimes possible to do striking service with bromide of potassium; but it will be necessary to accompany the treatment with strict orders as to generous diet, and very likely with the administration of cod-liver oil."

"Having decided that bromide of potassium is the proper remedy, we must use it in sufficient doses. Not even epilepsy itself requires more decidedly that bromide, to be useful, shall be given in large doses. It is right to commence with moderate ones (ten to fifteen grains), because we can never tell beforehand that our patient is not one of those peculiar subjects in whom that very disagreeable phenomenon — bromic acne — will follow the use of large doses. But we must not expect good results till we reach something like ninety grains daily. Let me add that it is not, so far as I know, by reducing any 'hyperæsthesia' of the external genitals, of which the patient is aware, that the

remedy acts. I have not seen such a *nexus* of disease and remedy in these cases.”

It should be added to the above that the daily dose, whatever that may be, that is sufficient to control the neuralgic condition, should be continued for several weeks after the pain is subdued, or no permanent relief will be secured.

Headache, that accompanies grief, anxiety, bereavement, or any sort of mental worry, yields readily to the bromide of potassium. But pain in the head, that ushers in an attack of fever, or accompanies any acute inflammation, as pneumonia or pleurisy; or that arises from constipation, or deranged digestion, or cold, and the like, — is rarely even palliated by the bromide. Whenever headache arises from anæmia of the brain, it is more likely to be aggravated than relieved by bromidal medication.

Persons, especially females of a nervous or hysterical diathesis, who are subject to that form of sick headache in which the cerebral symptoms not only precede, but predominate over the gastric ones, often derive considerable benefit from the bromide of potassium. It should be administered as soon as there is the slightest warning of a coming attack, and in a dose of not less than twenty grains. This should be repeated every hour till the nervous system is brought thoroughly under

its influence. At the same time, the patient should remain quietly on a bed or sofa, with the dress loosened so as to allow of an unimpeded circulation, and the extremities kept warm, till the usual period for a threatened attack has passed by.

In some cases, a better way than this is to give the continued dose daily for several months, during the intervals between each attack. By such a procedure, the intervals are prolonged, the severity of the headaches diminished, and occasionally the attacks arrested. The experienced practitioner need not be reminded that this course alone, however much it may palliate, rarely, if ever, eradicates sick headaches. They are too deeply grained into the constitution, by long-continued errors of diet or regimen, or by unhealthy modes of life, or unhealthy surroundings, to be rooted out by an agent that simply diminishes cerebro-spinal hyperæmia and reflex sensibility. In the administration of the large dose, at short intervals, first mentioned, a combination of carbonate of ammonia, or of the aromatic spirits of ammonia, with bromide of potassium, gives speedier relief than the latter alone.

4th, *A Controller of Reflex Power in Convulsive Diseases.* — The most important sphere for the employment of the continued dose of bromide of potassium is to be found in the application of its physiological action to the pathological conditions

of convulsive diseases, especially of epilepsy and epileptiform maladies. Its use in this way is of recent origin. For our present knowledge of its control over many forms of convulsion and spasm, we are indebted to some of the ablest living observers; especially to Sir Charles Locock, Drs. Radcliffe, Reynolds, Mac Donnell, Duckworth Williams, Echeverria, A. Voisin, Bazin, Hardy, and most of all to the distinguished Brown-Séquard, whose personal labors two continents have reaped the advantage of, and whose researches are valued wherever medicine is recognized as a science.

It would require a treatise on epilepsy, as well as one on the bromide of potassium, to point out precisely how the physiological action of the latter can be advantageously adapted to the different forms and phases of the former. The limits of this paper do not admit even of a sketch of epilepsy; and I must content myself, therefore, with a statement of the obvious fact, that the more accurate a physician's knowledge of the disease in question is, the better and more satisfactorily will he be able to employ bromidal and other medication in the treatment of it. The extent of our present knowledge of it can be ascertained by an examination of the researches of Brown-Séquard, Dr. Radcliffe, and Dr. Reynolds, and especially of the recent admirable work on epilepsy by G. Echeverria, of New

York. The knowledge obtained from these or from kindred treatises, supplemented by his own clinical experience, must teach the practitioner how to use the bromide of potassium in the treatment of this terrible disease.

The following directions for its use, from the pen of one, not less familiar with the physiological action of the bromide than with the natural history and pathology of epilepsy, possess the greatest practical value, and deserve the physician's careful attention.

A. Voisin says : * " It is only within the last twenty years that the therapeutics of epilepsy have acquired any fixed principles. Herpin of Geneva first, during this period, affirmed the curability of epilepsy, which to-day has become assured.

" The largest degree of success at present is due to the bromide of potassium. First employed in England, in 1853, by Locock, it was first used in France by Bazin and Hardy ; and in the hands of a large number of physicians has yielded excellent results.

" The bromide of potassium should be pure, free from iodine and chlorine. It should be given a few minutes before meals, in doses very gradually increased, and varying from two to twelve grammes (30 to 180 grains), or more, daily. But as the

* Bulletin Général de Thérapeutique, May, 1871.

doses employed must vary largely with individuals, according to their age, constitution, and force, I have employed for many years a method which has given me the best results, and which consists in determining the condition of reflex nausea, by introducing a spoon as far as the epiglottis. I have remarked that a therapeutic dose of the bromide of potassium is not attained till reflex nausea is suppressed: it is not till then that the bulb is certainly acted on, and its excito-motory force diminished. I have been fortunate enough to have this criterion of the therapeutic action of the bromide of potassium approved by M. Cl. Bernard, in his lectures at the College of France.

"The study of other reflex phenomena, such as lachrymation, cough, and sneezing, enables us to follow the action of the medicament upon the bulb and the spinal cord.

"The dose of the drug should not be increased beyond the suppression of reflex nausea; but it should be given continuously, and with perseverance, for years together, if the malady is ameliorated, or in process of cure. At the end of two years of amelioration or of cure, the remedy, instead of being administered every day, may be given every second, third, or fourth day, provided reflex nausea is always and certainly absent. It is only after several years have passed, without epileptic phenomena, that treat-

ment should be discontinued. Earlier than this, the administration of the remedy should always be continuous. Intermission is a great mistake. A chronic malady demands chronic medication. The bromide of potassium should almost be made the aliment of an epileptic, till he is cured.

“Certain therapeutic indications, peculiar to the bromide of potassium, always make me augur favorably of its action in epilepsy. Thus, hypnotic manifestations, general lassitude, an easy and rapid disappearance of reflex nausea, and an anaphrodisiac action, are favorable auguries in the treatment of an epileptic by the bromide of potassium. When, on the contrary, the anaphrodisiac, hypnotic, and sedative action is negative, and when the reflex nausea is slow to disappear, there is reason to believe that the bromide will produce no effect, and that it will be necessary to resort to other medication.

“The bromide of potassium can be advantageously employed in all forms of epilepsy, idiopathic and symptomatic, as well as in cases of epileptiform phenomena, even when they are allied to idiocy and cretinism. Not that it can cure them all, but it can mend them all; and the explanation thereof is perfectly physiological. Because all convulsive phenomena of an epileptic character are the product of an exaltation of the excito-motory force of the bulb,

the bromide of potassium can always moderate and calm, if it cannot suspend them. But while recommending the employment of the bromide of potassium, in preference to other medicaments, for all convulsive affections of an epileptic character, I consider that its utility is the greatest in cases where epilepsy is idiopathic; or where it is the result of great impressionability, or exaltation of sensibility; in those where it has been produced by intense emotion, painful impressions, fear, onanism, and venereal excess; in those, finally, where it is the hereditary consequence of neuroses, like hysteria, chorea, and even of epilepsy itself. Moreover, if the bromide of potassium does not always cure, it nearly always moderates the malady; and diminishes, or almost suppresses, the nervous erethism, shocks, and twitchings of the epileptic.

“The bromide of potassium can suppress the aura, even when unable to dispel completely the attacks. It has less influence over absent-mindedness [*les absences*] and vertigo than over the attacks.

“The proportion of those with whom I have been able to suspend the epileptic phenomena has gradually become larger and larger, since I discovered the criterion of reflex nausea. In reality, whilst I was able to report, in 1866, a suspension of the malady in one-fourth of the cases, I can now

obtain the same result in one-half of the adults treated. With children, on the contrary, the proportion of success is scarcely one-fourth.

"Pidoux and G. Sée think that the bromide of potassium does not cure epilepsy; and that, if it suspends or retards the attacks, it does so by replacing them with preludes and incomplete attacks. In the first place, this opinion is not tenable in face of the observations, already numerous, that establish a cure, without a trace of the evil left; and then it is to be remembered, that the principal indication of the cure of epilepsy is to be found in this, that the attacks begin to be replaced by preludes and incomplete attacks, just as confirmed epilepsy is always preceded for a certain period by preludes and incomplete attacks. So that when, under the influence of any medication, an epileptic has only incomplete attacks and preludes, he should be considered on the way to a complete cure.

"The administration of the bromide of potassium demands, when it is to be long continued, certain precautions, without which there is danger of being obliged to suspend its employment. Thus diuretics should be regularly given, in order to increase the urinary secretion, and the elimination by the kidneys of the bromide of potassium, and to prevent certain cutaneous eruptions, that patients find very disagreeable. Iron should be frequently associated

with the bromide of potassium, so as to prevent the anæmia and cachexia that its long-continued use is apt to induce, and to prevent certain affections of an evil character, that may occur with those who take large doses of it for many years.

"I have noticed that the bromide of potassium generally succeeds less well with children than with adults; perhaps, because the epilepsy of childhood is more frequently allied, than the epilepsy of adult age, to congenital states of the nerve centres; or to cerebral lesions of a scrofulous or tuberculous nature; or, more likely still, as the drug is very rapidly eliminated in childhood, only a slight impression is made on the spinal cord, and the reflex actions, of which I have spoken, are with difficulty suppressed. From eight to twenty-two grains may be given to children, two or three years old; from thirty to seventy-five grains, to those between five and ten years of age; and from thirty-five to one hundred and eighty grains, to those between ten and fifteen years old.* The bromism, which I have often observed in children, and which is characterized by depression, loss of appetite, great prostration of strength, and pulmonary catarrh, is never grave, if the drug is immediately suspended.

* These quantities refer to the amount taken through the whole of each day, not to each individual dose. — TR.

In adults, on the contrary, bromism is manifested by the gravest phenomena of pulmonary catarrh and adynamia, or rather of the most intense ataxia. The action of the bromide of sodium is the same as that of the bromide of potassium. The doses of it are not quite so large."

The testimony of Dr. West, the eminent London professor and sagacious physician, to the efficacy of the bromide of potassium, in the treatment of the epilepsy of children, is a valuable confirmation of what has been previously stated with regard to the bromidal medication of epileptics. He says: *
"I may be expected to say something as to my experience of specifics for epilepsy. I have tried all, or almost all, in favor of which any reasonable evidence could be adduced, and all have failed. The only one which has appeared to me to exert any specific power over epilepsy is the bromide of potass; and in a few instances its results have been most remarkable. It hardly ever fails to arrest the frequency of attacks; now and then it has seemed entirely to prevent them; and the crucial test of arresting fits by bromide of potass — of suspending the remedy and seeing the fits return, and of once more putting a stop to them by the resumption of

* Lumleian Lectures, on some disorders of the nervous system in childhood, by Charles West, M.D., pp. 45, 46. Am. ed. 1871.

the medicine — has, on some occasions, established its value beyond question. In the great majority of cases, however, the amendment has not entirely maintained itself: the system has, after a time, become habituated to the remedy; and after several augmentations of the dose, each of which has seemed to renew the old influence, I have been compelled to discontinue it, in consequence of the depression of the pulse, the general loss of power, and the appearance of the peculiar pustular eruption, which occasionally follows its long-continued use. In other cases, too, the agent which at first worked wonders ceased to have any influence. The constitution tolerated the increased dose, but so did the disease: the patient continued to take the medicine, but the fits, though once controlled, returned after a time just as before.

“Still, with all these drawbacks, the bromide remains the only agent which, in my hands, has made the least approach to the character of a specific. I always employ it, when I can find no distinct indication to guide me. I confess that I use it empirically; for I have found no means by which to distinguish beforehand the cases where the bromide will do permanent good, from the other, apparently similar, but much more common instances, in which its influence is merely temporary.”

My personal experience of the bromide of potassium, in the treatment of epilepsy, is so small that it scarcely deserves mentioning, after what has been previously quoted from Voisin, West, and Echeverria. I should not allude to it, were it not that out of the twelve cases, five males and seven females (two being under eight years of age, and ten adults), that my note-books have a record of, three seem to have radically recovered. Neither of these three has had a fit for many years; and every case of recovery from this sad disease deserves to be published, for the encouragement of physicians and patients alike. Six of the remaining nine are under treatment at the present time; and three of these have not had an attack for a year. Of the other three, one has died, and two have not been benefited by treatment. The whole twelve were treated by the large and continued dose that has been described. Perhaps it should be mentioned that this small group of cases occurred in private practice.

Hysteria. — The paroxysms of ordinary hysteria are more advantageously treated by such remedies as cold affusion, inhalation of ether, and what are called antispasmodics, than by the bromide of potassium. But if the paroxysms are epileptiform, their treatment by this remedy is nearly always successful.

The course pursued should be the same as in the treatment of epilepsies, except that it need not be continued so long. A course of from six to twelve months, depending on the severity of the case and its duration previous to the commencement of treatment, is commonly sufficient.

As a prophylactic in hysteria, uncomplicated with epileptiform convulsions, bromidal medication often yields a precious service. The continued dose quiets the hysteric or hyperæsthetic temperament, and bridles it, so that the necessary crosses of daily life — the irritations of existence — are less likely to excite an explosion. Many cases might be given in illustration of this remark, but to do so would only add to the bulk of this paper, which has already largely exceeded the limits originally intended for it.

While administering the continued dose in cases of hysteria, the practitioner should remember that it is not curative: it simply holds the nervous system quiet, controls an abnormal excitability for the time being. Other remedies, often moral, sometimes dietetic or hygienic, sometimes tonic, and sometimes purely local, must be used in conjunction with the bromide, so as to remove the cause of the malady.

This last remark leads to another, in reference to the opinion quoted from M. Voisin in a preceding paragraph, viz., that the bromide of potassium *cures* epilepsy. In the first place, the word *cure*, as indi-

cating the action of drugs, is inappropriate ; secondly, I conceive that the bromide acts in epilepsy as in hysteria, simply by keeping off the attacks long enough for the organization, by constructive metamorphosis, to rebuild nerve tissue, so that the latter becomes incapable of epilepsy. When a surgeon applies a splint to a broken bone, the splint holds the bone still, so that osseous reconstruction is possible. What a splint is to a fractured bone, bromide of potassium is to an epileptic medulla, or to hysteric nerve centres. The medulla is kept quiet long enough for it to grow into health, if it is capable of doing so. Neither the splint nor the bromide can be properly called curative, though they may be indirectly so. The practical advantage of looking at the action of the drug in this way is, that while the physician keeps his patient's nervous system under the control of the continued dose, he will, with this notion in his mind, be likely to look carefully after the equally important matter of reconstructive metamorphosis.

Bromide of potassium is not often used in the treatment of chorea, but it occasionally does excellent service in that complaint, especially when associated with Fowler's solution of arsenic.

5th, *A Vascular Sedative in Hyperæmia of the Nerve Centres.*—Brown-Séquard, Laborde, Voisin, and others, have demonstrated, what has already

been largely insisted on, that the arterioles of the cerebro-spinal axis are constricted by the action of the bromide of potassium, so that the nerve centres are made by it to carry less blood than they otherwise would. Whether this is accomplished by the direct action of the salt on the central or peripheral extremities of the nerves, or on the capillary blood-vessels themselves, is matter of greater interest to the physiologist than to the therapist. The latter is concerned chiefly with the important fact, that the bromide of potassium furnishes him with the means of diminishing to a limited extent, and at will, the amount of blood circulating through the brain and cord. This action underlies and explains the physiological phenomena, and consequent therapeutic indications, that have hitherto been pointed out. Little remains to be said, then, under this head, except to refer to the fact, that in cases of spinal irritation and spinal pain, and neuralgia anywhere, dependent on spinal congestion, the obvious indication is to employ the continued dose long enough to re-establish permanently a normal circulation in the nerve centres. I have often used it in this way, and with the happiest results.

When speaking of the value of the continued dose in dissimilar diseases, no allusion was made to its employment in ovarian and uterine difficulties, because there was a practical advantage in

reserving that to the present time. Every physician is familiar with the neuralgia, reflex excitability, and hyperæsthesia that is so apt to accompany these complaints. Apart from whatever local treatment may be necessary, there is probably no drug which affords greater relief than the bromide of potassium to these distressing symptoms. But it is to be remembered — and this is a sufficient reason for introducing the subject in this connection — that neuralgia, reflex excitability, and hyperæsthesia arising from spinal congestion and spinal irritation, may exist in the uterine region, without a trace of uterine disease. These symptoms do not necessarily imply disorder of the sexual organs of the female, and do not always demand a local examination. When they are dependent upon spinal hyperæmia, a larger and more permanent relief may be rationally expected from continued bromidal medication than when local uterine and ovarian disease causes or complicates them. When they are dependent on spinal derangement, local uterine treatment is more apt to aggravate than relieve them. There are many cases, especially among the unmarried, with whom it is desirable to try the continued dose of the bromide of potassium before resorting to a local examination.

ANTAGONISM OF BROMIDE OF POTASSIUM
AND STRYCHNIA.

M. Saison* has called attention to the physiological antagonism of bromide of potassium and strychnia. This antagonism is most marked in the action of the two agents upon the medulla oblongata and the cord, and least marked on the brain. The bromide produces capillary constriction and oligæmia of the bulb and cord; strychnia produces capillary dilatation and hyperæmia of the same parts. The bromide relaxes, and strychnia causes convulsions. The bromide produces relaxation and deficient reflex excitability; strychnia causes contraction and increased reflex excitability.

M. Saison says: "I have made numerous comparative experiments of these two antagonizing agents, — injecting strychnia into one limb and bromide into the other. There were convulsions and tetanic stiffening, with lengthening of the strychnized foot: no convulsions and relaxation of the other. Next I injected a mixture of the solutions of strychnia and bromide. The convulsions were very feeble, their total duration abridged,

* Thèse. Paris, July, 1868.

and the animals lived longer than after an equal dose of either agent singly. I have even been able to keep alive a strychnized frog more than an hour, by injecting bromide from time to time."

Here, as elsewhere, clinical observation supplements and confirms physiological experiment. When these two agents are administered simultaneously to man, a larger dose of both of them is required in order to bring about their specific action than when they are given separately. My attention was first called to this antagonism by Professor Brown-Séguard, in a consultation with him. I have since noticed it in several cases. Ordinarily, bromide of potassium and strychnia should not be administered together; yet it would be rational to give them simultaneously, provided it was desirable to obtain the maximum action of the bromide on the brain and bulb, and its minimum action on the cord. By their conjoint exhibition the influence of the bromide of potassium upon the circulation of the cord is antagonized, but not that upon the brain. Strychnia exerts its minimum action upon the brain, and its maximum action upon the cord. There are congestions of the brain, especially of its gray matter, which it is desirable to diminish; while it is equally desirable, at the same time, to keep up the nutrition, so as to prevent oligæmia of the cord. When bromide of potassium is used in such cases,

the addition of strychnia antagonizes the action of the former on the cord, without materially interfering with its influence over the encephalic circulation. At any rate, this is the best explanation I can give of the happy conjoint action in certain cases of these two drugs, whose physiological action on the cord is so opposite.

The following case,* reported by Dr. Charles B. Gillespie, of Freeport, Penn., is a clinical illustration of the physiological antagonism of these two agents, and of the control of the toxic action of strychnia by bromide of potassium.

CASE VIII. — "I was called, December 17, to a man, some miles in the country, who, the messenger reported, had fallen down in a fit, and had violent cramps. I found the patient lying on his face, on a small trundle-bed, with his hands tightly clutching the bed-frame, and, at every movement of the attendants, thrown into the most violent clonic spasms. On lifting his head, I recognized the patient as one who had, that same morning, purchased from my clerk three grains of strychnia, for the alleged purpose of killing rats. It was evident that he had taken the poison himself; and the wretched man confessed that he had taken nearly all the

* American Journal of Medical Science, Oct. 1870, p. 420.

strychnia some two hours before, for which he was now heartily sorry, and begged me to save him, solemnly promising that, if his life were only spared this time, he would never attempt the like again.

"This short explanation was interrupted half a dozen times by the most terrible spasms. His pulse was 70, hard and contracted; respiration good. The whole surface of the body was quite cold; great anxiety in the expression of the face; sight and hearing perfectly normal. On giving him drink, the great difficulty was in getting the cup to his mouth, without throwing him into convulsions; but when once there, he would gulp the contents down spasmodically in great mouthfuls. He had but little control over his arms: as soon as he let go his grasp on the bedstead, they would jerk violently, and continue thus until he laid hold of something solid and immovable.

"The spasms were evidently becoming more violent and frequent, and beginning to implicate the muscles of respiration. Not having the remedy I desired with me, I gave him a teaspoonful of the fluid extract of hyoscyamus; and then hurrying home, weighed out one ounce of bromide of potassium, which I dissolved in three ounces of water. Of this solution I ordered one half-ounce every thirty minutes; and I felt so confident of its efficacy in this case, that I intrusted the administration of the

remedy to a carefully instructed attendant, and did not revisit the patient till next morning, when I found him out of danger. The paroxysms had gradually become less violent and frequent; and by the time the last dose of bromide was taken, at midnight, he was able to get up without assistance, and walk to his own room. The only bad effects remaining were excessive muscular and nervous prostration, with an occasional slight convulsive shudder, which, however, entirely passed off through the day; and in thirty-six hours' time he was up, and at his usual business."

It is to be regretted that the above report does not give the total quantity of bromide of potassium which the patient took. Each half-ounce of the solution contained eighty grains, and he was ordered to take this every half-hour. How many times he took it does not appear. It is fair to infer, however, that he took more than half an ounce in the course of two or three hours, and possibly the whole ounce.

BROMIDE OF AMMONIUM.

Physiological Action. — The behavior of the bromide of ammonium in the human body, so far as its absorption and elimination are concerned, has been found to be the same as that of the bromide of potassium. What has been said of the latter in this respect, therefore, may be applied to the former. There is the same facility of absorption and of elimination, and the same variations of them with varying conditions of the stomach and its contents. The taste of the bromide of ammonium is rather more strongly saline and disagreeable than that of the bromide of potassium, and is therefore less readily taken. When swallowed, the stomach tolerates one as well as the other; at least this is true of moderate doses. In large quantities, the ammonium salt is more irritating to the mucous membrane than the potassium salt. The two may be united in the same prescription, if there is any reason for doing so; and they will pass into and out the body as readily as if they were not travelling in company.

It appears, moreover, from the researches of physiologists,* that the bromide of ammonium, while in

* *Vide* Experiments with the Bromide of Ammonium, Part 2.

the system, exerts upon it an action similar to that of the bromide of potassium. It may be given so as to deaden the reflex sensibility of the fauces and palate, to diminish the cerebro-spinal circulation, and to lessen general reflex sensibility. It is also apt to produce acne on the cutaneous surface, of the same character as that which so often accompanies the exhibition of the other bromide. Mental activity is repressed by it; and large and continued doses will induce a sort of hebetude and intellectual dulness. Dr. Brown-Séquard is of opinion that the bromide of ammonium exerts a special influence over the medulla oblongata and upper parts of the spinal cord,* and deduces some important therapeutic indications therefrom.

But, notwithstanding the similarity of the physiological action of these two salts, the more unpleasant taste and greater irritating qualities of the bromide of ammonium render it less agreeable to patients, and less convenient of administration than the bromide of potassium.

Therapeutic Action. — The bromide of ammonium is not largely used alone. It has been recommended by a few practitioners in pertussis, and is undoubtedly capable of rendering some service in that com-

* Lectures on the Diagnosis and Treatment of Functional Nervous Affections, p. 82.

plaint, in the way of diminishing spasmodic action, and especially of allaying hyperæsthesia of the pharynx and larynx. It has also been recommended in nervous affections, particularly those of the ganglionic system, and in glandular enlargements. From my own observation of its action in these affections, I am not inclined to regard it as equal in therapeutic value to the bromide of potassium.

Its principal therapeutic value is to be found in its association with, and not in its substitution for, the potassium salt. I have not observed that the hypnotic action of the single dose of the latter agent is increased by associating bromide of ammonium with it; but the sedative influence which the continued dose of the bromide of potassium exerts over the reflex power of the nervous system seems to be increased by such an addition. Ten grains of the bromide of potassium, with three or five grains of the bromide of ammonium, given together, three times a day, produce a greater sedative influence than twelve or fifteen grains of either of them administered three times a day separately. Professor Brown-Séguard first called attention to the increased sedative power obtained by the association of these remedies. Speaking of their united action, he says: * "I have observed a very curious fact in

* Lectures, ut supra, pp. 86-7.

employing together the bromide of potassium and the bromide of ammonium. I have ascertained that, without producing the phenomena which constitute what has been called bromism (anæsthesia of the throat, nostrils, &c., weakness, especially of the neck and spine, lack of will, sleepiness, stupidity, &c.), I could give in a day sixty grains of the bromide of potassium and thirty grains of the bromide of ammonium, while, if I replaced the thirty grains of this last salt by only twenty grains of the other salt, so as to give eighty of the bromide of potassium alone, *bromism* was usually produced. And also, if, in place of the sixty grains of bromide of potassium, I added to the thirty grains of bromide of ammonium from twenty to twenty-five grains of this last salt, *bromism* was again produced. So that ninety grains, *i.e.*, a larger dose of the two remedies taken together, did not produce *bromism*; while a smaller dose of either employed alone did produce it. If we call bromism a bad effect, and if we call a good effect the favorable influence of these remedies in epilepsy and other neuroses, it can be said that their association in certain doses diminishes their bad effect, while it increases their good effect."

Fcheverria * states, on the contrary, that he has

* On Epilepsy, p. 316.

not "recognized any marked adjuvant effect" from the addition of the bromide of ammonium to the bromide of potassium, — a mixture "which renders more unpalatable to the patient the already disagreeable taste of the solution of bromide of potassium." My personal experience, based not so much on the treatment of epileptics as on that of neuroses in general, leads me to coincide with the opinion of Professor Brown-Séguard. The combination of the two salts exerts a happier sedative influence than either of them separately.

It is interesting and instructive, in this connection, to compare the rules laid down by Voisin, for the exhibition of the bromide of potassium in epilepsy, which have been previously quoted, with those laid down by Brown-Séguard for the exhibition of the mixture just described in the treatment of the same disease. The similarity of the two statements enhances the value of each. Brown-Séguard says: * "There are rules relative to the treatment of epilepsy by the bromides of potassium and ammonium, employed together or separately, which are of so great importance that I will take this opportunity to mention them briefly, postponing the details till I treat especially of epilepsy. These rules are: —

"1. That the occurrence during the day of the sleepiness caused by those remedies can be avoided by giving relatively small doses in the daytime, and a much larger dose late in the evening.

"2. That the quantity of these medicines to be taken each day must be large enough to produce an evident, though not complete anæsthesia of the fauces and upper parts of the pharynx and larynx: that daily quantity being (according to the idiosyncrasy of the patient) from forty-five to eighty grains of the bromide of potassium, and from twenty-eight to forty-five grains of the bromide of ammonium, when only one of these salts is employed, and a smaller quantity of each, but especially of the second, when they are given together.

"3. That, considering that the bromide of potassium (and, in a small degree, also the bromide of ammonium) very rarely produces any good effect against epilepsy, without producing also an acne-like eruption on the face, neck, shoulders, &c., and that there seems even to be a positive relation between the intensity of the eruption and the efficacy of the remedy against epilepsy, it is most important to increase the dose when there is no eruption, and also when the eruption is disappearing, unless the dose given in the twenty-four hours is already so large that any increase of it produces great sleepiness in the daytime, a decided lack of will and

of mental activity, dulness of the senses, drooping of the head, considerable weakness of body, and a somewhat tottering gait.

"4. That it is never safe for a patient taking either of the bromides, or both, and receiving benefit therefrom, to be even only one day without his medicine, so long as he has not been at least fifteen or sixteen months quite free from attacks. Indeed, it is very frequent that patients neglecting this rule are seized again with fits, after an immunity of several or of many months, one, two, or only a few more days after the interruption of the treatment. In several cases, even after an apparent cure of ten, eleven, or twelve months, and, in one instance, of thirteen months and a few days, there has been a reappearance of the disease, after the treatment had been abandoned for only a few days, or a week.

"5. That the debilitating effect of the bromides in patients already weak — as in most epileptics — ought to be prevented or lessened by the use of strychnine, arsenic, the oxide of silver, ammonia, or cod-liver, cold douches or shower baths, and, of course, wine, and a most nourishing diet.*

* In making use of strychnine or arsenic, it must be kept in mind that not only the bad influence of the bromides, but also their favorable influence against epilepsy, can be diminished by these powerful agents (especially strychnine), and that it is, therefore, necessary, when these agents are used, to increase the

"6. That iron and quinine — which are generally injurious to epileptics, except in cases in which their nervous affection is caused, or at least aggravated by chlorosis, anæmia, or malarial cachexia — are more particularly injurious in cases in which the bromides are taken.

"7. That a gentle purge every five or six weeks usually gives a new impulse to the usefulness of the bromides against epilepsy."

Dose.—The bromide of ammonium may be given in the dose of thirty grains or less: more than that amount given at once is apt to irritate the stomach. It may be administered in water or syrup, or with a bitter infusion or tincture. If there are indications for doing so, it may be united in a prescription with bromide of potassium, iodide of potassium, iodide of ammonium, iodide of sodium, bromide of lithium, carbonate of ammonia, valerianate of ammonia, carbonate of soda, chloric ether, and the like.

dose of the bromides. The antagonism between strychnine, which acts in increasing the reflex faculty of the nervous centres, and the bromides, which diminish this faculty, may be so great as to produce almost a complete annihilation of the influence of the bromides and partly that of strychnine. In one case 132 grains a day of the bromides were taken without the least appearance of bromism, and without any controlling effect over epilepsy, when the patient was taking about one-third of a grain of strychnine a day; while he was strongly bromized under the influence of 80 grains a day of the bromides, when he was not taking strychnine."

BROMIDE OF LITHIUM.

The bromide of lithium is a white, deliquescent salt, having a saline and somewhat bitter taste. On account of its deliquescence, it should be exhibited in solution and not in powder. It contains about 92 per cent of bromine; and in this respect differs from the bromide of sodium, which contains 78 per cent of bromine, and from the bromide of potassium, which contains 66 per cent.

The physiological action of the bromide of lithium is very similar to that of the bromide of potassium and bromide of ammonium. It produces sleep, diminishes reflex sensibility and muscular power. According to Weir Mitchell,* it causes more rapid and intense sleep than the bromide of potassium. I am not aware of any experiments that have been made with it for the purpose of determining its rate and time of absorption and elimination. It is probable that in these respects it resembles the bromide of potassium, as it does in its therapeutic action. My clinical experience with it, which is not large, confirms the statements of Professor Mitchell in the article just referred to;

* American Journal of Medical Science, Oct. 1870, p. 443.

viz., that it "acts efficiently in some cases of epilepsy where bromide of potassium has failed; that it is thus efficient in lesser doses than the salt just named; and that, as an hypnotic, it is superior to the potassium salt and the other bromides." The only objection that I know of to its use is its cost, which, at present, is so great as to prevent its general employment. When the bromide of potassium fails to exert its ordinary physiological action, — a failure which sometimes, though rarely, occurs, — or when the stomach becomes disgusted with it, or the system unpleasantly affected by it, the bromide of lithium may be advantageously substituted for it. I have met with cases in which the bromide of potassium produced quiet and pleasant sleep for a time, and then failed to do so, and in which the lithium salt at once acted as the potassium salt did at first.

It may be given in the dose of from ten to twenty grains or more, three times a day. It is not often that it will be requisite to give sixty grains a day. Like the bromide of potassium, it may be exhibited in the form of a single comparatively large hypnotic dose at night, or in the form of the continued dose, repeated several times a day and for weeks together. The continued use of it will produce acne as rapidly and as decidedly as the bromide of potassium.

BROMIDE OF SODIUM.

The bromide of sodium closely resembles in its appearance, taste, solubility, and physiological action, the bromide of potassium, bromide of ammonium, and bromide of lithium. Its taste is, perhaps, rather less unpleasant than the others. M. Voisin regards its physiological action and therapeutical value as equivalent, or nearly so, to the bromide of potassium. Dr. Amory has been led by his experiments to regard it as a less valuable therapeutic agent than the potassium salt. It possesses no decided advantages over the other bromides just named, and therefore it is not desirable to substitute it for them in the treatment of disease.

PART II.

EXPERIMENTS

ILLUSTRATING THE PHYSIOLOGICAL ACTION

OF

THE BROMIDE OF POTASSIUM AND
BROMIDE OF AMMONIUM

ON MAN AND ANIMALS.

By ROBERT AMORY, M.D.,

ANNUAL LECTURER FOR 1870-71 ON THE PHYSIOLOGICAL ACTION OF DRUGS ON
MAN AND ANIMALS, IN THE MEDICAL DEPARTMENT OF HARVARD
UNIVERSITY; FELLOW OF AMERICAN ACADEMY OF ARTS
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MEDICAL SOCIETY, ETC.

PROPOSITIONS.

A. — Bromide of Potassium is absorbed readily by any portion of the healthy mucous membrane with which it is placed in contact.

B. — This drug is largely and mainly eliminated with the urine; during the first day the largest portion passes out of the system, less during the second day, and so on until there is none left in the system.

C. — The skin assists in the elimination of this drug from the system on the second as well as the first day.

D. — The loss of reflex action is due to the diminution of blood in the periphery of the nerves, and also of the central nervous system; this last occurring after the first.

E. — The action of Bromide of Potassium on the nervous system may be explained by its action on the capillary, arterial, or central circulation.

PHYSIOLOGICAL ACTION
OF
THE BROMIDE OF POTASSIUM
AND AMMONIUM.

CHAPTER I.

ABSORPTION.

BROMIDE of Potassium is absorbed readily by the mucous membrane of the mouth. This proposition is illustrated by the following experiments:—

Exp. I.—Under the effects of ether, a dog was operated upon for ligature of the œsophagus. When this had been accomplished, a solution containing 160 grains of this salt was placed in the mouth of the animal. In ten minutes after the contact of the drug with the buccal mucous membrane, some blood (3j.) was drawn from the carotid artery, and, examined by means of chlorinated water and bisulphide of carbon, gave the peculiar reaction of the liberation of bromine; viz., a reddish-yellow color.

The bromide must have been absorbed by the mucous membrane of the mouth and pharynx, for

great care was taken to prevent the contact of the solution with any other tissue.

EXP. II. — A strong solution of this same salt was retained in the mouth for five minutes, and then thoroughly ejected; the mouth was carefully rinsed out with fresh water and wiped dry, and again rinsed. The solution was kept in the anterior portion of the mouth, and by the tongue prevented from touching the pharynx.

The examination of 25 cubic centimetres of urine, passed two hours and a half afterwards, indicated the presence of a large amount of the bromide.

In these and other experiments not here related the bromide was present in the blood of dogs and in the urine of man, to whom the drug had been administered by means of the mucous membrane of the mouth *only*; and it is thus proved that bromide of potassium can readily be absorbed by this portion of the mucous membrane. There is no doubt that the absorption is rapidly accomplished. This is shown in these two experiments and by the following: —

EXP. III. — Ten grains in an aqueous solution were introduced by an œsophagean tube into the stomach of a rabbit. Six minutes after, 3 iss. of blood taken from the carotid artery were carefully

analyzed * and found to contain (by calculation from the amount of bromine obtained) three and three-fifths milligrammes (or $\frac{55}{1000}$ of a grain) of bromide of potassium. We supposed the weight of the rabbit to be 6 lbs. or 5,250 grains; by calculation, the inference seems reasonable that, if there was as much of this salt in the rest of the blood as in this specimen, we had recovered about one-third of the whole quantity given. Considering that in an analysis of thirty-five centigrammes of bromide of potassium, which had been previously dissolved in an ounce of urine, one-tenth part was not recovered in the process, it is fair to suppose that more of the salt might have been recovered in the above-named experiment than we actually obtained. In six minutes, therefore, a large portion of the drug was absorbed. Compare this with an experiment made upon man:—

EXP. IV. — Eight grains of the salt were swallowed, and the mouth carefully rinsed out with water and wiped several times. Five minutes after, ʒ ij. of saliva were collected, which, analyzed qualitatively, was found to contain a large amount of a bromide; an intense brownish-yellow tinge

* The details of this analysis will be reserved for another portion of this paper.

was given to bisulphide of carbon by the addition of two or three drops of strong chlorine water. In another experiment, a *slight* indication of the presence of a bromide occurred in urine collected twenty minutes after the ingestion of twenty grains.

EXP. V. — Some blood, drawn from the carotid artery of a rabbit ten minutes after the exhibition of 10 grains by the stomach-tube, failed to show the presence of any *free* bromine. By adding, however, the chlorine water, a bromide was decomposed, liberating the bromine.

EXP. VI. — The body of the experimenter was immersed for fifteen minutes in a warm bath (96° F.), containing an ounce and a quarter of bromide of potassium to 20 gallons of water. The urine passed during the night and following morning was retained, and then a portion carefully tested for a bromide. No indication of its presence was discovered. In this case no eruption of the skin occurred, showing that prolonged contact of the drug does not irritate the skin.

EXP. VII. — At another time about 3 ij. of this salt were dissolved in a foot-tub containing five gallons of water. The feet and ankles were then immersed for 18 minutes, the temperature of the water being kept at about 72° F.

The urine passed three hours after showed, by the usual test, that a salt of bromine was present in it. It is important to state that no bromide had been taken for four weeks previous to this experiment.

SUPPLEMENTARY EXP. (a). — Thinking that the results of these two experiments might be doubted, they both were repeated under somewhat different conditions. I asked my friend Dr. — to dissolve ℥ x. of br. of pot. in xx. galls. of water at a temperature above 98° F. He informed me that there was not quite enough water to cover his whole body, which was kept immersed for 12 minutes, the temperature of the solution varying from 108° to 102° F.; he afterwards washed the body with fresh water, and then wiped it dry. He reported that he felt more languid than usual after a hot bath (the temperature of the water was very high), and imagined that he experienced a saline taste half an hour after the bath. I carefully analyzed his urine (℥ v.) passed during 12 hours after the bath, but could not find the *least* trace of a bromide.

(b) At night I soaked my feet for ten minutes in a solution* of this drug, and the next morning took a cold sponge bath containing ℥ ij. of the bromide to a pail of water. ℥ iv. of urine passed during that day gave a very decided reaction of a salt of bromine. Thus by a warm bath no bromide had

* Temperature of 70° F.

been eliminated nor absorbed; while after a cold bath its presence in the urine proved its absorption by the skin. This agrees fully with the statement quoted by Dr. Stillé,* that in a warm bath at 96° F. the body exhales, and at a temperature below 80° the body imbibes moisture.

This drug can be absorbed also by the rectum; because, in the following experiment, —

EXP. VIII. — A rectal injection of beef tea, containing an ordinary dose of bromide of potassium, was given to a patient, and the urine passed during the next 18 hours collected. ℥ ij. of this gave a decided reaction of a salt of bromine. This and other experiments since undertaken prove that the rectum will absorb this drug, when dissolved in a vehicle which will prevent the local irritation of the mucous surface. When given in a *small* amount of warm water by the rectum, irritation may be induced, with a tendency to diarrhœa and tenesmus.

PROP. A. — These and other experiments not here related prove that bromide of potassium is absorbed readily and rapidly by the mucous membrane, *generally*, and that it is not readily absorbed by the skin except at a temperature below that of blood heat.

* *Materia Medica and Therapeutics*, vol. i. p. 52.

Is bromide of potassium decomposed in the system, and may a chemical transformation explain its method of action?

Dr. Bill, in a number* of the American Journal of Medical Sciences, states that there may be a chemical interchange *in the blood* between chloride of sodium and bromide of potassium, and says that when bromide of potassium meets chloride of sodium, chloride of potassium and bromide of sodium result; that is, outside of the body. He also states that, as there is an excess of chlorides eliminated after the use of this drug, perhaps its action may be explained by there being a diminution of the chlorides in the blood. I have taken considerable trouble to determine the correctness of this theory, and can find no other authority for this chemical reaction, and cannot see how such a theory can be proved by the known methods of chemistry.

His argument is based upon the fact that there is an increase in the amount of chlorides eliminated by the urine after the ingestion of the bromide in doses less than what may endanger life. He tabulates a report of the quantity of chloride of silver obtained from the urine of a person taking daily doses of the bromide; and, also, finds an increase

* July, 1868.

in the amount of potassium eliminated by the kidneys. He does not, according to this table, separate the bromide of silver from the chloride of silver.

Consequently an increased amount of the mixed bromide and chloride of silver (which are thrown down *together* by nitrate of silver), found in the urine after the use of this drug, proves no more than that the bromides and chlorides are eliminated together in the urine. In some analyses which were conducted under my supervision by Dr. Wood,* it was found that this increase in amount of the nitrate of silver precipitate was due to the union of bromine and chlorine with the silver, and the bromine was then separated, leaving, I should judge, only the normal amount of chlorine behind.

In our experiments the proportion of bromine to chlorine eliminated was as 2 : 1.

Another refutation of this theory might be adduced from the fact that bromide of sodium rarely, if ever, produces a physiological action which is similar to that produced by the bromide of potassium.†

* Instructor in Chemistry Med. Dept. Harvard University.

† Though it is stated by Voisin that the action of bromide of potassium and of bromide of sodium is the same, this is not confirmed by my experiments with the latter. Bromide of *lithium*, on the contrary, does produce an action similar to that of bromide of potassium, and is used by Dr. S. Weir Mitchell in practice on account of its more intense action. If a solution

CHAPTER II.

CHEMICAL PROPERTIES OF BROMIDE OF POTASSIUM.

It would be in place here to mention some of the chemical properties of bromide of potassium, and especially to give in detail the process by which our investigations were conducted.

This is a very fixed salt, losing no weight by fusion at a red heat. The stronger acids with difficulty liberate the bromine at an ordinary temperature. Potassium has a stronger affinity for chlorine than for bromine, and a stronger affinity for bromine than for iodine. If to a solution of bromide of potassium a drop or two of strong chlorine water be added, the bromine is set free in the liquid; and ether, chloroform, or bisulphide of carbon will absorb the gas, producing a strong brownish-red tinge to either. The bisulphide of carbon we found the most serviceable in this process.

This is a very delicate test, M. Rabuteau* having

of the bromide of lithium is poured into the ear (previously reddened by stimulation) of a rabbit, it causes a sudden pallor of the ear, which lasts for several hours after, the temperature also being noticeably lower.

* Gazette Hebdomadaire, April 24, 1868.

discovered an exceedingly small quantity; the only objections to this method being that the organic matters in the urine interfere with its reaction, and that an alkaline fluid may also prevent the decomposition. To overcome these difficulties, we evaporated the urine to dryness, and then ignited the residue, keeping it at a red heat for about half an hour. Then to the solution a drop or two of nitric acid was added, until blue litmus paper was changed to red. Next the chlorine water was added, drop by drop, until the peculiar reddish color was visible. This color was concentrated by the addition of two or three drops of the bisulphide of carbon, which, on agitation, absorbed all the bromine and settled at the bottom of the test-tube. Too much chlorine forms a white precipitate, chloride of bromine; therefore caution is required in adding the chlorine water. Sometimes in the decomposition of the organic matters the bromine escapes, so that the addition of a small fragment of pure soda or potassa may be placed in the urine to take up the bromine.* M. Rabuteau prefers the soda to potassa, because the former is more easily decomposed by nitric acid and chlorine. This was our test for the presence of a bromide.

The process for calculating the amount of a bro-

* *Op. cit.*

mide present may be best described by giving a detailed account of *one* experiment:—

EXP. IX. — Thirty-five centigrammes of bromide of potassium were dissolved in an ounce (31 grammes) of urine. The urine was evaporated to dryness, charred and ignited. The residue was then treated with boiling water and filtered from the carbon. But little of the coloring matter of the urine was present in the filtrate. Nitrate of silver was then added in excess, and the mixture allowed to stand twenty-four hours. The precipitate was washed thoroughly with boiling water, acidulated with a few drops of nitric acid. This precipitate consisted of a mixture of the bromide and chloride of silver, with some of the coloring matters of the urine. To free the latter, an excess of ammonia was added to dissolve the mixed bromide and chloride, leaving the coloring matters behind. The residue was washed with water. The filtrate was acidulated with nitric acid, and bromide and chloride of silver again precipitated. This precipitate was then washed with acidulated water as before. The filter paper had previously been dried and weight ascertained. This, after being dried, was now weighed with its precipitate and found to have increased to the amount of 6.075 grammes. Of this a portion was placed in a crucible, the weight of which had been previously ascertained.

The weight of crucible without contents was 6.705 grms.
 The weight of crucible with contents was $\underline{7.025}$ grms.

Thus the bromide and chloride of silver
 weighed $\underline{.320}$ grms.

This portion was then fused in the crucible, and chlorine gas, washed in sulphuric acid, was passed over by means of a porcelain tube fitting into the platinum cover of the crucible. The chlorine displaces the bromine which is set free. (This process must be continued till the crucible ceases to lose weight.) From the loss in weight the amount of bromine may be calculated from the following proportion: * —

1. "The difference between the equivalents of chlorine and bromine : the equivalent of bromine = the loss of weight : \times ." Thus $44.54 : 80 =$ loss of weight : \times

From the amount of bromine originally in the crucible may be calculated the amount of bromine in the whole precipitate as follows:—

2. Weight of the whole mixed precipitate : weight of that in the crucible = \times (bromine in the whole) : bromine in the crucible.

From the amount of bromine in the whole mixed precipitate, the amount of bromide of potassium recovered may be determined thus:—

* Quantitative Chem. Anal. Fresenius, by Bullock & Vacher, p. 446, 1865, Churchill, London.

3. Equivalent of bromine : equivalent of bromide of potassium = weight of bromine found in the mixed precipitate : \times (or bromide of potass.).

From these three problems the result of the preceding experiment was obtained. It was supposed that the bromine discovered in this process was united with potassium which was found in the urine. The method of obtaining the amount of this is so difficult and protracted that we are contented with Dr. Bill's * statement, that in his experiments the potash was increased "fourfold" in the urine when bromide of potassium was taken.

The result obtained was as follows : —

Weight of whole mixed precipitate . .	= 0.607 grms.
" " crucible with contents . .	= 7.025 "
" " " without " . . .	= 6.705 "
	—
" " bromide and chloride of silver	= 0.320 "
First weighing after passing over the	
chlorine	= 7.020 "
" loss of weight	= 0.005 "
	—
Second weighing after continuation of same	
process	= 7.012 "
" loss of weight	= .013 "
	—
Third weighing	= 6.991 "
" loss	= .034 "
	—

* American Journal of Medical Sciences, July, 1868.

Fourth weighing = 6.965 grms.
 „ loss = .060 „

Fifth weighing = 7.025 „
 „ loss = .060 „

Sixth weight the same. Then using the rules of proportion above stated, —

$$44.54 : 80 = .060 : X = 111 \text{ grm. or bromine in crucible.}$$

$$320 : 607 = .111 : X = .211 \text{ grm. or bromine in the whole amount of precipitate.}$$

$$80 : 119.11 = .211 : X = .314 \text{ grm. bromide of potassium.}$$

Thus of .350 of a gramme dissolved in urine

.314 „ „ was recovered.

.036 lost by impure chemicals and an insufficient laboratory.

This was the result of our first quantitative analysis for bromide of potassium, and the process is given in detail to show that all ordinary caution was exercised that could occur to our minds.*

The details of the analyses to be hereafter mentioned will not be transcribed.

M. Rabuteau mentions in a recent publication,†

* In these analyses the ordinary commercial nitrate of silver (lunar caustic) was used, which may be the cause of our not obtaining more accurate results. This would not, however, interfere with the *relative* results, which are the main points to be considered.

† Gazette Hebdomadaire, 1868.

that having tested the urine for two months, and having found a salt of bromine each time, and this when only one gramme had been given, he was so much surprised that he obtained some urine from a person who had not been taking a salt of bromine, and still found a trace of bromine present by the qualitative test before mentioned. In seeking for an explanation of this phenomenon, he ascertained if a quantity of urine exceeding one hundred and fifty grammes ($\bar{3}$ vj. +)* was employed he almost invariably detected some bromine. In any less quantity no bromine was perceptible in ordinary urine. Therefore he is disposed to add this metalloid to Bernard's list † of fourteen simple bodies found in man and the higher order of animals.

* We never employed in our analyses more than one hundred grammes at any one time.

† See Cl. Bernard, *Sur les Substances Toxiques et Médicamenteuses*, Paris, 1867, p. 40.

CHAPTER III.

EFFECTS UPON THE SECRETIONS.

WE will now consider the effects of bromide of potassium upon the secretions. The quantity of the saliva does not appear to be modified in any degree. This drug appears to a very great extent in this secretion, and can be detected for twenty days * after one gramme has been taken. Several times I have detected its presence in the saliva within a very few minutes after its administration, and have proved its presence for a long time afterwards, almost as long as it is present in the urine. Voisin states that this drug appears very early in the saliva, and remains there as long as it can be detected in the urine. His statements are confirmed by some experiments of Rabuteau, before alluded to; and, as I have not found any cause to doubt these observers, the details of my experiments have not been given. There seems to be no chemical decomposition with the gastric juice.

When pure, it at first *may* stimulate the mucous membrane to throw out its mucus; but, after one or

* Gazette Hebdomadaire, 1868, p. 582.

two days' use, its tendency is to dry up this secretion in the mouth and fauces, and especially in the excreta of the intestinal canal, which, with a few exceptions, are dry, hard, and infrequent.

Excretions. — With regard to its effect upon the kidneys there is much debate. Does it or does it not produce diuresis? It is difficult to judge of this from various reasons. The quantity of urine passed in twenty-four hours varies in different persons, and in the same person at different times. The state of the weather, of the skin, of the general health, diarrhœa, constipation, quantity and fluidity of blood, all show their effect upon the urinary secretion. Therefore, it is almost impossible to place an individual constantly in the same relations. This may explain some of the inconsistent results of various experimenters.* If bromide of potassium does augment this excretion, it is probably due to the change of blood tension in the kidneys, on which Bernard has found that the activity of kidney secretion in part depends.† Dryness of the mouth, fauces, and of the excreta of the intestinal canal follows its continued use, and the stools become dry, hard, and infrequent. The constipating effect upon

* Gazette Hebdomadaire, 1868, p. 582. Damourette and Pelvet, Bulletin Général de Thérapeutique, vol. lxiii. p. 296.

† Liquides de l'Organisme, Baillièrè et fils, t. 2, p. 155.

the intestine, shown by these effects, is probably caused by a diminished secretion from the mucous surface, by a diminution of the reflex sensibility and of the muscular contractility. This may be seen by its action on the pharynx and all the external portions of the mucous membrane. That this effect is not caused by the immediate contact of the drug may be known from the fact, that the injection of a weak or a strong solution of this salt into the rectum will create an irritation of the bowel, causing the evacuation of any fæces contained therein.

I have heard of two cases of chronic constipation relieved by a dose of the bromide, and where have been taken large doses of the ordinary cathartics without producing an intestinal discharge; in other instances one or two doses* of the bromide have caused an evacuation of the bowels. These fæces, carefully and repeatedly analyzed, give no indication of the presence of a bromide.

In such cases the primary effect of the drug seems to be exerted upon the muscular fibres, inducing their contraction and thus causing an excessive peristalsis, from which there results, sometimes, a violent expulsion of the fæces. When, however, the use of the drug is prolonged, this

* In these cases, if the use of the bromide was continued for a longer time, the fæces gradually became more solid in character, and finally the bowels became constipated.

sensitiveness is less marked; and the reflex action becomes diminished.

Other cases have been *recorded* where this hypercatharsis was so marked that the drug was discontinued.

Out of thirty-seven cases treated for epilepsy by this drug,* two patients had to discontinue its use, because catharsis was produced. These cases are, however, very rare; and we are disposed to place them all under the same conditions.

The excretion from the pulmonary mucous membrane, after the continued use of this drug (that is, when the system is under its influence), is diminished; and, if the influence is maintained, a dry and annoying cough may be induced.† Hoarseness, aphonia, dry cough, laryngeal pain, sub-crepitant râles,‡ all demonstrate this dryness of the mucous surface. If, however, the drug is impure, it having been sometimes combined with the iodate of potassium, opposite results may take place; that is, a catarrhal affection of the mucous surfaces. The difficulty of expiration,§ oppression, &c., tend to show a loss of muscular contractility in the pulmonary tissue.

* Williams, abstract in Boston Medical and Surgical Journal, lxxi. p. 422.

† Hameau, Gazette Hebdomadaire, 1868.

‡ Voisin, Bulletin Général de Thérapeutique, lxxi. p. 101.

§ Ibid., p. 102.

Milk drawn from the breasts of a lady who had been regularly taking bromide of potassium was analyzed for the bromide, and no trace of the salt could be detected.*

CHAPTER IV.

ELIMINATION.

LET us next pass to the elimination of this drug from the system, its ways and conditions, before examining its action upon the economy. Voisin† has stated that, as the breath smells strongly of bromine after the continued use of bromide of potassium, it may be partially eliminated in this way. If this is a fact, then this salt must be decomposed, and the bromine, being volatile, may escape. We find a bromide in the saliva, urine, and sweat, and in each of these a large amount of potash.

EXP. X. — We find that three different persons exhaling for fifteen minutes, after the continued use of bromide of potassium, through glass into a test-tube filled with water and bisulphide of carbon, do

* Medical Times and Gazette.

† Op. cit.

not produce the yellow color of bromine. On adding a few drops of strong chlorine water, the bisulphide does not change its color. Therefore we conclude that bromide of potassium is neither decomposed nor eliminated by the breath. The peculiar smell this eminent experimenter distinguished is probably no other than that produced by other salts of potassium, such as the chlorate of potassa and the iodide of potassium.* As this drug, passing through the mouth, mingles with the saliva and the mucus from the mouth, pharynx, and nose, there could not be any use in analyzing the excretions from the mucous surface of the lungs.

I do not consider that the saliva assists in the elimination of any drug, because, unless accidentally expelled, it passes into the stomach and is again absorbed into the economy. The ease and rapidity of the absorption of this drug by this secretion have already been mentioned.

That bromide of potassium is expelled with the urine has been noticed by Voisin, Damourette and Pelvet, in the "*Bulletin Général de Thérapeutique*," and by many other observers. My experiments

* It may perhaps be noticed that after the use of certain alkalies a fetid smell is given off by the mouth, and a disagreeable taste experienced by the patient; so also is the same effect noticed in certain persons who have a habit of biting and chewing up portions of the lining membrane of the inside of the mouth and lips.

and observations have been made with the particular view of determining under what conditions this occurs; and if certain conclusions here mentioned are not altogether new, the recital of them may be pardoned, inasmuch as the results arrived at are independent of others, and because the same chemical process* has not been carried out by any of the above writers. Great care and much time have been devoted to this subject; and the results, it is hoped, may be of practical value.

It has been already stated that M. Rabuteau has found bromine in normal urine. This, however, could be found only in a quantity much exceeding one hundred and fifty grammes. It would be proper to state that at no time did we use so large a quantity as this in our analysis. This observer states that he has found for twenty days traces of a bromide in the urine of a person who had taken only one gramme (grs. xv.) of this salt, and that traces could also be found in the saliva of the same person during the same period.

In our experiments we could find traces only at the end of forty-eight to fifty-two hours after a single dose. If, however, the dose was continued for a few days, the presence of a bromide was apparent for a much longer time, varying with the

* Vide p. 127 *et seq.*

amount taken and the time the exhibition of the drug was continued. The results of the experiments of M. Voisin * must be doubted, if M. Rabuteau † is correct; the idea of the former being that there is a small quantity of bromine present in normal urine; for in their chemical analysis, 325, 400, and 1,000 grammes of urine were used; and the quantity of pure bromide of potassium crystals varied considerably in each analysis. From the 400 grammes, .40 were obtained; from 1,000 grammes, .095; and from 850 grammes, 3.75 grammes. Their method of analysis is not related.

Always, during the first forty hours after an ordinary dose, I found distinct signs of the presence of a bromide. The experiments were repeated very often, and the same result was obtained.

EXP. XI. — During twenty hours, fifty grains of bromide of potassium were taken in five different doses. The urine passed during the first twenty-four hours was preserved, and amounted to fifty-one ounces. Of this about two ounces were analyzed for the quantity of bromide eliminated by the kidneys; from this amount a little more than one grain, and, by calculation, from the whole fifty-one ounces $28\frac{72}{100}$ grains were recovered. Thus more than one

* Op. cit.

† Vide p. 131.

half the amount of bromide of potassium was eliminated during twenty-four hours after the first dose was taken.

Another experiment was undertaken for the purpose of finding how much of the drug was eliminated during the second twenty-four hours after a dose of the drug whose action we are considering.

EXP. XII. — Ten grains were taken, and, of the thirty ounces of urine passed during the second twenty-four hours, two ounces were carefully analyzed; and, by our process and calculations before mentioned, there were recovered about three and three-quarters grains. Thus a third of this salt is eliminated during the second twenty-four hours.

These, combined with other experiments for qualitative analyses for a bromide, show that —

PROP. B. — Bromide of potassium is largely and mainly eliminated with the urine, and during the first day the largest quantity passes out of the system, and less during the second day, and so on till there is none left in the system.

Several times were the fæces analyzed and tested for the presence of a bromide, but always with a negative result. A large amount of caustic soda was added before each analysis to allow any free

bromine, which might have been volatilized during the ignition of organic matters, to combine in the formation of bromide of sodium. We are forced to conclude either that our chemical process in itself was deficient, or that bromide of potassium is not eliminated with the fæces. In some subsequent investigations for the action of bromide of ammonium, the fæces were carefully collected and analyzed by two members of my class, and no trace of a bromide could be detected. Considering that so large an amount of the salt is eliminated by other organs and the easy absorption by the mucous membrane, it is fair to suppose that, ordinarily, the bromide of potassium, when given in small doses, does not pass through the intestinal canal, but is absorbed before it can mingle with the effete contents of the bowels.

M. Voisin stated that, because an eruption of the skin occurred after the continued use of this drug, this organ assisted in its elimination. Acne may be produced from the action of this drug; but why may it not be caused by the altered condition of the capillary circulation, and thus induce those inflammatory conditions of the skin due to an obstruction of the circulation? Indeed M. Hardy in his lectures (*Sur les Maladies Cutanées Accidentelles*) considers modification of the circulation an important and often neglected cause of acne. As

we shall endeavor to show hereafter, bromide of potassium does produce a certain effect upon the capillary circulation. To show that this salt is eliminated by the skin, the following experiment was tried, and repeated twice with a similar result.

EXP. XIII. — In the first experiment, forty grains of the drug were taken in two doses three hours apart. Immediately after the second dose I entered a hot-air (commonly called a Turkish) bath, and remained in it one hour, and during that time collected four ounces and a half of perspiration. By a careful analysis, there was found little more than one-third of a grain of bromide of potassium in this amount of sweat. It may be remarked that this amount of excretion from the skin was abnormal; but, by the researches of Valentin,* the daily amount of sweat is about $2\frac{3}{4}$ pounds, or ℥ xxxii . According to approximate calculation, about two grains might have been eliminated in twenty-four hours through the skin.

This, confirmed by repetition at other times, proves that the skin assists in the elimination of this drug; and moreover we are able by —

* Text Book of Physiology, Valentin, translated by Brinton, London, 1853, p. 258.

EXP. XIV. — To determine whether during the *second* day the elimination by the skin continues. Five ounces of sweat were collected in a hot-air bath, entered thirty hours after a dose of eighteen grains of bromide of potassium. This sweat, treated in the usual manner, showed the presence of a large amount of a bromide.

We may then conclude that —

PROP. C. — The skin assists in the elimination of this drug from the system during the second day as well as the first.

Summary of the Means of Elimination.

Of the various organs which carry off the effete matters of the human economy, two only eliminate this drug; viz., the skin and urine. In the exhalations from the lungs and the contents of the rectum, we cannot find any evidence of the presence of this drug.

CHAPTER V.

EFFECT ON THE BLOOD-VESSELS.

WHEN bromide of potassium is applied in an aqueous solution to the interdigital membrane of one posterior extremity of a frog, the web of whose other foot is observed through a microscope, the circulation in the arterioles is seen to be hurried, and the venules become filled with blood of a lighter shade than is generally observed. Soon the circulation grows slower in the arterioles and the calibre of these vessels diminishes, and the supply of blood in the capillary system is scanty, whilst there is less than before in the venules and arterioles.

Half an hour or more after this, when the animal has become calm, the blood returns to the capillary system in rather larger amount than before; and in a little while the constriction or tetanus of the arterioles is noticed, which continues some time. The blood in the venules diminishes and approaches more to the color of that in the arterioles.* If the

* While making these investigations, I attempted some observations on the circulation in the crania of a frog. During the manipulation some blood-vessels were severed, and the field of vision became afloat with blood corpuscles. The addition of

muscular tissue be now observed without the aid of a lens, it will be found to be pale and exsanguine, which is due to this modification in the supply of blood to the capillary system. This same pallor of skin has been noticed by Voisin in his patients who have been for some time under the influence of bromide of potassium.

Meuriot explains the action of this drug upon the circulation, as compared with atropine, in the following words: "It is seen that bromide of potassium acts much more energetically upon the contractility of the vessels than atropine. . . . The bromide of potassium exaggerates the arterial tonicity, tetanizes the arterioles, slackens or arrests the circulation, and produces an oligæmia of the tissues."*

Some experiments have been undertaken in Berlin, by which it has been proved in a satisfactory manner that upon frogs the sedative action of this drug is upon the vasomotory nervous system. The translation of one of these is here given:—

Two frogs were selected, as nearly as possible

the solution of bromide of potassium changed their color to a peculiar rose-red. This occasioned some surprise, but was supposed as something, perhaps, accidental, though unaccountable. However, on reading a memoir by M. Meuriot, I find this same observation with regard to the color produced by the bromide of potassium. This bright red color is probably due to an excess of arterial over venous blood in the capillary system; and, as the tissue around is pale, this color is remarkable.

* *L'Étude de la Belladonne*, Paris, 1868, p. 50.

of the same size : one was used to correct the experiment ; the other was poisoned with potass. bromid.

FROG NOT POISONED.

The metronome was regulated to 100 vibrations per minute. The legs of the animal were loosely bound together in the middle with soft woollen cords, which would not compress the limbs. A vessel of a given size, and with an estimated quantity of distilled water, was placed under the feet ; then quickly, and at once, all six toes of both feet were cut off at the same height. The time, during which the observation was carried on, was two minutes, or 200 vibrations of the metronome.

The blood, flowing by drops, from each foot was counted, and received into the vessel. (The binding together of the legs being easy had no influence on the value of the *experiment*.)

Number of drops falling into the vessel : —

<i>Right leg.</i>	}	in two minutes.	<i>Left leg.</i>
1	}	in two minutes.	2
1			1
1			1
1			1
2			2
1			1
1			1
8			9

FROG POISONED.

(This frog before poisoning drew his foot out of the sulphuric acid mixture, after nine beats of the metronome.)

Waiting till the reflex power in the left leg had sunk to thirty, and in the right to forty-five beats ; then all six toes of both feet were cut off at the same level.

In two minutes only two drops exuded from the right leg.

The left plexus ischiadicus was then divided.

In two minutes ten drops of blood flowed from the left leg.

This is a very valuable experiment, the results of which were confirmed by repetition ; and shows conclusively, in another way, that the action of this drug is through the vasomotor nerves upon the blood-vessels.

CHAPTER VI.

EFFECTS ON THE NERVOUS SYSTEM.

IT might be supposed, from what has been said, that the nerve-cells are impaired by the action of this drug, and that the conductivity of nervous impressions is interfered with. Nerves from animals poisoned by this drug will convey an electrical current, and electricity will pass through a strong solution, or even through the solid salts of bromide of potassium, isolated in a glass tube, without any diminution of the electric current. The retardation of the circulation must have some dependence upon the vascular nervous system.

M. Laborde* made some experiments to determine the condition of reflex action, which are well worthy of examination.

He, at first, caused a frog to absorb by the interdigital membrane three centigrammes of this drug. The animal immediately moved spontaneously after the poison was absorbed. Then he remained quiet, but withdrew the extremity if irritated by pinching, pricking, or galvanism. This re-

* Archives de Physiologie, 1868, p. 422.

sponse ceased in twenty minutes, in the posterior extremities first, and then in the anterior. In another experiment with the same dose the heart pulsated for two hours after cessation of *responsive action*. In several of these experiments with this same dose, he reports that a state of tetanism, lasting two minutes, occurred in eight to ten minutes after the absorption of the poison, which was then succeeded by a collapse. Also at first the muscular fibres contracted, afterwards became relaxed, and would not contract when stimulated.

Now these phenomena all point to the same effect as that noticed in the circulation: over-stimulation of the power of contractility, soon followed by a state of relaxation or collapse.

To what may this be due? To the direct contact of the salt with the tissue? We have seen that almost immediately a large portion of this drug is absorbed and carried by the blood through the various organs and tissues. We have seen no cause to suppose the decomposition of this salt, but that it is bromide of potassium in the blood, in the urine and the sweat.

An experiment was suggested to me by this thought.

EXP. XV. — Both of the sciatic nerves of a frog were exposed and were isolated by glass rods.

Galvanism caused an equal amount of contraction in both limbs. A sponge was then saturated with distilled water and placed on the right sciatic nerve, and another sponge was saturated with a solution of bromide of potassium (3 j. = grs. xiiij.) and placed on the left nerve. The galvanic current was then applied to each in turn. The right foot responded to the stimulation. The left foot did not respond to the stimulation. The left was then thoroughly washed with distilled water from a wash-bottle, and then the galvanism applied. The left foot now responded; the bromide sponge was again applied, and the response ceased. The nerve and tissues were again washed, and the bromide sponge was applied to the right nerve, the water sponge to the left. The left foot contracted by the stimulation. The right foot did not contract by the stimulation.

This experiment was repeated several times with a similar result, the bromide sponge always preventing transmissibility of the shock through the nerve, while the other, water sponge, did not. These sponges were then applied to the brachial plexus of each side, the nerves being isolated on glass rods. The poles of the battery were applied one on the nerve, the other on the extremity. The same result followed the application.

This experiment did not hold good with other animals, such as dogs and rabbits, in all of which the

transmission of electric current was not prevented by the saturated solution of the drug. It is probable that the local irritation of the drug may in some way have caused a partial anæsthesia of the nerve operated upon.

M. Pelvet,* in speaking of this drug, says that it successively attacks the properties of the sensitive and motor nerves, the brain, cord, medulla, and the muscles. The contractility of the heart outlives every other organ. Respiration is indirectly affected.

Eulenberg and Guttman† say that two to four grammes (3 ss. — 3 j.) injected ‡ hypodermically into rabbits kill them in ten minutes, with signs of paralysis of the heart. Internal administration had the same effect. Sensibility and the power of voluntary movement were diminished. They observed always a corrosion of the mucous membrane of the stomach and infiltration of blood. In smaller doses they noticed quiverings in the muscles. They considered that this acted like other salts of potassium, and presented nothing characteristic of bromine. Pure bromine injected in much larger quantities had no such effects, and did not cause death.

On the contrary, M. Laborde considers that bro-

* Gazette Hebdomadaire, Dec. 6, 1867.

† Idem, July 5, 1867.

‡ Near the vicinity of the heart.

mide of potassium is the only drug that produces this peculiar action. Bromide of sodium and potassium had an entirely different effect, even when the latter caused death.

With this last observer I am more disposed to coincide, for his experiments were made with much care and ingenuity, and more clearly demonstrate his views. He states that potassium exalts the power of motility. He endeavors to show, by a very interesting experiment, that bromide of potassium does not destroy the volition, but affects the spinal cord and reflex system only.

One frog is decapitated and laid on the table; in another he causes the absorption of twenty-five centigrammes (four grammes or less). The first loses the sense of reflex response to stimulation, and afterwards exhibits the usual symptoms of tetanus, &c. The decapitated frog shows no loss of reflex action, but is now caused to absorb the same dose of this drug. The absorption occupies a longer time; but when it is accomplished this animal also loses reflex response to irritation, and is soon in the same condition as the first frog. From this M. Laborde concludes that bromide of potassium produces paralysis of reflex action, and has nothing whatever dependent upon the volition of the animal experimented upon. In Eulenberg and Guttman's experiments, it may be noticed that they supposed paralysis of voluntary

movement in warm-blooded animals. This, however, would be difficult to determine from paralysis of the sensitive nerves; and, as M. Laborde* by his experiments on frogs would show, that not only is there voluntary movement in one or two of these experiments, but that, in the two decapitated frogs (in which volition was put in abeyance), the power of reflex action is not lost until after the probable absorption of the drug; and, as we know that this reflex action is very persistent and of long continuance in beheaded frogs, is it not possible that MM. Eulenberg and Guttman confounded the absence of volition with the loss of reflex action?

PROP. D. — The loss of reflex action is due to the diminution of blood in the periphery of the nerve, and also in the central nervous system, this last occurring after the first. Thus we may get loss of sensation first, and then paralysis of reflex action. This is not strange if we compare the syncope produced by excessive hæmorrhage, in which there is anæsthesia and loss of reflex action. Primarily, increased rapidity of the heart's action is caused by the obstruction to the circulation in the smaller arteries and capillaries, from reduction of their calibre. This is a physiological law laid down by Marey.† But, probably, the same influence which

* *Op. cit.*, p. 423. † *De la Circulation du Sang*, Paris, p. 307.

the drug exerts upon the muscular contractility of the arteries would eventually enervate the cardiac pulsations.

The first effect produced by a moderate dose is acceleration of the pulse, which in an hour is succeeded by a retardation and diminished impulse. Thus, this drug has been recommended in nervous irritability of the heart where there is hypertrophied muscular tissue from disease of the mitral valve. Eulenberg and Guttman showed its local action upon the heart, and they thought that the drug caused paralysis of that organ.* In a large dose applied locally, this would very naturally happen; but when applied to an extremity, slowly received into the circulation, a less amount would produce the physiological action peculiar to the drug, without producing paralysis of the heart. In large, or very poisonous doses, Laborde noticed that frogs died very rapidly in a state of muscular relaxation. In moderate doses producing the poisonous action more slowly, the period of tetanism of the muscles occurred first, and subsequently relaxation and death, in which state the muscles remained relaxed for some time.†

* Stillé, *Materia Medica and Therapeutics*.

† This apparent difference may be understood, if we consider that an over-dose would not allow the blood-vessels to contract and to pass through the succeeding steps that we have endeavored to point out in the observations on the capillary circulation.

We have seen by direct experiment that when bromide of potassium in solution, or in a solid form, is placed upon the muscular substance, and electricity is applied, the muscular fibres contract both in frogs and warm-blooded animals. Therefore this drug does not destroy muscular contractility. M. Laborde,* however, observes that the peripheral extremities of a nerve in a frog under the action of this drug, separated from its central portion by a ligature, conduct electricity and produce contractions in the limb; but the central portion (above the ligature), stimulated by electricity, does not produce contractions in this limb. From this he infers that the action of this drug is upon the spinal cord, and not upon the extremities of the nerves; in other words, he infers that in frogs, in other animals and even in man, bromide of potassium arrests the reflex functions of the spinal axis, and that afterwards the extremities of the nerves lose their vitality, and lastly the muscular fibres their power of contractility. Now following out this theory with regard to the

In this case, the vessels are paralyzed and the blood becomes stagnant, thus producing congestion where a therapeutical dose produces *oligæmia*. Congestion in the brain would cause the stupidity and torpor which occurs. There is the same harmony of action upon the blood-vessels and the muscular fibre: where we have tetanus of the former we have tetanus of the latter; relaxation of the former, relaxation of the latter.

* *Op. cit.*, p. 439 — Exp. VII.

heart, we should have the same phenomenon; viz., the nerve (par vagum perhaps) is paralyzed by the drug in the ordinary sequence, — that is, after the nervous centre has lost its vitality, — but that the muscular contractility is preserved, keeping up the cardiac pulsations for a longer or shorter time afterwards. This would seem a very plausible explanation; but then we must not lose sight of the fact that Eulenberg and Guttman, in large doses injected near the region of the heart, produced paralysis of this organ. Was this caused by enervation of the nerve, commencing at its central portion, or by destruction of the muscular contractility? If both of the pneumogastric nerves are severed, the animal may live several hours with great impediment of circulation and respiration, and finally die in a state of exhaustion. Taking into consideration this fact, and that muscular contractility persists after death, we should infer that the drug causes paralysis of the nerves which regulate the heart's action. Now in frogs the power of muscular contractility is very active and persistent, much more so than in any warm-blooded animals.* Laborde's observations were

* We know that cardiac nerve-ganglia maintain their vitality and the cardiac pulsations continue even after the heart is separated from the body; and the ventricle will beat even when separated from the auricle *in frogs*. Likewise respiration in frogs is maintained by the skin, as has been before mentioned.

founded on experiments performed on this animal only, and therefore must be accepted with due caution in regard to the action of this drug on the warm-blooded animals, and especially on man, in whom the nervous system is arranged with so much more perfection, and so much more widely distributed, and the functions more subdivided. In all the experiments which I have observed on warm-blooded animals, the cardiac pulsations ceased within a few minutes after the signs of respiration. Electrical stimulation produced muscular contractions, whether applied to voluntary or involuntary muscles, to nerves either peripheral or central.

PROP. E. — The action of bromide of potassium on the nervous system may be explained by its action on the capillary, arterial, or central circulation; it modifies reflex action, by over-stimulation and subsequent paralysis of the vasomotor system, thus producing oligæmia of the tissues and nerve substances, depriving the latter of the vitalizing properties of the blood. *There is probably no alteration of the nerve substance or cells.*

In what other way can be the explanation of the efficacy of this drug in certain forms of epilepsy, accompanied by a capillary injection of brain or spinal axis, or in hysterical epilepsy caused by exaggerated reflex sensibility? Bromide of potas-

sium, though the most certain of all remedies to reduce the number of epileptiform convulsions in certain cases, rarely produces a permanent relief after the omission of the drug.

The efficacy of belladonna may be explained in the same manner, though the action of this drug* on the capillary circulation is perfectly distinct from that of bromide of potassium.

We repeat, then, that the action of this drug is perfectly explicable, by its action upon the circulation, and that the modifications of reflex sensibility may be due to the same cause. If the circulation in a limb is temporarily or permanently arrested by disease or ligature, that limb loses reflex action, and likewise sensibility. Is it necessary to lay the blame upon the spinal axis? But it may be said that this method of reasoning does not explain the primary excitement caused by this drug. It most certainly does; for we have always an excitement of the circulation, both capillary and central, when this drug is first received into the economy, and then a subsequent sedation of the circulation.

* Vide Boston Medical and Surgical Journal, March 11, 1869.

CHAPTER VII.

CONCLUSIONS.

I. — Bromide of potassium is easily absorbed by the mucous membrane wherever they are placed in contact.

II. — This drug is *easily* absorbed by the skin, provided the water in which it is dissolved is below the temperature of 75° F. If the temperature is above 96° F. it is not absorbed.

III. — The elimination is conducted by the skin and kidneys; as the saliva is a secretion, its presence in this fluid is not a proof of its elimination.

IV. — In therapeutical doses, bromide of potassium is not eliminated by the intestines or lungs.

V. — Bromide of potassium passes out of the system without decomposition. As most of the chemical transformation of drugs takes place, according to Bernard, in the laboratory of the kidneys, Dr. Bill's theory in regard to the interchange between chlorine and bromine in the blood, probably,

is erroneous. If there is an interchange, it is in the kidneys, or outside of the body (in other words) that the transformation must occur.

VI. — The effects of the drug are produced by its direct action upon the blood-vessels or the vasomotor system which control the contraction of these vessels, which explanation may account for all the physiological or therapeutical conditions brought about by the exhibition of this drug.

VII. — There is probably no different or opposing action in proportion to the dose administered. The larger* the dose, the more intense and the longer the action upon the vasomotor system.

VIII. — Its action upon the general nervous system is secondary, and dependent upon that of the vasomotor nerves. That it affects certain parts where there may be a determination of blood is not contrary to the known laws of physiology. Lack of healthy resistance to disturbing influences allows the blood-vessels to be dilated, and, consequently, surcharged; the presence of this drug stirs up the opposing influence which contracts these vessels. This influence would be exerted upon the diseased portion of the system more powerfully than upon the healthy portion.

* Not exceeding forty grains

IX. — Bromide of ammonium, in *almost* every respect, has the same action as bromide of potassium. This, I infer, from the results of more than twenty experiments (some of which are herewith appended).

EXP. XVI. — A guinea pig.

At 0 0' 0". — 4.30 grammes (sixty-one grains about) of bromide of potassium in solution, dissolved in 3 vj. of water, was injected by means of an œsophagean tube into the stomach.

0 5' 0". — Respiration 108 and regular, though inclined to be spasmodic; circulation very rapid.

0 15' 0". — Temperature (rectal) 34.8' (C.); * the animal is sluggish, though sensibility is still preserved.

0 20' 0". — Pulse about 60, and from this time increased in rapidity though it decreased in force.

0 25' 0". — Death, preceded for a few minutes by gasping and spasmodic respiration. Heart ceased beating within a very short time of the cessation of respiration.

Autopsy — immediately after death. — Trachea and œsophagus uninjured. The heart contracts by stimulation. The stomach was finely injected on the external surface, though pale on the internal

* Normal rectal temperature in this animal is 38° C.

surface, with here and there a few dark-colored (hæmorrhagic) spots, at which the mucus is easily separated from the submucous cellular tissue. The brain substance and spinal cord were pale. The membranes at base of the brain and around the spinal cord were injected with venous blood.

EXP. XVII. — Forty-five grains of bromide of ammonium in half an ounce of water were injected, in the same manner as above, into the stomach of a guinea pig.

3'. — The rectal temperature is 38° C.

5'. — The respiration becomes jerky, — 125 to the minute.

10'. — Cardiac pulsations 108. The animal seems stupid, but sensibility to irritation preserved; unable to walk; lays on its belly, with the legs extended helplessly behind it.

13'. — Gasps for breath; rectal temp. 36.5° C. On pinching in the vicinity of the brachial plexus, or the crural, clonic convulsions are produced, speedily becoming tonic, with marked opisthotonos, and in this state the animal —

28'. — Dies, and the muscular spasms are relaxed. At the moment of death the fæces and seminal fluid or mucus (a gelatinous cylindrical mass) were ejected.

Autopsy — fifteen minutes after. — Heart and mus-

cles contracted to electric stimulation. Stomach had the same vascular injection as in Exp. XVI. on its external surface. The contents were squeezed out, and the cavity, blown up with air, was dried and varnished. The veins of the cerebral membrane were injected, as well as the venous sinuses at the base. Lungs normal, float on water. Heart normal.

EXP. XVIII. — 3 ij. of bromide of ammonium in 3 iij. of water were placed in the stomach of a large-sized healthy rabbit.

3'. — Begins to show signs of drowsiness, stopping in his jumps and letting his head fall over to one side; sensibility unaffected. Expels some fæces.

7'. — Pulse 400.

9'. — Falls on to his belly, all extremities extended; sensibility heightened, starts at a sudden sound or touch; head turned to one side.

14'. — Is taken up by the ears, and then is seized with clonic convulsions, accompanied with cries; pupil is dilated; lays quiet upon the floor. Cardiac pulsation 80, irregular; spasmodic muscular contractions of face and forelegs.

23'. — Another cry, followed by convulsions. Sensibility to touch subsided.

28'. — Another slight convulsion, followed by muscular relaxation and death.

Autopsy. — On opening the skull, a gush of dark venous blood came out; capillaries not injected, and consequently could not be distinguished; brain-substance pale, cerebellum as well as the hemispheres; veins at the base of the skull injected; a clot in pia mater of middle lobe of hemispheres; on either side of the choroid plexus were clots, the plexus itself being distended; a clot in left lateral ventricle almost filling it; lungs floated on water; little urine in bladder, — none had been injected from commencement of the administration of the drug. Grs. $\text{vi.}\frac{3}{10}$ of bromide of ammonium were collected from the contents of the stomach.

EXP. XIX. — A piece of the skull of a rabbit ($\frac{3}{4}$ of an inch \times $\frac{1}{2}$ an inch) was carefully removed, exposing parts of both hemispheres. Ten minutes after the operation, grs. x. of the same salt, dissolved in water, was placed into the stomach through an œsophagean tube. The blood-vessels of the membrane covering the exposed surface of the brain were plainly visible to the naked eye or through a lens, and were filled with dark blood.

Seven minutes after, a contraction of the vessels and a shrinking of the brain-substance were plainly apparent. Ten minutes after, the color of the blood gradually changed to a peculiar light-red (rose-red).

45 min. Capillary injection and expansion of the brain-substance; animal is quiet, and the capillary injection is less marked. Slight muscular spasms along the muscles of the back. The brain resumes its natural prominence, then becomes slightly shrunk; and the capillary injection entirely disappears, leaving the brain pale. Two drops of a strong solution of the same salt are applied to the brain; a few minutes after, the capillary injection, caused by the application, is succeeded by anæmia, in which the veins are injected, the capillaries empty, and the brain-substance expanded. This is soon succeeded by the same effects as noted above, and the brain remains pale and shrunken, in a state of oligæmia, in which the veins as well as the other vessels are diminished in calibre and devoid of blood. The animal was then killed, as there was no time for further observation. The urine showed the presence of a bromide.

EXP. XX. — The nerves of a frog's leg were dissected out as high up as the lumbar vertebræ, and soaked in a strong solution of bromide of ammonium; electricity, applied above and below, caused muscular contractions in the limb. The central end of the nerve was cut off at the spinal cord. The nerve of the other leg, treated in the same manner, caused the same result.

EXP. XXI. — The soft parts and bone of a frog's thighs were cut off, leaving the sciatic nerves untouched. The nerves were immersed in a bath of a saturated solution of bromide of ammonium, the extremities emerging upon one side of the bath and the trunk upon the opposite side. The poles of the electric battery were applied to different parts of the trunk and to the extremities. The current was transmitted in every case, producing muscular contractions in the trunk and limbs. One nerve was then divided, and the poles were applied upon the trunk and upon the cut nerve in such a way that the fluid conducted, though feebly, the electric current.

EXP. XXII. — Perspiration collected during a Turkish bath, without any of the drug being taken, gave no sign of a bromide on analysis.

EXP. XXIII. — $\bar{3}$ iij. of urine collected during twelve hours after a rectal injection of bromide of ammonium, grs. xx. in beef tea, showed the presence of a bromide.

EXP. XXIV. — $\bar{3}$ j. of gastric-juice containing bromide of ammonium, grs. x., treated with caustic soda and then tested, indicated the presence of a bromide.

EXP. XXV. — Grs. x. of bromide of ammonium were given in a piece of meat to a dog with gastric fistula. Seven minutes after, 3 j. † of the contents of the stomach were drawn off, which, twice carefully analyzed, indicated no trace of bromine.

EXP. XXVI. — Less than a grain of the bromide of ammonium, placed upon the web of a frog's foot, caused, in the other foot, observed under the microscope: 1st, a contraction of the arterioles and venules; 2d, dilation of the artery only; contraction of the venules persists.

Ten minutes after the application —

3d, the arterial pulsations remain about the same in force and frequency; the arteriole is contracted to half its first capacity; current moves more slowly.

EXP. XXVII. — Grs. ij. of bromide of ammonium were placed upon the web of a frog's foot, and the other foot placed under the microscope.

In twenty minutes the arteriole became contracted as above. The pulsations in the arterioles gradually decrease, and the blood from the venules is received into the larger veins, which, after a while, in turn become emptied, thus producing what is called oligæmia, or exsanguineous tissue. In all these cases observed, when there was struggling,

the circulation moved more rapidly, and the blood-vessels were filled with more blood.

EXP. XXVIII. — One of the students in my class took at 7, P.M., grs. xl. of bromide of ammonium in $\frac{3}{4}$ j. of water. Went to bed at 10.30, having noticed only a slight excitement of the circulation, flushing of the face, prickling sensation in the skin, and tightness at the temples.

At 2.45, P.M., on the next day, took a rectal injection of grs. xl. in some mucilage of starch.

In 45 minutes experienced the same excitement of the circulation as noticed above, besides feeling a slight nervous excitement, such as he has after taking wine.

1 00'. — Pulse 81.

1 10'. — Pulse 80.

1 15'. — Pulse 81.

1 30'. — The nervous and vascular excitement subsided.

2 00'. — Felt as usual; spent the evening in joviality and felt no sleepiness. At night, pulse 75, slept well, and had a good appetite for breakfast; dejection normal, but less in quantity. Urine, passed twenty-three hours after the last dose, gave distinct indications of the presence of bromine.

EXP. XXIX. — Another of the students took at

10, P.M., grs. xl. of bromide of ammonium in a claret-glass of water, on an empty stomach. Pulse, before taking the dose, 80.

15'. — Pulse 88.

30'. — Pulse 80.

40'. — Vascular excitement, and exhilaration as after taking morphine. This gradually decreased, and was lost in a fit of drowsiness.

1 15'. — Found himself nodding, and then retired; respiration was normal; skin cool and moist.

Arose the next morning at half-past six, feeling as well and bright as usual. Had a dejection during the day. Towards evening he noticed uneasiness in the bowels, and the next day decided diarrhœa set in, and lasted for twelve hours. No griping or distress was induced, except that the abdomen felt as if distended with flatus. He never had diarrhœa, and could see no cause for this attack except from the drug.

EXP. XXX. — At 12 o'clock, before retiring to bed, the same experimenter took ammonii bromidi, grs. xx., on a full stomach. Within half an hour, felt as though he had taken a dose of opium, though less excited. Thinks that he fell asleep without the aid of the drug; dreamed of trying to pass urine into a bottle, but could not do so on ac-

count of being constantly in a crowd of men and women.

Took the same quantity at 5.30, A.M., on an empty stomach. Collected the urine before taking the second dose, which on analysis showed the presence of a bromide.

CHAPTER VIII.

EXPLANATION OF THE ACTION OF THE DRUG.

WHEN the drug has been received into the circulation, its action is exerted upon that branch of the vasomotor system, which causes the contraction of the arterial vessels, thus reducing the supply of blood to all tissues, but acting more especially upon those which are superabundantly supplied. At first, for a short time, there may be some vascular excitement; within an hour, and especially after the continued use of the drug, the arterial sedation is accomplished, and may last for several hours. The central organ is also quieted, and thus we obtain a diminution of blood in the nervous centres, as well as elsewhere, modifying the activity of their functions.

Professor Brown-Séguard has reported some experiments in the first volume of his *Journal de*

Physiologie, which illustrate many of the symptoms peculiar to large (but not poisonous) doses of bromide of potassium. In these experiments it is well shown that muscular irritability could be excited by the injection of red blood, even after cadaveric rigidity had ceased, and that ligature of the aorta could prevent this muscular irritability in one hour and thirty-six minutes from the time of occlusion of the artery.

I know of no authentic case of poisoning in man from bromide of potassium. I have no doubt that death could be induced, but the size of the dose must be very considerable. That much harm may be done by too indiscriminate a use there can also be no doubt, as probably a continued use of the drug will interfere with the process of assimilation. I consider its continued and prolonged use contra-indicated in anæmia or chlorosis. That it is a specific against epilepsy is erroneous. Such cases as proceed from anæmia of the cord or any part of the brain will not be ameliorated by its use. When there is congestion, there will be benefit. Again, if the dose could be administered only when an attack is anticipated, it would be following out the indications of its physiological action; and in some cases this idea could be prosecuted.

I cannot conclude this paper without publicly expressing my sincere thanks to those gentlemen of

the Medical Classes of 1868-69 who gave me their thoughtful and attentive assistance, and of acknowledging that many of the results derived from the foregoing experiments would not have been attained had I not received such skilful and careful aid.

INDEX

Table of contents listing various sections and page numbers, including sections like 'Introduction', 'Chapter I', 'Chapter II', etc.

INDEX.

A.

	PAGE
Absorption, by the stomach, aided by combination with an alkali	10
Absorption by the mouth	116
by the skin	12, 118
by the rectum	13, 120
rapidity of	116
Acne sometimes follows continued dose	39
description of, and cause	39, 139
Ammonium, bromide of	102, 158
elimination of	163
therapeutic action of	103
therapeutic dose of	109
physiological action of	161
in combination with bromide of potassium	104
Anæmia and chlorosis, use of bromides in	168
Anaphrodisiac action	71
Anæmia of the brain	23
Anæsthesia of the pharynx	41
of ejaculatory ducts	48
Anæsthetic, bromide of potassium not always an	29
Angina pectoris	76
Anodyne in various neuroses	75
Aphasia, caused by continued dose	50
Aphonia, an evidence of excessive dose	43
Assimilation, secondary, modified by continued dose	55
Asthma, and Trousseau's prescription for	77
Aura, in epilepsy	87

B.

	PAGE
Bladder, inflammation of, not improved by bromide	74
Blood, circulation of, how influenced by bromide	142
globules not altered by bromide	38
Brain, experiments illustrating action on	161
Bromide of potassium, decomposition in the system and theory of Dr. Bill	121
Bromide, changes color of blood to rose-red	142
in normal urine	128
does not appear in secretion from mammæ	134
Bromism, cases illustrative of	60-63
a possible death from	63

C.

Capillary circulation, effects of bromide on	142
Chemical analysis of bromide, qualitative	124
quantitative	125
Circulation, affected by continued dose	34
single dose	21
Coffee, used in conjunction with bromide of potassium	65
Conclusions from physiological action	156
Constipation produced by bromide of potassium	131
Convulsive disease, the controller of reflex power in	82
Cure, meaning of this word	93

D.

Death, rarely caused by a large dose	60
Decomposition of bromide of potassium	121
Deglutition, difficult, a case of with use of bromide	70
Diarrhœa, occasional production of by use of this drug	132
Doses, single	17
therapeutic action of	18
continued, physiological action of	34
difference between single and continued	35
toxic	36

E.

	PAGE
Elimination, ratio of, to absorption	14, 134
exhalations of lungs	134
by fæces	139
by saliva	135
by the skin	140
summary of methods of	141
ways of	134
Epilepsy	82
action of bromide explained in	154
signs of favorable effect upon	86
idiopathic	87
of children	90
rules for treatment of	107
Erethism	72
Erysipelas, use of bromide in	51
Excretions, on the urinary	131
Exhibition of bromide of potassium, rules to guide in	12
Explanation of the relief of insomnia by bromide of potassium	23
Explanation of physiological action of drug	167
Experiments of Laborde to show maintenance of volition and diminution of reflex action	149

F.

Fetid breath, following continued use	41
occurs in those who neglect to cleanse their teeth	60
attributed to its effect upon mucous membrane (note)	135
Frogs, physiological action of bromide on	150
its local contact with nerves of	146

G.

Globules of blood not altered by bromides	38
---	----

	PAGE
H.	
Headache	81
Hearing and vision not affected by bromide	37
Hyperæmia of nerve centres	94
Hyperæsthesia modified by the use of bromide	55
Hypnotic action dependent on condition of brain	21
Hypnotic dose	19, 44

I.

Incontinence of urine	74
Indications and contra-indications	26
Insomnia, cases of, accompanying teething	29
following mental anxiety, &c., cases of	27, 29
physiological causes of	20
Iron, to be used with bromides	88

L.

Length of time of presence of bromide found in urine	136
Lithium, bromide of	110
its use when bromide of potassium fails	111
experiment illustrating local action of	122

M.

Masturbation	79
Memory and impaired mental activity a result of the con- tinued dose	49
Menopause, functional derangements in, how controlled	75
Metamorphosis of tissue, increase of destructive	56

N.

Nausea and vomiting, reflex	73
Nervous irritability relieved by bromide of potassium	27
Nervous conductivity, modifications of	146
Nervous system, effects on	145, 162
Neuralgia	78
Nymphomania	72

O.

	PAGE
Œdema of uvula, a sign of bromal intoxication	58
Oligæmia, caused by bromide of potassium	21, 142
Opium, bromide of potassium in connection with	31
explanation of their combined action	32
Ovarian diseases, disturbances in	95

P.

Paralysis of heart caused by concentrated local action of bromide	151
Pathological conditions in which the bromide of potassium can be used	66
Powdered bromide irritates mucous membrane	11
Prophylaxis in hysteria	93
Puche, investigations of, on bromide of potassium thirty years ago	53
Propositions, A.	120
B.	138
C.	141
D.	150
E.	154
Pulmonary mucous membrane, excretion of	133

R.

Reflex sensibility diminished by continued dose	52
Reflex response, Laborde's researches on	149

S.

Secretions, effects on	130
Sedation, of heart	151
Seminal emissions	72
Sensations blunted by the continued dose	54
Sensibility, dulness of, induced by continued dose	38
Sexual desire sometimes repressed by continued dose	47
Single dose	17

	PAGE
Sodium, bromide of	112
Strychnia, antagonism to bromide of potassium	97
case illustrative of	99
foot-note on	109
Summary of therapeutic and toxic phenomena as effects of bromide	64
Summary of physiological action of bromides	156

T.

Temperature, lowered, a sign of bromal intoxication	59
Tetanism of muscles and vessels due to contact of drug	146
Therapeutic applications of bromide of potassium	65
Therapeutic and toxic group of phenomena following use of bromide	64
Toxic dose of bromide	36
its action	57
symptoms of	58
Typhoid fever, use of bromide in	31

U.

Uterine diseases, disturbances in	95
---	----

V.

Vascular sedative, experiment to illustrate	144
Vision and hearing unaffected by bromide	37
Vomiting, use of bromide generally contra-indicated	11

W.

Wakefulness, from exhaustion, not relieved by bromide	20
experiments to show action of bromide upon	19, 22
Whooping-cough	76

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