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FOR REVIEW.

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Med. Dept., Room D, up stairs.

A MANUAL

OF

HYPODERMATIC MEDICATION:

THE

TREATMENT OF DISEASES BY THE HYPODERMATIC OR SUBCUTANEOUS METHOD.

BY

ROBERTS BARTHOLOW, A.M., M.D., LL.D.,

Emeritus Professor of Materia Medica, General Therapeutics, and Hygiene in the Jefferson Medical College of Philadelphia; Honorary Fellow of the Royal Medical Society of Edinburgh; Honorary Member of the *Société Médico-Pratique de Paris;* Fellow of the College of Physicians of Philadelphia; Member of the American Philosophical Society; Fellow of the Medico-Chirurgical Faculty of Maryland; Honorary Member of various State and local Societies; Author of a Treatise on the Practice of Medicine; of a Treatise on Materia Medica and Therapeutics; of a Manual of Medical Electricity; etc., etc.

FIFTH EDITION.

REVISED AND ENLARGED.

PHILADELPHIA:

J. B. LIPPINCOTT COMPANY.

LONDON: 10 HENRIETTA STREET, COVENT GARDEN.

1891.

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Je pense même, à raison de ces circonstances, que l'absorption sous-cutanée, qui n'a été employée jusqu'ici sur l'homme que par exception, devra devenir méthode générale pour l'administration de tous les médicaments énergiques, et à l'état de pureté.

Bernard.

Who that has suffered from a painful local affection can think of the alleviation of his sufferings which follows from the subcutaneous injections of an anodyne without gratitude?

Sir W. Jenner.

Die neueste Zeit, mehr und mehr einer nicht skeptischen aber rationell critischen Auffassung in therapeutischen Dingen zuneigend, hat diesen gewaltigen Apparat pharmaceutischer und dynamischer Mittel grossentheils über Bord geworfen, und beschränkt sich auf wenige, aber in eminenter Weise bewährte, locale Methoden. Dieser glückliche Uemschwung knüpft sich zum Theil an die Einführung der *hypodermatischen Injectionen*, welche die symptomatische Behandlung der Neuralgien ausserordentlich vereinfacht und vervollkommnet, die meisten älteren Verfahren ersetzt und überflüssig gemacht haben.

Eulenberg.

PREFACE

TO THE FIFTH EDITION.

ANY one familiar with the former issues of this manual will discern that many important alterations have been made in this edition. In fact, the book has been recast, many of the articles have been rewritten, much new matter has been introduced, and the various remedies have been arranged according to the terms of a classification compiled for this purpose. These changes have increased the size of the book by about two hundred pages, and as the page has been enlarged in both directions, the capacity of the book has been materially enhanced.

These additions had become the more necessary because of the increasing importance of the hypodermatic method since the germ theory has so closely occupied the etiological field. It is by means of the injection instrument that in so many instances pathogenic organisms can be reached and effectively treated. It is partly in this way that the subcutaneous method and related forms of injection therapeutics have become essential parts of a physician's equipment.

In selecting the new matter, I have sought to obtain that entirely pertinent to the subject, and in the literary execution have made the attempt to be at once exact and comprehensive. If error has occurred, it is in the direction of admissions to the list of remedies of those that may

appear to be useless or unfit, rather than in the exclusion of those considered by others of my readers as distinctly meritorious. I may venture to hope that this edition of the manual will serve the purpose of uniting the *technique* of the art with the knowledge now possessed of the pathogeny of microscopic organisms.

It is more especially in the production of synthetic remedies that such phenomenal activity has characterized the later chemical contributions to the Materia Medica. Besides this material, the product partly of scientific and partly of commercial chemists, the increased work devoted to experimental therapeutics has resulted in so much that the task of discrimination between the remedies thus brought forth has greatly added to the labor of preparation for this edition, but I could do no less, seeing that the unwearying kindness of my readers demands from me careful attention to their needs, which is the best assurance of my gratitude for their continued favor.

It gives great pleasure to say that in preparing this edition I have had the assistance of my son, Dr. Paul Bartholow, A.B. (*Harv.*), M.D. (*Jeff.*), who has made notes, verified references, and read proof, thus materially lightening my labors.

ROBERTS BARTHOLOW, M.D.

PHILADELPHIA,
September, 1891.

PREFACE

TO THE FOURTH EDITION.

The rapid progress made in therapeutical science renders necessary frequent revision of any work devoted to its exposition. This is especially true of hypodermatic therapeutics, which deals with the active principles,—the newest products of chemical research, which may be made available for this method of administration. Hence, since the publication of the third edition of this manual, so much has been contributed to this subject, that many changes, and considerable addition of new material, have been found necessary. I have rewritten much of the work, and have added new matter to the extent of one hundred and fourteen pages of text. As heretofore, I have incorporated those new contributions to therapeutics which seem so well grounded as to be permanent additions to knowledge.

In the substitution of the term *hypodermatic* for the familiar word *hypodermic*, my action may or may not be generally approved, but the change is urgently demanded in the interests of a correct nomenclature. To make the attempt at substitution successful it will be necessary to have the co-operation of medical authors. The unanimity of scholars in regard to the incorrectness of *hypodermic* is surely sufficient justification for combined effort.

When referring to the subject of "iridium points" for

needles, I did not know the precise origin of the application of this remarkable metal for this purpose. I have learned since the printing of that part of the work that we owe this important improvement to Dr. William Judkins, of Cincinnati.

R. B.

1509 Walnut Street,
Philadelphia, Pa.

PREFACE

TO THE THIRD EDITION.

Several years having elapsed since the publication of the second edition of this manual, important alterations have been rendered necessary by the advance in knowledge. But few changes seem desirable in the first part, devoted to "History, Technology, and General Therapeutics," but many changes and numerous additions have been made in the second part, or "Special Therapeutics." Chapters have been added on the following topics: The Morphine Habit and its Treatment, Duboisine, Pilocarpine, Chloroform, Chloral Hydrate, Apomorphine, Aquapuncture; and all of the other chapters have had important additions made to them, and some of them have been entirely rewritten. The size of the volume has been considerably increased, and its usefulness enhanced, it is believed, by these alterations and additions.

As this is now the only work on the subject in the English language before the profession, and as this embodies the results of the most recent investigations, the author ventures to express the belief that it must continue to be useful to those for whom it was originally intended. The exhaustion of two editions and the demand for a third indicate that the manual supplies an existing want. The author has, therefore, felt encouraged to increase the size

and enlarge the scope of the manual, so as to make it still more worthy of the approval of the medical profession.

The hypodermatic method has been greatly extended in range since it was first employed for the relief of pain. The applications of various agents by this mode to the treatment of different morbid states are even more important than the use of anodynes, and it is probable, as other active principles are discovered, the method will receive still greater extension. As, however, no good can exist in this world without a corresponding evil, the usefulness of the subcutaneous medication is embarrassed by a most serious abuse in the employment of the hypodermatic syringe for the purpose of narcotic stimulation. It is no exaggeration to say that this abuse is becoming a gigantic evil, to the extent and dangers of which the medical profession should be fully alive. The author has set forth this subject, as amply as the limits of such a manual will permit, in a chapter on the morphine habit, and he begs now to add another warning in regard to the danger of the lengthened use of morphine subcutaneously; for no matter how much the original prescription may have been justified in the condition of the patient, and how conscientious the physician in his efforts to prevent abuse, if the habit be formed, the mental and moral degradation which ensues will always be referred to as the blunder or the crime of Dr. So-and-so.

R. B.

1509 Walnut Street,
Philadelphia.

PREFACE

TO THE SECOND EDITION.

This edition is not a mere reprint of the first. Numerous and important additions have been made in various parts of the work. I have sought to incorporate every real improvement in hypodermatic medication which has been announced since the appearance of the first edition. Much has been proposed that does not appear to me to be of permanent value, and hence I have omitted it, in conformity with my original design of keeping on the strictly practical side of my subject. Whilst I have omitted much that seemed wanting in the essential quality of utility, I have not felt at liberty to reject from consideration any remedy a knowledge of whose uses might aid the physician in an emergency.

Now that the first enthusiasm which attended the introduction of this method has died away, we are in a position to estimate accurately its true merits. It is gratifying to me to observe that the judgments pronounced in the first edition, in regard to the various agents employed in this way, have been confirmed by a larger personal experience and by the general voice of the medical profession. The hypodermatic method is, certainly, a very important addition to our resources, and no physician can be considered as doing justice to his *clientèle* who does not give

them the advantage, in suitable cases, of its great curative value.

In conclusion, I have to express my obligations to the reviewers for their very favorable notices of the first edition, and to the medical profession for the estimate which they have placed on my labors.

R. B.

27 West Eighth Street,
Cincinnati.

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PREFACE

TO THE FIRST EDITION.

As a teacher of Therapeutics, and as a practitioner, it has frequently been brought to my notice that the information existing in our language on the subject of hypodermatic medication is exceedingly meagre. I have been urged by students and practitioners to prepare a convenient manual, to embody in small compass what is really known of value on this subject. This little work is the result.

Those who do me the honor to read my book will find that I have drawn largely upon my personal experience in the use of the hypodermatic method. This fact, together with the necessity I was under not to enlarge my work beyond the boundaries of a "manual," will, I trust, excuse the apparent dogmatism of my statements. As, however, the experience and observation of one individual, how great soever may have been his opportunities, must necessarily, in so extensive and important a subject, be incomplete, I have not neglected the contributions of English, French, and German physicians to this department of practical medicine.

I am indebted to the present resident physicians of the Good Samaritan Hospital for important aid. Drs. De Courcey and Rutter, with a scientific zeal which does them honor, submitted themselves to experiments in order

to elucidate some important points in the physiological action of morphine and atropine. Dr. Galbraith made and recorded the observations.

Dr. J. S. Unzicker, of this city, a very capable physician and pharmaceutist, has placed me under obligations for numerous careful experiments, to determine what agent, if any, is best suited to prevent change in solutions prepared for hypodermatic use.

R. B.

CINCINNATI, OHIO.

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THE TREATMENT OF DISEASES

BY THE

HYPODERMATIC, OR SUBCUTANEOUS, METHOD.

HISTORY OF SUBCUTANEOUS MEDICATION.

With the opening of the present century began attempts to utilize the skin as a medium for the introduction of medicaments into the blood. Chrestien, of Montpellier, who is also celebrated for his researches on the medicinal value of the salts of gold, published in 1804 a treatise on the iatroleptic method. This work was translated into German by Bischoff the following year. Various papers of minor importance appeared in French and German literature during the first quarter of the century. Lembert, in 1828, and Richter, in 1835, discussed, in more or less elaborate essays, the endermatic method, and Madden, of Edinburgh, in 1838, published an experimental inquiry into the physics of cutaneous absorption. It is in a high degree probable that Madden's research had its inspiration in the recent developments in regard to the curative effects obtained by the inoculation and implantation of medicines. About 1836, Lafargue had published the results accomplished by his method; that is, the insertion of morphine into the skin along the trajectory of the nerve affected with neuralgia. Lafargue invented a needle-tro-

car, with which he could effectively deposit morphine in the form of a paste in the skin. Ascribing the curative results of this practice to the pustules that formed at the site of the inoculations, he studied with care their development and structure. Although it was early discovered that the benefit derived from the inoculation of morphine was in no way related to the pustules produced, the good results of the method were most conspicuous, and attracted wide-spread attention at that time. Valleix, Cazenave, Malgaigne, Hayem, and others in France, Langenbeck, Bertrand, and Von Bruns in Germany, Rynd in Dublin, and Drs. Washington and Taylor in New York, repeated the practice of Lafargue, in some instances modifying the method. These observers, and probably the most of those who practised the inoculations, were not concerned, as was the originator of the method, as to the mode of development and the special forms assumed by the pustules, but referred the curative effect to the action of morphine on the sensory nerves of the part. It is not surprising, then, that modifications in the mechanical details were soon introduced. In 1839, Drs. Taylor and Washington, of New York, on becoming acquainted with Lafargue's method and the important curative effects obtained from the inoculations, also inserted morphine along the course of the affected nerve in cases of neuralgia. Instead of inserting morphine in a paste by the inoculation plan, they injected a solution of morphine beneath the skin with an Anel syringe, an opening having been made previously for this purpose. Anel's syringe, the real progenitor of the modern hypodermatic instrument, is a small syringe having an elongated tapering nozzle, fine enough for entrance into the lachrymal duct. To convert this into an instrument for subcutaneous injection it is

only necessary to put a cutting point on the small extremity of the canula.

About the same time, and no doubt influenced by Lafargue's successful practice, Dr. Rolland, as Dr. Wilson* informs us, "cured a case of neuralgia by inserting $\frac{1}{16}$ of a grain of morphine in four punctures over the deltoid." It was also, there is reason to believe, the publication of Lafargue's results which induced Mr. Rynd, of Dublin, to set about the invention of a complicated instrument for introducing under the skin a solution of morphine by its own gravity. Besides the inoculation method, the endermatic use of morphine began to be discussed and to be much employed about the twentieth year of the present century. Brown-Séquard has always advocated the endermatic method, which he holds is in some respects superior to the subdermatic. Sieveking† has found the endermatic plan work well in cases of persistent neuralgia, and this experience extends back beyond the period when was brought forward the hypodermatic method, with which he compares the endermatic. There was, therefore, an abundant experience in the local use of morphine just before the introduction of the hypodermatic method. It was not, however, until the experiments of Dr. Alexander Wood, of Edinburgh, were published, that the method of subcutaneous insertion of morphine began to be properly appreciated. Doubtless also in imitation of Lafargue, Wood began in 1843 the use of a crude syringe (similar to the Anel), with which he injected a solution of morphine through an opening previously made in the skin. In 1855, or twelve years after the first attempts to execute his

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* St. George's Hospital Reports, vol. iv. p. 19 (foot-note).

† The Lancet, 1861, vol. i.: "Clinical Remarks on Neuralgia."

conception, Wood published* an account of his method. It is certain, however, that the physicians of Edinburgh had become familiar with subcutaneous medication by personal communication with Dr. Wood before any account of it had appeared in the journals of the day. During this time Mr. Rynd, of Dublin, was carrying on his investigations, and he affirms that "the subcutaneous injection of medicinal substances to combat neuralgia was first used by myself in Meath Hospital in 1844."

It is obvious that the practice as thus far developed had for its chief, if not only, object, to obtain the local effects of morphine. Even so late as 1861, Dr. Sieveking was concerned chiefly about the local action in the endermatic and subdermatic application of morphine. We find that Dr. Wood began with the same notion, for he strongly insisted on the importance of injecting the medicament into spots painful on pressure. "The local effect depends," he says, "much upon the affinity between the particular medicine administered and the tissue to which it is applied." Not, like Lafargue, seeing a relation between the forms of pustules and the curative action on the diseased nerves, but an "affinity" between the morphine and the morbid state of the nerves; and to the local action Wood attributed the cures effected by the new method. He did not fail to observe, as, indeed, he graphically described, the systemic or general effects which so speedily follow the subcutaneous injection.

The question of priority of discovery has been warmly disputed. As is usual when great improvements are made in the arts and the sciences, the way to discovery is prepared by the work of many investigators. The inventor

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* The Edinburgh Medical and Surgical Journal, 1855.

finally co-ordinates the results of his predecessors, and adds the experiment or the needed acquisition which completes the discovery. Wood established his right to be regarded as the discoverer of the hypodermatic method, by using the syringe for injecting a solution of morphine, and by the publication of his experiments and their results. Mr. Rynd, who claims to have been the first to employ the new method, must be ranked with those who were working in the same direction,—like Drs. Taylor and Washington, of this country,—but who failed to make public their improvements or discoveries in time to substantiate a claim to priority. Dr. Sieveking asserts that "Dr. Kurzak, of Vienna, was the first, I believe, to employ the subcutaneous or hypodermic method, which was then largely used by Dr. Wood, of Edinburgh." * There is no reference to the authority for this statement, hence we are compelled to resort to contemporaneous German works for evidence. The treatise of Professor Eulenberg,† the most thorough and elaborate which has thus far been published on this subject, and which is peculiarly rich in its bibliographical titles, contains no reference to Dr. Kurzak's claims to priority, or to any work done by him on this subject. Dr. Eulenberg also, in a more recent publication‡ on the same topic, Dr. Erlenmeyer,§ and Dr. Lorent‖ are equally unmindful of Kurzak's claim to be recognized as the discoverer of hypodermatic medication.

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* The Lancet, 1861, vol. i. p. 105. *Supra.*

† Die hypodermatischen Injectionen der Arzneimittel, etc. Berlin, 1867, p. 10.

‡ Percutane, intracutane, und subcutane Arzneiapplication, Allgemeine Therapie, i. 328.

§ Die subcutanen Injectionen der Arzneimittel, p. 1.

‖ Die hypoderm. Inject. nach clinischen Erfahrungen. Leipzig, 1865, p. 1.

How far, if at all, the progress of physiological research influenced the endermatic and subdermatic application of remedies cannot now be stated with precision; nevertheless there are some important facts which have a distinct relation to the subject under consideration. The first research into the action of a medicament made by the physiological method was conducted by Magendie, about 1819, upon the *upas* and *nux vomica*, and on *strychnine.* In the course of this research Magendie first demonstrated that poisons acted by absorption into the blood. To ascertain the general effects of the remedy being examined, he introduced some of it *under the skin of the thigh*, and then observed the actions as they occurred. This experiment was performed in 1819.* In the course of this research, also, he tested the rate of absorption from different parts, including the veins. Subsequently, Bernard, pursuing his investigations into the action of curara, and also in his studies of the poisons, introduced the medicament, the subject of experiment, under the skin.† It was, therefore, perfectly well known to physiologists that medicines introduced under the skin were rapidly absorbed, producing their characteristic effects, at the time when Lafargue was studying the forms of pustules caused by the endermatic application of morphine, and Mr. Rynd, of Dublin, was inventing an instrument for the more efficient introduction of morphine into the skin.

It is the more surprising that the progenitors of the hypodermatic method should have referred the curative action of morphine to the local impression, since they observed that it produced the most decided systemic effect.

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* Ann. de Chim. et de Physiol., vol. xvi., 1819.

† Leçons sur les Effets des Substances toxiques et médicamenteuses. Paris, 1857, p. 272.

Although Wood directed that "the instrument is not to be put into the place where the patient complains of pain, but into the spot where you find you can awaken pain on pressure," he accurately describes the rapidity and extent of the narcotic impression. The injunction to insert morphine into the spot painful on pressure had its origin in the practice of Villeix, who, in his work on neuralgia, then in the first flush of its popularity, had recommended the method of Lafargue. That Wood fully appreciated the extent of the systemic effect of morphine when administered hypodermatically is evident in the following passage:

"It is truly astonishing how rapidly it affects the system. If you throw in a large quantity of morphine, you will see the eyes immediately injected and the patient narcotized, and in a few minutes afterwards you will see him in a profound sleep."

Making such observations, it is impossible that he should be unaware of the effect of the remedy thus administered on the centres of conscious impressions; but he yet attributed the curative effect in neuralgia to the local action.

It was reserved for Mr. Charles Hunter to demonstrate the important fact that the application of the injection to the painful points, as contended for by Wood, was really unnecessary, and that equally good effects followed the introduction of the injection into a distant part. Mr. Hunter's first paper appeared in 1859, and was entitled "Experiments relative to the Hypodermic Treatment of Disease." These experiments, made on animals, demonstrated that hypodermatic injections "acted by absorption; that they acted quicker than by the endermic method, or than stomachic doses; that they acted more effectually; and that a small injected dose was equivalent to a much

larger one by the stomach." Mr. Hunter was permitted to use the method of Wood on two patients afflicted with neuralgia, in care of Dr. Pittman in St. George's Hospital. As "both had abscess in the neuralgic site, from the continuance of the localization," the point of introduction of the injection was varied, and it was found,—"first, that in neuralgia equal benefit followed distant injection of the cellular tissue as followed the injection of the neuralgic site; secondly, that localization was not necessary to benefit a given part; and, thirdly, that for certain reasons it was better not to localize,—the chief being: 1, the infliction of unnecessary pain; 2, the almost certain risk of irritating, thickening, or inducing matter in the part from repetition; and, 3, it became evident that a large class of neuralgia would be excluded from this treatment if it was necessary to inject the neuralgic site."

Great praise must be awarded Mr. Hunter for his success in demonstrating these important conclusions, and for popularizing his method. His industry in collecting facts and presenting them to the profession was indefatigable. His views were perseveringly advanced, with an intelligent appreciation of the nature and importance of his facts. He read papers before societies; he published articles in the *Medical Mirror*, *Lancet*, *Medical Times and Gazette*, and *British and Foreign Medico-Chirurgical Review;* he issued a pamphlet* containing all of his previous papers and some additional facts, and he enlisted, by personal effort, many of the physicians and surgeons of London in a trial of the new therapeutical expedient.

It was thus, chiefly through the efforts of Mr. Hunter,

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* On the Speedy Relief of Pain and other Nervous Affections by means of the Hypodermic Method. Churchill, London, 1865.

that the method of Wood, previously confined to Edinburgh and to Dublin, became naturalized in England. Mr. Hunter's papers in the *Medical Times and Gazette* attracted the attention of Courty, of Montpellier, and Béhier, of Paris, who popularized the new method in France. It was soon after tried and reported upon favorably by Scanzoni, of Wurtzburg; Oppolzer, of Vienna; Graefe, of Berlin, and numerous other eminent authorities on the Continent. In 1865 a small treatise, by Dr. Lorent, of Bremen, appeared at Leipsic. A monograph, by Dr. Erlenmeyer, passed to the third edition in 1866. In 1867 the second edition of the elaborate work of Dr. Albert Eulenberg was published in Berlin. Dr. Eulenberg gives a list of two hundred and twenty articles and essays in various languages, but chiefly in German, which appeared on this subject from 1855 to the date of publication of the second edition of his work. From these facts may be seen the extraordinary extension which has been given to this method of treatment on the Continent.

The method of Wood, as defined and extended by Hunter, met with a more favorable reception on the Continent than in the country of its origin. According to Dr. Anstie,* "it is still very much unappreciated" in England. It is true that the principal English physicians and surgeons think highly of the method, and now employ it largely, but, as Dr. Anstie informs us, there are "practitioners who will not admit that there *can* be any particular advantage in it which the old way of giving medicines does not offer."

The hypodermatic method, soon after its publication by Wood, was introduced into the United States. Dr. Fordyce Barker, of New York, while in Edinburgh in 1856,

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* The Practitioner, July, 1868.

was presented by Professor Simpson with a hypodermatic syringe. Soon after his return home, in May, 1856, he used this instrument, and was, consequently, the first in this country to practise the method of Wood. Dr. Barker's syringe was the model from which Tiemann's instruments were made. In August, 1857, the late Professor George T. Elliot published some observations on the hypodermatic method. Dr. Ruppaner published, in 1860, in the *Boston Medical and Surgical Journal*, the first account of the new method in print in this country.

It seems proved that the hypodermatic method was practised in New York before Wood made public his discovery, or before the earliest date assigned by Mr. Rynd, of Dublin, for his use in this way of remedial agents. Dr. Isaac E. Taylor, in a communication to the *New York Medical Gazette*," * shows that Dr. Washington and he used practically the same method in the New York City Dispensary so long ago as 1839. The idea was suggested to them by the results of Lafargue's method of inoculation. Instead, however, of inserting the solid medicament by means of a grooved needle, as was Lafargue's practice, these gentlemen punctured the skin with a lancet, and by means of an Anel syringe threw a solution of the medicine under the skin. This mode of operating was the same practically as that suggested and used by Wood in 1855.

When the first edition of this work was published (1869), I was not aware of the above facts in regard to the introduction of the hypodermatic method in this country. It affords me sincere pleasure to attribute to my own countrymen the credit to which they are justly entitled.

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* April 23, 1870.

HYPODERMATIC MEDICATION.

The Method.

Definition.—Mr. Hunter, in 1859, proposed the word *hypodermic* as the name of the new method, in imitation of terms already in use, as *epidermic*, etc. The word hypodermic is compounded of two Greek words, ὑπο, *under*, and δερμα, *the skin*. This word is condemned by all scholars, who are unanimous that the term should be—in accordance with the rules of construction—*hypodermatic*. That eminent philologist and Oriental scholar, Mr. Fitz-Edward Hall, D.C.L., assures me that under no circumstances is hypodermic allowable. It is, however, so firmly established, and in such universal use, that the substitution of the more correct term can be accomplished only by combined effort. In the earlier editions of this work I have followed the general custom in using *hypodermic*, but in the former and present edition, and in the later editions of my "Practical Treatise on Materia Medica and Therapeutics," I have departed from the common usage to do my part towards the introduction of the more correct term, *hypodermatic*. The word *subcutaneous* expresses the same idea, and is in all respects appropriate.

By this method the medicament is introduced beneath the skin, usually into the subcutaneous areolar tissue, but also into the muscles and into the parenchyma of organs. Further, the instrument may be employed to inject medicines into the serous cavities, into the veins, and into the

tissues of morbid growths. Although these topics in some respects differ from subcutaneous medication, it is my purpose to include them in the present edition, since the same process is followed practically in all cases when the hypodermatic syringe is the instrument employed. The method consists in:

1. A suitable solution of the medicament;

2. An instrument for injecting the solution beneath the skin, into the subcutaneous areolar tissue, or into the tissues of muscles, organs, or new formations.

THE SOLUTION.—A medicine employed for hypodermatic use should be capable of perfect solution in the vehicle, which is usually water. Particles of medicine undissolved are not only not readily absorbed, but also act as irritants, producing inflammation and abscess.

The solution should be free from dirt or foreign matter of any description, and should be neutral, or, at least, without decided acid or alkaline property. Any substance which will coagulate the blood, or produce violent irritation, is unfit for hypodermatic use.

A solution, even of a neutral substance, should not be too concentrated. Pure water is entirely harmless, and the quantity of fluid injected, within certain limits, need not be considered, provided suitable care be used in selecting the site and in injecting. Concentrated solutions, *cæteris paribus*, are more apt to produce local irritation than dilute solutions. Moreover, if the solution of a powerful alkaloid be very concentrated, a drop too much injected may produce dangerous symptoms. In ordinary syringes, a few drops remain at the bottom of the cylinder and in the needle; hence it is difficult, in using a very concentrated solution, to inject the precise amount desired, or, indeed, to approximate to it very closely.

As regards their preparation and preservation, hypodermatic solutions may be *extemporaneous* or *permanent.* For reasons to be detailed presently, extemporaneous solutions are generally to be preferred. The agent to be injected should be dissolved, at the moment when required, in water that has been boiled and filtered. Distilled water is not essential: it is not even better than ordinary river-, spring-, or well-water free from visible impurities. Distilled water quickly becomes cloudy on exposure to the air, because of the growth in it of a minute but visible vegetable organism. I find, after ample experience, that river-water which does not contain recognizable impurities is perfectly suitable for the solution of alkaloids and other agents used subcutaneously. If distilled water be employed for making the solution, it should be freshly distilled.

The water used for preparing solutions should always be boiled in advance. The reasons are,—first, that alkaloids are, as a class, more readily soluble in hot water; in the next place, the water is sterilized by boiling.

For the purpose of preparing extemporaneous solutions, powders of a given weight are made in advance. It is, unfortunately, quite impracticable to properly subdivide and make into powders those alkaloids that are given in hundredths of a grain. Morphine, morphine and atropine, pilocarpine, apomorphine, and some others may be put up in powders for solution as required, but the same arrangement is not practicable for many other remedies. Gelatin tablets, containing a definite measure of the medicament incorporated with gelatin when fluid, have been in use for several years, especially in England. The gelatin disks or "tabloids" are slow to dissolve, and the absorption of the gelatin is imperfect, so that local irritation is apt to result from them.

The most important improvement lately made in this respect is the "hypodermic tablets" now prepared on a large scale by the manufacturing pharmacists.* They are compressed pellets, containing definite measures of the agents usually employed mixed with sulphate of soda, or, when the dose is of sufficient size, without any addition to the mass of medicament. The compression is effected by a machine, and the tablet, when complete, is a circular disk, about one-fifth of an inch in diameter and a line in thickness. The quantity of sulphate of soda in each tablet is one-fourth of a grain, which is intended to furnish a proper basis and to aid in the solution of the alkaloid. All agents now employed hypodermatically are put up in this form and furnished to "the trade" in quantity. When it is proposed to use a tablet subcutaneously, it is dissolved in sufficient water that has been boiled for the purpose, and is then drawn up in the syringe in the usual way. Tablets that have become old dissolve slowly, and careful and patient trituration may be necessary to effect a perfect solution.

Improvements have been made recently in the preparation of tablets (called *tabloids* by the English). Many alkaloids of which the dose is not less than one-fifth of a grain are now compressed into tablets without the aid of some material for giving solidity and form to the mass.

Permanent solutions are prepared from formulæ and kept on hand for use as required. The most carefully prepared solution rapidly deteriorates by keeping. In a few days a faint cloud appears, and soon after the solution becomes turbid. The cloudiness and turbidity of an alkaloid solution, made with pure distilled water and free from visible

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* The Wyeths, of Philadelphia, were the first to prepare them.

impurities, are due to the development of a minute organism,—the *penicillium*. This plant grows partly at the expense of the alkaloid, and hence while the solution increases in turbidity it declines in power. Filtration removes the visible impurities, but a solution which has once been turbid is ever afterwards unfit for subcutaneous injection. A solution long kept, although it may not be turbid, or if turbid has been filtered, may, when injected, cause an indurated and painful swelling, which remains for months, and is slowly absorbed or suppurates. In some cases a cyst forms at the site of such an injection, slowly enlarges, and when finally emptied is found to contain gelatinous, purulent matter, with a small slough of connective tissue.

If permanent solutions are to be used, it is extremely desirable to prepare them with menstrua that will not undergo change, or to make such additions to ordinary solutions as will prevent the growth of the penicillium. The distilled waters of cherry-laurel and of eucalyptus, and chloroform especially, have been used successfully, and solutions made with them do not exhibit any change for several weeks at least. They are not irritating, and do not affect the system in the quantity required for subcutaneous administration. The *aqua chloroformi* has been much used in the last few years for the solvent, and is preferred by those who have become familiar with its valuable properties. It is antiseptic, somewhat analgesic, and permanent.*

Within the last few years the oil of vaseline (liquid vaseline) has been used for the making of certain solutions. This substance is neutral, unirritating, and a solvent of extensive range. It will take up and deposit some very

* Certain alkaloids, cocaine notably, lose strength in solution.

irritating articles, and no indurations or inflammatory deposits of any kind are produced.—*Dujardin-Beaumetz.**

The addition of certain antiseptics to the aqueous solution of an alkaloid is an efficient method of preventing change. Two to four minims of carbolic acid to the ounce of solution of morphine will act efficiently for several weeks in preventing the growth of penicillium. A minim of carbolic acid to the drachm of solution is not enough to act injuriously, and will continue an antiseptic action for several months. This agent increases a very little the pain and smarting which attend the injection at the first moment, but then a state of lessened sensibility follows. Two to four grains of salicylic acid to the ounce of solution will also prove effective in preventing change, but it increases the irritation—the smarting—which attends the injection. Resorcin may be substituted for salicylic acid, as it is almost free from irritating qualities and is equally as effective as an antiseptic. Boracic and benzoic acids, like carbolic acid, have the power to stop the growth of the penicillium, but are more irritant than the latter or than resorcin. The mineral acids are effective both to prevent change and to increase the solubility of many of the alkaloids, but they are much too irritating to be employed for the preparation of solutions for subcutaneous injection. Indeed, the acids are responsible for most of the abscesses, the sloughing, and the tetanus which have followed the injection of medicaments. My conclusion is that it is far better to make extemporaneous solutions than to rely on any formula, how well adapted soever it may appear to be to the purpose in view. The mineral acids should never be employed for the preparation of hypodermatic injections.

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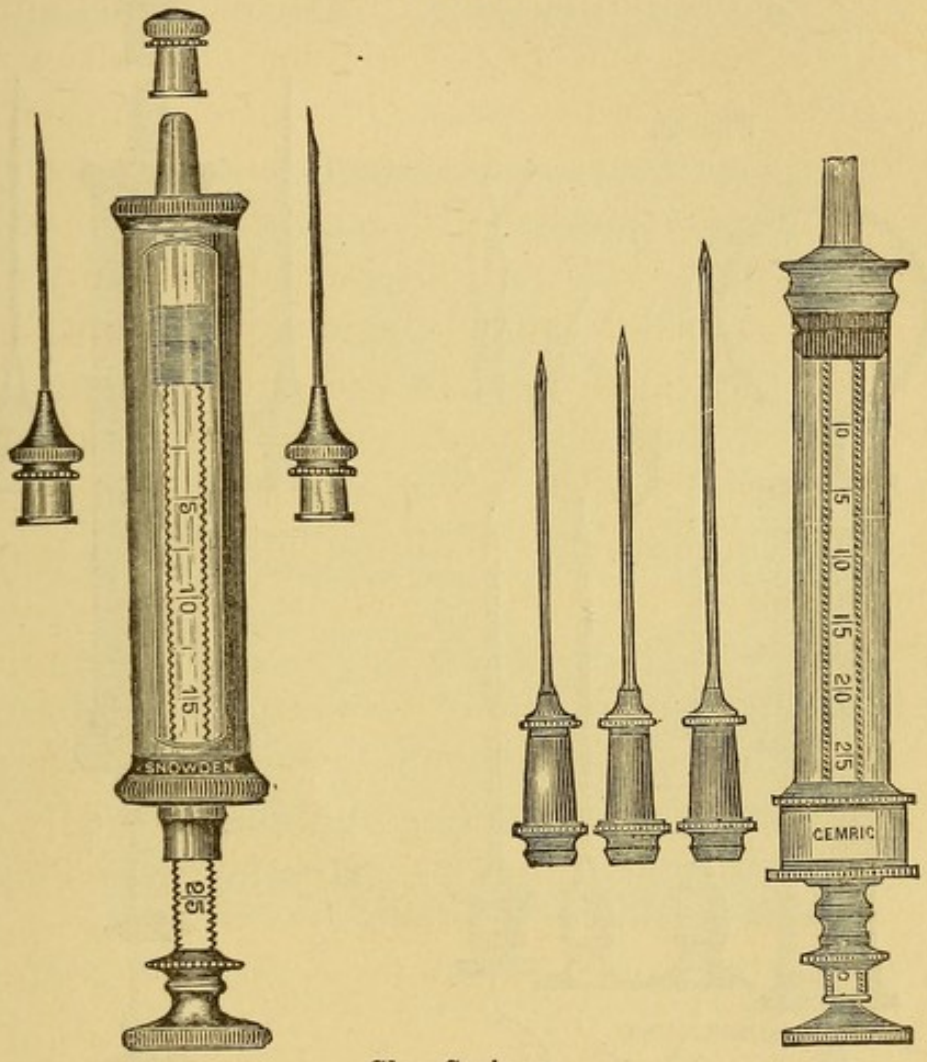
* Bul. Général de Thérapeutique, vol. cxii p. 97.

THE SYRINGE.—The instrument used by Wood in his first experiments was a Fergusson syringe, intended for the injection of liquor ferri chloridi into nævi. This instrument, like the Anel and the Pravaz syringe (French), required a preliminary opening to be made in the skin,

FIG. 1.



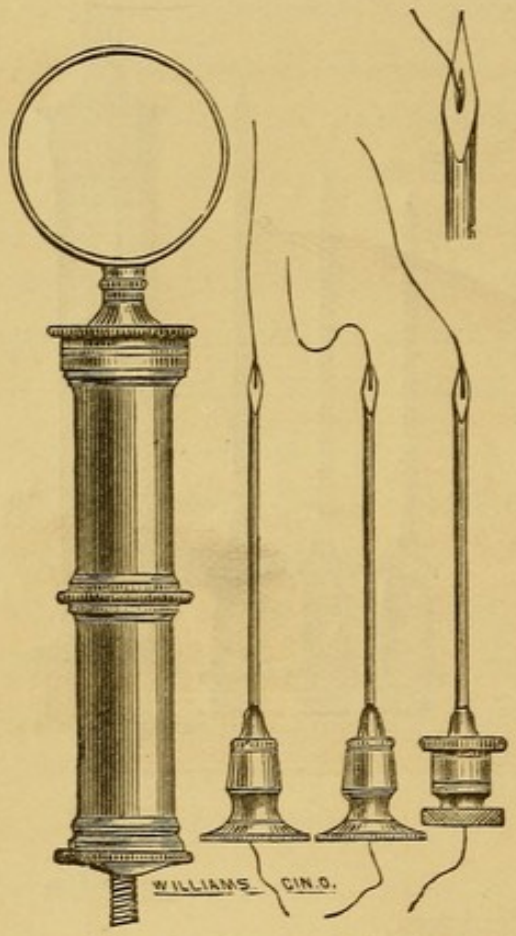
Glass Syringes.

through which the canula could be passed. Mr. Hunter made a most necessary and important improvement when he had a cutting point put on the canula for transfixing the skin.* The details of the manufacture have been fur-

* On the Speedy Relief of Pain and other Nervous Affections, etc. Pamphlet. London, 1865.

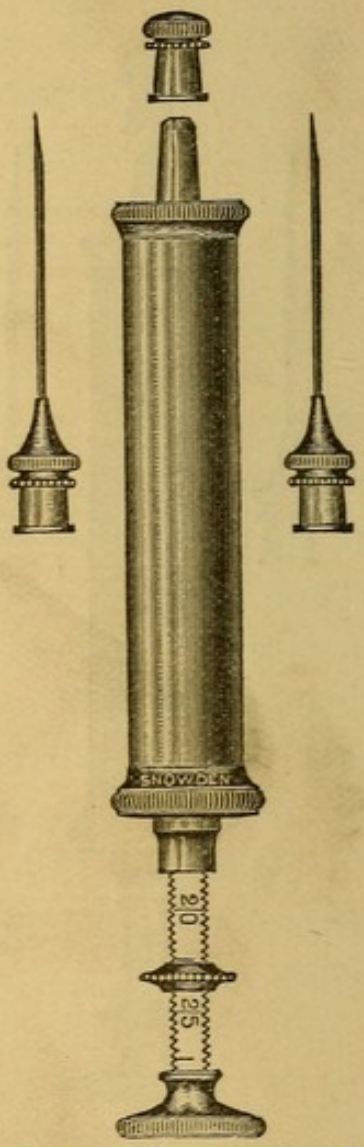
ther elaborated, and now very perfect instruments can be obtained. The material of which the barrel is constructed is glass, hard rubber, celluloid, German silver, pure silver, or gold. Glass is fragile, and the bore of glass tubing is

FIG. 2.



Silver Syringe and Needles.

FIG. 3.

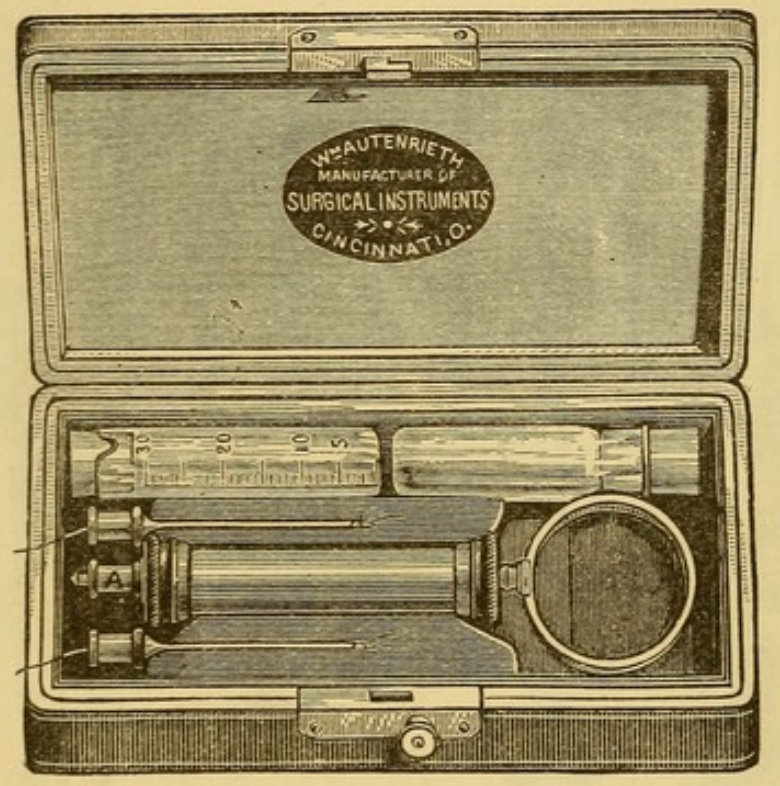


German Silver Syringe.

so unequal that it is difficult to obtain a piece uniform in calibre throughout. The fragility is corrected by enclosing the tube in metal, leaving a slit through which the contents can be inspected and the graduation read. In the original glass syringes, and in the inferior ones now

made, the mountings of the cylinder are fastened on by sealing-wax or other cement, and hence loosen easily, and leak, or give way altogether. The new material known as "celluloid" is well adapted to the making of cylinders. As it is moulded in a soft state, perfect uniformity in the calibre can be secured, and as it can be made transparent, the contents are visible. Although possessed of a trans-

FIG. 4.

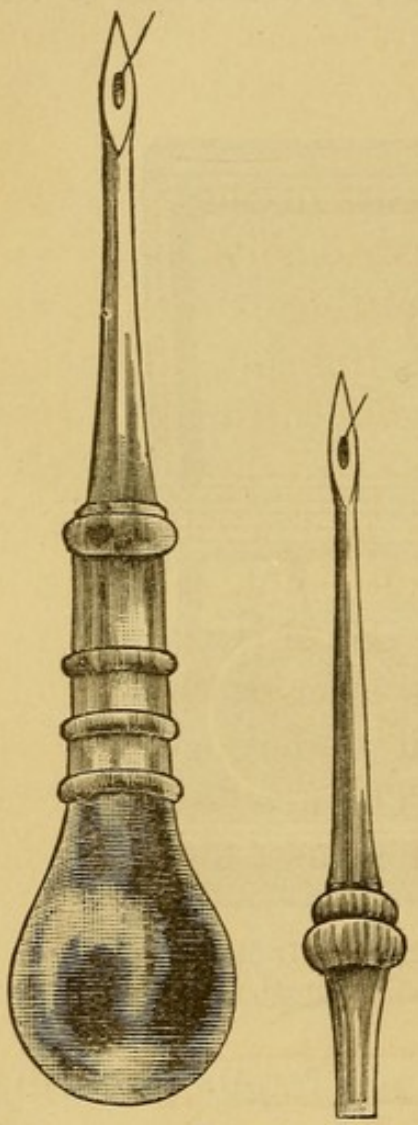


The Author's Silver Syringe, with Gold Needles, Iridium-pointed, as made by William Autenrieth, Cincinnati, Ohio.

parency almost equal to glass, it is not fragile, and will not break by falling on a tiled or stone floor. On the other hand, it is soluble in chloroform, and when the syringes made of it require repairs they can be made only at the shops of the celluloid company. Hard rubber is a suitable material for syringes, but they are usually made very poorly. An exception to this statement is the syringe of

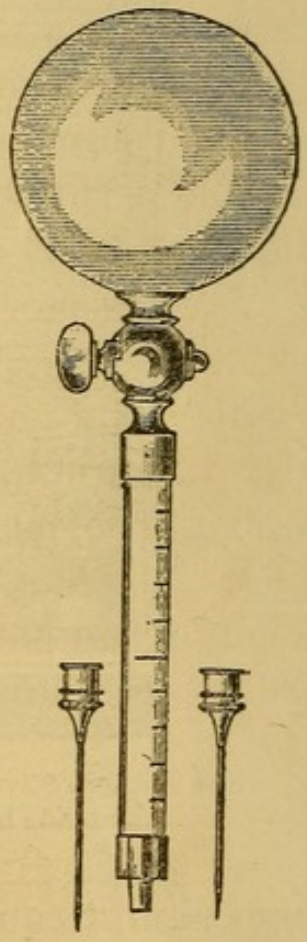
Leiter, of Vienna, made so that the parts fit accurately without screws, and can be therefore readily cleaned, and they are very durable. Of course the contents of a hard-rubber syringe are not visible, but the graduation of the piston may be accurate.

FIG. 5.



Hypodermatic Injection-Tube of Dr. John J. Thomas, of Youngstown, Ohio.

FIG. 6.



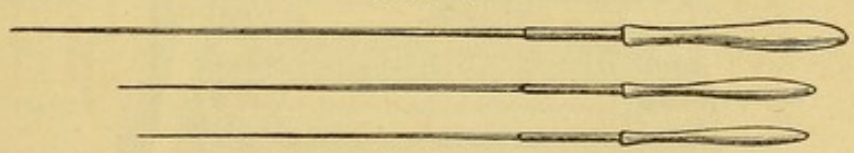
Koch's Syringe, as devised by himself.

Silver, according to my experience, is the best material for making hypodermatic syringes. It is practically indestructible, and is not acted on by any fluid introduced into

the tissues. The barrel can be constructed with a uniform bore, and an accurately-fitting piston assured. The objection to it is that its contents are invisible; but the piston-rod can be graduated with the utmost nicety. German silver may be substituted for pure silver, as no solutions are injected that would corrode the material. Gold has also been utilized for the construction of syringes. They are beautiful in appearance, durable and satisfactory in usage, but they are expensive, entirely out of proportion to their utility.

The needle is a very important part of the instrument. The needles furnished with most instruments are too large, and have an abrupt shoulder at the cutting extremity, which makes the perforation of the skin difficult. The needle should be as small as possible, and the cutting part should have a lancet-shape, but without the groove or depression which some makers put in. The best needle is a gold one, with a hardened or an iridium point, as now made by Mr. Autenrieth, of Cincinnati. Steel is the usual material, but it is more apt to cause after-troubles, such as nodules, abscesses, etc., because it undergoes oxidation, especially when put away damp. The needle should have a wire passed through it when not in use, for the double

FIG. 7.



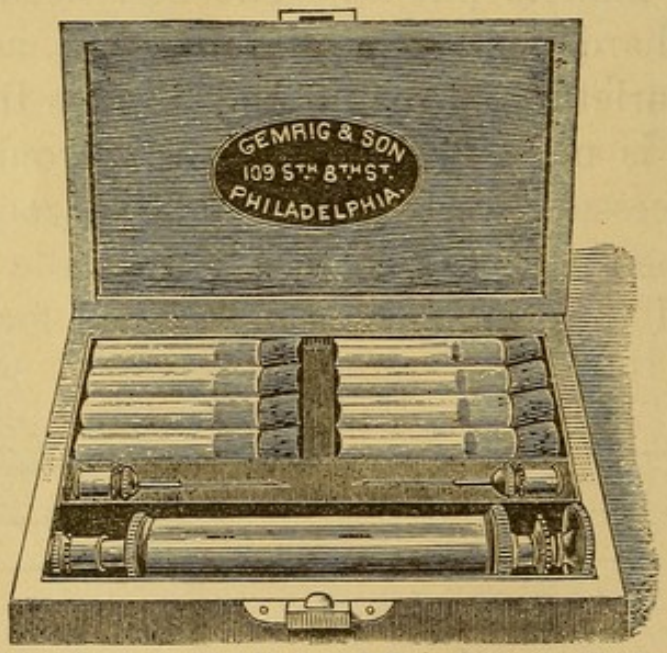
Rimmers.

purpose of excluding any solid particles and preventing the closure of the calibre. Every instrument should be provided with several "rimmers,"—long, tapering, and very fine steel rods used by watchmakers,—which are very

useful for cleaning out obstructed needles. As in the intervals of the use of syringes the piston dries and will not work properly, the barrel should be closed by a cap, which is put on or screwed on when the needle is removed. A few drops of water may be drawn in, and then the cap adjusted. In this way the piston is kept moist and in working order as effectively as if it were in frequent use. Dr. Whittaker, of Cincinnati, first proposed to use them. Weiss, of London, has invented a new piston, which promises to be very useful. It is made of hard rubber, thin enough to be flexible and adapt itself to the barrel of the syringe, so that no leather packing is required. The superiority of this piston in neatness, cleanliness, and effectiveness is obvious.

Undoubtedly the utmost circumspection is necessary in

FIG. 8.



Box containing Syringe, Needles, and Hypodermatic Tablets, proposed by Dr. J. W. White, and made by Gemrig.

the use of the needles,—for diseased blood, or specific virus, may be transmitted from one person to another. Besides

the cleanliness enjoined, the practitioner must see to it that needles used in infected persons are not employed in those free from infection. The usual means for antiseptic treatment of the instrument, as a whole or in part, must not be overlooked.

There are several methods by which the hypodermatic syringe may be charged with the required dose of the solution. The fluid may be drawn up into the barrel by aspiration, or the cap of the barrel may be unscrewed, the piston removed, and the solution poured into the barrel. The former is more convenient. If air enter when the fluid is being drawn up, it may be readily expelled by inverting the barrel and moving up the piston until a drop of the fluid presents itself at the orifice of the needle. In using a glass instrument which is graduated, more of the solution should be drawn into the barrel than it is contemplated to administer, and, fixing the eye upon those divisions of the scale representing the amount to be injected, the piston is made to traverse slowly the proper space. In filling my silver instrument I pursue the following method: I pour into a minim-glass the proper quantity of the solution. The needle being screwed into its place, I insert the point into the solution and draw the whole amount into the barrel of the syringe by slowly elevating the piston, inclining to one side the minim-glass, in order to take up the last drop. If air have entered, I invert the syringe and push up the piston slowly until it is all expelled. An allowance of one minim should be made for loss when more than ten minims are used.

Mode of Injection.—Take up between the thumb and forefinger of the left hand a loose fold of skin in some convenient situation. Push in the needle with a quick and decided motion, parallel with the direction of the fold,

at the same time pressing or pinching the skin with some firmness to lessen or prevent the pain of the little operation. The resistance ceasing, it will be known that the needle has perforated the skin, and the point of the needle may also now be freely moved about in the subcutaneous areolar tissue. It is better to pass the needle for a half-inch or more under the skin, to have sufficient space for the fluid. The injection must be made slowly, drop by drop, so that the fluid may diffuse itself without rupturing any small vessels or the fibres of the connective tissue. When all has been injected, withdraw the needle slowly, pressing at the same time upon the puncture to prevent escape of the fluid. A few minutes' pressure will suffice to retain the fluid, and to arrest the little bleeding which sometimes takes place. A bit of plaster may also be applied to the puncture, but this is generally unnecessary. By some operators, when practising an injection subcutaneously, the fluid is thrown into the muscular tissue, as this does not proceed to suppuration as readily as the connective tissue. In the treatment of the paralyses, strychnine is injected into the affected muscles. The intra-muscular injection of anodynes is, however, an infrequent mode of hypodermatic treatment, but is growing in favor. To inject into a muscle,—for example, the brachialis anticus, —make it tense by flexing the forearm, and then by a quick motion thrust the needle directly into the muscle. It is claimed for this method that it is less painful and less liable to be followed by abscess than by the injection under the skin, but it is obviously improper if any considerable amount of fluid is to be injected.

In practising the hypodermatic injection, it is important to avoid puncturing a vein. Serious depression of the powers of life, fainting, and sudden and profound narco-

tism have been produced by injecting a solution of morphine directly into a vein. Fatal collapse might be induced by injecting air into a large vein along with the solution.

Bony prominences should also be avoided, for in these situations the skin is not sufficiently loose to permit the ready entrance of the fluid, and inflammation and abscess may follow a too forcible injection.

The puncture should not be made, as a rule, into inflamed parts. I have known a bad phlegmon produced by injection into the tissues of an inflamed wrist.

It is not necessary to follow the original method of Wood, and inject into those points in which pain can be awakened by pressure. Some exceptions to this rule undoubtedly exist, as will hereafter be shown, but they are not numerous. The arm, the outer face of the thighs, the calves, the abdomen, and the back are suitable places for the injection. The arm, about the insertion of the deltoid, is generally selected when option allows. Eulenberg makes the assertion that the effect is slower when the injection is made in the back than in any other situation.* I have not been able to observe any difference in the rapidity of effect as influenced by the site of the puncture, except when thrown into a vessel, or in some specially vascular place. If, as sometimes happens, the patient prefers injection into the painful part, it will be well to yield to his prejudices, provided no contra-indication exist thereto. Sometimes redness and swelling take place at the site of the injection. This is best relieved by a cold wet compress.

If the patient be timid and intolerant of pain, the sen-

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* Die hypodermatische Injection, etc., op. cit., p. 62.

sibility of the skin may be lowered by ether or rhigolene spray. A piece of cotton cloth moistened with chloroform and held on the skin a few minutes is nearly as effective as the spray, and much more convenient.

When an agent is used that, like chloroform, is very painful in the effect which follows as well as attends the injection, a small amount of cocaine can be thrown under the skin of the part to be operated upon. The antagonisms of the various remedies must be borne in mind when about to use cocaine. It is antagonistic to morphine, to atropine, to physostigmine or eserine, and some others.

LOCAL AND SYSTEMIC EFFECTS OF SUBCUTANEOUS INJECTIONS.

All agents injected under the skin, even water, produce some irritation at the point of puncture. Smarting, burning, followed by redness, and a more or less extensive swelling or wheal, are the usual phenomena. Very acute pain is caused when a nerve is punctured. When a few drops only are injected, there may be some trivial redness to indicate the point where the needle entered, and no after-swelling or irritation. The resulting wheal, when considerable fluid is injected, resembles the swelling of urticaria or of *erythema nodosum*. An indurated nodule may form, to suppurate slowly, and discharge after some weeks or even months. In such a case more or less sloughing usually occurs, including the areolar tissue and a portion of the skin, a depressed cicatrix resulting. Sometimes a frank abscess, sometimes an induration, and, not infrequently, a cyst are produced by the injection. There can be no doubt that, if the proper precautions are taken, and the tissues of the individual injected are sound, no induration or inflammation will result from the injections, if materials like morphine be injected; but when cocaine is used, cysts more frequently form. If the rules already laid down for the preparation of solutions are not complied with; if the syringe or needle is dirty or rusty; if injury is done by rough handling; or if the patient is in a cachectic state, the local accidents above described may

happen. Inflammation has resulted from partial puncture of the skin and forcing in the fluid violently. In some of the reported cases, all accessible parts of the body have been covered with cicatrices, partly-healed sores and ulcers, and recent abscesses. Making due allowance for the sensational spirit in which these cases have been narrated, there are still facts enough to show conclusively that, through carelessness in the preparation of solutions, in the treatment of the syringe and needles, and in the method of injecting, inflammation and abscesses may result. The puncture of a vein may cause some loss of blood, or the formation of a purpuric spot, and the fluid may be thrown directly into the blood, or be drawn into the vein through the opening made by the needle. In the former case there will be an almost instantaneous action of the medicine; in the latter, slower yet rather quick and powerful effects. These will be described when the remedy concerned is under discussion. In a few instances, the injury of nerves at the site of former punctures has induced tetanus, but the nervous system was prepared by the disease for which the injections were originally used, or by the cachexia induced by the chronic morphinism.

Further observations on the local effects of the injection are considered because of certain results which have been arrived at since the fourth edition was published. Such agents as cocaine, chloroform, and ether cause more inflammatory action and more decided after-effects than morphine, atropine, and many others. It is the nature and the results of the inflammatory action caused by cocaine, more especially, that are to be taken up here. Under some circumstances considerable swelling and tenderness follow the cocaine injection. The tissues are irritated to a considerable extent, and blood is effused,

the amount of this being dependent on the looseness and permeability of the parts. Suppuration does not follow. Foreign bodies thrown under the skin set up inflammation and suppuration in the connective tissue; but in the case of some irritating alkaloids the congestion of the tissues gives rise to hemorrhagic extravasation, and this in turn develops into a cyst, the contents of which undergo slow changes, becoming first a thin bloody fluid somewhat gelatinous, after a time assuming a less blood-like appearance and a more gelatinous character, and finally a semi-transparent, colorless liquid, having the appearance of blood-serum, but more consistent. Subsequently renewed activity takes place in the cyst, and an effort at extrusion of its contents occurs. The central part of the summit of the cyst grows red and tender, and finally the tissues are divided by ulceration and an escape of the contents takes place. If laid open before the completion of the changes mentioned above, the discharge is more or less bloody in character.

If the swelling formed soon after the injection is opened, the fluid flowing away is bloody in appearance, and is blood mixed with a gelatinous material. If opened early by a small trocar, an aspirating needle, or bistoury, the cyst will close, and the cavity left slowly fills up. Some sloughing of the overlying tissues may take place, and now and then a deep, dark slough extending through the skin to the subcutaneous tissue will form; nevertheless, healing will usually occur promptly when the blood is drawn off from the cavity.

The systemic effects produced by the hypodermatic injection of remedies must now be compared with the stomachal administration. A remedy entering the blood through the stomach is affected in its physiological and

therapeutical action by the condition of that organ. Disease—for example, gastric catarrh—may hinder, if not entirely prevent, diffusion through the mucous membrane. The rate and extent of absorption are influenced by the presence of other ingesta, by the state of repletion of the veins, and by the condition of the liver. The digestive fluid undoubtedly exerts a chemical action on many remedial agents, forming combinations sometimes more, sometimes less powerful. Again, as the state of the nerves has an important influence on absorption, it is obvious that those remedies which depress the nervous system must constantly lessen, by repetition, the power of the stomach to convey them into the circulation. On the other hand, when a medicine suitable for the purpose is thrown under the skin, its physiological and therapeutical effects are produced in the fullest degree and in the most characteristic form. It follows that the therapeutical properties of a drug must differ not only in degree, but also in kind, according as it enters the blood through the stomach or by the subcutaneous areolar tissue. Experience and observation abundantly demonstrate the truth of this statement. The subcutaneous use of certain drugs has developed very valuable therapeutical properties, which the stomachal administration had not even suggested. Bernard* affirms that this mode of administering remedies, which has hitherto been the exception, must become the general method for the use of active principles. The advantages of this over other methods, considered from the point of view of practical therapeutics, are manifold.

The effect is produced more speedily, and the whole effect of the quantity introduced.

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* Archives Générales, 1864.

The results are more permanent and curative.

Gastric disturbance rarely occurs, and irritation of the stomach is avoided.

The administration may be made to persons unwilling or unable to swallow.

It follows, then, that remedies suitable for this purpose may be used hypodermatically, to produce:

1st. All of the physiological and therapeutical effects which can be accomplished by them when given by the stomach; and,

2d. The physiological and therapeutical effects peculiar to this method.

The hypodermatic method may be employed for:

1st. A local action only.

2d. General or systemic effects.

The general effects of remedies administered by the hypodermatic method are to be distinguished from those due to the inherent qualities of particular and individual agents. It is necessary to consider those results of the administration common to all remedies.

As respects the general effects of this method we have to note, first, that a remedy entering the blood by the subcutaneous channel acts according to its own nature, is individualized, so to speak, and is not modified by its environment. On the other hand, medicaments introduced by the stomach may be modified in structure and altered in chemical constitution by the stomach and intestinal juices.

The rate at which given agents act when injected varies with their nature and power of diffusion,—using this term in its technical sense and as a synonyme for absorption. Studied as agents having power to traverse animal membranes, they are arranged in two classes:

Those having the power to traverse animal membrane

with the maximum facility are called *crystalloids;* those having the minimum power of diffusion, *colloids.* The former usually have a crystalline structure, whereas the latter are gummy or glue-like. Ready solubility is an important factor in the character of these bodies. For the most part, the alkali-like substances, or alkaloids, derived from so many sources, are the most useful of agents for this kind of practice. There are some agents—as potassii iodidum—which surpass the alkaloids of botanical source in the rapidity with which they enter and pass out of the system; but the crystalloids diffuse through the body with astonishing rapidity. As the round of the circulation is made in about one minute, all soluble substances diffusing through the body complete the circuit in this time. Some agents occupy much more time than one minute; others act so rapidly that insertion of the medicine and the appearance of lethal or toxic action seem to be manifest simultaneously, or nearly so. Prussic acid furnishes a good example of this rapidity of action. Also, the effects of medicines are as nearly pure or typical of their real action as can be obtained, for they are not qualified by an impression, chemical or otherwise, acting upon them by passing through the stomach and liver.

Another fact of great importance is that the character of the medicament is unchanged by successive administrations. No accumulations, in the sense in which *cumulative* action is now held, take place; but the power exerted by the remedy after it is taken is the more strongly felt because of the more rapid absorption, and again, the power declines with greater rapidity because of the more prompt and rapid excretion. The excretion of remedies given hypodermatically occurs under the same condition as when administered by the stomach.

CLASSIFICATION OF REMEDIES USED BY THE HYPODERMATIC METHOD.

In the several editions of this work, hitherto, I have not made use of any system of classification, but have arranged the various articles according to the usual position assigned them therapeutically. It seems to me desirable, however, to pursue some arrangement by which the various facts can be properly classified, and according to which the agents used hypodermatically may be grouped in methodical order.

The arrangement now submitted is based on the physiological actions of the remedies. Those acting on the whole system are first considered, and those acting on special functions follow in the order of their importance.

CLASSIFICATION.

A. Remedies Affecting the Nutrition.

1. *Remedies Increasing Waste* . . . . . — Bichloride of Mercury, Peptonate of Mercury, and other Salts. Iodine and its Salts. Pilocarpine. Salines.
2. *Remedies Promoting the Nutrition* . . . — Iron. Arsenic. Transfusion. Oils, etc.

A. Remedies Affecting the Nutrition.—*Continued.*

3. *Antiseptics*
- Carbolic Acid.
- Creosote.
- Antipyrin.
- Resorcin.
- Pyrodin.
- Euphorin.
- Orexin.
- Saccharin.
- Thallin.
- Creolin.
- Blood-serum.
- Pyoktanin (Blue).
- Cantharidin
  - Cantharidates of Potassium, Sodium, or Ammonium.

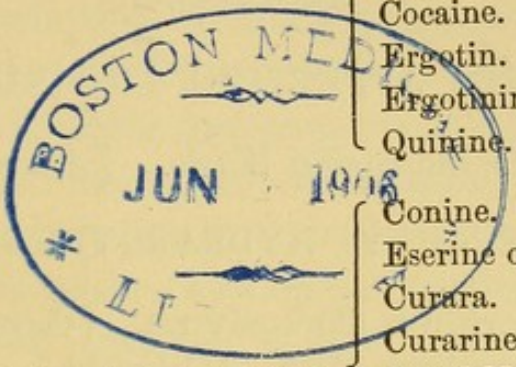
B. Remedies Affecting the Nervous System.

1. *Anodynes*
- Morphine.
- Codeine.
- Atropine.
- Homatropine.
- Hyoscyamine.
- Hyoscine.
- Duboisine.
- Solanine.
- Chloroform.
- Ether.
- Chloralamide.
- Chloral Hydrate.
- Bromoform.
- Urethan.
- Amylen Hydrate.
- Methylal.
- Exalgin.

2. *Excito-motors*
- Strychnine.
- Brucine.
- Picrotoxin.
- Hydrastine.
- Hydrastinine.

B. Remedies Affecting the Nervous System.—*Continued.*

2. *Excito-motors*
- The Digitalis Group.
  - Digitalis.
  - Sparteine.
  - Convallaria.
  - Strophanthin.
  - Adonidin.
  - Blattic acid.
- Cocaine.
- Ergotin.
- Ergotinine.
- Quinine.



3. *Depresso-motors*
- Conine.
- Eserine or Physostigmine.
- Curara.
- Curarine.
- Amyl Nitrite and Nitrites.
- Lobeline.
- Nicotine.
- Hydrocyanic Acid.

C. Remedies Affecting the Alimentary Canal.

Emetics and Cathartics
- Apomorphine.
- Apocodeine.
- Podophyllin.
- Aloin.

D. Irritant Injections
- Aquapuncture.
- Osmic Acid.
- Aqua Ammoniæ.
- Nitrate-of-Silver Solution.
- Saturated Solution of Common Salt.
- Tincture of Cantharides.
- Chloride of Zinc.
- Pepsin.
- Carica Papaya.

ACTIONS AND USES OF THE REMEDIES EMPLOYED BY THE HYPODERMATIC METHOD.

A. REMEDIES AFFECTING THE NUTRITION.

1. *Agents Increasing Waste.* [*Alteratives.*]

MERCURY: HYDRARGYRUM.

Hydrargyri Chloridum Corrosivum. [*Corrosive Sublimate.*]
Hydrargyri Chloridum Mite. [*Calomel.*]
Hydrargyri Oxidum Flavum. [*Yellow Oxide of Mercury.*]
Hydrargyri Cyanidum. [*Cyanide of Mercury.*]
Albuminate or Peptonate of Mercury.
Ammonio-peptonate of Mercury.

Preparations.—The rule has been to employ only those preparations soluble in water, but numerous departures from this plan have been made from time to time. Recently it has been maintained that such an insoluble preparation as calomel acted the more efficiently, since it is kept in contact with the tissues so much longer because of its insolubility; whereas the soluble pass into the blood so readily, and are so quickly eliminated, that the time is insufficient to permit the necessary action to take place. Scarenzio* was probably the first to make use of calomel, having in 1864 published his first observations. He suggested the suspension of calomel in water by means of glycerin. Hebra soon after proposed the administration

* Eulenberg, op. cit., p. 307.

of sublimate (gr. i–℥ss of water). Lewin* was the first to apply sublimate solution on a large scale, the method being illustrated by extensive clinical observations, the whole appearing in a considerable volume. Lewin especially advocated the administration of weak rather than strong solutions of corrosive sublimate (½ of a grain to 1 ounce of water). He added morphine sulphate (gr. ss–℥i) to obviate the pain which, to a greater or less degree, attends the subcutaneous injection of the corrosive chloride. The strength of the solution employed by Lewin was one grain to the ounce. Liégeois† has conclusively shown, also, that strong solutions are not only injurious, but unnecessary.

So many local troubles (abscesses, ulcerations, sloughing) attended the use of calomel, at first, that it soon fell into disuse; but a revival is again manifest, and calomel suspended by glycerin, by olive oil, and other menstrua, has come into large use, the theory being that an insoluble preparation, as already stated, is more lasting in its effects. The yellow oxide of mercury is also employed in a similar manner, and is objected to for the same local results. Besides the irritant effects of such an agent, when retained for some time in contact with the subcutaneous connective tissue, the menstrua used for suspending the salt are liable to decomposition, and cause abscesses and ugly ulcerations, with much pain and considerable constitutional disturbance.

In consequence of the local ill results of insoluble preparations, the soluble are more generally employed. Besides the sublimate, the salts of mercury now proposed for subcu-

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* Lewin, Bul. Général de Thérapeutique, 1869, vol. ii. Also from Dr. F. Bricheteau, De l'Application de la Méthode hypodermique au Traitement de la Syphilis par les Préparations mercurielles.

† Ibid., 1869, vol. ii. p. 158, par Liégeois. Also ibid., Août, 1880.

taneous administration are the succinate, the benzoate, the cyanide, and the albuminate. Dr. Vollert,* of Strasburg, has advocated the *succinate of mercury* as a highly-eligible preparation. He uses a solution of one to two to 100, giving a syringeful (equal to xx ♏), the dose of the mercury being one centigramme. Vollert asserts that the succinate solution causes but little pain when introduced, and is rarely followed by inflammation and abscesses or ulcerations. The number of injections in ordinary cases required for the disappearance of the symptoms varied in different subjects, and ranged between 19 and 35. For 28 subjects recorded in his tabular statement, 523 injections were required,—an average of 19 for each patient (pp. 408–412). Another soluble salt of mercury has been suggested by the Russian professor, Dr. Stoukovenkoff,†—the *benzoate.* Although this salt of mercury is but slightly soluble in water, it dissolves readily in water containing some common salt. The proportions advised by Dr. Stoukovenkoff are nine (9) parts of the benzoate to two (2) parts of the chloride of sodium. The formula for the injection is twenty-four (24) grammes (℥vi) of the benzoate, six (6) (¼ gr.) centigrammes of chloride of sodium, and distilled water thirty (30) grammes (℥i). No pain, no induration, no abscesses or ulcerations follow the injections of this salt, according to its proposer.

The double salt of iodide of mercury and sodium was suggested to Dr. Bricheteau by Pharmacist M. Bouillon, as a medicament especially adapted to hypodermatic use. The main objection to this salt is the difficulty in pre-

* Therap. Monatshefte, September, 1888. Ueber Succinimid-Quecksilber eine neues Mittel zur subcutanen Injection. Dr. Vollert, from Wratsch, No. 4, 1889.

† Bul. Général de Thérapeutique, 1889, vol. i. p. 525.

paring it, and hence it has never come into general use. The dose for administration subcutaneously is $\frac{1}{4}$ of a grain, which is contained in fifteen minims of the solution given below:

℞ Hydrargyri et sodii iodidi, gr. xxiv;
Aquæ destillatæ, ℥iii. M.
Sig.—Fifteen (15) minims contain $\frac{1}{4}$ of a grain.

This salt, as Dr. Bricheteau* ascertained, was very well adapted to the purpose, and no doubt it would have gone into general use if the difficulty of its preparation had not proved so serious an obstacle.

The cyanide has become very popular with those who have been prevailed on to make use of it; but it is painful, so much so as to render patients unwilling to have it inserted after the first trying experiences. It has been ascertained that if the cyanide be pure it is not severe, even but little painful. Sigmund and Güntz† used it with remarkable success, and Mandelbaum‡ maintains its superiority over all other preparations of mercury used hypodermatically in the treatment of syphilis. It has been proposed to combine morphine or cocaine to remove the severe pain which attends the injection at once and for some time afterwards. It should be remembered that the cyanide must be made afresh for each treatment by injection (Sigmund and Güntz), if local troubles are to be prevented. It is necessary, also, to avoid large doses with a view to more prompt cure; for experience has shown that the large doses are more apt to cause inflammation and induration of the tissues, salivation, and

* Bul. Général de Thérapeutique, De l'Application de la Méthode hypodermique, etc., 1869, vol. i. p. 297.

† Wien. Med. Presse, quoted by Virchow and Hirsch, 1879.

‡ Vierteljahrschrift für die Dermatol. in Syphilis, 1878, p. 201.

ulceration of the gastro-intestinal mucous membrane, and these untoward results more than compensate for the gain in time of the larger over the smaller doses.

Some recent experiences have confirmed former reports on the utility of the cyanide (M. Horovitz,* Mandelbaum,† Sigmund and Güntz‡). All agree that this salt sets up horrible pain when thrown under the skin, if not pure, and hence the usual practice has been to combine morphine or cocaine with it to lessen the suffering. Besides the pain, there are no other local complications caused by the cyanide,—no indurations, no abscesses. Recently our German colleagues, especially, have brought into use a new preparation of mercury called *hydrargyrum thymolo-aceticum*, made by Merck, of Darmstadt, for subcutaneous injection. To prevent too rapid absorption and excretion, the solution of this new medicament is thickened somewhat by the aid of mucilage and liquid paraffin.

The formamide, peptonate, and albuminate of mercury have become more generally popular than the other salts of mercury, because nearly free from the serious local effects, including pain, which attend on the use of the soluble, especially of the insoluble, salts of mercury. The formamide was first proposed by Liebreich,§ of Berlin. He advised the preparation of this substance by dissolving the freshly-precipitated red oxide of mercury in formamide. It was ascertained at once that this preparation was superior to all others in respect to the local complications,—the pain, inflammation, and abscesses,—which almost never occurred.

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* Liebreich, Centralblatt für die gesammte Therapie, 1883, p. 95.

† Mandelbaum, ibid, 1886, p. 522.

‡ Güntz, Therapeutische Monatshefte, October, 1890, p. 494.

§ Sigmund, quoted in the same article.

Bamberger first proposed the use of albuminates or peptonates of mercury for subcutaneous injection. These have since come into general use, by reason of their comparative freedom from the unpleasant results attending on the use of insoluble and other irritating salts of mercury. Peptonates are prepared by dissolving corrosive sublimate in a solution of pepsin. Staub was probably the first to make use of the albuminate, which is prepared by dissolving the mercurial salt in a solution of egg albumen.

The formulæ for this, as for other salts of mercury, are given below.

The author has always used the corrosive sublimate, as follows:

℞ Hydrargyri chloridi corrosivi, gr. i;
Aquæ, ℥i. M.

Sig.—Should be dissolved by heat at boiling temperature and then filtered. The dose is ten (10) minims, which contains $\frac{1}{48}$ of a grain. This is a sufficient dose for the beginning of the treatment, but it can be increased with the progress of the case.

Liégeois recommends the following,—the morphine added to lessen the pain of the operation:

℞ Hydrargyri chloridi corrosivi, gr. iii;
Morphinæ sulph., gr. iss;
Aquæ destillatæ, ℥iii. M.
Sig.—Fifteen (15) minims contain $\frac{1}{32}$ of a grain.

Vollert recommends that the succinide solutions have the strength of 1.30–2 to 100. Of this solution he administers a Pravaz syringeful, which is about twenty minims' capacity, and contains one centigramme of the mercurial salt.

Bamberger's solution of albuminate consists of two preparatory solutions, one of albumen and another of corrosive sublimate. The albuminate is made by dissolving 200 c.c.

of albumen in 300 c.c. of distilled water. The solution of corrosive sublimate is of the strength of 5 parts to 100. Of the sublimate solution 60 c.c. are mixed with 100 c.c. of the albumen solution. A salt solution of the strength of 20 per 100 is also prepared, and of this 60 c.c. are added to the albuminate and corrosive chloride solution. The preparation thus made is allowed to stand for two days, when it is filtered and then is ready for use. The dose of this solution is 20 c.c. The peptonate is far more easy of execution. The following are the formulæ most in use:

Pepsin, 1 gramme (15½ grains);
Water, 50 c.c. (7½ grains). M.

Filter. To this solution of pepsin is added the solution of chloride of mercury having the strength of 1 to 500, 20 cubic centimetres of salt 20–100 solution (16 c.c.), and sufficient distilled water to make up to 100 cubic centimetres. Each cubic centimetre contains 1 centigramme of mercury.*

The salt added increases the stability of the solution and lessens the pain and inflammation at the site of puncture.

Delpech used the following formula, substituting chloride of ammonium for the chloride of sodium in the albuminate preparation. He affirms that this is the most eligible solution now in use for hypodermatic purposes. The mode of preparing this solution is far less complicated than is the albuminate. It consists in dissolving an ammonia-sublimate powder in distilled water and glycerin, as follows:

Powder of ammonia (mercurial peptone), .50;
Distilled water, 25.00;
Glycerin, 5.00. M.

Each syringeful (20 ♏) of this solution contains 10 milligrammes of mercury.

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* Dujardin-Beaumetz, Leçon de Clinique Thérapeut., vol. iii. p. 548.

Besides the forms for injections given above, I must not fail to mention the blood-serum vehicle proposed by Dr. Max Bockhart, of Wiesbaden.* The blood of cattle, sheep, hogs, etc., can be utilized for this purpose. The serum is first filtered, and to the filtrate, of 40 cubic centimetres (1⅓ ounces) contained in a graduated glass, is added a warm solution of bichloride of mercury of the strength of 46 grains to the ounce of water. The precipitate thus obtained is dissolved in a solution of common salt,—105 grains in five drachms of water. This solution, containing three per cent. of mercury, is mixed with distilled water up to 6¼ ounces, and has the strength, therefore, of one and one-half per cent. of mercury. It must be kept in a cool, dark place. The dose is 12 drops given every day, the patient thus receiving ⅙ of a grain each time.

Kaposi, Boer, Mandeville, Bamberger, Martineau, and others, contrasting the efficiency of the various solutions, differ somewhat in their estimate of their respective value, but the majority hold to the superiority of the simple sublimate solution, except in respect to the local trouble, the sublimate causing induration, inflammatory tumors, and abscesses more frequently than the peptones and albuminates, which are said to be free from such complications; but there is a general agreement that sublimate is far more painful than the peptonates and albuminates. The author's experience is distinctly in favor of the simple sublimate solution, which, although painful, has never been followed by local complications of importance in his experience, which has been considerable.

I must insist on the need of care in preparing and ad-

* The Therapeutic Gazette, 1886, p. 68. The London Lancet, July 17, 1886.

ministering solutions of mercuric chloride or of any other mercurial. The syringe must be of glass or hard rubber, and no metallic appendages of the instrument should come into contact with the mercurial. The needle should be clean—absolutely clean—and aseptic, and it is the better if made of gold suitably hardened, and provided with an iridium point. The ordinary steel needle will suffice, however, if kept properly clean and sterilized, especially if plated with platinum.

Actions and Uses: Local Effects.—What salt of mercury soever is used, there can be no question that severe pains attend the introduction of the preparation underneath the skin. The pain differs in degree somewhat, but is never absent. It is asserted that the peptonates are least painful, and that the cyanide causes the maximum suffering, but increasing experience shows the futility of all such assertions. Each occasions sufficient local distress to render the method repugnant to sensitive patients, and not infrequently induces them to avoid their physician, and yet more surely to avoid the clinic.

The alkaloids morphine and cocaine added to the solution are not to be depended on when several hours have passed from the time of making, for they are precipitated as amides in a little while. As, however, physicians are urged to prepare a fresh solution for each day,—better still, for each patient,—the diminishing effect of the narcotic may thus be prevented. It is unfortunate that a distinct interval exists between the time of the injection and the beginning of the anodyne effect. The better plan, therefore, is to select the site for the injection, and then insert a sufficient dose of cocaine a few minutes before the other solution is to be made use of.

The mercurial solutions may not cause any more dis-

turbance than the morphine, if sufficient care be used. Bamberger asserts that his peptonate causes no more pain than the injection of morphine does.

Besides the pain, various local disturbances may ensue. A swelling quickly forms and has a tensive feeling, as if pus were confined beneath; a considerable wheal develops about the site of the puncture, and sometimes to a considerable extent over the limb and on other parts. The local swelling may go on to the formation of a cyst, or suppuration may occur. The cyst is to be expected if a considerable hemorrhagic extravasation takes place, and if the blood is confined to the part it subsequently slowly proceeds to seek an outlet, setting up an ulceration to make the necessary way to the surface. The pus formed has a gelatinous and bloody appearance, and it obeys the usual law and seeks to escape at the point of least resistance. The severe pain and the inflammation may cause various nervous symptoms, the most severe being tetanus. It has been questioned, however, whether such an accident as tetanus really takes place as a consequence of subcutaneous injections, unless the most unconscionable carelessness is manifested.

When large doses of the mercurial are administered, in some states of the system mercury can be found in the urine after an hour or two, and ptyalism may be expected after a few doses have been given. The number of injections that may be practised before this symptom appears varies in different individuals, constitutional peculiarities being an element in the causation; but the dose is more influential than any idiosyncrasy. The initial dose of the sublimate ranges from $\frac{1}{30}$ of a grain to $\frac{1}{6}$ of a grain. Calomel is given in quantity from $\frac{1}{2}$ grain to 5 grains. The other insoluble salts, as the black and red oxides, the

salicylate, etc., are given in about the same quantity as calomel. M. Staub,* who was among the first to make use of sublimate in solution with alkaline chlorides and albumen, gave one centigramme (15 minims) daily of his preparation, equivalent to $\frac{1}{30}$ of a grain, at the outset of the treatment.

As to absorption, it should be noted that mercury given subcutaneously will, if no obstacle exists, appear in the urine on the second day.

The ptyalism induced by the subcutaneous injection of mercurials is not different from the same state caused by the stomachal administration. The gastro-intestinal catarrh and ulcerations, the state of the nutrition, and condition of the blood are also the same whether one or the other mode of administration be followed. As respects the hypodermatic method, it is to be observed that the effects follow more promptly and excretion is more rapid. In cases under treatment, if the mercury be not detected in the urine on the second day, it may be questioned whether the preparation used is a good one.

The number of injections required to effect the removal of the visible signs of syphilitic infection varies in different individuals. The number of injections to cause salivation is determined chiefly by the dose. To remove the external symptoms of syphilitic infections from five to thirty injections are required, the average being about ten, yet some have been cured by four injections.

Results.—To come to a definite conclusion regarding the curative power of mercurial injections it is necessary to compare them with the standard set up by the methods hitherto in use,—with the results of the stomachal admin-

* Archives Générales de Médecine, July, 1872.

istration, the fumigations, mercurial frictions, etc. Abundant data exist for determining the position in the scale of the various methods in use.

One of the earliest to begin the hypodermatic method in this disease, in the treatment of large numbers, was Lewin, of Berlin, whose book embodying the results of his investigations was an epoch-making publication. In a series of experiments on a group of one hundred and forty-four, there were fifty-one cases of salivation. On the other hand, Liégeois,* who employed a much weaker solution, had but four cases of salivation in one hundred and ninety-six subjects. Besides the dose, there was no difference in the solutions or in the methods of employing them. If we examine further, we find that Lewin treated three hundred and fifty-six patients by injections of sublimate, aided by some other remedies, and of these the relapses were eighty-nine, or twenty-five per cent. When ordinary means of treatment are made use of, the relapses average eighty-one in one hundred cases. The superiority of the injections over the stomachal administration is thus clearly shown.

The most conspicuous example of the utility of the hypodermatic method in specific infection is that of M. Martineau at the Lourcine Hospital. He has formulated the results of the treatment of one thousand cases of syphilis, and he affirms that, with his ammonia-peptone solution of corrosive sublimate, there have been no accidents,—no local inflammation, no abscesses, no ulcers, no ptyalism, no gastro-intestinal catarrh, etc. Thus the cures have been effected promptly and without any mercurialism. As respects the pain of the procedure, Martineau affirms

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* Bul. Général de Thérapeutique, 1869, vol. ii.

that it is not greater than the least irritating remedy employed in that way.*

M. Vidal tried the method of Martineau in thirty cases of venereal disease with excellent results, and has formulated his conclusions as follows:

Of the thirty patients, four had ptyalism to a sufficient extent to require the suspension of the treatment. With every precaution taken to avoid accident, some of the cases were annoyed by the formation of nodosities which were more or less persistent, and in some there was a good deal of pain, but abscesses never occurred.

It is generally held that the best places in which to insert the mercurial solution are in the muscles of the back and especially in the buttocks, where there is much connective tissue and the muscles are prominent. The best procedure is to make the insertion intra-muscular, —to thrust the needle into the muscle and not confine the injection to the connective tissue beneath the skin. In this way room is had for the syringeful of solution, and the pain of the operation is much less. If, however, the pain be objected to, it may be obviated by making a preliminary injection of cocaine, $\frac{1}{12}$ to $\frac{1}{6}$ of a grain. When anæsthesia is induced, the needle can be thrust into the muscles quickly and deeply without fear. It is especially desirable to avoid the prominences of bone,—that is, to insert the needle into the muscular masses on each side of the spine, and not over the posterior or transverse processes of the vertebra, or over the sacrum, or prominences of the ilium, or the trochanter. The fluid should not run out, as it may cause pain by passing over the raw tissue, and be followed by a slough. The orifice made by

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* M. E. Callamand, Journal de Thérapeutique, 1882, p. 47, *et seq.*

the needle should be accurately closed by the index finger of the other hand pressing easily but firmly on the site of the puncture as the needle is withdrawn.

It has been stated, *supra*, that the needle with which injections of mercury are made should be carefully sterilized after cleaning. The material of which made is preferably hardened gold, if the expense is justifiable; if not, steel coated with platinum comes next in value for the purpose. The material of the syringe should be glass or celluloid, and the piston should operate so completely that none of the fluid can reach and act on the metal piston-rod.

The needle should be sterilized for each operation, and the fluid or mercurial solution should be made afresh every day. Indeed, it were better if there be an interval of several hours between, that a fresh solution be prepared for each patient. A daily injection is the usual practice at the outset of the treatment.

THERAPY.—As the use of mercury hypodermatically is almost entirely confined to the treatment of syphilis and its complications, this method, as a means of more speedy and effective relief, is to be discussed here for the most part.

It is the opinion of the most eminent specialists, among whom may be mentioned Kaposi, of Vienna, Vidal and Martineau, of Paris, and Bloxham, of London, that the hypodermatic method is far in advance of all other means of treatment if the occasion and the local conditions warrant.

My own judgment is that it is equally adapted to the treatment of the indurated sore as for the constitutional states. As Mr. Hutchinson has recently taught, the infection of the system is synchronous with the first appearance of the induration,—the characteristic quality of the true

infecting chancre,—and that a course of mercurial treatment, judiciously carried on, will prevent or suppress the so-called secondary stage. It may seem a supererogation to say that my own practice has been, for many years at least, to begin the mercurial treatment when induration is found to exist, and in this way no secondary symptoms, except in a very modified form, appear thereafter.

No one at this day questions the propriety, indeed the necessity, of giving mercury for the secondary stage, especially if no mercurial course had been instituted. It is a mistake to suppose that the use of mercury must be lavish, or carried up to the development of mercurialism. Salivation is not necessary; indeed, it retards rather than promotes the cure. We have in the statistics of Lewin and Liégeois, respectively, a demonstration of the superiority of smaller over the larger doses of mercury. We find that in Liégeois's cases no salivation occurred, but the cures were permanent and the relapses far less, comparatively, in numbers; but a somewhat longer time was required for the complete result than when larger doses were given. This conclusion is further supported by an immense amount of clinical experience in the practice of Martineau, Delpech, Mandelbaum, Sigmund, Bamberger, and others. It has been shown conclusively that when the smaller doses are administered the nutrition of the body improves, the blood becomes richer in red-blood globules, and the organs in general perform their functions with increased facility and power. It is essential to this improvement in nutrition that mercurialism be avoided, for salivation and the gastro-intestinal disturbances would surely prevent any gain in material.

Corrosive sublimate is the salt of mercury which most

improves the bodily condition, as has been shown by Keyes and Wilbouchewitz; but this power is available only when small doses are given and the interval between the doses is long rather than short.

These facts in regard to the influence of mercury on nutrition can be as well seen when the method of administration is by hypodermatic injections as by the stomach; indeed, rather more certainly, for by way of the subcutaneous areolar tissue the stomach is not interfered with and, the digestion continuing unimpaired, the secondary assimilation remains unaffected.

For the so-called "secondary symptoms" there can be no question as to the value of mercury or as to the subcutaneous use of the agent. There is, however, no common agreement as regards the so-called "tertiary symptoms" and their treatment by mercury. Having had some experience in the hypodermatic treatment of this stage of the disease, I may venture my opinion in regard to its utility. When there are present no signs of phagedæna, no evidences of seriously-impaired nutrition, no injury of the viscera, it can be used with more benefit, more curative power, than iodine in its various forms.

In cases where the progress of syphilitic ulcerations threatens serious impairment, even destruction, of an organ, the injections of mercury are especially indicated. In ulceration of the vocal bands, or gummata, or other form of specific outgrowth impinging on the peduncles of the cerebellum, on the medulla oblongata, on the crura cerebri, or in other situations, the rapid progress of the disease may require the use of the most active and quickly-operating medicaments. In cases of ulceration involving the larynx, where life is threatened by the extension of the process to the vocal chord, and suffocation is immi-

nent, timely injection of mercurials has averted a fatal termination.

The results of the treatment which most recommend the method to the unfortunate subject are, first, the celerity of action, the absence of complications, the infrequency of relapses, and the cleanliness of the means used. To these favoring circumstances should be added the relief from stomachal medication, which is annoying from the necessity of swallowing drugs and their untoward effects on the gastro-intestinal mucous membrane.

Besides the uses of mercury in the treatment of syphilis, there is one condition in which an injection of bichloride of mercury proved highly beneficial,—in the algid stage of cholera. The reporter of this remarkable case was Surgeon Baker, of the Indian Medical Staff, who published an account of it in the *Indian Medical Gazette* for July, 1889.* The patient, a seaman almost *in extremis*, was given an injection of $\frac{1}{3}$ of a grain of corrosive sublimate, the needle being inserted in the gluteal region. The next day the reaction was complete, and in ten days he was dismissed from the hospital cured. By administering the corrosive chloride the physician avails himself of its germicide power, by means of which the bishop bacillus —which is the parasite causing cholera, according to the great master, Dr. Koch—is destroyed.

I must add to this account of the hypodermatic use of mercury the late experimental work on *intra-pulmonary injections*. There is no difficulty in performing the injection. It consists in passing through the chest-wall, at an

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* The Therapeutic Gazette, 1889, vol. xiii. p. 753.

intercostal space lying over the diseased area, the needle, which must penetrate the part diseased, into which the solution is injected.* Some favorable results have been given out; but a remarkable case, proving fatal, has discouraged further attempts by the advocates of this method. In the case in question, the very thin outer wall of a cavity communicating with a bronchus was penetrated by the needle, and in consequence the air poured out into the cavity of the thorax, the lung collapsed, and in two hours the patient was dead.

If we are called on to dispose of the question as to the mercurial best suited for hypodermatic injections, it were better to decide from the statistics now available for the purpose. The largest number of injections practised by any single operator are those of M. Martineau, whose experiences were obtained at the Lourcine Hospital in Paris. He lately reported one million of injections, and has had no untoward consequences,—no abscesses, no after-indurations, etc. He attributes his remarkable success to the use of ammonio-albuminate of mercury. Next to Martineau comes Lewin, of Berlin, with three hundred thousand injections and twenty abscesses; but he makes use of a solution of corrosive sublimate.

Dr. Watraszewski, of Warsaw, has used with great satisfaction the red and black oxide of mercury, after experiencing much disappointment with calomel. He suspends these preparations with mucilage in water, and gives a grain at a dose. In the course of two hundred injections he had no unpleasant after-effects in any case, and no pain occurred that required attention. He found two to five injections sufficient to effect a cure, and he allowed an

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* Lépine, Bul. Général de Thérapeutique.

interval of two to five days between each injection. If these statements were substantiated by satisfactory evidence, no one could fail to use these oxides in the treatment of syphilis by the hypodermatic method; but the facts are too remarkable to be dealt with in any other spirit than incredulity.

One of the most effective of the mercurial remedies is the cyanide, but there is a serious objection in the severe pain which attends the injection. The succinide, the iodides, the albuminates, the peptonates, and the ammonio-peptonate of mercury are soluble preparations popular with specialists in the order in which they are named,—the last having the highest number of adherents.

Of the insoluble preparations, calomel, from the time of Scarenzio, has been most used. Pronounced objections are entertained against it now because of the local complications to which it so often gives origin. The oxides of mercury—black and red—seem to have little action on the tissues, and are very effective, if the reports published are to be credited. In respect to curative power, it is alleged that the insoluble preparations have the signal advantage of being more actively curative because of their long retention in the system. In consequence of this belief the insoluble preparations of mercury are again coming into more general use.

The weight of evidence is in favor of the ammonio-albuminate of mercury as possessing the highest advantages, confirmed by each succeeding observer, and therefore worthy of full confidence. The latest publication of statistics by Martineau confirms all previous reports regarding the efficiency of this preparation, and freedom from all local and systemic disturbances or complications.

IODUM: IODINE.

Tinctura Iodi. [*Tincture of Iodine.*]

Liquor Iodi Compositus. [*Compound Solution of Iodine.*] Dose of either from ♏i–♏v.

Iodoformum. [*Iodoform.*] Dose from gr. i–gr. v.

Potassii Iodidum. [*Iodide of Potassium.*] Dose from gr. v–gr. xv.

Sodii Iodidum. [*Iodide of Sodium.*] Dose from gr. v–℈i.

These preparations, except iodoform, are administered dissolved in water. The tincture may require one to three grains of iodide of sodium or potassium to effect a perfect solution. The liquor iodi comp. contains five parts of iodine and ten parts of potassium iodide in one hundred parts of water. It is obvious that the quantity of potassium iodide is here adequate to effect a perfect solution, and is in a quantity sufficient to make an impression therapeutically.

The water with which a solution is made should be sterilized by boiling and filtration. It is important to use as dilute a solution as possible, for the more concentrated the preparation the more irritating to the tissues.

Potassium iodide is very freely soluble in water, so that from five to fifteen or more grains can be dissolved in a half-drachm of water; three of the salt to four of water is a suitable proportion. The dose for hypodermatic use will range from five to thirty grains, the actual amount being determined by the various circumstances of the case.

Sodium iodide may be administered subcutaneously in doses of from five to fifteen grains more than potassium iodide. The same rules obtain as regards the preparation of the solution and its administration as have been

stated for the potassium salt, but the sodium salt is less irritating and safer.

The other iodides have not been used subcutaneously; if desired, they can be employed as the potassium and sodium salts are, and administered in the same manner and under the usual circumstances.

Physiological Actions.—When the tincture or the salts are thrown under the skin, vivid pain and burning are experienced, and a considerable swelling remains at the site of puncture, but it usually disappears in a few days. The pain from the tincture may be slight, and no swelling result; on the other hand, there may be very severe pain and considerable swelling at the site of the puncture. This lump may slowly disappear or gradually suppurate. The iodides with alkaline bases have a remarkable power of diffusion. In a few minutes after a full dose enters the stomach it has made the round of the circulation and appears in the saliva and in the urine. When thrown under the skin, of course, the rate of diffusion is so much the greater, and merely seconds are occupied in making the complete circuit.

The affected areas acted on by an iodide dispose of their pathological new formations, which are rapidly extruded, leaving intact the normal tissue. Such action has been called "alterative," and is supposed to be a special endowment of a few medicaments. The iodides increase waste, and are therefore classified with the group of remedies, such as mercury, which act in a similar manner.

The injection of large doses of the preparations of iodine, especially if frequently made, will bring on a morbid state called *iodism*. The amount of iodine necessary to cause this state differs in different subjects. A rather fanciful division into *acute iodism* and *chronic iodism* has

been made; but time has less to do with it than the amount given, or than the susceptibility of the individual.

Iodism is manifested by injection and redness of the eyes and some swelling of the eyelids; a little later the lips are somewhat swollen, the throat becomes red and irritable, the voice husky, and the taste lingering in the mouth is bitter and saline. Patients unfamiliar with these conditions fancy a severe cold has come on, but no one having seen the fauces could be mistaken. A more or less severe coryza attends on the other symptoms, and a cough husky and strident completes the resemblance to a "cold in the head." General *malaise*, more or less pain in the back and limbs and in the forehead, contribute to the distress; the appetite fails, the stomach is somewhat distressed, and the stools are rather loose than confined. The cough which the original irritation brought on was faucial, but this is succeeded by an irritating cough, which is added to the other symptoms when the hyperæmia extends to the larynx and bronchial tubes, and paroxysms of difficult breathing, asthmatic in character, occur. In a case of œdema of the glottis, due to the administration of large doses of potassium iodide, narrated by Dr. Fenwick,* of the London Hospital, the patient had taken a few doses, each of ten grains of iodide of potassium, when he was attacked with the usual symptoms of acute iodism, including violent laryngeal symptoms of a severe type which required tracheotomy to save life. Four similar cases are narrated by Dr. Groenouw,† of Breslau, which, although not so severe as Dr. Fenwick's case, were sufficiently serious to excite grave apprehensions as to the result.

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* The London Lancet, November 13, 1875, p. 698.

† Therap. Monatshefte, March, 1890, p. 105, *et seq.*

Dr. Fenwick regarded his case as the most severe that had ever been reported, but any example of the kind attacking the larynx is formidable enough. In one instance coming under my notice, the croupy cough, the husky voice, and the asthmatic breathing were clearly indicative of the degree in which the larynx was involved.

It is, I think, a fact that the free or lavish use of the iodides tends to diminish the sexual power in men,—to a much less degree in women; but in the former slow changes take place in the testes of an atrophic kind, and the organs become soft, even flabby, and are distinctly wasted after some months. With this local change there is associated a mental state of a peculiar kind,—hypochondriacal, melancholy, and suspicious, with a fear of impotence, etc. It has seemed to me probable that the mammæ of women were more or less wasted after the use of the iodides for some time. It is quite difficult to procure the assent of middle-aged women to an inspection of the mammæ, now pendent and rather unsightly objects. How much of low and depressing spirits come of the change in the mammæ I do not know.

Considerable attention given to the question has also inclined me to believe that the free and long-continued use of the iodides—especially of potassium—affects the kidneys unfavorably, and causes Bright's disease or its equivalent. It is now known that the salts of potash are hurtful to the kidneys, and hence the change in the organs in question may be due to them. How or why the effect is produced may still be questioned, but that after a course of potassium iodide extending over months and years the presence of albumen in the urine is ascertained, is not an infrequent incident. The relation of cause and effect is hardly doubtful under these circumstances.

THERAPY.—The practical outcome of the hypodermatic injection of iodine has become rather promising. Properly speaking, the method by which iodine is chiefly employed is not hypodermatic, but parenchymatous.

By *parenchymatous injections* is meant the injection of medicaments into the substance of enlarged glands and other organs, into the various cavities, and into the interior of tumors. We are here concerned with iodine only as the material to be injected.

Davaine* was the first to use the preparations of iodine (the tincture) by subcutaneous injection, applying the method to malignant ulcer (charbon). His first communication was made to the French Academy in 1873. Several years afterwards Richet took up the same subject at the Hôtel-Dieu, Paris, and again demonstrated the truth and utility of the previous observer's method. Richet† employed, as Davaine had, the solution of iodine, consisting of 1 part of the tincture (French Codex) to 2 parts of distilled water. A syringeful of this solution (20 ♏–3ss) was thrown into the substance of the ulcerating mass several times a day. Richet was followed in this practice by Thévenot,‡ whose experiences, much later in date, confirmed the observations of those who had preceded him. His practice was also directed against *malignant pustule* (charbon), and by means of solutions of iodine of varying strength. He ascertained that the microbe, the *bacillus anthracis* of malignant pustule, was prevented spreading on all sides by the injection made in a line around the base of the ulcer, and those contained in the mass, after the

* Recherches sur le Traitement des Maladies Charbonneuses chez l'Homme. Davaine, Journal de Thérapeutique, 1880, pp. 631–638.

† Journal de Thérapeutique, 1883, p. 325.

‡ Ibid., 1881, p. 621.

injection of the iodine, were found to be inactive and without the remarkably strong infective power of the uninjured germ. The number of injections ascertained to be necessary ranged from two or three a day to a dozen or more, according to the condition of the mass and the state of the patient, especially in respect to systemic infection, which it may be well supposed increased the gravity of the disorder in every way.

The solutions of iodine have been applied successfully to the treatment of *cysts* and *cystic tumors*. I have seen some tumors of the neck, partly *cystic* and partly *glandular*, rapidly cured by these injections. My experience is that the undiluted tincture must be made use of to secure closure of the cyst. In but one case did the reaction approach the danger-point, and this was a case of cyst in the thyroid gland. I should have known then the danger of this procedure, but did not. As has happened many times when the iodine is thrown into the interior of a thyroid cyst,—as in my case, after allowing its contents to escape,—a high degree of constitutional disturbance followed the little operation, much sloughing occurred, and a septicæmic state came on. The patient—a girl in domestic service—was pulled through with great difficulty.

Goitre, when simple,—*i.e.*, without calcareous or other forms of degeneration,—is cured by injecting the tincture of iodine or Lugol's solution into the interior of the enlarged portions of the gland. The dose of the tincture of iodine should be from 2 to 5 minims or drops in each lobe of an ordinary goitre, but if the tumor is large, 5 drops in each injection—there being several—would prove too much; of the compound tincture twice as much. The number of injections and the time occupied in the treatment will depend on the duration, size, and condition

of the enlarged gland, and somewhat on the patient's state and hereditary influences.

Parenchymatous injections of iodoform, in the proportion of 6 parts of iodoform to 20 of glycerin, were proposed and used by Thomann * in the treatment of these and other local affections. As iodoform is soluble in ether and glycerin, it was proposed to dissolve in ether first, and then add glycerin in the proportion given above,—*i.e.*, 6 grammes (or 93 grains) of iodoform to 20 grammes (or 7 drachms) of glycerin,—nearly equivalent to 1½ drachms of iodoform to 1 ounce of ether and glycerin.

Other cystic diseases have been successfully treated in the same manner. *Spina bifida* is now frequently cured by the method of Morton, which consists in the injection through a canula of an iodo-glycerin solution. The following is the formula for this solution:

> Tincture of iodine, 0.50 gramme = 7¾ grains;
> Iodide of potassium, 1.50 grammes = 23 grains;
> Glycerin, 30 grammes = 460 grains. M.

Several precautions are necessary to secure the best results. The canula should be large enough to fill out completely the opening, to prevent the escape of the spinal fluid and the admission of air and other foreign bodies. Treated on this plan, Morton † had, out of fifteen cases, twelve successful ones,—the unsuccessful having had complications. Watt had four successful, and Chassaignac had no failures in his cases.‡ A highly-instructive example is that narrated by Mr. Coates: an infant of three months injected with an iodine solution of the strength of 15 parts of

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* Bul. Général de Thérapeutique, vol. ciii. pp. 47, 285.

† The London Lancet, 1876, vol. ii. p. 776. ‡ Ibid.

iodine to 75 parts fluid. Notwithstanding convulsions, the child recovered entirely. Many other cases are on record, but these will suffice to illustrate the method and its practical outcome.

Echinococcus or *echinococci cysts* are also curable by the injection of iodine, if so situated as to be within reach from without. The site most usual, as might be expected from the position and character of the organ, is the liver. A single echinococcus cyst may form, by gradual accumulation of its contents, an enormous body, filling up and pushing out the right hypochondrium. It has been proved that mere puncture and evacuation of the contents of such a cyst will sometimes effect its destruction. The results of the injection are far more satisfactory, for when the iodine solution is thrown into the cyst-cavity sufficient adhesive inflammation is excited to close the cavity and ultimately obliterate it entirely. Although in a few instances some constitutional disturbance has taken place, the method almost invariably results *cito, tute et jucunde.* Surgical incisions, drainage-tubes, and all the paraphernalia of the modern surgeon, with his antiseptic precautions, may be invoked should the milder expedients fail to effect a cure. Other *cystic tumors*, such as those formed by the obstruction of the sebaceous gland-ducts, and which are often seen on the heads of those fearing a surgical operation, may be quickly cured by inserting ½ of a drachm of the tincture of iodine, some of the fluid contents being previously removed, or an aspirator needle inserted, the contents being fully squeezed out, and then sufficient iodine injected to change the action of the lining membrane of the sac.

As for a period subsequent to the operations on cysts and hypertrophied organs, mentioned above, the methods of antiseptic surgery, as now known, were undeveloped;

the troubles incident to the opening and withdrawal of the contents of cysts were hardly understood. The same procedures, carried out with antiseptic precautions, would not now, it is believed, be followed by such ill results. These facts are well illustrated by the cases of *spina bifida* reported by Mr. Berry.* Of three cases treated by the method of Mr. Morton, two recovered and one died. The failure in the fatal case was attributed to the fact that the canula did not fit the opening made, air entered the sac, decomposition ensued, and severe constitutional disturbance followed, ending in death.

In making an injection into a full and hard cyst, or into a hypertrophied gland, some care should be exercised to secure the entrance of the solution into the interstices of the organ. If the piston of the syringe is arrested by the needle impinging upon some hard tissue, so that no fluid can pass, the syringe should be drawn back a little to give the necessary space.

The treatment of *abscesses* and other purulent collections is most successfully accomplished by injecting into the cavity sufficient tincture of iodine to well distend it. Should the abscess be already full and tense, so that no additional fluid can enter, sufficient pus should be withdrawn to permit the necessary amount to be introduced. The undiluted tincture, the compound tincture, or such extempore solutions as may be formed with the tincture of iodine and iodide of potassium, can be employed for this purpose. The number and strength of the injections depend on various circumstances.

The treatment of *cold abscesses* by injections of iodoform is now common practice in European countries, but is not

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* The London Lancet, 1876, vol. ii. p. 881.

so well known on this side of the Atlantic. Editorials on the effects of the iodoform as an antiseptic, and urging its employment, appeared in the *New York Medical Record* for March 12 and May 28, 1887. In a letter to the editor of the same journal (April 2), Dr. Reineking points out the efficacy of injections of iodoform, and shows how excellent were the results in Billroth's and Von Bruns's hands. The preparation used by Billroth is a ten-per-cent. solution of iodoform in glycerin. The abscess is drained through a canula and the injection of 40 to 50 grammes (about 1½ to 2 ounces) is then made through the same canula, but the sac is not irrigated. If iodoform is dissolved in glycerin or oil of vaseline these operations are painless, but if ether be used as the solvent, much pain is caused by it. Dr. Reineking is a strong advocate of this practice, especially when the abscess opens at some distance from the real seat of the disease. The iodoform injection is not to be repeated until all trace of iodine in the urine has disappeared, which may be several days, even weeks.

The reason for awaiting the disappearance of iodine from the urine is that its presence indicates the persistence of the action of iodoform. If continuous doses were given, a toxic action would take place, and the mental disorders characteristic of this agent, when given in excess or too long, might occur as it accumulated in the system. The subsequent exhibition of the remedy will therefore be in order whenever it is prudent to give it, to be decided by the absence of those symptoms indicating accumulation.

Dr. Jasinski has treated eighty-six cases of cold abscess by injections of a mixture of iodoform and glycerin ten per cent. in strength. He made the injections through the canula of a trocar, with which he punctured the sac. Many of them were cured by a single injection; others by two

or three injections; eleven gave way spontaneously after the iodoform injection was practised. These last cases got well speedily. In nineteen of the cases the abscess was laid open, drained, and the cavity washed out with the iodoform solution, and drainage maintained.

Hydrocele has many analogies with the cystic diseases above described, and may therefore be properly considered here. For many years, until recently, since the advent of antiseptic surgery, injection of the undiluted tincture of iodine was the "cure" in general use, and it is yet preferred by many operators. But of late carbolic acid, originally proposed and used by Dr. Levis, of this city, has been adopted by an increasing number of surgeons and is rapidly growing in favor. It is less painful than iodine, and it seems to be rather more effective. They are employed in the same manner. The fluid is drawn off after puncture and carbolic acid or the tincture of iodine is injected through the same canula. The iodine or the phenol excites sufficient plastic inflammation to close the sac.

Those *pelvic abscesses* which succeed to various disordered pelvic functions and to various operations on, in, or about the uterus, or induced by spontaneous pelvic peritonitis or septic peritonitis, are, in these days, emptied most carefully, if at all, or under the most painstaking antiseptic precautions,—emptied with the trocar and canula, injected with iodine or iodoform, according to the recipe of Billroth and Von Bruns, or, in like form, a mixture of iodoform with glycerin. Treated thus with the careful modern methods of antisepsis, they can now be successfully managed in the mode indicated above.

Probably the most instructive example of the curative effects of solutions of iodine or of iodoform is the injection of them into the pleural cavity subsequently to

the operation of tapping. When the case is one merely of accumulated serum (dropsy of the chest so called), and no other than the serous exudation has occurred, a cure is not infrequently effected by draining the cavity, without the introduction of any topical remedy. When, however, abundant masses of semi-solid or purulent exudation are present, or when the exudation is entirely purulent, some solution of iodine becomes necessary. The strength of the solution used in injecting the pleural cavity varies somewhat according to the views of operators, but the main point is to obtain such a change in the condition of the pleura that a reaccumulation of the fluid cannot take place: Lugol's solution, the compound tincture of iodine, carbolic acid, and various solutions in strength going from the mildest up to the tincture. The last mentioned —the tincture—is best suited for injecting the parenchyma of organs.

During the decade just passed there were various attempts made to treat phthisis, especially those cases having cavities, by means of parenchymatous injections of iodine, or by various solutions for washing out cavities and disinfecting them. The tincture of iodine, Lugol's solution, and the compound tincture have been used for this purpose; also mixtures of iodoform and solutions of iodoform. Various surgical expedients have been tried at different times within the last two hundred years, and the opinions of the last quarter of a century just passed have crystallized into a plan for curing consumption by means of injections made into the pulmonary tissue, and not merely to wash out cavities known to have formed.

In a paper on Intra-Pulmonary Injections in Phthisis, Dr. Beverly Robinson assigns the credit for making the first injections of iodine into the pulmonary paren-

chyma to Dr. William Pepper in contradistinction to the surgical methods of Mosler, who proposed washing out cavities by introducing the solutions through the chest-walls and the lung-tissue intervening. Dr. Robinson gives a fact which answers his own statement. He quotes from *Langenbeck's Archiv* a paper by Dr. Wilhelm Kock, giving an account of experiments on dogs, showing the effects of iodine as injected into the lungs of these animals, and recommending its use "in the treatment of certain pulmonary affections in man." It is obvious that Dr. Kock had in view the same mode of using iodine that Pepper afterwards took, and with praiseworthy diligence made the method his own.

Two very instructive papers on the intra-pulmonary injections of iodine have been published by Dr. John Blake White,* who reports a very serious case that recovered by this mode of management. In these papers we are informed that carbolized iodine is preferred as in the following formula:

℞ Atropini sulph., gr. $\frac{1}{3}$;
Morphini sulph., gr. ii;
Tinctur. iodi, ʒiii;
Acidi carbolici, gtt. xx;
Glycerini, ʒiss;
Alcohol, dil. (20 to 30 per cent.), ℥iss. M.
Sig.—15 to 30 minims a dose.

The considerable pain attending the injection, and the violent cough which so often comes on, induced Dr. White to add morphine and atropine to the solution, and in this way obviate the objections of patients to the distress occasioned them. Besides the anodyne effects of atropine as

* The New York Medical Record, November 13, 1886, p. 536.

it is here in combination with morphine, it makes an impression on the lungs of a distinctly beneficial kind; it stops the sweating and the diarrhœa, which are serious wasting processes.

Dr. Robinson,* whose paper I have referred to, uses Lugol's solution for injecting, and Professor William Pepper, M.D., prefers the liquor iodi comp., which he at first had diluted to fifteen per cent., but subsequently increased in the proportion of one to five.

Ransome, of Manchester, England, has had instructive experiences regarding intra-pulmonary injections of iodoform in five cases, four of them phthisical and one of gangrene. The case of gangrene was carefully managed, and repeated injections were given, the result being a cure,—not an unprecedented thing without such remedial measures.

The iodoform was dissolved in ether, olive oil, or eucalyptus oil,—the last mentioned the operator preferred for this purpose. Some improvement was noted in several, although only from two to eight injections were practised in each of the phthisical. In one, symptoms of iodoform-poisoning came on, one had a temporary pneumothorax, and one a hemorrhage (the gangrene).

The parenchymatous injection of liquor iodi comp. in a case of pneumonia† succeeded perfectly in effecting a cure, or, as it may be more correctly stated, a case got well in which iodine was used. A case of meningitis is reported in the *Centralblatt für die Med. Wissenschaft* as cured by the injection of the tincture of iodine.

Professor Sée reports remarkable success with iodoform

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* The Medical Record, 1886.

† The Medical News, Philadelphia, January 9, 1886.

injections in some cases of tuberculosis. In addition to the numerous cases of *charbon* already referred to as yielding to injections of iodine, Mesnard gives an account of numerous others which have been reported since.

As respects the immediate effects of the injections, comparative observations have been made which show that the lungs of dogs can be injected without any injury remaining visible after the death of the animal. Hemorrhage appears not to have occurred, and pneumonia has not been caused by it thus far. The lung-tissue in human subjects, at the points where the iodine has been inserted, becomes denser and harder through fibroid change.

When the injection of iodine is practised a severe pain comes on, although in a few instances the pain has been rather trifling, a very violent cough supervenes, and profuse purulent or muco-purulent matter is expectorated. There may be some fever, but hitherto it is not sufficient to require special treatment.

Although distinct improvement has been noted in almost all cases, Dr. White reports but *one cure* that was substantiated, and this case at the outset was rather unpromising.

Among the most important of the uses to which iodoform, iodine, and the iodides are applied subcutaneously is for the cure of *syphilitic infection*. Thomann * was the first to employ iodoform subcutaneously in this condition of things, and his solution consisted of iodoform 6 parts and glycerin 20 parts. It should be remembered that common glycerin contains more or less sulphuric acid, which is highly irritating and causes intense burning pain when thrown under the skin. The usual dose of iodoform is

* Bul. Général de Thérapeutique, 1882, vol. ciii.

from 1 to 5 grains, but Thomann injected 4½ grains, first insertion. It is one of the cumulative poisons. Although a portion diffuses from the blood into the urine within two hours after injection, the greater portion of any quantity given remains much longer in the system, and the accumulation continues and increases with each dose if prescribed to be taken at the usual intervals. The peculiar mental states which iodoform sets up are forms of mania, melancholia, dementia, etc. The composition of iodoform explains its peculiar powers in this respect; hence if the mind exhibits any peculiarity during a course of iodoform, a careful inquiry should be made and the remedy, if necessary, be suspended. How much, when given hypodermatically, may be necessary to bring about the delirious state has not been clearly ascertained; but it is quite well known that the idiosyncrasies of the patient's system have an important influence on the result.

Notwithstanding iodoform has such a large per cent. (93) of iodine, it is not considered equal to the iodides of sodium and potassium in curative power in the various manifestations of the syphilitic infection. There are now in existence many papers in reference to the hypodermatic injection of these salts of iodine, but it seems to me that they are now but little used, mercury being rather freely given this way in all the forms of the disease. There is, however, some conclusive evidence as to the safety of this expedient and the curative results obtained by it. Fränkel,* in 1882, demonstrated the nature of the impression made on the lungs by various medicaments injected into them, and asserted that this mode of treatment of tuberculosis promised the best results for the

* The London Medical Record, 1882, vol. x. p. 272.

future. Although for the primary and secondary disease mercury exhibited in some form must continue to be the most important remedy, for the later *secondary and tertiary forms* the iodides, for the most part, must remain the best. Whenever the iodides are administered, and the stomach becomes rebellious, the hypodermatic method is the best resource available for giving these medicines. Of the potash and soda salts, respectively, there can be no question of the greater toxic power of the former; but as respects therapeutical activity, there is little difference, although the proportion of the iodine may be somewhat less in the soda salt. The local effects of the two agents differ much: the potash salt gives great pain, causes inflammatory swelling, and an induration remains which very slowly disappears after many weeks or months, it may be; the soda salt causes little pain, and, if not too large in amount as to the solution, or too concentrated, will produce no inflammatory swelling or any induration.

When an attack of iodism of great severity occurs, especially if œdema of the glottis supervene, there can be no doubt of the impropriety of the subcutaneous injection of iodides, or of their exhibition in any form, and iodism is only increased by giving the iodide subcutaneously.

Cases of cerebral syphilis—the symptoms caused by the pressure on important parts—require the most prompt and effective measures. The point of election for the deposit of gummata is the middle fossa of the skull, near the *cella turcica*. In this situation the *crura cerebri*, the *pons*, and many of the cranial nerves come into relation with the gummata, whence it follows that the symptoms indicate the position of the neoplasm. Pressure on the nervous elements deranges their functions, and when cranial nerves are impinged on, the muscles they supply are first thrown

into a condition of spasm, and, as the pressure increases, the nerves become softened, disintegrated, and paralysis succeeds to the condition of heightened reflexes. It is most important, therefore, to prevent or arrest the pressure, and thus save from a deformity that is usually permanent. When pain is the prominent feature in cases of cerebral syphilis, the sensory nerves come into relation with the syphilitic exudation, and therefore the fifth nerve, its trunk or main branch, is usually the nerve affected. If pain disappears, then it is obvious that the nerve has passed into the stage of softening and can no longer transmit impressions. This change in the morbid state of the nerve is manifested in loss of sensation where before pain was felt. Anæsthesia and pain are signs, therefore, of the progress of the local disease. So great may be the injury done that the first onset of the malady should be attacked with vigor.

As regards the selection of a remedy for the cerebral mischief, there are several points to be considered. Shall iodine be used hypodermatically? It is the universal opinion that iodine should be so used if the stomach gets rebellious. On the other hand, it is widely held that mercury in some form is almost always preferable.

If a preparation of iodine be decided on, shall iodine or iodoform be used? Differences of opinion prevail, but it is generally conceded that, if rapidity of action and decided effects are to settle the question, the choice must rest with iodoform. There are compensations, however, in some respects, for iodoform is greatly more apt to induce a toxic action which will enforce change in the remedy. As respects rapidity, it has been shown that when iodoform has been administered the iodine appeared in the urine within a half-hour.

A considerable number of practical physicians prefer iodoform to the iodides of sodium or potassium. Thus, of the Spanish we have Villar and Flores;* of Italians, Arcari;† of Germans, Lewin,‡ Mosetig-Moorhof,§ and many others; Martineau‖ and others, of France. It need hardly be stated that these names represent but a few of those who have been engaged in this method, but they show the drift of opinion.

PILOCARPINUM: PILOCARPINE.

Alkaloid of Pilocarpus Pennatifolius, of the Rutaceæ.
[*Jaborandi.*]

PREPARATIONS.—Pilocarpus contains two alkaloids, *pilocarpine* and *jaborine*. The latter, although closely related to the former in composition, differs in the arrangement of its molecules, and hence possesses different qualities and powers. Jaborine is formed chiefly, there are reasons for believing, in the course of the preparation of pilocarpine, and hence that process is best which separates the largest quantity of pilocarpine and the minimum of jaborine.

Jaborine is antagonistic to pilocarpine, and hence under

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* The London Medical Record, January 15, 1886.

† Gaz. Med. Lambord. Quoted by The London Medical Record.

‡ Berliner klinische Wochenschrift, 1888.

§ Centralblatt für die Chirurgie, 1882, No. 4. Quoted by The London Medical Record, July 15, 1882.

‖ Centralblatt für Prakt. Med. und Pharm. Quoted by Therapeut. Monatshefte, 1889.

any circumstances it is better to make use of *pilocarpine*, the alkaloid, than of any preparation of pilocarpus, the crude drug.

A proper formula for the subcutaneous injection of pilocarpine is the following:

℞ Pilocarpin. hydrochlorat., gr. i;
Aquæ, ʒi. M.
Sig.—Six minims contain $\frac{1}{10}$ of a grain.

As pilocarpine is somewhat deliquescent and is readily decomposed, solutions should be kept in a cool, dark place, and only enough for immediate use should be prepared. The tablets as now made are also convenient for this purpose. Caution is necessary.

The initial dose for an adult, given hypodermatically, is $\frac{1}{10}$ of a grain, and this may be increased to $\frac{1}{4}$ of a grain when necessary. A sufficient effect is produced in vigorous subjects, as a rule, by $\frac{1}{5}$ of a grain; but children are not as susceptible to its constitutional impress as adults, and therefore there need be but little variation from the regular dose.

Pilocarpine acts better, it is agreed by all, when given subcutaneously.

Physiological Effects.—Within a few minutes (two or three) after the injection of the active principle, a subjec tive sense of heat, accompanied by a feeling of fulness of the head, is experienced, followed speedily by a flush extending over the face, forehead, ears, and neck. Simultaneously the action of the heart increases, but there occurs at the same time a general fall of the blood-pressure. The most characteristic effect is the increase of the perspiration and the secretion of the salivary glands. As the flushing of the face takes place the saliva begins to flow plentifully,

a profuse perspiration breaks out over the whole surface of the body, the nasal and bronchial mucus and the tears are also increased, and sometimes a profuse watery diarrhœa occurs. When the dose is large the amount of perspiration discharged from the skin is enormous, and the salivary flow is measured by pints. It sometimes happens that the amount of saliva is immense and the perspiration small, and *vice versa*, but usually both secretions are very greatly increased. A distinct fall of temperature—from 0.5°–2° Fahr.—takes place when the sweating occurs, and is maintained for about four hours. Pallor of the face succeeds to the flushing, the pulse becomes weak, drowsiness, an extreme degree of languor, and chilliness of the surface are experienced. These effects of pilocarpine are due to the action of this agent on the vaso-motor nervous system. Paresis of this system causes dilatation of the arterioles, whence the afflux of blood to them, the flushing, and the increased action of the heart. The sphygmographic and kymographic tracings show a considerable lowering of the vascular tension, and to this diminution of the vaso-motor tonus is the increased secretion of saliva and sweat due; for, as Prevost has demonstrated, ablation of the spheno-palatine ganglion is followed by an enormous effusion from the Schneiderian mucous membrane. The reduction of temperature is referable to the discharge of fluid from the salivary glands and skin, the evaporation from the surface cooling the subjacent tissues, and a portion of the heat of the body being converted into another mode of motion.

Pilocarpine contracts the pupil, and the accommodation is impaired. In the language of Mr. Tweedy,* when pilo-

* The Lancet, vol. xi., 1875.

carpine is instilled into the eye, it causes "contraction of the pupil, tension of the accommodative apparatus of the eye, with approximation to the nearest and farthest points of vision, and amblyopic impairment of vision from diminished sensibility of the retina."

In consequence of the great loss of fluid by the skin the urinary secretion is diminished in amount, and, as more or less urea and salts are contained in the sweat, the urine is pale and watery. The bladder is irritable, and pain is felt usually along the course of the urethra, and the glans penis sometimes becomes painful and highly sensitive, and, rarely, considerably swollen.

Characteristic effects are experienced in the gastro-intestinal canal. After a lethal action is caused in the dog or cat, if the abdomen is opened at the period of maximum action, the intestines will be found in active movement, rhythmically contracting and enlarging as is the mode peculiar to the organic muscular fibre. M. Morat,* who has examined these movements with great particularity, found this to be the case. That these actions were incident to the impression made by pilocarpine was further shown by the introduction of the antagonist atropine, for when $\frac{1}{6}$ of a grain was given an immediate cessation of the intestinal movements occurred, and within one minute the increased action was arrested when one centigramme was thrown into a vein.

As regards the secretion of the various organs of the abdomen, it is certain that the biliary and pancreatic secretions and those of the glands of the intestinal mucous membrane are increased, the pancreatic notably so, by the action of pilocarpine, and accordingly this agent takes

* Journal de Thérapeutique, No. 1, 1881, p. 918.

its place among the cholagogues. It is in consequence of this physiological action, no doubt, that certain cases of icterus are cured, but for more intimate knowledge of them the reader is referred to the Therapy.

One of the most important questions connected with the action of pilocarpine is the impression made by it on the heart and general circulation. I have several times witnessed considerable depression, nausea, and weak circulation—faintness—during the first stage of the effects, just before the fall of temperature takes place, but never any symptom to awaken anxiety. I had an unpleasant experience but a few months ago which demonstrates the necessity of care and caution. I gave to a lady of 60 years, hypodermatically, a pellet said to contain $\frac{1}{20}$ of a grain of hydrochlorate of pilocarpine, and she reported no effects. I then gave her another, making the dose $\frac{1}{10}$ of a grain, and in ten minutes she grew "deathly sick," and I found her lying on the hall floor with a pallid face, cold perspiration, sunken countenance, and a very weak circulation; but a tablespoonful of brandy brought her around, and in a half-hour she walked home without difficulty. There was no more failure of the heart than is caused by severe nausea, and at no time was the rhythm of the pulse changed. Her intelligence was intact throughout the whole action of the medicament.

In many cases, after the action is over, a feeling of drowsiness deepening into sleep is experienced, and thus a calm, natural, and refreshing slumber is obtained. As it is not often necessary to prescribe more than one dose a day, that should be administered at or just before bedtime, so that sleep follows easily and pleasantly, especially if the wet skin be dried and the damp garments removed.

The action of pilocarpine on the temperature of the body is now manifest. Coincidently with the free action of the excretory organs,—the skin and gastro-intestinal canal, the salivary, and others,—the body-heat, increased during the first or stimulant stage of the action, declines, and at the end of the action is found to be somewhat below normal; but it is to be observed that in the healthy state the temperature of the body is not so readily influenced as in the febrile condition. The causes of the decline of the temperature are not far to seek. The conversion of the surface-heat into another mode of motion is the true explanation; for as the pouring out of fluid goes on, much of the fluid passing into vapor, the heat is employed in effecting the change of physical state,—in other words, into "another mode of motion."

The toxic action of pilocarpine is much influenced by idiosyncrasy. Some persons are in a high degree susceptible to its action, while others remain unaffected by considerable doses. A sufficient dose will kill in all cases. The lethal amount cannot be stated with precision. Thirty (30) centigrammes of the alkaloid will kill a dog of medium size, according to Vulpian.* In the human subject other considerations besides weight have to be taken into account, especially idiosyncrasy, temperament, and education.

The effects of pilocarpine on the system are exactly opposed by atropine, and in the whole range of physiological antagonisms there is not one so thorough and complete as that of pilocarpine and atropine. It is to be understood, of course, that atropine, for the quantity,—

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* Vulpian, Leçons sur l'Action physiologique des Substances toxiques et médicamenteuses. Paris, 1882, p. 116, *et seq.*

grain for grain,—is far more powerful than pilocarpine, and hence, in treating cases in which the antagonism is availed of, the quantity given of each must be determined by the results of the administration and the doses necessary to maintain the physiological action. The antagonism covers the whole ground of the impression made by each, and includes the nervous, digestive, muscular, circulatory, and glandular systems. The most obvious and characteristic symptoms—the salivation and the sweating—are very soon brought on; indeed, in a minute after the injection of pilocarpine. The salivation is more prompt to appear after the pilocarpine than is the sweating, and is also the first to be effected by atropine,—a fact of which I assured myself fourteen years ago *in propriâ personâ*. The surface —pallid, cool, clammy, and reeking with a cold perspiration—soon becomes dry and warm, the secretions of the intestinal organs are soon arrested, and the action of the heart, during the period of lowest temperature rather feeble, rises in strength, the pulse becomes fuller and stronger, and a genial warmth steals over the body, the face flushes a little, and the normal state is completely restored.

As regards the pathological changes caused by pilocarpine, not much information is available, very few fatal cases having occurred. Some cases of "heart-failure" have been induced by its administration during the course of such maladies as cardiac dropsy, scarlatina, etc.; but it is not easy to say how much was due to pilocarpine and how much to changes in the heart's structure. General congestion, sometimes quite intense, has been observed in the various organs.

THERAPY.—The physiological actions of pilocarpine are so well defined that they are immediately available for application in the treatment of disease. As it causes con-

siderable loss of material, and makes the outgo larger than the income, it belongs to that class of remedies known as agents that increase the metabolism of the body, or that promote the retrograde metamorphosis, or waste.

Pilocarpine having the power to increase excretion by promoting the activity of excretory glands, it becomes an important remedy in those diseases characterized by deficient depuration. In inflammatory states after the subsidence of the acute symptoms, exudations remaining, it is in a high degree serviceable. For the removal of the *exudation of pleurisy* and of the inflammatory products forming in the eye and in other organs, it has been proved effective. A great many observers have reported cases in which pleural exudations and the large accumulation of fluid—the so-called dropsy of the chest—have been made to disappear when the most approved measures of other kinds had failed. Although it is the usual practice to administer pilocarpine after the acute symptoms have subsided, yet Gubler* maintains its curative power in the disease from the time of its earliest manifestations. The fact is, however, that the special utility of pilocarpine in pleuritis is the removal of inflammatory deposits and exudations, and large or small effusions in the thorax. In the *subacute* or *chronic inflammatory thoracic diseases* it is precisely indicated, and has proved exceptionally useful.

When inflammatory exudates appear in the eye, in *iritis* and *irochoroiditis*, and in *detachment of the retina*, pilocarpine has been successful in a high degree; but the removal of the deposits of specific inflammation by mercury is not a corresponding action, and when these agents are given

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* Journal de Thérapeutique, 1874. Quoted in the Dictionnaire de Thérapeutique, tome iii. p. 210.

simultaneously, the results achieved by each should not be confounded.

The curative influence of pilocarpine in detachment of the retina is by no means generally admitted. The views of ophthalmologists are diametrically opposed, and the greatest names hold to the view of its inutility. Thus Wecker, Grandemont, Galezowski, Diavaux, Landesberg, and others among the French and German ophthalmologists assert its uselessness in detachment of the retina or choroid; Ramorino,* on the other hand, reports a case in which the injection of pilocarpine was promptly and completely successful. Dujardin-Beaumetz† also reports cases of detachment of the retina cured by the injections. Landesberg,‡ subsequently to his first success with the pilocarpine in these cases of retinal detachment, had some unfortunate experiences,—four cases in which cataract formed, as he supposed, because of the action of the pilocarpine. On the other hand, some observers have had excellent results from this treatment. Dr. Josso§ has had four cases of cure without relapse, and four other cases in which decided amelioration took place. Dr. Debierre‖ had equal success, but he did not confine his treatment to the administration of pilocarpine, but employed other approved measures in conjunction therewith. In 1881 there was a division of opinion on the question of the utility of pilocarpine in detachment of the retina. Now, it must be admitted that there exists an increasing scepticism—indeed, a nearly general disbelief—in its virtues in the malady in question.

Pilocarpine has been used successfully in certain diseases

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* Dictionnaire de Thérapeutique, p. 221. † Ibid.

‡ Journal de Thérapeutique, 1883, p. 198.

§ Ibid., 1881, p. 822. ‖ Ibid.

of the ear. Those examples of Ménière's disease, due to effusion into the semicircular canals of a serous or hemorrhagic kind, are often remarkably improved by the injection of this agent. When a hemorrhage has taken place in the canals, pilocarpine is less immediately beneficial, but the ultimate result is good in promoting the absorption of the liquid part of the exudation (Politzer).

Kosegarten* has had good results in cases of *catarrh of the middle ear*, and also in inflammatory troubles and exudations in other parts of the middle and internal ear. Other aurists who have made use of it under the same conditions, report corresponding results when the same state of the ear exists as mentioned above.

In the removal of the *exudates of inflammation of the cerebral and spinal membranes*, and of the cavities of the body lined with serous membrane, with or without association with specific treatment, pilocarpine performs an important service by increasing the activity of glands and other organs excretory in function. Having myself devoted considerable attention to this subject, I may say that the value of the agent in appropriate cases is very great; but much depends on the manner in which it is given. It is not necessary to administer the remedy frequently,—not even twice a day unless special circumstances require other and different measures. Once a day, in the cases above mentioned, or on alternate days, or at longer intervals even, is it required as a means of promoting excretion. In this way the actions of specific medicines are promoted and the progress of cure much facilitated.

I should not fail to mention that pilocarpine has proved successful in *œdema of the glottis*, more especially in cases

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* Centralblatt für die gesammte Therapie, 1887, p. 209.

due to local causes, as in croup, and also in cases due to constitutional causes, as sequelæ of typhoid fever and in diphtheria. No doubt it will prove equally effective in cases of œdema of the glottis due to uræmic poisoning, or to the conditions present in septicæmia.

In various spasmodic affections of the respiratory apparatus, such as *spasmodic croup* so-called, really *laryngismus stridulus*, in *singultus* (hiccough), and in *spasmodic asthma*, it has proved to be a very certain remedy. Certain precautions are necessary, however; the most important of these is the presence of bronchorrhœa. If to the large quantity of mucus then present in the tubes should be added the increased secretion furnished by the action of pilocarpine, a dangerous access of difficult breathing might come on, and several cases of the kind have been reported. On the other hand, it is a very effective remedy in cases of *bronchitis* with deficient secretion, or during the stages of dryness in an acute attack. It plays the part of an expectorant, therefore, in such cases. The author has witnessed remarkable results in *capillary bronchitis* by the administration of pilocarpine. The mechanism of the action, so to speak, consists in the liquefaction of the tough mucus which fills the finer tubes and restricts the passage of the air into the air-sacs, whence it follows that the supply of oxygen is insufficient and dyspnœa and cyanosis come on.

Dr. L. Riess* reports the use of pilocarpine in the bronchial catarrh accompanying various *chronic cardiac and renal diseases*, and in the *pulmonary œdema* attendant on cardiac obstruction, in all of which he had excellent

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* Berliner klinische Wochenschrift, No. 15, 1887. Quoted in Centralblatt für die gesammte Therapie, 1887, p. 303, *et seq.*

results, in a degree, however, varying with the extent and permanent character of the original affection. It was mentioned above, as the outcome of the author's experience, that the injections of pilocarpine are especially serviceable in the various inflammatory affections, and in those characterized by a viscid, tenacious mucus lining the mucous membrane, or by a dry state of the membrane accompanied by whistling and sonorous rhonchi or râles. The spasmodic diseases of the breathing organs are also specially affected by pilocarpine, both for the removal of merely temporary states and for the cure of more permanent maladies. Riess* instances the difficult breathing due to catarrh and to spasm, as in *emphysema*. In pneumonia he finds it of great value during the course of the disease to determine the *crisis* or *lysis* when the change seems impending and does not occur, or to cause the absorption of deposits in the lungs which linger and manifest a tendency to undergo caseation.

Of all the pulmonary troubles of a spasmodic kind in which pilocarpine is used, it is most effective in asthma, singultus, and whooping-cough. Of the troubles affecting the broncho-pulmonary mucous membrane, the most serious malady in which pilocarpine has had trial is *membranous croup* or, as it is now designated, *diphtheria*. The theory of Guttmann,† in accordance with which it is used in this affection, implied the detachment of the false membrane by the greatly-increased secretion from the mucous membrane, and the change of action whereby the mucous surface could not reproduce it successfully. The favorable reports first published by Guttmann were much too san-

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* *Supra.*

† Guttmann, Berliner klinische Wochenschrift, October 4, 1880.

guine. Dr. Wendt, of New York, published experiences very favorable to its use. On the other hand, Dr. Neuverster reported cases—twenty-one in number—in which the result was not wholly negative, but positive for injury to some of them. Dr. Gréza Faludi found it serviceable in many cases; but his enthusiasm for the remedy leads him to form an extravagant estimate of its power.

Archambault* has made a well-considered contribution to this subject, in which he indicates the special conditions for determining the administration of pilocarpine. He shows that when the false membrane extends to inaccessible places, pilocarpine may be given; when, however, only the pharynx, nares, and mouth and tongue have been invaded it is not advisable, for other and far safer remedies that are more efficient for detaching the false membrane may be employed.

The objections to pilocarpine, which also are strongly emphasized by him, Paynardeau† holds, are its unpleasant, nauseating effects, vomiting, cramps, and gastralgia. Vomiting may come on in a very violent manner, and diarrhœa may ensue that leads on into collapse. Extreme prostration will then occur and a fatal result be induced by cardiac paralysis.

At the same time the memoir of Dr. Tayac‡ appears, in which he commends in strong terms the use of pilocarpine in diphtheria. He says its action is prompt and energetic, and that it detaches the false membrane when a smart flow of saliva takes place. This loosening and separation

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* Archambault, Journal de Thérapeutique, 1881, p. 879.

† Paynardeau, Thèse de Paris, 1881; also Journal de Thérapeutique, 1882, p. 259.

‡ Tayac, Thèse de Paris, 1882; also Journal de Thérapeutique, 1882, p. 260.

of the false membrane, he says, is often followed by a sensible amelioration in the general state of the little patient. If administered at the outset of the case, the development of the disease is hindered. As to the mode of administering pilocarpine, a considerable majority of those who have prescribed this remedy made use of the hypodermatic method. It is generally accepted that this method is far in advance of the stomachal or of any other, and many hold that it should be valued as twice as effective, in point of curative power, as that of the stomachal administration.

We find, however, that the results of M. Archambault's treatment by pilocarpine were by no means favorable, for of twenty-one patients, nine recovered and twelve died. Demme also has advocated the use of pilocarpine in diphtheria, and his statistics are favorable to its administration in this disease. As I have already stated, opinions vary greatly. Whilst Demme and others quoted favor, many are opposed to its employment in this disease; but those who uphold its use do not agree with Guttmann that it is a specific by the effect of the greatly-increased flow of the mucus and saliva detaching the false membrane. They admit that the injections are frequently followed by nausea and vomiting, but they avoid the ill effect of this on the circulation by administering an ounce or two of brandy, the more especially to prevent failure of the heart. Professor Lashkewich, of Russia, treated ten cases of diphtheria; following strictly Guttmann's plan, he gave pilocarpine, and all the cases died.* Again, Dr. Warschauer† had under treatment a number of very severe

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* Wratsch. Quoted by The London Medical Record, 1881, p. 491.

† Ibid.

cases, and all recovered. As so much depression attends the action of pilocarpine, Dr. Warschauer advises the coincident administration of stimulants.

We find that American opinion is equally discordant with European. There are those who commend the remedy; there are others who condemn it just as strenuously. One of our best authorities—Professor Abram Jacobi,* of New York—finds pilocarpine practically valueless in the treatment of diphtheria, and not without danger. He therefore advises against its use, except when the false membrane is limited to inaccessible parts, and when in the hands of physicians acquainted with its powers and its lethal activity. Some practitioners in this country were at first quite enthusiastic over the new diphtheria cure, but their zeal cooled when the remedy proved uncertain. Dr. A. Ady† had four severe cases, but all of them got well; Dr. Townsend‡ reported a group of seventeen cases, five of which were malignant, and only one died,—that one belonging to the malignant class. Dr. J. Gerard§ reported a hopeless case, *in articulo mortis*, which improved immediately on administering pilocarpine, and quickly recovered. Dr. E. C. Wendt published an account of three severe cases that got well on the pilocarpine treatment. Professor Prentiss also had a recovery, under the same remedy, of a most severe case.‖ Dr. W. N. Ames¶ had similar experience in a single example of the same kind.

It is useless to multiply examples. When the first experi-

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* Treatise on Diphtheria, New York, 1886.

† The New York Medical Record, 1881, vol. xix. p. 474.

‡ Ibid., 1882, vol. xxii. p. 335.

§ Ibid., vol. xx. p. 598.

‖ The Philadelphia Medical Times, August 13, 1881.

¶ The Medical and Surgical Reporter, 1881.

ence with the new remedy came out, there was much expectation of the benefit to be derived from it; but the high hopes gradually fell off into the ordinary state of variation in professional opinion, and while some looked for further advances in the treatment (the optimists), the pessimists congratulated themselves on that conservatism which refused to be hasty in forming an opinion as well as in applying it to practical affairs.

When the mouth and pharynx are persistently too dry and the saliva deficient in the proper constituents, pilocarpine affords relief by acting on the salivary apparatus, increasing its functional powers.

The parotid gland, a member of the same system, is acted on in a similar manner. For this reason it has been employed in the disease known popularly as *mumps*,—a specific inflammation of the parotid gland,—and in the metastatic inflammation of the testis in the male, which is quite common, and of the mamma in the female, which is uncommon. A few injections of the $\frac{1}{16}$ of a grain, as a rule, suffice.

Cough maintained by habit and various forms of spasmodic cough, as already mentioned, are relieved by pilocarpine; sometimes cured by a single injection. Other neuroses of the respiratory tract are helped by the giving of this agent, provided they are not paralytic in form.

Pilocarpine is effective in some diseases of the skin,—diseases of the dry and scaly variety,—and favorable reports have been made regarding its curative powers in *fetid sweating of the feet.* Thus Dr. Armaingaud finds that by local injections, from six to eight in number, the character of the fetor is changed, its pronounced foulness is so modified as to be borne without disgust, and after a few more doses the disagreeable disorder is wholly ended. There

has not been, as yet, sufficient time to ascertain whether the cures have been permanent, yet Dr. Armaingaud reports additional cases in which this treatment was entirely successful. The probabilities are that at least assuagement of the fetid sweat has been effected, and doubtless a certain number of them have been cured. To cure sweating by the exhibition of a remedy that causes sweating may have a singular sound in this place, and may prove a shock to some of the weaker brethren, but no homœopathy is concealed under the fact: it is simply a process of antagonism between the two forces,—between the morbid action on the one hand and the influence of the remedy on the other.

In *unilateral sweating of the head and face, of the side, and of single members* pilocarpine has proved very useful, even curative, in some of them. It is necessary, however, to remember that the attacks of sweating may be due to reflex causes, one of the most frequent of which is disorder of the stomachal or intestinal digestion. Again, sweating of one-half of the head and face is often caused by aneurism within the thoracic cavity, or other tumor, pressing on the branches of the sympathetic ganglia and some of those belonging to the nervous system of animal life. Under such conditions no remedy could act more than temporarily and very imperfectly on the sympathetic system unless procuring the removal of the tumor, so that the pressure should cease. Having an effect on the same tissue, the morbid influence and the remedial influence come into a position of antagonism, and one or the other must yield: in this case the morbid influence yields, and the *status quo* is restored.

Cases showing the power possessed by pilocarpine to break up the morbid complex of ague have been published

from time to time. I have had some personal experiences of the same, which I will presently narrate. Has pilocarpine any germicide effect in respect to Lavaren's parasite? It is to be remembered that antiseptic agents vary greatly in their power to destroy or inhibit micro-organisms, and it is probable that pilocarpine has no action upon the microbe of intermittent fever, but it exerts a powerful action on the physiological functions of the skin and kidneys. Dr. Griswold,* Interne of Bellevue Hospital, was the first to make observations upon the effects of this agent on the morbid process by substituting a sweating stage for the chill and fever. For this purpose it should be administered when the chill is about to come on. It was soon found that an acute intermittent was merely modified in appearance during the action of the pilocarpine, and its subsequent behavior was not changed from the original type, and required the usual treatment to stop permanently. It is true, as already remarked, that the treatment by quinine is made more prompt and thorough; but pilocarpine, of itself, is not sufficient.

Of those who have made trial of pilocarpine I find that the last statement is generally, if not universally, accepted. In *chronic malarial poisoning* it is probable, on the other hand, that pilocarpine has more sustained power and more decided curative effects. It is probable—almost certain—that future developments will be in favor of this view. In a very severe and protracted case of the chronic form coming under my care recently, the effects of the remedy on the cold stage were immediate: the skin became warm generally, the face flushed, and some temporary headache followed; but in a short time the sweat poured out, and the

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* The New York Medical Record.

sweating stage was thus substituted for the chill and fever. It was concluded that if this were the case each intermittent could be suppressed permanently. This fortunate result was not justified by further observations; but although the cure was not effected, it was certainly true that the force of the disease was broken, and a recovery was far more easy to accomplish. These remarks are to the purport, therefore, that at first the results of the use of pilocarpine were restricted to the abolition of the chill and fever stages, and the merging of the morbid process into a mere sweating stage or process.

The first and most important use of pilocarpine, soon after its introduction into professional notice by Professor Gubler, was in the treatment of *anasarca from albuminuria*, especially as this occurs towards the end of pregnancy, with the alarming convulsions. The great value of the new medicament, in causing excretion of the materials which should be eliminated by the kidneys, was the fact which most visibly affected the medical profession. Its utility in albuminuria was a conspicuous fact. If a dose of $\frac{1}{8}$ of a grain were given hypodermatically, the enormous output of saliva and sweat gave great relief, and when repeated often effected cures. *Convulsions* due to uræmia or urinary retention, such distention of the pleural and peritoneal cavities as will interfere with the proper movements of the lungs, and the spasmodic difficulty of breathing known as renal asthma are conditions that pilocarpine can remove by the stimulating effect it has on certain organs of excretion. The sweat, when urinary retention or suppression occur, contains the solid matters which the kidneys should have excreted, and hence the action of the skin is supplementary to that of the kidney. These facts form the basis of the therapeutical diagnosis in *acute* and *chronic albuminuria*.

The remarkable effects of pilocarpine in acute albuminuria were early shown when the first trials of the agent were made. Thus Mr. Marshall* gives an account of a case of general anasarca, with enormous swelling of the limbs, abdomen, and extreme difficulty of breathing, which he relieved by ¼-grain doses of pilocarpine, and cured in a few weeks by continued use of the same, and without any other medication that could especially influence the result. After two weeks of the injections ⅕ of a grain was found to be sufficient, two a day in number; and, finally, when a cure could be foreseen, the administration was reduced to alternate days only.

Very many instances of the successful use of pilocarpine were shown in those cases of albuminuria that were more or less advanced in pregnancy. An important distinction must be made between those cases of pregnancy in which the disease occurs in the early and those in the later months. When albuminuria appears during the first three months of pregnancy, the effect for ill is far greater, as respects the fœtus, than the same condition much later on; but as respects the mother, it must be admitted that the influence of that state of the system is more hurtful when near the end of pregnancy, for the renal and mental symptoms in the latter months are more certainly dependent on structural changes. A question much discussed now is the effect of pilocarpine on the uterine contractions. It is maintained by many that it has the power to initiate them, and by others that it can only promote uterine action after it has been established. The former is held by a minority only, and can, I think, be readily enough demonstrated incorrect. There can be no doubt that, by

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* The London Lancet, December 22, 1888.

reason of its power to increase the contractile efforts of the organic muscular fibre,—the uterus fully developed and its contractile energy distinctly acting, even if not very strongly,—pilocarpine can increase the contractions of the womb muscles and thus produce the abortifacient power. In giving pilocarpine, then, it is necessary to bear this fact in mind. Miscarriages have occurred under its use, but they were not necessarily due to the pilocarpine, for other conditions may have existed that were sufficient to bring about the same result. When the woman is in such a state that a miscarriage may be looked for, it is necessary to exercise great care in using pilocarpine. With this exception, and another to be mentioned further on, there is no doubt of the good, even admirable, effects of pilocarpine. To use the agent when the action of the heart is weak from a morbid state within, or when it is obstructed by some mechanical cause from without, is bad practice.

Several instances have been reported in which death ensued from obstruction of the trachea by a quantity of tenacious mucus suddenly poured out, and coincident with a great flow of sweat and saliva. If the patient should be unconscious from any cause, there must be great danger of asphyxiation under these circumstances. One is said to have perished and two others were reported as in great danger, but survived, the conditions above described being present in all. Sänger reports three cases, two of whom died from the asphyxiation and one only recovered.

There can be no question as to the value of this remedy in *eclampsia*, especially in those cases complicated with albuminuria. The usual doses in the treatment of such cases is 1 to 2 centigrammes ($\frac{1}{8}$ to $\frac{1}{4}$ of a grain).

In the case of *polyuria*, the evidence of the good effects

of pilocarpine is clear. That form of the disease known as *diabetes insipidus* is the form in which it is more especially useful. By increasing the action of the skin the morbid flow by the kidneys is antagonized.

In diabetes of the saccharine variety,—*diabetes mellitus*,—and the mild form of the same, which is now spoken of as glycosuria, pilocarpine has good effects, although not curative. It lessens the amount of urea and sugar and improves the general condition. If it is asked, How can a remedy which acts as a diuretic under some circumstances afford relief to a malady signalized by an excessive flow of urinary water? it can be answered that an antagonistic action is quite evident between the forces,—medicament and the kidneys; one or the other must yield. In this case the amount of water and solids is lessened, and hence the morbid process yields.

There are no cases of true diabetes that have been really cured, although much amelioration has taken place in many by the reduction in the amount of sugar and urea present in the urine before the administration of the remedy. It is in polyuria, however, rather than in *diabetes insipidus*, that the most decided effects are produced. Numerous cures have been effected by it. At the same time, it is important to differentiate between those having their origin in some disease of the cerebellum or medulla oblongata, those arising from syphilitic lesions, and those due to obscure affections of the organs of nutrition. The more nearly they conform to the type of syphilitic affections the more readily are they cured. If so, a combination of agents—pilocarpine, regulation of the diet, and exercise—are the fittest for this purpose.

Pilocarpine has been used successfully in the treatment of certain convulsive disorders. These are represented

by hydrophobia, tetanus, histrionic spasm, writer's cramp, whooping-cough, etc.

It was alleged a few years ago that pilocarpine had a distinct curative power in *hydrophobia.* Some of these "cures" have been reported; but no one can examine the details without feeling a sense of insecurity and the fallacy underlying all the reports. There is, first, the case of Denis Dumont, which was being treated by bromides, codeine, and chloral without any symptoms of improvement; but when pilocarpine was administered the result was that an immediate change for the better occurred, and one dose three times a day by subcutaneous injection speedily effected a cure. On the other hand, by a careful investigation of the disease on the smaller animals, M. Nocard* demonstrated its entire inefficiency, and proved that it is neither prophylactic nor curative, nor does it have a sedative effect, although it is said of several cases unsuccessfully treated by it, that soon after receiving the first injection there was immediately induced an apparent state of relief, but which was of brief duration. The very few successes are much more than counterbalanced by the reverses; for, whether tried in warm-blooded animals or in man, the same result is observed,—the cases of hydrophobia prove fatal whether pilocarpine is given or not, and, as it appears, in the usual manner of this disease.

In *poisoning by atropine* and the other members of the mydriatic group, pilocarpine is an antidote that acts by virtue of its physiological antagonism, exactly fitting in, as it were, the depressions of the one to the elevations of the other,—waves meeting in opposite phases, and one neutralizing the effects of the other, so that calm results.

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* Journal de Thérapeutique, October 10, 1882, tome ix. p. 721

This takes place by virtue of the physical law: "to every action there is an exact and equal reaction."

I have already, in another part of this work, discussed the question of the antagonism of pilocarpine and atropine, and need not, therefore, go over the subject here.

The same principles govern the treatment of poisoning by the other members of the group,—hyoscyamine, duboisine, daturine, hyoscine, etc.

As regards poisoning by pilocarpine, we have to note that severe symptoms occur without a lethal action ensuing. In most cases the unpleasant symptoms connected with heart-failure ensue. There are profuse sweating and salivation, with pallor, small, contracted pupil, the heart's action feeble, the mind clear but inactive. The exhibition of ammonia, but especially of atropine, affords prompt relief in every direction. I can speak of the action of atropine from the point of view of my own bodily experiences, having, when pilocarpine first came out, taken a dose to insure the accuracy of my own conception of its physiological powers. The effect of $\frac{1}{6}$ of a grain having reached its maximum, I then injected the $\frac{1}{100}$ of a grain of atropine, with an immediate and most gratifying result. Within one minute the wretchedness experienced from the pilocarpine was disappearing, the coldness and dampness of the whole surface was replaced by a genial glow due to the quickened action of the surface capillaries, the saliva, which had just then been pouring out, stopped, the mouth becoming rather dry, and the heart, which had been beating slowly and feebly, quickly returned to its habitual pace both as to time and as to force and volume. The subjective sensations of the inner consciousness, which had been miserable, gloomy, and depressed, were replaced by good humor, even gayety of

disposition. It was a most pleasing experience,—that is, the sudden exchange from a gloomy mind to a natural state of feeling and being. In fact, there is no example of antagonism between two remedies so complete as this; not one in which the excessive action in one direction is just compensated for in the lessened action of its opposite.

The treatment of toxic symptoms caused by pilocarpine consists in the use of atropine in the proportion of the $\frac{1}{100}$ of a grain to $\frac{1}{2}$ of a grain of pilocarpine, together with such stimulants as chloral, whiskey or brandy, ammonia, and injections of ether. If rightly adjusted in respect to time and quantity, the administration of atropine is of itself sufficient.

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2. *Agents Promoting Nutrition.*

FERRUM: IRON.

Ferrum Dialysatum. [*Dialyzed Iron.*]
Ferri Tartras. [*Tartrate of Iron.*]
Ferri Citras. [*Citrate of Iron.*]
Ferri Citras Ammoniatus. [*Ammonio-Citrate of Iron.*]
Liquor Ferri Peptonatis, Dialysati. [*Peptonated Solution of Iron, Dialyzed.*]
Liquor Ferri Albuminati. [*Solution of Albuminate of Iron.*]

These preparations have been utilized by various clinicians, and are therefore urged by them as suitable for hypodermatic use. The first to use iron subcutaneously was Professor J. M. Da Costa, M.D., of this city. Some obscure references have been made to Continental authorities said to have anticipated Da Costa in this practice, and

by this means a question of priority may be brought forward. It is more important, however, to determine a principle. It is of comparatively little consequence who was the originator of this practice, but the merit belongs to Da Costa of having presented this subject in a tangible form, and of having familiarized the profession with it, explained its nature, and demonstrated its limits. In a communication recently had with Dr. Da Costa he informs me that he has been disappointed in the use of the dialyzed iron, because of its inferior quality and the presence in it of the chloride of iron, but he still maintains the superiority of hypodermatic injections of iron to the stomachal administration, when the conditions are urgent.

There should not be a hard and fast rule regarding the salt of iron used for hypodermatic injections, for sometimes the mildest chalybeate may cause not a little irritation, while the toxic combinations of iron may be used freely without distress. The list of iron preparations contains combinations with vegetable acids, which were contrived to obviate the tendency to irritate the tissues which the combinations with the mineral acids are more apt to do. The views of physicians are as varied as the preparations are numerous. Kuthe* always made use of the albuminate of iron. Neuss,† who made an experimental study of this subject, concluded that the phosphate of iron with citrate of soda was the best. Losio,‡ the Italian observer, always made use of the ammonio-citrate, but he regarded the lactate as next in value. On the other hand, Eulenberg held that the lactate is specially objectionable

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* Küthe, Virchow und Hirsch, Jahresbericht für 1887, p. 388.

† Neuss, ibid., 1881, p. 302.

‡ Losio, ibid., 1887, p. 388.

because it causes lasting indurations and frequently suppuration.

In an elaborate study of this subject, Hirschfeld* comes to the following conclusions:

(1) The subcutaneous injections of iron are painful.

(2) The injections of iron are not efficacious.

(3) This method is rather difficult of execution in private practice.

(4) Actually there does not exist a single preparation that realizes all the desirable conditions necessary in this mode of treatment.

PHYSIOLOGICAL ACTIONS AND THERAPY.—The effects of iron, as studied from the clinical stand-point, are referred to its power over the process of assimilation and to its influence over the composition and oxidizing power of the blood, which it is supposed to improve. The action of iron is favorable only under two conditions: in improving the process of construction of tissue, when the desire for food and its assimilation are increased. According to Brown-Séquard, iron can act only by promoting the primary assimilation by increasing the appetite and the function of digestion. Foods, as is now well known, contain sufficient iron for the nutrition of the red-blood globules. If iron at the same time supplies a need of the red-blood globules and promotes oxidation, its position as a remedy must be higher even than it has hitherto occupied.

From what point soever the iron is introduced into the system of man, it enacts the *rôle* of an agent promoting the constructive tissue metamorphosis by the effect it has on the primary assimilation, and in this way it raises the general tone and vigor of the organism.

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* Hirschfeld, Bul. Général de Thérapeutique, 1886, p. 86.

The elimination of iron takes place in part through the kidneys, in large part by the liver and intestines. Jacobi,* in a series of experiments to ascertain the rate of elimination of iron, found that when injected beneath the skin iron could be detected during the first day in the urine. Elimination goes on for about three days, but it lessens in amount proportionately as time passes. As is the case with the metals in general, no doubt iron is strained out of the blood, so to speak, by the liver, which seems to have the property of retaining the metals in its own structure. As the continued addition of iron to the blood would have the injurious effects of iron medicinally administered for too long a time, it may be a function of the liver to prevent too great an increase of this metal in the blood. This fact is certainly true of the other and more deleterious metals, such as arsenic, antimony, gold, silver, etc. (Glaeveck). When iron is injected directly into a vein, the route through the liver is not included in the circuit; hence to this the difference in the result may be due.

Mori† reports three cases of *extreme anæmia* occurring in pregnant women, for whom he prescribed citrate of iron, injecting each time a syringeful of a one-per-cent. solution. In two weeks, it is said, a cure was practically effected in one, one is reported as recovering, and the third as somewhat benefited. Nussbaum‡ finds that in *chlorosis* there is little difference in the result whether the iron be given subcutaneously or by the stomach, but the former mode of administration secures more prompt and lasting curative effects. He holds, further, that the iron administered enters into the formation of the red-blood globules,

* Schmidt's Jahrbücher, 1887, Band ccxv. p. 20.

† The New York Medical Record, July 24, 1886.

‡ Therap. Monatshefte, October, 1887, p. 369.

and that it does not merely increase the activity of the assimilative functions.

In anæmia, Da Costa had excellent results from the injection of dialyzed iron. He administered 15 minims of this preparation daily, and the rapid improvement was demonstrated by the increase of the hæmoglobin, as well as in a rise in the general nutrition and in the vigor of the body.

What opinion soever we may form in regard to the mode of action of iron, it remains that in *anæmia* and *chlorosis* it is, next to arsenic, the most important remedy. It raises the globular richness of the blood to the normal standard, and by the hypodermatic way more quickly than by the stomach, and especially also when the stomach and intestinal canal cease to assimilate iron.

To that albuminous material with which iron is associated in the economy Bunge* has given the name *hæmatogen*, and to this compound he ascribes the property of assimilating iron, maintaining that this constituent of the blood is not derived from inorganic salts, but is supplied to the blood-globules by an inorganic compound contained in plants and foods. If these observations are correct, it must be admitted that the best preparation of iron for *anæmia* and *chlorosis* is the albuminate, and this preparation is better suited for hypodermatic use than the inorganic salts.

Sometimes, for a state of depression coming on suddenly and requiring the use of stimulants, the tincture of the chloride of iron is given subcutaneously; but it is not good practice, for there are other agents used in this way far more effective.

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* Bunge, The London Medical Record, January 15, 1886.

ARSENIUM: ARSENIC.

Acidum Arseniosum. [*Arsenious Acid.*]
Acidum Arsenicum. [*Arsenic Acid.*]

PREPARATIONS.—*Liquor Potassii Arsenitis.* [*Fowler's Solution.*]
Liquor Sodii Arseniatis. [*Pearson's Solution.*]

ACTIONS AND USES OF ARSENIC.—The preparation known as Fowler's solution, which has been almost wholly used in making hypodermatic injections of arsenic, is an arsenite, while the combination of sodium with arsenic acid is an arseniate. The latter is much weaker, because containing a greater proportion of oxygen.

There is but one objection to the liquor potassii arsenitis: the tincture of lavender is an ingredient inserted to give some odor and color to the solution. This is objected to because it is irritating to the tissues and causes considerable pain at the time it is injected beneath the skin.

The liquor sodii arseniatis (Pearson's solution) is a compound with an alkaline base, and an *ic* acid; the difference in quality is due to the fact that more oxygen is contained in it, in consequence of which there is less arsenic. It must be given in larger doses,—about one-fourth more.

The following formulæ can be used for hypodermatic injections:

℞ Liq. potassii arsenitis, ℥i.
Sig.—Inject from one to three times a day from five (5) to twenty (20) drops.

℞ Liq. sodii arseniatis, ℥i.
Sig.—Inject from one to three times a day from ten (10) to thirty (30) drops.

If Fowler's solution is to be used, the tincture of lavender should be omitted for the reasons above mentioned, as it does not contribute to the therapeutical actions.

The powers of arsenic, in its relations to physiological action and therapy, are little different whether given by the stomach or injected beneath the skin. By the latter method the medicament passes into the blood more quickly, and accordingly the results of its action are sooner achieved.

The peculiar characteristics of arsenical action are exhibited when thrown under the skin, as, for example, the nausea and vomiting, the diarrhœa, the puffiness of the eyelids, the breathlessness on making any exertion, and the swelling of the ankles. It is by these signs that the toxic effects should be recognized, especially when large doses have been taken for some time. The later manifestations of the arsenical action, such as altered locomotion, neuritis with neuralgic affections, paresis,—afterwards paralysis, etc., come on,—sometimes appear quite insidiously after the appearance of the morbid complexus almost too indefinite to be recognized. When the maximum doses are taken, close attention should be given to the ordinary symptoms of arsenical poisoning, that it may be early recognized.

Such neuroses as *chorea*, *neuralgia*, and *epilepsy* have been successfully treated by arsenic hypodermatically administered.

The first person to make use of arsenic hypodermatically was Dr. C. B. Radcliffe, and the first announcement made by him appeared in the "System of Medicine"* edited by Dr. Reynolds, of London. "This patient had suffered from a distressing choreal affection of certain muscles of the neck, by which the head was kept continually bobbing and turning. Various modes of treatment had been tried without the least benefit. . . . The idea of injecting arsenic hypo-

* System of Medicine, vol. i. p. 712, *et seq.*

dermatically occurred to me on the 12th of January, 1866, and was carried out the same day. Fowler's solution was chosen, and the part selected was the most tender point over the contracting muscles. Commencing with 3 minims, the quantity injected was finally raised to 14 minims. Before the fourth injection was practised, a marked change for the better had taken place; before the eighth, the choreal movements were almost at an end, and a change for the better had gone on steadily from the beginning."

Dr. Radcliffe reports another case in which amelioration, equally as great, was produced by the hypodermatic injection of arsenic, the patient being a lady 60 years of age. He has also employed, "with results more or less satisfactory, the hypodermatic injection of arsenic in certain cases of neuralgia, epilepsy, and other affections of the nervous system."

In the cases of chorea above referred to, Dr. Radcliffe's "object in introducing the arsenic hypodermatically was not to escape gastric irritation, but to produce some local change in the nerves of the parts which were the seat of the disorder, as well as to bring about some more general change in the system."

Dr. Radcliffe employed for these injections at first the undiluted Fowler's solution, but as considerable local irritation followed, he afterwards diluted it by one-half water. This proved much less irritant.

As the arseniate of sodium solution is free from an irritating constituent, it were better, probably, to make use of that; but we have no satisfactory information regarding the relative powers of these two, if any real difference exists. If, however, Fowler's solution is rendered unirritating by omitting the lavender, there can be no question as to the safety and utility of this formula.

As to the dosage in any case of disease requiring arsenic, the amount to be given at a time ranges between the limits mentioned above; but the largest amount should be reached only by carefully ascertaining the conditions present: the state of the patient, the existence of stomachal disorders, and the nature of the case.

The cases of disease requiring arsenic are nervous affections, disorders of nutrition, glandular enlargements, and tumors having the aspect of cancer or some form of malignant growth.

In certain stomachal troubles, such as *chronic catarrh*, *atrophy of the stomach glands*, *chronic ulcer*, and ulcers of the duodenum and other parts of the intestine, arsenic greatly benefits and frequently cures. If the stomach prove irritable, and irritability increases with the administration of arsenic, the subcutaneous injection becomes a precious resource. Somewhere in the walls of the abdomen the injection can be made, those places being selected where the connective tissue is most abundant and loose and extensible. From five (5) to ten (10) minims can be injected every day for this purpose. In *chronic diarrhœa* and *dysentery* the same remedy is most efficacious, especially if combined with a minute quantity of morphine,—from $\frac{1}{20}$ to $\frac{1}{60}$ of a grain. The same facts are true of ulcers of the stomach and of the duodenum, and of ulcers situated in other parts of the intestinal canal.

The neurotic affections benefited in a marked degree by injections of arsenic are *whooping-cough*, *habit cough*, *hiccough*, *asthma*, and the *spasmodic element* in emphysema. In administration by the stomach, good results are attained, but given subcutaneously, arsenic is much more effective in the cure of these maladies. The result in many cases is only reached by long and persistent efforts. The injection in

the more acute cases should be given every day, but in the chronic cases two or three times a week, and the dose should be about 5 to 10 minims at a time; those insusceptible to the action of arsenic should have a larger quantity at each visit.

Our French colleagues have for several years strongly advocated the use of arsenic in *chronic bronchitis*, *emphysema*, and *phthisis*, and have administered it by the stomach and by inhalation by means of the arsenical cigarette, which being inflamed, the vapor can be readily drawn into the air-passages. Not only in the modes indicated can arsenic be given, but also, and in a high degree effectively, by the subcutaneous injection.

Martelli reports a case of *asthma* that had resisted the most approved methods of treatment, promptly relieved and cured by the hypodermatic injection of arsenic. Fowler's solution, diluted in the proportion of one part to two parts of water, was the strength of the solution employed, and this was made use of two and three times a week until a cure was effected, and the cure followed in a few weeks. Besides the cases of asthma already mentioned, certain neuroses of the thoracic organs have been greatly relieved or cured by arsenic injections. *Pseudo-angina pectoris* and true *angina pectoris* are the maladies most successfully treated by the hypodermatic injection of arsenic.

So much has been accomplished since by the hypodermatic use of arsenic in *chorea*, and also by its stomachal administration, that some facts in addition to those already given should be entered here, to supplement the experiences of former years. One of the series of cases most surprising in the results obtained is that of Dr. W. B. Cheadle,* of

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* The London Practitioner, February, 1886.

London. After trying many plans of treatment, he finally resorted to the use of a remedy long known for its curative powers in chorea,—*arsenic*. The observations of Dr. Cheadle are based on a study of one hundred and sixty (160) cases. Cases for comparison, treated without arsenic and with it, gave the following results: the former cases (without arsenic) averaged a duration of forty days; cases of the latter (with arsenic) had an average duration of twenty-nine days. The last series of cases treated in the same way averaged only twenty-four days.

In ordinary *anæmia*, especially in *chlorosis*, arsenic has demonstrated a remarkable curative power. Twenty years ago, Dr. W. A. Hammond, formerly Surgeon-General, published an article in the *New York Medical Journal* on chlorosis, in which he attempted to prove that chlorosis is not an affection of the blood, but of the nervous system, through which proceeds the morbid influence to other functions,—the nutrition, in this case. He showed conclusively that arsenic is very much more effective as a remedy than iron. The patients suffering from chlorosis have done far better with arsenic alone, and especially without iron, which is so often combined with arsenic in the course of the treatment. This view of the utility of arsenic is coming to be generally understood at the present time.

That form of anæmia known as the "pernicious" is of course greatly more perilous than the simple variety. The *pernicious anæmia* is usually, probably always, a symptom of degenerative changes occurring in some important part or organ, more especially one or more concerned with the blood-making process. Arsenic is the one remedy that has exhibited curative power. The organs more immediately concerned are the liver and spleen, the supra-renal

bodies, and the lymphatics coming more immediately into relation with the semilunar ganglion and the solar plexus. Not only pernicious anæmia, but morbid states even more serious, and closely allied, have been cured in the hands of Tholen,* Israel,† Mosler,‡ Padley,§ Peiper,‖ of Greifswald, and others. Cases of this kind—associated even with such grave conditions as glandular swellings and sarcomata—have been treated successfully by the liberal use of arsenic in the form of Fowler's solution injected subcutaneously on the one hand, or directly into the mass of a tumor on the other. Mosler¶ has shown that the extreme anæmia of *leucocythæmia*, or *splenic leukæmia*, is best cured or improved by injection into the mass of the spleen. He advises, further, that the most prominent nodule, or part of the organ situated nearest the anterior abdominal wall, should be selected as the site of the injection. Some preparation he regards necessary. The point at which the needle is inserted is covered with an ice-bag both before and after the injection. A needle with a small point, but somewhat longer than the hypodermatic needle, and also made of hardened gold or of steel coated with platinum, is the proper one for penetration as far as necessary. Up to the present time, notwithstanding the undeniable dangers of such a practice, those injections have not been followed by any accident, but we should none the less avoid every movement that portends disaster. Now, it is considered wise, also, to take all kinds

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* Tholen, The London Medical Record, August 15, 1881.

† Berliner klinische Wochenschrift, December 27, 1880.

‡ The London Medical Record, June 15, 1886.

§ Padley, The London Lancet, November and December, 1884.

‖ Centralblatt für die gesammte Therapie, February, 1884.

¶ The London Medical Record, June, 1886, vol. xiv., *supra*.

of precautions that the antiseptic plan requires to prevent septic decomposition.

The various tumors of glands, such as Mr. Treeves,* of London, reports,—of the cervical glands, all of which increase much in size in the first stage of that dreaded disease, lymphadenoma,—are such that persistent injection of arsenic offers a means of relief to. Tholen † gives an account of lymphadenoma and cases of pernicious anæmia rapidly cured by injections of arsenic. Dr. Israel ‡ narrates his experience of a case of lymphadenoma malignant in character, which, under the stimulation of the arsenic injections, increased in volume and took on renewed activity; but presently, after the injection of considerable doses, it lessened in volume, then gradually atrophied, and ultimately disappeared.

Enlarged glands from external causes, as the increase in size due to malarial toxæmia, the enlarged spleen and liver, are quickly cured by the injections of arsenic. Peiper, of Greifswald, relates such cases of hypertrophied glands, and also Mosler, to whom reference has been made.

Arsenic has long been known to have exceptional powers in the treatment of diseases of the skin. That it has a special direction to the skin is shown in the several eruptions that appear during an arsenical course. There is a form of eczema and of herpes zoster (shingles) which arsenic may develop at an earlier or later period, according to the susceptibilities of individuals. Such a tendency proves the existence of an arsenical action on the skin. It can be readily supposed, I think, that the morbid action

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* Proceedings of the Clinical Society, The Lancet, April 2, 1887.

† The London Medical Record, August 15, 1881.

‡ Berliner klinische Wochenschrift, 1880.

of a medicament may oppose the morbid action which comes on spontaneously in the system. Two bodies cannot occupy the same space at the same time; one must displace the other, of necessity, and hence when an arsenical impression begins its development, the morbid action must yield in a corresponding degree. Such are the principles which underlie the applications of arsenic in the treatment of diseases of the skin.

The forms of skin-diseases in which arsenic is most useful are the dry and scaly eruption and the chronic forms of eczema. The first to use arsenic hypodermatically in the treatment of skin-diseases was M. Lipp,* and the reasons that moved him to the method were these: the result was more decided and occurred earlier, the stomach continued undisturbed, and the amount of arsenic used was much less. One of the most obstinate eruptions in respect to cure is *lichen rubra*, Hebra's disease; but Köbner† succeeded promptly and entirely in curing a case by the hypodermatic method.

TRANSFUSION

By the Subcutaneous, Intra-venous, and Intra-peritoneal Methods.

Blood. Milk. Alkaline and Saline Salts.

PRELIMINARY.—In former editions of this work I did not include the subjects embraced in this new matter of the present issue, for at that time they had exhibited little relevancy to the questions now under consideration.

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* Archiv für Dermatologie und Syphil., No. 3, 1869.

† The London Medical Record, March 15, 1881.

Transfusion means, according to the original signification, the transfer of blood from one person (the donor) to another person (the recipient), the latter being reduced by loss of blood to the verge of dissolution. Now, it is extended to mean the injection of any material suitable for the purpose into some vessel or vein, or into the neighborhood of a vessel or of a congeries of vessels, prepared for rapid absorption, as, for example, the peritoneum. In a rather indirect sense, therefore, certain instances of subcutaneous and intra-peritoneal injections belong to the transfusion group. The various injections entitled "transfusions" are the following:

Intra-venous Transfusion.

Peritoneal Transfusion.

Subcutaneous Transfusion.

Transfusion of Blood by Various Modes.—This consists in giving to a patient blood, transferred by means of a suitable apparatus to his or her system from the vein or artery of the person furnishing it. The method may be *mediate* or *immediate*, and the blood may be in its natural state or it may be defibrinated. To accomplish the removal of the fibrin, the blood is taken from the person furnishing it in a full stream, and is then received into a reservoir properly warmed and aseptic, where it is defibrinated, if that is the form in which it is to be injected. Whole blood in its fresh state is the ideal form, but when it has been brought in contact with the tubes and vessels its special vivifying power or attribute is lost, and then it has the *rôle* merely of any other fluid, for it has been shown that its corpuscles undergo changes that unfit them for the performance of their proper function.

Immediate transfusion is that form of the operation which unites the veins of the donor and of the recipient by

means of a simple tube provided with valves and stop-cock; but it is affirmed that even such transient contact impairs the powers of the red-blood globules permanently. The perforated needle inserted into the vein of the donor must be introduced parallel to the line of the blood-current, which, in the venous system, is upward towards the trunk, and also the needle transfixing the vein of the recipient must have the same direction. In this way fresh and whole blood is transfused into the system of the recipient, and this must be the ideal form, if it be true that the blood is in a condition to functionate in the new situation as it had been in the old.

The result of numerous observations in all parts of the world go to show that immediate transfusion is the ideal method, if all points are carefully observed and their meaning heeded. There are but two conditions in which whole blood is essential to the success of blood transfusion: where the loss has been so great that an insufficient number of red-blood globules are present to perform the necessary functions, and where the inhalation of chemical and poisonous gases and medicinal solids (phosphorus) have so far damaged the blood-globules that they cannot functionate. The filling of the veins and arteries by other indifferent fluids will not, therefore, suffice under these circumstances. There is, however, testimony of a positive kind against this assumption. Thus Dr. Eskridge, of Philadelphia, had in his ward at Jefferson College Hospital a man admitted in a state of complete insensibility, having fallen into a privy-vault, where he lay immersed in the fæces, only his face and mouth above the noisome mass. He was poisoned by the gases there generated, the chief one being carbonic oxide, a deoxidizing agent and one having a most destructive action on the red-blood globules. After a trial of

numerous restoratives which proved unavailing, Dr. Eskridge bethought himself of intra-venous injections of ammonia. The man was nearly moribund, and hence the result was the more wonderful. On the second day after his restoration to consciousness he was able to go about freely, without any ill feelings or derangements of any of the functions.

The success here was plainly due to the injections of ammonia. The number of the injections was considerable. For the first twelve hours a syringeful of the undiluted aqua ammoniæ was injected on an average of every fifteen minutes. After consciousness was restored the number of injections was diminished. In the arm at the bend of the elbow was the vein (median cephalic?) into which the ammonia was thrown. No after-troubles of any kind were observed except a small abscess at the site of the punctures, due to the irritation of the skin by the "stronger water of ammonia" which was administered, instead of the dilute solution which had been intended. The usual strength of the solution of ammonia for intra-venous injection is 2 parts of water to 1 of stronger ammonia; but it is clear that the *aqua ammoniæ fortior* can be used should any emergency require it.

The meaning of such a case should be well settled. If the blood-globules are damaged to such an extent that they cannot go on with their proper functions, is it essential that the vascular system shall be supplied with fresh whole blood? If ammonia can effect restoration in such a condition, the question must be answered negatively. If, however, in the case under consideration the condition of the system was one in which the reaction of the blood was changed to acid, which so affected the blood-globules as merely to impair and not destroy their function, it must

be concluded that ammonia proved to be so powerful a restorative because of its active alkalinity.

Before deciding on the question of blood transfusion the real state of the globules must be settled. Are they destroyed and wholly unable to perform their functions? Are they merely inhibited and capable of proper work on removal of the inhibition? In connection with this subject I shall instance two cases of poisoning from phosphorus and from carbonic monoxide respectively, that have been placed on record by Jürgensen.* In both the blood-corpuscles were materially changed, and in both an admirable cure was wrought by means of transfusion. For such cases other plans and devices have commonly proved fruitless. Whenever, therefore, the corpuscles of the blood are unable to carry on their work, it seems quite certain that the transfusion of fresh blood is necessary.

Dr. J.W. Howe, of New York, and Landois, Schafer, and Jürgensen, of Germany, also maintain the necessity of transfusion of whole blood in all cases, since the mixing of the blood-globules impairs the quality of all. Even persons of the same sex need the supply of blood of their own kind if the best performance of the mixture is to be obtained. At one time it was supposed that the blood of various animals could be substituted for human blood. Especially was lamb's blood praised, and the lamb itself exalted almost to the level of humanity as the donor of blood to the failing human subject. Lamb's blood "the era of a new-blood dispensation" is the phrase with which Gesselius† ends his book on transfusion. Not only were losses by uterine hemorrhage, by traumatism, and other causes to

* Berliner klinische Wochenschrift, 1871, Nos. 21, 22, and 25.

† Die Transfusion des Blutes, eine historische, kritische, und physiologische Studie. St. Petersburg, 1873.

be relieved by the transfusion of lamb's blood, but all specific maladies, all strumous or syphilitic affections, were to be thus cured,—the tainted blood to be withdrawn as far as possible and the pure blood passed in. It need hardly be observed that this scheme had some elements of truth and sound physiology mixed up with an intolerable deal of chaff.

The animal craze soon subsided, as it became clear that any individual requiring blood transfusion must have his own kind furnish it; that animal blood, or blood from any other race of man, even, acted injuriously on the red-blood globules.

Lamb's blood was well borne in a great many cases in which it was used, and it was not until Landois's observations on the evil effects noticed when the transfused blood was from a different animal, that a reaction set in against it. In this country we believe no one has utilized the new-blood dispensation and employed the lamb as a donor of the blood.

Mediate transfusion consists in interposing a vessel between the supply source and the receptive patient, to receive the blood, where it can be defibrinated, if that be necessary. As a rule, now, the mediate method of transfusion is limited to those cases requiring defibrinated blood. The vessel receiving the blood is kept warm (100° Fahr.), and the blood is rapidly whipped up as it flows until every bit of fibrin is coagulated. The fibrin is strained out by means of a cloth strainer, and this part of the process must be most carefully done, for should any solid particles of the fibrin remain in the mass and be injected, the results of multiple emboli must be expected, and a disaster inevitably occur. Blood from a human subject or from an animal may be caught in a suitable

vessel, and then transferred to the patient by means of a syringe; but I need hardly observe that such procedures are of the past and are no longer justifiable.

Of the various methods of effecting the intra-venous injection or transfusion of blood, there can be no doubt of the superiority of the immediate method. The blood of a healthy subject, of the same sex if possible, should be made use of. Direct communication between the vessels of the donor and of the recipient should be established, and a quantity of blood determined by the conditions present should be passed in. In cases of loss of blood from any cause, the amount of blood given need not, as a rule, be more than four (4) ounces, and very often half that quantity will suffice to put a very different complexion on the appearances of danger before so threatening.

The instruments now employed for this purpose are simple in construction and easy to manipulate. The apparatus which Roussel, of Geneva, has invented is the most popular in European countries, and is strongly advocated by those familiar with its working. Aveling's is most used in England and I believe in this country. It is similar to the Davidson enema syringe which is now so well known; but the ball-valves are made to work in the opposite direction, so that the blood passes on into the vein and cannot return back. The bulb is worked slowly and gently, and the blood admitted drop by drop. Force and hurry will spoil all; for if much fluid is thrown suddenly into a vein, the heart will be overpowered and come to a standstill. Besides these arrangements, the most rigid antiseptic precautions must be taken in respect to sterilization of all objects and instruments concerned in the operation.

If proper attention be given to all points the danger of immediate blood transfusion is not great. Defibrinization

was proposed originally because of the fear of embolism occurring as a consequence of coagulation of the blood in some parts of the vascular territory; but if the fibrin is removed no coagulation can take place, and hence no emboli be produced.

Various fluids besides blood are nowadays employed for intra-venous transfusion or injection. Milk for a time became a sort of fad. Numerous cases of its sucessful employment were published, and next to blood it was made use of most extensively. Hodder, of Montreal, was the first, it is most probable, to transfuse milk instead of blood. According to Brinton,* twelve cases are on record, of which Hodder had three, Gaillard Thomas, of New York, three, Howe, of New York, two, and Hunter, of Philadelphia, four, making in all twelve cases, and of these six were successful. Much depends on the history of the cases. Thus Meldon† used the intra-venous injection of milk in ten cases of *pernicious anæmia*, all of them "moribund" when admitted. Notwithstanding their unfavorable aspect, four were permanently cured, and life was prolonged in several which afterwards proved fatal. In a well-considered experimental paper, Vigezzi‡ has examined the whole question with great care. He finds that the chief danger of milk transfusion is the formation of emboli, due, he says, to the lactic and butyric acids produced in the milk. It is essential that the milk be fresh (milked at the time needed) and that it have an alkaline reaction. If any emboli are formed, a fatal termination only is to be expected. The amount of milk

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* The New York Medical Record, November 2, 1878.

† The London Medical Record, May 15, 1880, and ibid., March 15, 1881.

‡ Ibid., December 15, 1883.

required is from half an ounce to six ounces. It is rare indeed that a greater volume of fluid than six ounces can be injected with safety, and in this respect milk must be made use of in accordance with the same laws as other fluids used in this way. Vigezzi found the intra-venous injection of milk very effective as a remedy in *anæmia*, and in *pernicious anæmia* the results of the same treatment have been in a high degree favorable.

The general satisfaction of those who have made use of the milk injections should not blind them to unfavorable results which have occurred. It has been asserted that milk introduced into the circulation needed no digestion, that it is assimilated of itself; but the facts do not warrant such assumptions. It has been shown by Miglioranza* that the fatty and albuminoid substances of the milk are not utilized, but pass out by the kidneys. The undigested milk may be retained in the blood, giving rise to serious disturbances by the increased pressure of the vascular system and by vomiting and diarrhœa. The fat of the milk may accumulate in the kidneys, and albuminous and other organic substances may strain out through the kidneys, and hence it is that albumen has been so often detected in the urine of those having received milk by transfusion.

According to Brinton, the intra-venous injection of milk causes a disturbance of the system not unlike, but less pronounced than, that induced by blood similarly employed. The immediate symptoms are flushing of the face, tingling of the skin, and an eruption of urticaria; a chill occurs, followed by febrile reaction, and the general signs of an increased vital activity are manifested on all

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* The London Medical Record, August 15, 1883.

sides. The globular richness of the blood is improved, and there is a greater excretion of certain products of tissue-changes (urea, etc.), but a considerable proportion of albumen appears in the blood, and sometimes—emboli blocking some of the pulmonary capillaries—great distress in breathing is experienced.

The operation of transfusion of milk is a simple one. All that is required consists of a flexible tube having a funnel at its proximal and a suitable perforated needle with a cutting point at its distal end. The milk, carefully filtered and warmed to 100° Fahr., is then poured into the funnel and conveyed by gravity into the venous system. A vein at the bend of the elbow is usually selected. In several instances, in deference to the need of having the milk absolutely pure and good, and without changes in its composition due to standing in ordinary vessels, goat's milk has been used, and the animal taken into the house to be milked at the time needed.

Various solutions have been employed for intra-venous transfusion. Solutions of chloride of sodium (common salt) are most important, but they are variously modified. One of the most useful, as it has been successfully employed, is that of Jennings.* He entitles it "saline alcoholic solution," and as it contains alcohol as well as salines, it is suitably named. The composition of this solution is as follows:

Chloride of sodium, 50 grains;
Chloride of potassium, 3 grains;
Sulphate of sodium and carbonate of sodium, of each, 2½ grains;
Phosphate of sodium, 2 grains;
Absolute alcohol, 2 drachms;
Water, 20 ounces at 100° Fahr.

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* The London Lancet, 1882, vol. ii. p. 436.

In a case of exhaustion by *hemorrhage* (*placenta prævia*) 16 ounces of this fluid (temperature 100° Fahr.) were injected into a vein of the arm, with complete success. An immediate revival took place, the patient emerging from a moribund state, and recovery ensued without accident. Dickinson, also, in a case of diabetic coma, used the salt solution by intra-venous injection.

The intra-venous injection of a saline solution has the same wonderful effect on the subject in a state of collapse as when immediate blood transfusion was the method pursued. It has been asserted by Jennings,* Ott,† and others that the use of the saline is just as effectual as blood transfusion, and that it is the amount, and not the character, of the fluid passed into the vein that brings about the desired result; for when blood is transfused the blood globules do not functionate in the normal manner, but are gradually eliminated through the kidneys as effete matters that have undergone the ordinary degenerative changes. It seems to be well established as a fact that blood lost by hemorrhage is not restored as rapidly by the accession of fresh blood as by the merely saline solution entirely free from putrescible elements. If these views of Ott's be accepted, and increasing observations seem to indicate that they are sound, the whole theory of transfusion, as respects the *rôle* of blood in that operation, must be materially modified.

In the algid stage of *cholera* it has long been known that the intra-venous injection of salines had a remarkable effect in bringing back to life those apparently dead. Unfortunately, most of those thus treated quickly relapsed

* The London Lancet, 1883, vol. i. p. 228.

† Inaugural Dissertation (Russian). Quoted by The Medical Record, 1882, 1883.

and died. Improved methods have rendered the operation of transfusion far less dangerous and the results more beneficial. For example, Cantani* has published a report of two hundred and twenty-six cases of *cholera* treated by saline injections, the mortality being at the rate of thirty-one per cent. As the usual mortality rate of cholera is fifty per cent., it is clear that this method affords better results than the treatment hitherto pursued. Aqua ammoniæ has been employed with remarkable success in the treatment of depression of the powers of life under various conditions. Thus Dr. Trusewicz † recommends the intra-venous injection of ammonia in *cholera.*

It has long been known that the intra-venous injection of ammonia is an effective remedy for the bites of the venomous snakes of Australia and of this country. We owe the original demonstration of this fact to Mr. Halford, of Australia. Although Brunton‡ has shown that it is unavailing as a remedy for the snake-poisons of India, it is certainly very effective against those of other countries.

Whenever the vital powers are greatly depressed from any cause, the circulation feeble, and collapse imminent, the intra-venous injection of ammonia is indicated, and may prove highly efficient. Also in various acute diseases, as in *pneumonia*, this remedial measure has proved its efficacy in many instances. When thrombi form, or emboli are circulating in the blood, there can be no doubt of the superiority of ammonia injections to all other remedies. It does no harm on entering a vessel; it maintains the

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* Il Morgagni, 1885, Nos. 6 and 7. Quoted by The London Medical Record, March 15, 1886, p. 108.

† The London Medical Record, 1885, pp. 69, 286. ‡ Op. cit.

alkalinity of the blood, and thus prevents the formation of, or dissolves, thrombi and emboli. There are many situations in which the exertion of this power would prove highly advantageous: in the case of thrombus of the pulmonary artery, of a vessel of the brain, or of such blocking of a vessel as occurs after a low fever,—viz., thrombus of the femoral vein, and the development of a case not unlike the "milk-leg" of the nursing woman.

Usually, diluted aqua ammoniæ is made use of: aqua ammoniæ, 1 part; distilled water, 2 parts, or equal parts, if considered necessary. Dr. Eskridge supposed he was using the diluted preparation, but actually had injected the ammonia fortior,—the stronger water of ammonia.

Peritoneal Transfusion.—This expedient for adding blood to the circulation was first conceived and carried out by Professor Ponfick, of Breslau. Defibrinated blood is used, and not whole blood. The principle of gravity can be applied to effect peritoneal transfusion. After the fibrin is separated, and the fluid properly strained and at the temperature of 100° Fahr., the amount decided on is then passed into the cavity. The apparatus required is simply a glass funnel, a flexible tube, and a trocar and canula. A suitable site being selected, the trocar (a small one) is thrust in, and this being withdrawn, the canula remaining, the blood is poured in through the funnel and tube until the necessary quantity has been received.

When Ponfick's account of peritoneal transfusion was published, his explanation of the results was examined into by Golgi and Bizzozero,* and they confirmed his statements at all points. It was ascertained that the glob-

* Berliner klinische Wochenschrift, 1880, No. 30.

ular richness of the blood is quickly increased and the percentage of hæmoglobin also. As peritoneal transfusion must largely supersede existing methods, if the good effects are confirmed and no accidents occur, it is desirable to have a clear view of its powers and of the results obtained by it.

As the transfusion of blood into the veins, whether by the mediate or immediate method, is accompanied by so large a mortality, if peritoneal transfusion is not dangerous to life and is easy of performance, it may take the place of the more fatal expedient. As already stated, peritoneal transfusion consists in the injection into the peritoneal cavity of defibrinated blood. What becomes of the blood after it is deposited in this cavity? Experimental investigations by Bizzozero and Sanguirico * have shown that the blood remains but a short time; in other words, the blood is quickly absorbed, and then the question arises whether it is in a condition to functionate, or merely as so much fluid occupies a space corresponding to the amount injected. As, in either event, additional material is contributed to the blood, it necessarily acts as a restorative. When, however, sudden hemorrhage threatens life, the restorative must act immediately if it is to serve any useful purpose, and therefore it may be necessary to perform immediate transfusion.

In some cases of peritoneal transfusion considerable tenderness of the abdomen follows, indicating the development of a local peritonitis. Fever, preceded by a rigor of less or greater severity, delirium rarely, profuse sweating, etc., may be results of the transfusion into the peritoneal cavity. These are exceptional results and purely

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* The London Medical Record, October 15, 1886.

accidental. Troubles may arise from the neglect of antiseptic measures in performing the operation, air may be admitted to the cavity, and various other accidents may occur.

In performing the operation, the point for inserting the needle-canula should be fixed on the central line of the abdomen two to four inches below the umbilicus. The blood should be drawn from the donor of the same sex as the recipient; if available, it should be received into a vessel kept at the proper temperature, then quickly whipped up to separate the fibrin, and strained. After straining the blood, the needle-canula for puncturing the abdominal wall should transfix it by a quick movement, the proper point having been decided on beforehand, and the blood should then be allowed to flow through the needle into the cavity. The blood should flow rather slowly into the peritoneal region, for as large as the space is, sudden distention may cause faintness, even alarming depression.

Peritoneal transfusion is adapted to the treatment of *anæmia*, especially the *pernicious* variety, to supply the vascular system in *sudden loss of blood* from disease or traumatism. When the anæmia is due to changes in the blood such as are caused by phosphorus or carbonic oxide, it is necessary to supply new blood to the vascular system of the recipient.*

It is probable that peritoneal transfusion is quite as effective as intra-venous transfusion with defibrinated blood. For most of the purposes for which transfusion into the veins is necessary, the peritoneal mode will suffice. Dozzi† reports two cases that were greatly improved by means of

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* Jürgensen, op. cit.

† The London Medical Record, March 16, 1885, p. 105.

peritoneal transfusion. But, on the other hand, Bareggi* deems this method of transfusion less preferable than the hypodermatic injections of blood, which, he says, are safer and more practicable.

Besides the intra-venous method, there is another mode of transfusion which has proved to be quite effective,—viz., *hypodermatic transfusion*, which consists in a deposit of blood, fresh and defibrinated, into the loose connective tissue of the flanks and back. Blood defibrinated and salines are employed in this mode of transfusion, and the syringe should be a large hypodermatic instrument.

It has been found that the hypodermatic transfusion of blood and salines has an action as prompt and efficient, nearly, as the peritoneal transfusion. Bareggi† finds that the hypodermatic injection affords better results than by any other mode. Saline solutions, consisting for the most part of sodium chloride, have been given subcutaneously in many instances. Also, the injection of defibrinated blood hypodermatically has proved equal to and far less liable to serious after-consequences than the peritoneal and intra-venous methods of administration. Thus Silbermann‡ reports two cases of complete success by the subcutaneous blood-injections, and Paladini§ gives an account of a case (one of the first) in which the same practice succeeded admirably. Similarly, various cases of cholera have been successfully treated by subcutaneous saline injections. Samuel reports cases of cholera treated by subcutaneous injections of salt solution and of simple water injections,

* Virchow und Hirsch's Jahresbericht, 1883, p. 311.

† *Supra.*

‡ The London Medical Record, March 15, 1885.

§ Ibid., January 15, 1884.

also subcutaneously, kept up for hours at a time, and they have, it is said, succeeded perfectly.

In a communication to the *London Lancet*, April 21, 1883, Dr. Murrell suggests saline intra-peritoneal injections as a remedy for poisoning,—for those organic poisons that cause great depression of the powers of life, including the phenomenon of heart-failure. The formula he suggests is the following:

> Common salt, 1 drachm;
> Bicarbonate of sodium, 4 grains;
> Chloride of calcium, 3 grains;
> Chloride of potassium, 1 grain;
> Water, 20 ounces, at a temperature of 100° Fahr.

We see thus that a largely-increased number of successful cases have been reported lately, giving us necessarily great hope of still further triumphs in this field.

Other Nutrient Injections.—Reports have been made within the past few years of cases in the condition of great depression of the powers of life, treated in the emergency by injections of cod-liver oil, beef-tea, and similar enormities. If the performers of these remarkable exploits can remember the length of time such articles require for their digestion, or for their diffusion into the blood-vessels, their zeal might be tempered with more discretion. It need hardly be said to any of my readers that such injections are wholly unsuitable; not only unscientific, but brutal; for we find usually at the site of the injection suppuration and sloughing, with the attendant phenomena of pain and septicæmic fever.

Injections of Oils.—For *struma* in its various manifestations, for incipient phthisis, for a low state of the vital powers, induced by *suppuration*, *diseases of bones*, etc., cod-

liver oil has been used—it is said—with advantage when administered hypodermatically. The sequel of such practice is rarely told, and the indurations and abscesses that follow every injection are studiously concealed.

Not long since, in a case of severe hemorrhage, and consequently a failing heart, it is narrated that *beef-tea* was injected, the result being most happy. It needs no elaborate argument to prove that the injection of such a substance cannot fail to be injurious, and hence I urge upon my readers that such practice is highly objectionable; for if decomposition should ensue, there must be more or less sloughing and purulent accumulation at the site of the injections. Other stimulants, as, for example, the injection of ether, can be used in an effective manner without causing any of the deleterious results of a decomposable substance, with the after-danger of septicæmia.

Brown-Séquard's Solution.—I should not close this part of the subject without giving some account of the new modes of treatment based on the modern bacteriological investigations and discoveries. The first in point of time is the fluid of Brown-Séquard,—a testicular juice which probably contains a leucomaine having special powers in connection with the organs of reproduction. The mode of preparing this solution is as follows: Two or more testes of one of the inferior animals (Brown-Séquard used the testes of guinea-pigs) are bruised in a sterilized mortar with a little sterilized water, and all the juice the testes contain expressed out of them, and the fluid thus obtained has in it an albuminoid substance which possesses special and remarkable powers. After it is filtered and sterilized, it is ready for use. A syringeful is injected into the loose connective tissue of the hips and buttocks.

If properly prepared and properly sterilized the solution will cause but little pain when injected, and will not give rise to any local trouble afterwards. If, however, it is carelessly prepared, and contains fatty detritus or decomposing material, it is certain to cause a good deal of mischief.

According to Brown-Séquard and other competent persons, it has remarkable effects on the constitution of man. It apparently revivifies the functions of animal and organic life, and sets back the progress of decay ten years or more. Similar powers have been ascribed to testicular fluid by the aborigines of the Rocky Mountains, especially by the Cheyenne tribe of Indians of Northern Texas, of the Staked Plain, and of Eastern New Mexico, according to my personal observations.* Other instances of traditional belief in the concealed, but stored-up, energy of the testicular fluid have quite supported the contention of Brown-Séquard; so that, whether true or false, historical beliefs should be added to the traditions of savages in favor of the existence of such a force.

It is asserted that spermine or leucomaine is a constituent of seminal fluid and of testicular juices, or that the powerful principle contained in it is of that character. When properly prepared, disinfected, and containing an antiseptic to prevent further changes, it can be injected

* In 1860-61 I was serving as an officer of the medical staff, United States army, at Fort Union, New Mexico. Attending one of the ceremonies of a band of Indians near the station, on one occasion, I saw a young buck eating a great mass of raw flesh, as it seemed to me, and with obvious difficulty, for as he ate he was pushing the testis (as I had learned it was) into his mouth with some difficulty, his cheeks distended, his eyes protruding, and liquid fat running out of the corners of his mouth and tears from his eyes. The testes were quite large and were those of the antelope, and the man was eating one because of the general belief in their power to raise the warrior to a high state of ability and courage, and also sexually.

with entire safety. There is no exact statement anywhere as to the precise amount required in any instance, but Dr. Brown-Séquard has indicated that the quantity of fluid he obtains from two testicles of a rabbit is a sufficient amount for one injection in an adult male.

The effect of this material on the organism of man is that of a vital stimulant. In a few minutes after it is injected the forces seem to take on new life, and soon the appetite and the assimilation are improved, an increase of weight takes place, and the muscular strength, the disposition to exertion, the sexual capacity, and all of the powers of body and mind take on new activity. It is these remarkable changes that have induced the enterprising newspaper men and other wits to dub the preparation "The Elixir of Life," etc. Great injustice was done Dr. Brown-Séquard in these ridiculous statements. His own modest story was to the effect that he had reason to believe such a solution would prove of benefit in some forms of disease.

It is in the decay incident to old age, or premature old age, that very considerable good is derived from it. Also in wasting diseases of various kinds the stimulating effects of the fluid may prove highly effective. Indeed, the maladies in which it may be expected to do good are situated in those organs upon which its action appears to be expended.

The albuminous substance, *spermine*, has recently been brought forward by Parke, Davis & Co., but doubts are entertained regarding its nature and character. It certainly has some relation to the active constituents of the testicular fluid, or it may be the most active constituent, and being rid of some associate principles that contribute to the reaction when the whole fluid is used, it

will ultimately fill its place in arranging for another solution.

In preparing testicular fluid, it is necessary to secure sound testes from a large domestic animal (the ram, the bull, the horse, the dog, etc.). All superfluous fat and fibre being carefully detached, the testis is rendered aseptic, the mortar and pestle are similarly treated, and, when ready, the organs are bruised in a mortar, the juice pressed out, filtered, rendered aseptic, and is then fit for use.

Koch's Lymph, for the Treatment of Tuberculosis.—As so much has been said regarding the properties and mode of using of the lymph, and the secular press has gone beyond its usual bounds to take up such medical affairs as the lymph is concerned with, little remains to be said on any part of the subject. I conclude, therefore, to add nothing to the great burden of the literature of Koch's method. Should the sixth edition of this book be called for within the next few years, and something of a permanent and unequivocal character be determined on by that time, I shall discharge my duty to my readers and present such an outline of the subject as truth, reason, and space permit.

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3. *Agents having the Power to Destroy Pathogenic Micro-Organisms.* [*Antiseptics.*]

Preliminary.—The group of remedies acting in opposition to disease-producing micro-organisms must of necessity have a general application, and cannot be confined

within certain anatomical bounds, but have communication with any or all parts of the system invaded by germs. Antiseptics or germicides are agents having the power to inhibit or destroy the pathogenic parasites. It is clear that no distinct differences exist between antiseptics and germicides, since the function of each one is to destroy germs. In actual employment these remedies seek out the germs, suspend their activity, or stop or destroy those physiological functions in which the germs only have power to produce a poisonous material inimical to man. Not all antiseptics can be used hypodermatically, because not soluble in proper menstrua. It is no part of my purpose to take into consideration those remedies of the antiseptic class unsuited for subcutaneous use.

As there is a close correspondence between the various members of the aromatic series, from which the antiseptics of the phenol group are derived, it has occurred to me that it were better to make a preliminary statement giving a general view of their properties.

All of the phenol group subsequent to carbolic acid have been introduced very rapidly within the last few years, partly because of the advances in chemistry and pharmacology, which compelled, as it were, their production, and largely because, being proprietary articles of commerce, it is the interest of the chemical manufacturer to push them forward as rapidly as possible. The reason assigned for giving a trade designation to a new medicament is that the chemical name is an impossibility for ordinary use.

The members of the phenol group in time of production subsequent to carbolic acid, and suitable for injection under the skin, vary somewhat in the amount of irritation caused by them, but rarely occasion inflammatory swellings or in-

durations, and still less frequently abscesses. They are remarkable also for their promptness in affecting the system at large and the rapidity of their actions, it being little more than two hours—when a toxic dose is taken—between the beginning of the effects and their termination in death.

The first systemic effect, when a sufficient dose has been administered, is usually dizziness followed by dulness and hebetude of mind, and passing into drowsiness, but without delirium. Next, trembling of the muscles and clonic convulsions appear; then increasing insensibility, passing into coma and followed by profound unconsciousness, come on in the order named, and finally respiration fails and the action of the heart ceases. With the development of the symptoms as just narrated, dilatation of the pupil ensues, the action of the heart increases, the peripheral circulation becomes more active, correspondingly, the face flushes, and presently a more or less copious perspiration breaks out over the whole surface of the body. During the normal state of man the temperature of the body undergoes no positive changes; if there be any deviation it is in the direction of elevation rather than fall of temperature; but this peculiarity may be due to the active muscular exertion rendered necessary by the clonic convulsions.

As respects the effects on the nervous system of animal life, it is to be noted that the action is central and not peripheral; that the muscles are paretic, not in consequence of any disease in them, but because of a change set up in the motor centres of the cord. Sensibility is simply reduced, but not abolished until the last period of the lethal action. As regards the functions of respiration and circulation, it is to be observed that both are first increased in force and frequency, but presently the force declines and the fre-

quency increases,—evidence that the vital powers are declining.

During the existence of fever, these remedies display a considerable power to lower it; in other words, they are antipyretic. In respect to this function, they exert a greater power of heat-reduction than any antipyretic medicines known to the medical profession. In practice certain disadvantages lessen the value of the antipyretic effect; for example, at the decline of the sweating stage a rigor of less or greater power comes on and may be so severe as to have the form of a pernicious chill, and may approach dangerously near to a lethal effect. When the diminution of the fever is as much as 2°, 3°, or 4° Fahr., the chill may be expected to correspond in severity with the amount of heat thus disposed of. This depressing chill constitutes a real danger in the case of many of these antipyretics, and only those will be retained permanently in the medical armamentarium that are not so objectionable in respect to this rigor. Besides the dangerous rigor, there is another point in which the new antiseptics are objectionable: they have a depressing effect on the heart, which is exerted more especially when the chill comes on.

As carbolic acid is the best representative of the group, and was the first to be known, it seems most appropriate to begin an account of the series with the consideration of this agent. The other members of the same group will also be considered in their turn, taking up those only that can be employed hypodermatically. Many of them are not soluble in any menstruum that can be utilized for hypodermatic use, because too irritating to the tissues. Such remedies are not proper, and hence of necessity many are omitted from this work.

ACIDUM CARBOLICUM: CARBOLIC ACID.

Phenol, etc.

PREPARATION.—For hypodermatic use the solution of carbolic acid in water is employed as follows:

℞ Acid. carbolic. purif., gr. x;
Aquæ, ℥i. M.
Sig.—Twenty (20) minims contain ½ of a grain.

Other solutions can be prepared, of course, according to the needs, or indications, or views of practitioners. There are distinct peculiarities as to the solution of carbolic acid. Different specimens, yet not varying from the normal standard, differ in solubility, and require other methods than the usual ones to augment the proportion in a given solution. By effecting a solution in small proportion, after a time another proportion will be taken up, provided that some care is used to bring it about.

The dose of carbolic acid ranges from ½ of a grain to 2 grains, if given by the hypodermatic method.

PHYSIOLOGICAL ACTIONS.—Even when given by the subcutaneous method at longer intervals than required by the stomachal administration, there may be danger-symptoms which demand attention. Hence careful consideration should be given to all signs indicating the approach of a lethal action.

The local effects of carbolic acid at the moment when the solution enters the areolar tissue are those of an irritant, and considerable smarting ensues, which, however, is soon followed by a loss of sensibility,—analgesia,—which extends a short distance beyond the area occupied by the injection. Some numbness and tingling combined are also

felt at and beyond the point of injection. By the application of undiluted carbolic acid to the skin of his own arm, Bill* ascertained that an analgesic and an anæsthetic area can be made coextensive with the application. He was soon after followed by Squibb, the chemical manufacturer, who ascertained the same fact. This effect is a local one, and involves only the skin at the point of application. When the mucous membrane is touched with the pure acid, and also the skin in a less degree, there appears a whitish but superficial eschar, and the place is benumbed and has a tingling sensation at the same time.

If the dose of carbolic acid be a small one, the local effects may alone be felt. On the other hand, systemic effects promptly follow when the dose is sufficient in size. Long-continued use of the syringe, even if the individual doses be small, may cause toxic symptoms. It is always wise, when the administration of the remedy for a long time becomes necessary, that frequent inspections of the urine be made. A persistent smoky appearance and a peculiar odor bode evil, and should be duly regarded.

When a lethal dose is taken hypodermatically, prompt action occurs. Dizziness, vertigo, headache with a tensive feeling, weak action of the heart, and drowsiness soon occur. The muscular system weakens, respiration becomes labored and shallow, the heart's action continues to decline, the pulse is irregular, and the drowsiness deepens into coma. Vision grows dim, the pupils contract, delirium occurs with restlessness, and death ensues in a state of profound unconsciousness, with failure of respiration and cessation of the heart's action. Fatal accidents by hypodermatic injection are exceedingly rare, if any

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* The American Journal of the Medical Sciences, 1870, p. 573.

have occurred. Poisoning is also rarely by design, but comparatively frequent by accident, solutions of the acid or the pure acid being swallowed by mistake.

The use of the hypodermatic syringe in cases of poisoning is restricted to the administration of the antidote. By the stomach the free use of mucilage (not oils!) and the alkaline sulphates are the chief antidotal means, and by the subcutaneous tissue the administration of atropine, as that is the antagonist. Under the therapy will be given further particulars on these points.

Besides the general effects of carbolic acid mentioned above, we have to note the actions of this agent on the heat function, on the secretions, and on the nervous system in respect to motility and sensibility. Carbolic acid is a paralyzer of the nervous system. The action is spinal, and not peripheral, the motor part being the seat of the effect.* Whether the spinal cord or the intra-cranial organs is the part on which it acts is much disputed. Salkowski maintains that the action is spinal; Husemann, that it is cerebral. Gies holds that the clonic convulsions which occur in cold-blooded animals are spinal, for they are found to occur in decapitated frogs. These clonic convulsions are succeeded by paralysis. In man the paralysis gradually develops from a condition of paresis, and convulsions are uncommon.

Carbolic acid also lowers the blood-pressure and enfeebles the action of the heart, the stand-still occurring in the diastole. It exerts a paralyzing action on the muscles of respiration, and death takes place by arrest of respiration.

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* Th. Gies, Zur Kenntniss der Wirkung der Carbolsäure auf den thierischen Organismus. Archiv für experimentelle Pathologie und Pharmacologie, Band xii. p. 401, *et seq.*

The dose that may be regarded a dangerous one cannot be fixed on with any certainty, at least within narrow limits. Six grains have been administered once a day for several days. Bouchard and Gimbert have gradually increased the dosage to 15 grains a day, in cases of phthisis; but great care was necessary to avoid upsetting the stomach.

To determine the presence of carbolic acid in the urine, the best procedure is to ascertain whether the sulphates are present or absent. If carbolic acid is in the urine it will unite with the sulphates to form the sulpho-carbolates, and consequently if the sulphates are absent, any test to show this will prove the point. The first step consists in acidulating the urine with strong acetic acid, then adding baric chloride in excess; if sulphates are present, baric sulphate is precipitated.

THERAPY.—By *parenchymatous injection* is meant the insertion of medicaments in the depth of muscles or organs. It was formerly used principally with solutions of carbolic acid, and was reserved as an especial method of giving this agent; but many others are so employed.

One of the most important of the maladies in which carbolic acid is used is *erysipelas.* The reports regarding its success in this disease are uniformly favorable. The mode of treating it consists in injecting a solution of carbolic acid at certain intervals in front of the advancing inflammation. A half-grain is injected about two finger-breadths in front of the redness and swelling. When the amount given reaches to 6 grains, it is usual to restrict the application to that amount, for toxic symptoms may be expected if more be given. Once a day is the usual number, and not more than three or four days are occupied in this treatment. Carbolic acid has proved highly satisfactory in the treatment of *malignant ulcer* or *charbon.* In this

malady numerous injections are made all round the tumor at about the same distance as in the case of erysipelas. The strength of the solutions used varies greatly, and ranges from one to ten per cent. In two or three days a great change takes place in the appearance of the ulcer, and it soon closes.

Analogous to these cases is the application of carbolic acid to the treatment of *diphtheria*. Taube,* of Leipsic, has used it with great advantage by injection beneath the mucous membrane and into the tonsils, in imitation of Dr. Edel, of New York, who was, no doubt, the first to practise this method.

Carbolic acid, given subcutaneously, has been much employed in the treatment of other affections of the skin, as *rodent ulcer, epithelioma*, etc. I have seen several cases of epithelioma, or a condition of the skin which seemed to justify this diagnosis, treated successfully by this plan. One of the cases referred to had been operated on for epithelioma and the disease returned twice at the site of the cicatrix. There were many injections made, extending over a year, nearly, and I learned recently, after many years of silence, that my patient is still living and there has been no return of the disease. The method of performing the injections is similar to the treatment of anthrax,—*i.e.*, a ten-per-cent. solution is so injected as that in turn each portion of the base of the growth is acted on directly. This little operation is not painful, and patients quickly acquire tolerance of the whole procedure.

Such glandular growths as *bubo* (local *tumors of glands*) are much improved by the parenchymatous injection. A

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*. The London Medical Record, October 15, 1878, p. 443. Quoted from Deutscher Zeitschrift für pract. Medicin.

solution of from two to ten per cent. can be used without any injury or accident. *Synovitis of joints* can be thus cured; also *bursæ*, enlarged and prominent, and *abscesses* are greatly benefited and cured by the hypodermatic injections. To these affections must be added *hydrocele* and *hemorrhoids*.

For a long time the tincture of iodine was the first of remedies for the cure of hydrocele. So many of the cases failed of benefit, however, that carbolic acid was, at length, substituted. We owe, I think, the use of carbolic acid in the cure of hydrocele to the late Dr. R. J. Levis, of Philadelphia, who used this remedy many times. The operative procedure is precisely the same as when iodine tincture is used: the sac is emptied of its fluid by the canula, and through this the carbolic acid is injected into the interior of the sac, and not allowed to pass into the several layers of tissue about the sac.

The injection of *hemorrhoids* with carbolic acid and glycerin is a distinct advance in the treatment of these bodies. The dose required depends somewhat on their size and condition. According to Dr. Kelsey,* who is an authority on this subject, the more recent hemorrhoids should be injected with diluted carbolic acid (1 part of acid to 2 parts of glycerin); but an old and large hemorrhoidal tumor can be injected with the pure acid, that there may be some sloughing. After the separation of the slough, and in the course of healing, the tumor will contract much and ultimately be entirely absorbed. Few methods of treatment are more signally successful than this way of treating hemorrhoids.

Besides these local uses of carbolic acid, there are sev-

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* The New York Medical Record, August 7, 1886.

eral points to be examined into regarding its application in internal maladies. It is reported by Tessier, of Mauritius, that *intermittent fever* can be cured by the injection of a solution of the acid,—¾ of a grain in 20 minims of water. Kunze asserts that the injection of the acid will procure resolution of the lung in cases of *pneumonia*. *Enlarged spleen*, the result of chronic malarial poisoning, can be reduced to the normal by an occasional injection of carbolic acid, tincture of iodine, and glycerin (1–1–2); probably once a week is often enough for this purpose. The hypodermatic syringe, provided with a long needle of small calibre, is a suitable instrument for this purpose. The same solution is proper for the treatment of *abscess of the liver* when it is sacculated, or early in the case, before the purulent accumulation is invested and held by a retaining membrane,—the so-called pyogenic membrane. *Abscesses* in other situations are treated successfully in the same way, —viz., by injecting into them a mixture of equal parts of carbolic acid and tincture of iodine. In these troubles, dilution of the injecting materials is not necessary. In a formidable case of *sublingual abscess*, carbolic injections proved entirely successful in the hands of Skibnivsky.* *Blood-poisoning*,† due to a poisoned wound of the hand, was rapidly cured by injections of carbolic acid (four per cent.) into the other arm, two injections being practised in twenty-four hours.

Treatment of Poisoning by Carbolic Acid.—Should a lethal action occur in consequence of error in the dosage or idiosyncrasy in the patient, or of an attempt at suicide,

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* Wratsch. Quoted by The London Medical Record, August 15, 1883.

† The Lancet, April, 1885, vol. i. p. 784.

the question for consideration is, What antagonistic remedies can be applied? It is evident that if the carbolic acid has been administered hypodermatically, no stomachal remedy is of any use; for the subcutaneous administration so quickly develops the symptoms, and beyond the reach of a chemical antidote, that it were idle to expect relief by any other mode of giving.

An antagonist which has the power to oppose the action of the poison at many points has been brought forward, but it has not attracted the attention it ought to have done. A distinguished surgeon of New York, Dr. Post, made me acquainted with it, and told me the particulars of a case in which he had used it with success,—the only case that had occurred in his practice or elsewhere. Dr. Post was induced to make use of atropine by observing that the pupils of his patient were minutely contracted. On learning these facts, I instituted a course of experiments in the Laboratory of Experimental Therapeutics of Jefferson College, and found that Dr. Post's observations were correct, and that the antagonism must prove a valuable means of saving lives. I ascertained that the antagonism between carbolic acid and atropine was similar to the antagonism between morphine and atropine,—that is, the depression of the circulation and of the respiration caused by carbolic acid is overcome by atropine, so that these great organs of life can maintain the vital powers until the depressing agent is eliminated. Besides the antagonism between the actions of both agents on the circulation and respiration, it should be noted also that it extends to the cerebrum, to the pupils, to the mucous membrane, and to the skin. It may be well to make some observations on these points. As regards the cerebrum, the hebetude of mind at the first onset of the toxic symptoms, and the

deepening of this impression into coma, are opposed by atropine, which acts in the opposite direction. The minutely-contracted pupil is due doubtless to the unopposed action of the third nerve, in consequence of paralysis of the sympathetic governing the radiating fibres of the iris; the filaments of the third nerve, as is well known, being distributed to the circular fibres, which contract the pupil, while the radiating fibres enlarge the pupil.

The quantity of atropine required to oppose the effects of carbolic acid can be determined only by trial. The state of the pupil, the degree of coma, and the manner of maintenance of the respiration are the signs by which the condition of the patient is made known, and also by which a judgment as regards the amount of the antidote may be formed.

CREOSOTUM: CREOSOTE.

Guaiacol.

The actions and uses of creosote are so nearly those of carbolic acid that any additional matter referring merely to the creosote would seem to be a labor of supererogation. There are, however, several special uses of creosote, or guaiacol, that may be mentioned here with advantage.

Ordinary creosote and guaiacol are not identical, but are so nearly so as to permit the substitution of one for the other. Guaiacol contains about seventy per cent. of pure creosote. Creosote differs from phenol or carbolic acid in several points, but the main difference just here is that creosote is obtained from the distillation of wood-tar, whereas carbolic acid is a product of coal-tar. Guaiacol is a specially pure creosote, obtained from guaiac, and is

therefore better for hypodermatic injection; but in the absence of guaiacol, ordinary creosote may be used. It should be the practice, however, always to make use of the purest attainable drug, for hypodermatic injection especially.

As creosote is not readily soluble in water, several expedients are practised to obtain the necessary strength in solution. In the first place, the beechwood creosote, or guaiacol, should be made use of, and with this it is easy to prepare a solution by dissolving 1 or 2 drops in 20 minims of distilled water, of chloroform water, or in oil of vaseline; after the solution of the first portion is effected, the remainder up to 5 or 6 drops can be dissolved in the same solution with persistent agitation. In this way as strong doses as are desired can be administered. The usual dose is from 1 to 10 or more minims, beginning with the minimum twice a day, and increasing as rapidly as may be until 10 to 15 drops are given. The injections should be made into the abdomen, hips, or back, as the patient prefers or as is expedient. Very little pain is felt. I have found that the guaiacol gives almost no pain, and is not objected to by the most fastidious person. While the hypodermatic injection is going on, inhalations of creosote may be practised twice or more a day. All authorities agree on the desirability of introducing into the patient's system the largest practicable amount of the medicament. According to Lublinski,* much depends on the purity of the preparation. He found that when the guaiacol was administered, the smoky and, after a time, the blackish discoloration of the urine never occurred; but from common creosote this was a constant result.

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* Centralblatt für die gesammte Therapie, November, 1887.

Dr. Schetelig* has published a novel and at the same time a most effective method for injecting creosote, if its proposer is found to state the truth or is to be credited. It is to dissolve creosote in pure oil of cloves of twenty to thirty per cent. strength, and administer four to twelve injections of 16 minims each. He finds that this causes no irritation and is very effective. The injections are practised every fifteen minutes to one hour, until the desired amount is received. The temperature of the phthisical patient was seen to be reduced several degrees by the creosote, and no disturbance of the stomach occurred in consequence of the administration of this remedy in any patient.

We find no other reference to the use of oil of cloves as a vehicle for the subcutaneous injection of creosote. Oil of cloves is an antiseptic and an analgesic locally applied, and because of these properties is the more useful as a vehicle.

Creosote may be tested as follows: Dissolve the supposed genuine creosote in 80 parts of water, and add to this solution 1 minim of liquor ferri perchloridi; a dark-brown precipitate forms; but with carbolic acid or impure creosote a blue sediment falls.†

The result of the treatment of phthisis by creosote is seen in diminution of cough and expectoration, disappearance of the bacilli, of night-sweats, of fever; improvement in the appetite and digestion, and gain in weight and in strength. As regards the effect of the remedy on mortality-rates, much depends on the stage of the disease, the character of the individual, and the time spent in carrying

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* The Therapeutic Gazette, 1889, p. 484.

† Bitclunsky suggests the following test: 1 c.c. of the creosote should be dissolved in 10 c.c. of a ninety-per-cent. alcohol solution, and 4 c.c. of this solution mixed with 10 c.c. of pure sulphuric acid. If guaiacol, the liquid is of a rosy hue; if common creosote, it is almost brown.

out the treatment. As is the case, necessarily, with all kinds of treatment, those patients do best that are seen earliest and in the very onset of the disease. The greater the damage done to the lung by induration, the product of catarrhal pneumonia, and by the formation of excavations, the more difficult the work of restoration. There are statistics available for the determination of the real value of the creosote treatment. Lublinski* has treated four hundred cases; but as he could keep under observation but two hundred and ten of these, he reported on these only. Of thirty-two cases treated at their own homes, there were eleven recoveries, and of one hundred and seventy-eight polyclinic cases, only twelve could be considered as cured.

Sommerbrodt† reports a series of five thousand cases treated by injections of creosote through a period of nine years, and, as a rule, in all cases not too far advanced this remedy gave surprising results. The effects noted were improvement in general condition, increase of appetite and of digestive power, diminution of cough and expectoration, arrest of the nocturnal sweats, and disappearance of all the physical signs of phthisis. In many cases ulcers of the larynx healed, and scrofulous tumors disappeared rapidly. He was able to say that many cases were apparently cured. The minimum duration of the treatment was one year. In the case of females the treatment was suspended during the menstrual period. The amount of creosote taken was considerable, from the minimum dose of 1 minim up to the maximum daily of 10 minims.

The experiences of Sommerbrodt induced Dr. Paul

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* Centralblatt für die gesammte Therapie, November, 1887.

† Berliner klinische Wochenschrift, 1887, No. 15.

Guttmann,* of Berlin, to essay the same practice, and his results, in the main, correspond with those of his predecessor.

As respects the uses of creosote hypodermatically, there are none others of importance requiring attention. It is true that in many of the uses assigned to carbolic acid, creosote may be substituted. This understood, much repetition may be avoided.

ANTIPYRIN.

PROPERTIES.—The name "antipyrin" is a trade designation, substituted for the impossible chemical name, *dimethyloxyquinicine*, and is made from a chief quality of this chemical product,—namely, the antipyretic quality.

Antipyrin is a white or grayish-white powder, soluble in all proportions in water. It has basic properties, and combines with acids to form salts. When given hypodermatically the dose may be five (5) grains to thirty (30) grains. The following solution is suitable for the purpose of subcutaneous medication.

℞ Antipyrin., ʒiv;
Aquæ destil., ʒi. M.
Sig.—Twenty (20) minims contain ten (10) grains.

As antipyrin is so freely soluble in water, the dose may be made to vary within wide limits; but in giving it by the stomach or hypodermatically it should be remembered

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* Berliner klinische Wochenschrift, 1888; also, Dr. C. M. Hopmann, ibid.; also, Dr. Von Brunn, ibid.; also, Dr. Kaatzer, ibid. Quoted by The London Medical Recorder, October, 1888.

how serious may be the consequences of an overdose, especially by the latter method.

Physiological Actions.—Locally, the effects of antipyrin are quickly displayed after the entrance of its solution into the subcutaneous tissue. In twenty minutes a portion of that given can be detected in the urine. It is largely excreted by the urine. There is, as a rule, but little pain caused by the injection; but now and then, owing to special susceptibility probably, excruciating pain is felt. This result can be obviated by adding a little cocaine to the solution,—say $\frac{1}{12}$ of a grain (Sée). Further, now and then, also, an inflammatory swelling is formed at the site of the injection which may proceed to suppuration.

There is much similarity in the action of the various members of the group. Nevertheless, antipyrin has its own form of action. This fact is shown by the rapidity with which symptoms are developed, and the clear-cut outline of each particular sign. In common with the general mode of action, antipyrin increases somewhat the action of the heart and of the respiration; the face flushes a little, and a general subjective sense of warmth is felt over the body; then perspiration more or less profuse comes on, and this ending, the pulse-rate and the temperature are lowered. In the normal state the body-heat is not affected, but when febrile heat occurs the decline of temperature is quite notable, reaching as much as 2° or even 4° Fahr. There can be but little, if any, doubt regarding the nature of the decline of temperature. The production of the water of perspiration and the conversion of this water into vapor can be accomplished solely by means of the liberation from the body of a large amount of heat, a loss that frequently occasions a marked diminution

of temperature. A similar phenomenon—the disappearance of heat during the boiling of water—was formerly accounted for by the theory of "latent heat," but is now explained by the supposition that the heat has been converted into another "mode of motion," to use the scientific expression now employed to explain the process.

When the sweating process is over, there is found to be a considerable lowering of the temperature,—from 1° to 3° Fahr., according to the dose. With this decline of body-heat the surface of the body is cool, and a sense of chilliness deepening into a rigor then comes on. There are great variations in the extent and depth of the cold stage, and in the algid condition as affecting the circulation and the respiration in the several members of this group employed in hypodermatic therapeutics. Some of them,—kairin, for example,—when given in full medicinal doses, cause such profuse sweating and such a decided rigor that the circulation becomes exceedingly embarrassed, the heart's action feeble and irregular, and all the signs of collapse appear. Antipyrin, fortunately, has little of the chill stage, or rigor, consequently it is far safer in actual practice than the other members of the same group. Serious and threatening symptoms are not to be expected from antipyrin when exhibited in proper doses.

Besides the effects above described, we have now to note with some detail the action of antipyrin on the nervous centres. In common with the other members of the same group, it acts on the central apparatus of the nervous system, especially on its sensory and motor tracts. It has a paralyzing action, and it modifies the state of the sensory centres, removing pain. It modifies the reflexes and lessens the receptivity of the cord. When large doses are exhibited a tetanic stage is observed in the lower animals

subjected to experiment, but no corresponding state has occurred in man.

Antipyrin acts somewhat on the walls of the vessels, increasing their tonicity and raising the arterial tension, thus causing a rise of arterial pressure at first, but afterwards relaxing the vessels. It diminishes the abnormal temperature of fever, but has no appreciable influence on the normal body-heat. The mode in which the reduction of febrile heat is accomplished is not agreed upon. Some hold to the theory of excitation of the thermogenic centre in the brain; others maintain that the diminution of nutritive activity suffices to account for the decline of fever-heat. The heat-centre is a hypothetical centre; it has no place at present in anatomical systems, and physiology merely speculates on its probable position, and does not define its powers or its inhibitions. On the other hand, antipyrin stirs up various parts of the system and sets up numerous changes in the tissues, altering the form and character of various secretions and parts, which must induce corresponding changes in temperature.

On the blood itself antipyrin has no decided action. It does not affect the hæmoglobin, nor does it cause the cyanosis or the oppression which attend the maximum action of some of the antipyretics, as kairin, acetanilid, and many others. It is the hæmoglobinuria which has such a baleful influence on the case, hastening the lethal action.

One of the first maladies for which antipyrin was prescribed is *acute rheumatism.* The testimony regarding its virtues in this disease is rather conflicting. According to Alexander,* who first prescribed it (1884), it is the best of

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* Breslauer aerztlich Zeitschrift, 1884, Nos. 11 and 14.

remedies for acute rheumatism. In two days the pain is relieved and the swelling of the joints lessened; but these effects are not permanent; relapses occur, and further use of the remedy becomes necessary. In treating rheumatism with antipyrin the remedy should be persisted in, and for a time after all rheumatic symptoms have disappeared, whether or not relapses occur.

As antipyrin exhibited so much power over the joint pain, Alexander concluded that it must be analgesic. On giving it for analgesic action, it was soon ascertained to possess the property of relieving pain *per se*, and could, therefore, be utilized in all neuralgic affections. It is especially in the neuralgic cases that the subcutaneous use of antipyrin has proved to be so highly effective.

Fränkel, Dujardin-Beaumetz, and other German and French physicians have contributed facts illustrating the same point. Before going into this subject, I would say something further regarding antipyrin in acute rheumatism. It is generally held that it is about as effective in acute rheumatism as salicylate of sodium, and the same rules obtain in respect to its continued use, to prevent relapses. There are no facts or statistics showing the comparative results as to heart complications, but the probability is that there are no real differences in this respect between the salicylates and antipyrin. There are, however, great differences in their power respectively in relieving joint pains, and thus lessening the patient's distress.

Most prominent among those who have signalized their clinical study of the actions and uses of antipyrin is Professor Germain Sée,* whom we find to have contributed the greatest number of facts to the existing knowledge

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* Comptes-Rendus de l'Académie des Sciences, Avril, 1887.

of its analgesic actions. The utility of antipyrin in acute rheumatism being demonstrated, the next step consisted in applying it to the treatment of *migraine*. The first reports of its utility spread through all civilized countries, and so far was it vulgarized that the sufferers from migraine, especially, went about with powders of antipyrin in their pockets to take when desired. By the subcutaneous method it was found that antipyrin was most effective as a remedy in cases of neuralgia. The forms of *neuralgia* in which it has proved most decidedly curative are the *tic douloureux* of the fifth nerve, *migraine*, and *sciatica*. The amount given in these affections will range from 5 to 15 or 20 grains, repeated several times in the twenty-four hours, if the severity of the case requires so much.

While antipyrin is effective against the neuralgias of common origin, the same result can hardly be expected when a tumor or an exostosis has, by pressure on a nerve-trunk, caused the pain. In this instance only temporary relief can be effected, and it may be that the transitory relief cannot be procured.

In the *neuralgia* of the cranium, of the *fifth nerve*, and of the *sciatic*, the best curative results are obtained by injecting deeply in the neighborhood of the affected nerve, but not so deeply as to bring the needle in contact with the nerve. The solution of antipyrin for this purpose may be equal parts, or one-half, or one-fourth. The repetition of the dose will depend on the nature of the inducing cause, on the curative effect of the first injection, and especially on the state of the nerve. It is well known that these conditions have a decided effect in favoring or retarding or preventing neuralgic seizures. Among those who have expressed themselves most decidedly on the analgesic effects

of antipyrin are Alexander (*op. cit.*), Demme,* Langgaard,† Fränkel,‡ Neumann,§ Dujardin-Beaumetz,‖ Mendel,¶ and others.

Professor Sée has shown that antipyrin causes a very notable diminution of the sensibility to pain in the limb into which the solution has been thrown, and above that of the other limb. The electric excitation of the sciatic in an animal under the influence of antipyrin does not produce any of those reflex contractions that indicate feebleness of the perceptive sense and of the reflex response of the spinal cord. Chouppe has shown experimentally that when sufficient strychnine to cause death is given to a dog under the influence of antipyrin, the characteristic strychnic convulsions do not appear. Antipyrin, it must be noted, is a tetanizer when large doses are given.

It is asserted by Sée that all kinds of pain are relieved with certainty by antipyrin, and among the most severe he mentions biliary colic (passage of gall-stones) and renal colic (passage of renal calculi), than from which man can suffer no greater pain, and they are forms of pain readily cured by this remedy. It may well be doubted if many of these are permanently cured; they are rather relieved for the time being, and reappear subsequently. Among the pains assuaged, often cured, by antipyrin are earache and toothache. From 2 to 10 grains thrown under the skin at the angle of the jaw will quickly afford relief, especially if the solution is deposited in the neigh-

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* Fortschritte der Med., 1884, Nos. 20 and 21.

† Therap. Monatshefte, 1887, p. 20.

‡ Ibid., p. 451.

§ Berliner klinische Wochenschrift, 1885, No. 37.

‖ Bul. Général de Thérapeutique, tome cxiii. p. 107.

¶ Therap. Monatshefte, 1887, p. 259.

borhood of the affected part. In otalgia, besides the external subcutaneous application, the ear may be filled with a warm solution of antipyrin.

Friedländer* relates his experience of the action of antipyrin in the painful affections of children, and he states that it is uniformly effective and is well borne by the little ones. Fränkel,† of Breslau, strongly urges a combination of antipyrin and morphine for subcutaneous injection in painful affections, notably *hemicrania*, *neuralgia* of spinal nerves, including the *sciatic*, and other diseases of the same character.

The hypodermatic injection of antipyrin has been used successfully in assuaging the pains of labor, while it does not retard the uterine contractions. There is an abundance of testimony in proof of this. Queirel,‡ of Marseilles, France, makes use of antipyrin, with or without morphine, for the relief of labor pain. Imbert de la Touche§ practised the same method, but combined cocaine with the antipyrin, thus securing the analgesic effects of both. The combination of antipyrin with cocaine has shown exceptional utility in the relief of painful states of various kinds. The anodyne and analgesic effects of this combination during labor are unquestionably effective in relieving "the pains," but it sometimes fails by reason of idiosyncrasy, probably. The administration of antipyrin during labor must be regulated by the effect it has on the real pain. The amount given is often larger than necessary. From five (5) to fifteen (15) grains—from 60 centigrammes to 1 gramme, according to the new notation

* Therap. Monatshefte, 1887, Band i. p. 302.

† Deutsche Med. Wochenschrift, 1887, Band i. p. 451.

‡ Dictionnaire de Thérapeutique, Appendice, tome iv. p. 810.

§ Bul. Général de Thérapeutique, tome cxv. p. 81.

—is sufficient in most cases to keep the pains within due bounds.

Other *pains* than those mentioned above are greatly relieved by the injection of antipyrin; for example, the *pains of tabes dorsalis* or locomotor ataxia. An analgesic must not be given too hastily, for much of the pain is the expression of a merely nervous state in a neurotic subject, prone to exaggerate his sufferings. Until it becomes manifest that the pains are genuine, it were better to withhold antipyrin and give such a placebo as water, which has some effect on local nerve-pain, and is not therefore such a placebo as implies fraud. When the nerve-pain of tabes dorsalis comes on, it occurs usually in the fifth nerve, in the cervico-brachial plexus, and in the sciatic nerve; in the last mentioned more frequently than in any of the others.

Injections of antipyrin are remarkably effective in the treatment of *lumbago.* A letter from Paris,* containing an account of a case of lumbago of great severity in the Hôtel Dieu, states that the condition of the patient was so bad that he could not rise up in bed, and could not sit down when out of bed. One injection of antipyrin brought about complete relief. Having very plain objective evidence of the existence of subacute rheumatism, the antipyrin was continued in the same dose morning and evening—*i.e.*, 7¾ grains—for some days longer; but the single dose sufficed for the lumbago, and no return or relapse occurred at any subsequent time. Such a case illustrates alike the curative effects of antipyrin and the value of the hypodermatic method (Lucking, Lepine, Sée).

In using the hypodermatic method it is better to insert

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* The British Medical Journal, September 1, 1887.

the needle so that its point is in the neighborhood of the nerve, but not actually touching it. That the injection is the better the nearer the material comes to the seat of pain, there is little doubt, although the fact is not universally admitted.

As regards the use of antipyrin in the painful diseases, it is clear that the remedy is far more effective when used subcutaneously than when given by the stomach. Professor Sée was the first advocate of its hypodermatic use, and speedily learned that its analgesic action is equal to that of morphine, and that it does not involve the formation of a habit and is more pleasant in action. In an investigation on this point he ascertained that in all painful affections of every kind, in which morphine had been used hitherto, antipyrin was equally effective in relieving the pain and equally curative in the various conditions present. Fränkel, Wolff,* and Hirsch have reported their experience with it, and they confirm on all points the statements of Sée. They also find that by subcutaneous injection antipyrin gives far more relief than when administered by the stomach. In summing up the forms of disease in which he has found it specially effective, Wolff gives the following: in muscular rheumatism, the chest-pains of the phthisical, neuralgia of the important nerves, etc. Sée finds that the maladies for the relief of which antipyrin has been used successfully are as follows: the neuralgic pains of nerve-trunks; chest-pains due to aneurism or valvular disease, etc.; pseudo-angina pectoris; all forms of colic,—hepatic, renal, uterine, and menstrual. Lumbago is especially amenable to the anodyne effects of antipyrin given subcutaneously. As this is often a very obstinate

* Therap. Monatshefte, June, 1888, Band ii. p. 279.

affection, and is so effectively treated by the antipyrin injections, they should be given in all suitable cases. There can be no doubt, also, that antipyrin is an effective remedy in dysmenorrhœa, when the pain is severe enough to require action (Dr. Windelschmidt).* The time for administering antipyrin is at the access of pain, whether before or after the appearance of the menstrual flow.

Finally, as respects the use of antipyrin subcutaneously in the treatment of painful affections, it may be said that it can be employed in all cases where pain is the essential condition. The dose for adults ranges between 5 and 20 grains, and the repetition of the dose depends on the effect of the first injection and on the degree and character of the pain. It is true, larger doses may be given; but when the method of use is by the hypodermatic injection, the quantity fixed on here will usually suffice.

As considerable pain usually attends on the injection of antipyrin, and as its curative power also is enhanced thereby, it has been proposed to add cocaine to each solution as follows (Martin).†

℞ Cocainæ hydrochlorat., gr. ii;
Antipyrini, ʒiii;
Aquæ, ʒi. M.

Sig.—The dose for hypodermatic use ranges from 10 ♏ to 20 ♏.

Sée‡ has also recommended the addition of some cocaine to the solution at the time of the injection. The quantity of cocaine should be sufficient only to stop the local pain. On the other hand, the proportion of cocaine in a solution

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* Allgem. Med. Central. Zeitung, Berlin, July 4, 1888.

† Therap. Monatshefte, 1888, Band ii. p. 185.

‡ Bul. Général de Thérapeutique.

of antipyrin must be greater or less as it is intended that the cocaine or the antipyrin shall dominate or merely support the analgesic effect. When the purpose is to allay pain, that being the substantive affection, the curative effect is decidedly the more decisive when the two agents are administered conjointly. Again, should the condition be one of tetanic spasm rather than clonic, the addition of cocaine is not proper, for in such cases its action would prove synergistic rather than antagonistic to the disease.

Spasmodic diseases of various kinds have been treated by antipyrin with varying success, it is true, but on the whole with distinct advantage. The first spasmodic affection in the treatment of which antipyrin was employed was *whooping-cough*. It proved useful, though not absolutely curative, for its powers are chiefly shown in lessening the violence and shortening the duration of the disease. Friedländer was among the first to prescribe it, in the Children's Hospital, for children under six years. He found that small doses did better than large ones, and that the children took the medicine readily when mixed with some raspberry syrup and water. Since that first period, antipyrin has been prescribed very largely for whooping-cough, and on the whole its use in this disease is amply justified. Friedländer found it exceptionally beneficial in the *bronchitis* of young children, first perceiving its utility in the cases of whooping-cough in which the bronchial inflammation was a pronounced feature. Although it was prescribed by the stomachal administration, it is nevertheless necessary to know that by the subcutaneous mode its power is the greater.

Chorea is one of the maladies in which antipyrin has seemed to be exceptionally beneficial. As the effect of this agent on *acute rheumatism* places it among the first of

remedies for this disease, the therapeutical kinship with chorea increases our belief in the essential character of each as related pathologically.

Epilepsy is another spasmodic disease in which antipyrin was at first greatly praised. It is not as effective as acetanilid, and, as considerable experience has now shown, neither one can take the place of the bromides.

As a remedy for chorea, however, we may admit that it has considerable merit. It is highly praised by Legroux, Hirsch, Fränkel, and Sée as a curative agent in this disease, the number cured being already considerable; but it is only rarely given by hypodermatic injection. Anticipations of its powerful curative action in *epilepsy* were at one time just as fondly entertained, but larger experiences, as we have seen, have disproved them.

The antipyretic effects of antipyrin is one of the fixed facts of the life-history of this substance, and as an agent for removing surplus heat it is one of the most certain and effective of remedies. It procures a more decided reduction of temperature, consistent with safety, than any of the newer remedies of the same group. When the dose is sufficient, the amount of heat disposed of ranges from 1° to 4° Fahr. Remedies of this kind, antipyrin excepted, have a uniform effect in causing more or less cyanosis when the sweat stage comes on; the cyanosis may appear with dangerous symptoms, which in some instances pass off quickly and do not bode ill, but more frequently the appearance of cyanosis signifies a separation of the hæmoglobin and disorganization of the blood. With the development of these toxic symptoms there ensues increasing weakness and irregularity of the heart's action, irregular and rapid respiration, often of the Cheyne-Stokes type. The vessels are dilated because of the paresis of their

muscular layer, and the sweat-glands being engorged and stimulated, pour out a profuse secretion which, beginning as a little moisture on the face, soon assumes the proportions of a tremendous sweat from the whole surface of the skin, and a chill inevitably follows. The action of antipyrin on fever has been confirmed by an immense experience; but, as has been stated, it affects only the elevated temperature of fever, and not the normal body-heat.

No remedy, in fact, has had a more abundant clinical experience to support a principle. From the time of its earliest introduction into medical practice it has been the object of extreme interest, and its antipyretic power is being constantly reaffirmed by the experience of all making use of it.

In connection with this subject it may be said in general that the antipyretics, now so much the fashion, do not modify the course, lessen the duration, or change the character of typhoid or any essential fever, or any form of inflammatory fever, or the fever of infection of any kind.

Although to reduce temperature in any form of fever by an antipyretic is of little avail, there is much to be said in favor of these remedies in respect to *hyperpyrexia*, a state of excessively high temperature brought on in the course of inflammations or fevers by causes, at present, little understood. In hyperpyrexia, as it occurs now and then in the course of *acute rheumatism*, the temperature reaches 106°, 107°, 108°, and 109° Fahr. rather suddenly, and is accompanied by new and alarming symptoms. The subcutaneous injection of antipyrin is a measure of great utility, and will accomplish relief in a short time, if relief be possible. Usually 7 to 16 grains suffice to bring down the temperature, but the dose can be repeated every two to

four hours. A dose ranging from 1 to 2 grammes two or three times a day is the dosage in rheumatism and fevers, as a rule.

Dr. Friedländer, in the treatment of *scarlatina*, found that the accompanying bronchitis was much benefited by antipyrin. He came to regard antipyrin, finally, as almost a specific in bronchitis of the eruptive diseases in young children; but it does not modify in any way the morbid complexus of any form of fever or inflammation, no matter in what degree it brings about loss of heat.

In certain neuroses of the heart we have, in antipyrin by subcutaneous injection and pyridin in vapor, remedies that relieve with promptness those unpleasant symptoms that indicate sudden failure of the heart. Pseudo-angina pectoris is one of these, but, of course, the true angina pectoris is far more dangerous; however, if administered in time, the relief is great, and the subcutaneous injection of antipyrin will not conflict with other remedies that may be necessary.

Notwithstanding the apparently harmless character of antipyrin, some cases nearly fatal and several deaths have occurred. Blore* was one of the first to publish an account of death from antipyrin. Forty-five grains in all were given, and there was nothing besides to consider important. Respiratory and cardiac failure were the immediate causes of death. Dr. Henderson,† of North Carolina, had one fatal case and one other on the road thither. In both he had given, with moderate doses of antipyrin, the extract of nux vomica. The first patient was dead in two hours. There is a distinct kinship in the physiological

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* Wien. Med. Wochenschrift, 1886, No. 15, p. 542.

† The New York Medical Record, January 22, 1887, p. 95.

actions of the two remedies, for both cause tetanic spasms and death by tetanic fixation of the muscles of respiration (Chouppe). By a vigorous application of stimulants the other patient was brought round.

RESORCINUM: RESORCIN.

History.—The name by which this agent is known is a compound word, made up by the discoverers from *resin* and *orcin*, because in some ways it resembles these substances.

Resorcin occurs in rather shining crystals, and presents a phosphorescent gleam when rubbed in the dark. It is whitish in color, but when exposed to the light and air the tint becomes yellowish and brownish, changes which signify ultimately a decomposition; but its properties are not altered so long as a brownish hue is not developing.

Properties.—Resorcin injected under the skin does not cause local irritation, and after the slight smarting passes off, it is not usual to have swelling and urticaria about the site. The powers of resorcin correspond to those of carbolic acid, although the latter is the more active. When a little resorcin is put on the mucous membrane of the lips, it will, if moistened, cause a whitish eschar, very superficial and but slightly painful.

It does not cause any stomach irritation, *per se*, when introduced into the stomach, no more than it does when thrown under the skin. When a lethal dose is taken, the first symptoms are dizziness, some dilatation and afterwards contraction of the pupil, trembling, clonic convulsions, etc. Up to this point there may be no change in the mind,—no impairment of intelligence,—but a hebetude

presently deepening into coma, and finally profound unconsciousness and complete muscular resolution occur. The clonic convulsions become more frequent and severe in proportion to the dose taken, and as the symptoms begin promptly, so they terminate quickly in death, about two hours being occupied with all the lethal phenomena.

As regards the effects on the nervous system, we find that the nerve-centres and afterwards the peripheral nerves are acted on; for when the sciatic is separated from the rest of the nervous system, and the blood-supply is cut off, the muscles of the leg are not affected by convulsions or in any other way.

Resorcin is an antiseptic of considerable power; but the high estimate placed on it by Andeer and others, when first introduced, has not been justified by later experiences. In some respects, however, it continues to hold a place because of its special utility, and to these instances reference will be made hereafter.

Soon after Andeer's* paper appeared, Brieger† made resorcin the subject of renewed investigation, experimental and clinical, with the result greatly to depreciate its medicinable powers. Brieger found that in small doses—less than 1 gramme (15½ grains)—it is not efficacious as an antipyretic, and to obtain an effect equivalent to a fall in temperature of 2° Fahr. a much larger dose must be given,—*i.e.*, from 15 to 60 grains,—and then there is danger of symptoms similar to those of poisoning by carbolic acid. Chemical effects are caused by resorcin in its passage through the system. It seems to be well established that

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* Centralblatt für die Med. Wissenschaft, 1880. Quoted by Dictionnaire de Thérapeutique, etc., 1882, tome iv. p. 427.

† Deutsche Med. Zeit., February 2, 1882. Quoted by The London Medical Record.

resorcin is excreted as ether and sulphuric acid, and consequently that the elements of ether, and also the acid, are excreted, thus depurating the system of important constituents and combinations (Brieger). Next followed the research of Dujardin-Beaumetz and Callias,* demonstrating the same facts. All recognized in resorcin antiseptic properties and a distinct germicide power comparable to that of carbolic acid, but were forced to admit its inferiority in respect to antipyretic properties. Indeed, with the possible exception of Lichtheim, authorities are agreed as to its danger in fevers; but as a disinfectant of typhoid stools it answers a most useful purpose, being relatively cheap and at the same time efficient. It is not as an antipyretic that resorcin is made use of, but rather as an antiseptic, an agent to prevent the extension of septic processes when employed in subcutaneous medication.

The following solution is a suitable one for subcutaneous use:

℞ Resorcini, ʒ ii;
Aquæ destillatæ, ʒ i. M.

Sig.—Twenty (20) minims contain five (5) grains of resorcin.

Bogouche† advises the following:

℞ Resorcini, 5 parts;
Aquæ destillatæ, 100 parts.

This is equivalent to resorcin 1½ drachms, distilled water 4 ounces. Either of these solutions is suitable for hypodermatic injections.

The most important applications of resorcin are those in which the agent is used by subcutaneous injection. When *erysipelas* is spreading, the solution of resorcin should be

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* Bul. Général de Thérapeutique, 1881, tome ci. pp. 3 and 49.

† Dictionnaire de Thérapeutique, tome iv. p. 434.

injected an inch in front of the margin of the point of inflammation, or in front of the advancing inflammation about a finger's breadth from the line of redness. It should be injected every three or four inches apart, and the needle, on being introduced, should point towards the inflamed area. The inflammation quickly subsides and the morbid process is extinguished in two or three days (Bogouche). In *malignant ulcer* the same procedure may be relied on as highly efficient. It has been used in place of iodine or carbolic acid, in the treatment of this disease, by injecting the solution about an inch from the ulcer and about two inches between each insertion.

At one time, soon after its introduction into medical practice, resorcin was highly esteemed as a remedy in *intermittent fever*, and it was supposed that a substitute for quinine had been discovered. Brieger first pointed out the errors of observation commended by Andeer and Lichtheim, and since then the general conclusion has been reached that it is inferior to quinine in all respects. It may, however, be used with advantage in cases of chronic malarial poisoning, when the objective symptoms are those indicative of enlarged liver and spleen.

In *diphtheria* the local application of resorcin has proved effective and is growing in favor; but the local action is the more effective when supplemented by injections of the same remedy in the neck and about the angle of the jaw.

The original conception of the action of resorcin was that no depression accompanied by heart-failure occurs, and that it was therefore safe in any reasonable quantity. This opinion must be modified. Resorcin is safe when given in small doses not exceeding 20 grains, but when the dose reaches 60 grains the danger becomes pressing, and to pass beyond this point is to incur most serious risk.

ACETANILID: ANTIFEBRIN.

The medicament known under these names is a derivative of the anilin series and a product of the amides. *Antifebrin* is a trade name designed to express the most distinctive property of the agent, but *acetanilid* is a truer and more appropriate designation, and this should be preferred in prescription-writing.

Acetanilid is a white crystalline powder, freely soluble in hot water, but sparingly soluble in cold water. As at a temperature of 105° Fahr. it will dissolve one part in fifty of water, the amount required for the hypodermatic injection can be given in a comparatively small quantity of fluid, if it be raised to that temperature.

It is prescribed but rarely—very rarely indeed—by the method of subcutaneous injection. The dose, comparatively speaking, for this mode of administration is from two (2) to four (4) grains. As it dissolves in chloroform freely (1 to 6), the menstruum chloroform water will probably take it up more readily than the other menstrua.

It is not irritating to the tissues and is diffusible, so that the effects occur promptly. In general it may be said that acetanilid follows the mode of action of the series to which it belongs: it lowers the temperature and at first stimulates the circulatory and respiratory apparatus, but the maximum being soon reached, the cardiac and respiratory organs decline in action correspondingly. At the same time the perspiration becomes abundant and the skin cool, and if the dose administered has been a large one the sweat is profuse and, instead of a light chill, a decided rigor may come on, and with it great, even alarming, depression of the vital powers. When a considerable dose is adminis-

tered cyanosis may appear, and this is a danger symptom when the amount of the medicament is larger than usual. Acetanilid is safer than its immediate congeners, chinolin, kairin, and thallin. Comparing it with antipyrin, we find that the latter must be given in considerably larger quantity, but acetanilid has less antipyretic property, and antipyrin is safer. Compared with thallin, acetanilid is not so powerful an antipyretic, but is more efficient in the treatment of some fevers, and has more analgesic power. It is of little importance to determine whether any one of these remedies is more toxic than another, for it must be confessed that none of them are free from a tendency to produce poisonous effects in the chill stage.

Comparing once more acetanilid with antipyrin, we find that although acetanilid is in other respects inferior to antipyrin, it possesses some special advantages as an antiseptic. Besides, it will be infrequently used as an antipyretic by subcutaneous injection. As an analgesic it compares favorably with the other members of the same group.

PYRODIN: HYDRACETIN.

Acetylphenylhydrazin.

Another antiseptic called *pyrodin* has recently been introduced to medical practice. The chemical name is *acetylphenylhydrazin*, which is too cumbrous for ordinary use. In the preparation of it the radical *acetyl* is substituted for an atom of hydrogen in *phenylhydrazin*. The name *pyrodin* is an improper designation according to M. Ed.

Egasse,* who has made a careful physiological and pharmacological investigation of its actions and uses. It has modes of action corresponding to the others in the same group. It lessens the number and force of the cardiac pulsations and of the respiratory movements. Its maximum effect is accompanied by profuse sweats, and the subsequent rise of temperature, after the abatement is brought about, is associated with a rigor of greater or less severity at the onset. It acts on the vaso-motor system, relaxes the walls of the vessels, and slows the heart. It abolishes the reflexes; but the motor nerves and muscles respond to stimulation and the muscles contract energetically on direct irritation, showing that the effect of the medicament is central and not peripheral.

Pyrodin is an antiseptic of considerable power, an analgesic, and an antipyretic. It is soluble very slightly in water, the proportion being 1 to 1000 of water. Dreschfeld† finds it to be an antipyretic of the greatest power, one which acts promptly and deeply, and maintains its hold on the body-heat quite persistently.

Pyrodin is actively toxic and must not be given more frequently than once a day, and the dose should not exceed 8 grains for an adult. It is a deoxidizing agent, and hence is very destructive in its action on the blood, attacking the red-blood globules, and it should not be administered, even in proper doses, for a longer period than one to four weeks.

Although pyrodin has received the above mention, it can hardly be considered a suitable medicament for hypodermatic injection, and is admitted here more as a warning of its dangerous character.

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* Bul. Général de Thérapeutique, tome cxvi. p. 498.

† Ibid., loc. cit.

EUPHORIN.

This medicament, a recent contribution to medical practice, is a *phenyl-urethan* and a derivative of the anilin group. It is slightly—very slightly—soluble in cold water, but is more soluble in alcohol and in a mixture of alcohol and water, so that a hypodermatic solution can be thus made: ¾ water, ¼ alcohol. Although an antiseptic, antipyretic, and analgesic, euphorin does not harm the blood, nor is it actively toxic. It is therefore a desirable agent for subcutaneous use, if its solubility can be increased. It has been ascertained that the combination of euphorin with an alkali increases its solubility to a sufficient extent for the purposes of hypodermatic medication.

The taste of euphorin develops rather slowly in the mouth, becoming ultimately similar to cloves. Whether thrown under the skin, into the peritoneal cavity, or into the veins, it does not affect the pulse, respiration, or temperature, if the amount given is a small one. Animals killed by a toxic dose pass into collapse, the temperature falls, and muscular resolution, anæsthesia, insensibility, and abolition of the reflexes complete the morbid complexus. When the excretion is ended, *para-amido-phenol* is found in the urine.*

Euphorin is not a deoxidizer; it does not reduce the anatomical elements, and the blood remains normal.†

In physiological actions and in therapy euphorin does not differ qualitatively from the other members of the amides, and the fatty and aromatic series of synthetical bodies. It is an antipyretic, but in the quantitative effect it falls

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* Merck's Bulletin.

† Sansoni, Therap. Monatshefte, September, 1890.

behind many others. The lowest stages of the decline of temperature is reached in three hours, sometimes not until six hours. The maximum action having been reached, the lessening of the body-heat may extend to two degrees below the normal, and when the decline of temperature has been considerable, profuse sweating and a severe rigor usually occur; but under the ordinary circumstances, with doses of suitable size the action of euphorin is free from any objectionable features, and entirely so in respect to the changes induced by the other members of this group in the blood.

Euphorin is employed for the diminution of fever-heat, or antipyretic action, for lowering the rate of movement of the heart and arteries, for analgesic effect in cases of notably severe pain in rheumatismal affections, and for the relief of convulsive disorders. The action is prompt, beginning in a half-hour or hour, reaching its maximum in three hours, and the effects are not entirely expended in eight or even twelve hours. Although from the effects of small doses some perspiration and chilliness appear, no symptoms of collapse come on, and but little cyanosis; but in large doses it is probable that the same results will occur as from most of its congeners in the same group of remedies. To produce an antipyretic effect, Merck* advises that relatively large doses be prescribed rather than numerous small ones.

Euphorin has proved to be an efficient antiseptic, removing the odor and changing the character of any open ulcer or wound.

Larger experience is necessary to develop the real powers of euphorin and to prove its therapeutical effects.

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* Merck's Bulletin, January, 1891, p. 8.

OREXIN.

Still another new remedy of the chinolin series appeared recently under the proprietary designation *orexin*. It is not readily soluble in water, and its use, therefore, is very limited in hypodermatic treatment.

It is supposed to be remarkably effective in promoting appetite and the primary assimilation. As more or less irritant, it will probably prove more useful by injection subcutaneously than by the stomach. Further investigations are needed to develop its uses and to assign it to its true place as a medicament.

SACCHARINUM: SACCHARIN.

Orthosulphaminbenzoic Acid.

It is a seeming paradox to say in ordinary language that an acid is a sweet; but saccharin is really an acid, and at the same time is the sweetest substance in nature. The name *saccharin* is a proprietary designation, and is apt in expressing the main sensible property of the medicament, and a convenient designation for commercial uses. The name and the drug are patented, and cannot, therefore, be made for the market by any other firm. The chemical name is simply an impossibility for ordinary uses.

Properties.—Saccharin is an amorphous powder, white or pale buff in color, and its sweet taste has a slight flavor of bitter almonds. It is two hundred times sweeter than cane sugar, and it is this physical quality which induced

its use in medical practice. It is soluble in cold water to a slight extent, in hot water more freely, in ether and alcohol still more freely. It can be used hypodermatically dissolved in water at the temperature of 100° Fahr.

In the course of its medicinal uses it can be readily enough dissolved in such foods as a child may be taking, and thus act the part of a food and a medicine. I have found it exceedingly useful as a remedy in the bowel troubles of children when pain was present, the fermentation and the formation of gases being the chief or only cause of the distress.

It has the usual qualities of the other members of this group to which it belongs,—*i.e.*, the antiseptic,—and, as an acid, combines with bases to form salts. For example, saccharin and bicarbonate of sodium form saccharate of sodium, and carbonic acid is given off. As saccharate of sodium is freely soluble, that preparation may be utilized for making hypodermatic solutions. The degree of solubility of saccharin in various liquids is given in the table below.

In boiling water, 0.60 parts per 100 by volume.
In cold water, 0.20 parts per 100 by volume.
In alcohol, 4.25 parts per 100 by volume.
In ether, 1.00 part per 100 by volume.
In chloroform, 0.20 parts per 100 by volume.*

Saccharin is sparingly soluble in glycerin.

As an antiseptic it ranks with salicylic acid. As it is harmless to the tissues, it may be used hypodermatically in the infective diseases. The following formula is a suitable one for subcutaneous injection:

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* The Therapeutic Gazette, 1887, p. 823.

℞ Sodii bicarb., ʒi;
Saccharin., ℈ii;
Aquæ destillatæ, ʒiv. M.
Sig.—Twenty (20) minims or a syringeful, as required.

The subcutaneous injection of saccharin may become an important remedial means in the infectious and septic maladies and in fevers of specific type. But this method is not as yet developed, and we may never see any further additions to our resources in that direction. I give the few points that have occupied professional attention to any important extent.

THALLINUM: THALLIN.

Thallin must not be confounded with "thallium," one of the elements and a metal. Thallin is an artificial name,—a trade and an officinal name. The chemical designation is tetrahydroparamethyloxyquinoline,—obviously much too long and too difficult of pronunciation for ordinary usage. The name thallin was adopted because it expressed one of its most notable reactions occurring when a few drops of ferric chloride are added to a solution of one of its salts.

Thallin is a basic substance which combines with acids to form salts, as the following:

Thallini sulphas (sulphate of thallin).
Thallini hydrochloras (hydrochlorate of thallin).
Thallini tartras (tartrate of thallin).

The substance thallin, in its natural state, is a liquid, oily material, but the salts occur in large fine crystals, which dissolve in water in sufficient amount to make the solution available for subcutaneous use. The solubility of the sulphate of thallin is as one to seven. The following formula is suitable for hypodermatic use:

℞ Thallini sulphat., ℈i;
Aquæ chloroformi *vel*
Aquæ destillatæ, ℥ii. M.
Sig.—Each minim contains one-sixth ($\frac{1}{6}$) of a grain.

The dose for stomach administration for children is from 1 minim of this solution to 5 minims, and for adults about twice these quantities.

Actions and Uses.—Thallin is one of the derivatives of the coal-tar series, and is similar in source and action to antipyrin, antifebrin, and others. As respects therapeutic action, they agree in the lowering the temperature of the body when in a febrile state, in reducing the rate of movement of the heart and lungs, and in causing at the termination of their action much sweating and a rather severe rigor.

Thallin has in its physical qualities many peculiarities. It is a whitish powder, crystalline in appearance, but has not a crystalline structure. It has an odor of aniseed. It is soluble in five times its weight of cold water, and very freely soluble in boiling water. Exposed to the light it rapidly becomes brown, and in presence of an oxidizing agent turns to green. The most significant action on the body is the reduction of temperature. The decline begins within an hour, and falls to the maximum degree in the succeeding two to three hours, the reduction finally reaching the normal several hours afterwards. At this period in the cycle of changes a mild or severe chill occurs, the surface being wet and cool. The amount of perspiration varies with the quantity of thallin taken. The final cessation of the sweating is coincident with the lowest temperature, or nearly so.

The heart's action and the respiration decline with the temperature, and the blood-pressure falls in the same ratio.

As respects the nutrition of the body, thallin lessens the excretion of urea and of carbonic acid, and hence it may be concluded that the oxidation process is impaired. In fact, thallin is a deoxidizer, and consumes the oxygen in a free state in the blood, as well as that which is being constantly admitted; thus destroying, or at least diminishing, the oxygen-carrying capacity of the red-blood globules. The antipyretic properties of this medicament can be explained by reference to this deoxidizing action, the cessation or diminution of the great function of oxidation necessarily limiting, in regular proportion, the production of heat.

Thallin causes curious changes in the color of the blood, which becomes brownish, approaching black, and more or less of a bluish discoloration appears on the skin when the action is at its maximum. The latter are not permanent alterations, but disappear when the action of the medicament has been expended.

Long-continued use of thallin is not without danger. Asphyxia may be eaused by it when a sufficient amount of the drug has been given by the way of the stomach or injected under the skin. It dissolves and destroys the hæmoglobin. After the lowering of pulse and respiration the final termination is by arrest of the heart in diastole.

THERAPY.—The chief function of thallin is to lower febrile temperature, and this is accomplished without any nausea, chills or sweats, or other unpleasant phenomena. Opinions are divided as to its power over pyrexia. The testimony of Jaksch,* Karst,† Steffen,‡ and others, and more recent observers, is decidedly in favor of the view

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* Zeitschrift für klinische Medicin, 1884, Band viii.; also Therap. Monatshefte, 1888, p. 188.

† Wratsch, 1886, No. 2. Quoted by The Therapeutic Gazette.

‡ Jahrbuch für Kinderheilkunde, Bde. xxv., xxvi.

that it possesses a distinct antipyretic quality. In a comparison of the mode of treatment of typhoid fever by hydrotherapy and by thallin, the result was distinctly in favor of thallin. As the mortality-rate under thallin was less than under the cold water, and as there were no untoward after-consequences, the adverse testimony, which is merely negative, must be regarded as of doubtful authority, supported as it may be by names even of the highest authority.

Steffen is especially enthusiastic as to the value of thallin in the *febrile affections* of childhood. He administers this medicament in doses of ½ of a grain up to 2 grains, and these are given twice in twenty-four hours. It is to be presumed that the hypodermatic method is employed only in case the stomach is unable to dispose of the remedy, especially when children are the subjects.

Although only an exceptional subject for subcutaneous injection, it may be well to observe that thallin has decided antiseptic power, and is especially active against that minute organism, the gonococcus, which it destroys. Cases of gonorrhœa are treated successfully by this remedy, the average duration under thallin being about one-half of that usually required under other modes of treatment.

If a large quantity of thallin is necessary to effect the reduction of temperature, it is better to administer smaller doses more frequently. It has been found by Erlich * that in this way the more disagreeable or dangerous effects are eliminated,—the sweats, the rigor, the weakness of the circulation, and the hyperpyrexia which may otherwise come on with the advent of the reaction fever after the decline. The duration of the antipyretic effect of thallin

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* Therap. Monatshefte, 1887, p. 53.

is from one to four hours, but this varies with the amount given. It should be understood, however, that the period of apyrexia is rarely so long as four hours, and this only when maximum doses are administered. In no case should doses above 5 grains be given, especially when the condition of the heart and arterial system is abnormal, or when the respiratory organs are in a state of advanced phthisis. Should symptoms of cardiac failure become manifest, the subcutaneous injection of atropine or of ether, or both, should not be delayed. Notwithstanding the apprehension that existed regarding the depressing effect of thallin, more recent experiences have taught a different lesson, and clinical reasons have been adduced to prove its comparative, if not absolute, safety. Much larger doses have been given within the past two years than were considered at all safe when this remedy was first brought into use.

The remarks just made on the apyretic effects of thallin are based on its use in typhoid. What has been said in regard to this is equally applicable to other forms of the essential or the eruptive fevers. Thallin is a constant, but not an absolutely invariable, apyretic, according to some of the best authorities. Jaksch,* who first studied it, says thallin is an excellent antipyretic, although he found there was now and then some sweating at the end of the action; but there were no accidents, no *malaise* or other untoward results. As regards the amount of antipyretic effect, it is agreed that thallin reduces fever-heat from one to three degrees; but Huchard† maintains that with the rise of fever succeeding to the fall there is free sweating and rigors come on, together with a sense of feebleness

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* *Supra.*

† Annuaire de Thérapeutique, 1886, p. 186.

and exhaustion. In many other forms of fever besides typhoid it was found that the remedy exerted no other effect than reducing the range of fever, and did not in any way modify the morbid process.

It was at one time held that chinolin and the group of allied remedies possessed the antiperiodic power in some sense comparable to quinine, but this was soon disproved. Thallin abates the temperature of intermittent fever, but it does not change its character.

To sum up my views on thallin, I have to say that it can be used hypodermatically in the treatment of disease.

That it is an efficient antipyretic, probably the most efficient for lowering the body-heat.

That in depressing the temperature it does not change the morbid state.

That in large doses it is apt to cause a more or less severe chill and a profuse sweat.

That in smaller doses and less decided action there are no unpleasant effects,—no chill, no sweat, no depression of the circulation, no after-effects of any extent.

CREOLIN.

Continuing our comments on the recent contributions to the antiseptic class, we shall consider briefly the most promising.

Creolin was first introduced by Von Esmarch, whose authority brought it into immediate notice. Liebreich * gave it an examination, the result of which proves that it

* Therap. Monatshefte, 1887, Band i. p. 442.

is not a chemical compound but a mechanical mixture, and that it is identical with sapocarbol. The composition is perhaps a matter of mere curiosity; if known, the ingredients may not illustrate the action; it is rather a question of what the agent or combination of agents accomplish as a remedy.

Creolin does not dissolve in water, but remains suspended, and can thus be injected subcutaneously. It is not specially irritating to the tissues, but suppuration is apt to follow, probably due to the sapolo constituent.

In common with all the agents of the chinolin series, creolin affects the temperature, the pulse, the respiration, and the sensory nervous system. It is an active antiseptic, and has proved highly successful in the treatment of foul-smelling and eroding ulcers, sinuses, and malignant tumors. It is safe to use because not active as a toxic substance, large quantities being required to bring about a fatal result. Its most important property is the antiseptic, and it is now freely used for these purposes, and by the hypodermatic injection will rarely, if ever, be called into use.

The dose of creolin ranges from 2 to 5 to 15 grains, according to the age of the subject and the character of the malady.

BLOOD-SERUM.

Late experimental and clinical observations have shown that blood-serum is distinctly hostile to minute organisms.

The blood-serum common to all warm-blooded animals is not always of the antiseptic variety. That which possesses this antiseptic property is the kind that is used in

the cases under consideration. It need hardly be explained that the serum must be got in contact with the parasite, and hence if the pathogenic germ is in the blood, the intravenous injection becomes necessary; if in the pulmonary parenchyma, the walls of the chest should be transfixed and the tubercular deposits or the cavities injected. If the object of the treatment be *lupus* or *lymphadenoma*, or any other malady requiring this form of treatment, the serum should be so inserted as to act directly on the *materies morbi.*

Besides such uses of blood-serum, it has been proposed to utilize this fluid for making hypodermatic solutions. It is antiseptic, unirritating to the tissues, and it has considerable solvent power. Corresponding solutions are made of the insoluble and also soluble salts of mercury and blood-serum. The blood of the dog, the hog, and other domestic animals is used for this purpose.

To the above list of animals I should have added lamb's blood, which Gesellius so strongly eulogizes. The serum of lamb's blood is readily obtained, of course, and the animal submits with little opposition to his loss of blood, so that the affair can be conducted with ease and certainty.

NOTES.—*Turpentine* has been used with a measure of success, by hypodermatic injection, in cancer, the agent being thrown directly into the mass of the tumor. It causes exquisite pain, and probably few can be found who will submit to the operation.

Lactic acid has been used, injected into the neck, in cases of epithelioma of the larynx, and, it is said, with success. Lactic acid has been used in its unadulterated state and diluted according to the necessities of individuals.

In selecting the remedies for hypodermatic injection out of the large number of antiseptics lately brought forward,

it is necessary to avoid those insoluble in the ordinary menstrua and those manifestly inferior in their powers and attributes.

PYOKTANIN (BLUE).

Methyl Violet.

One of the more recent contributions to the antiseptic class introduced into medicine is pyoktanin. The name given it is an artificial product of word-building, and signifies that this agent has the property of inhibiting pus formation. It is one of the aniline series of coloring agents, and imparts a blue color to the anatomical elements, especially the cells; but the staining does not extend to all parts of the cell, for the nucleus is colored but in part. It is in especial this staining power that has introduced it to the notice of pathologists, for on this depends what specific action it has, if any, on malignant growths. On its antiseptic power depends its utility in the treatment of certain morbid states. For example, pyoktanin has displayed special utility in the treatment of gonorrhœa, the gonococcus, or the microbe of that affection, being inhibited by it.

As I am concerned only to chronicle its use in hypodermatic injection, I must needs speak of those properties which enable it to be employed in that way. *The solution that may be injected with the best results is the one-per-cent. solution.* It should be entirely clear,—that is, free from undissolved particles.* Although not freely soluble in water, a one-per-cent. solution can be made free from cloudiness. As it is injected for the purpose of reaching and staining the cells, it is essential that the solution be a perfect one,

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* Therap. Monatshefte, February, 1891.

that it may permeate the tissues and reach to and stain its cellular elements, thus destroying their vital powers.

The first paper treating of its physiological actions and therapeutical properties was by Professor Stilling,* who first demonstrated its power to inhibit pus formation; but we owe to Professor Mosetig-Moorhof† the discovery of its remarkable property of diffusing into tumors of a malignant character and staining the cell so that the growth of the tumor is arrested, its nutrition impaired, and its atrophic degeneration secured. Although sufficient time has not elapsed to determine its real powers, the results obtained are highly satisfactory. Some growths have been arrested in their progress, and in some instances such a degree of atrophic degeneration secured as to promise the most successful outcome in the future to this plan of treatment.

Much depends on the manner in which the pyoktanin is used. In the first place, as I have already stated, it is essential that the solution be free from all solid particles, that it be injected by the syringe into all parts of the tumor, so that the diffusion into the cellular masses be complete and the staining be sufficient to arrest the cellular life and thus prevent further development of the tumor. As these are the necessary conditions, the number of injections must be regulated by the results achieved. It is well, also, to inject into the normal tissues about the new formation, that the outward growth of the cancerous mass be prevented; indeed, this should always be a part of the injection treatment.

It may appear to the reader an unwarranted egotism that I mention some experiences of my own, but I may be in-

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* Merck's Bulletin, June, October, November, 1890.

† Ibid., March, 1891.

dulged so far as to say that some fifteen years ago I essayed the arrest of growth and the cure of epithelioma by injecting a solution of carbolic acid in glycerin and water beneath and around the morbid mass, so that its nutritive supply was prevented reaching the growth. Treated in this way, I succeeded in curing an unquestionable epithelioma which had been twice removed. Such a result has greatly increased my confidence in the success of the method employed by Mosetig-Moorhof.

In support of the theory of Mosetig-Moorhof, it may be well to mention, also, some of the cases which he has treated with apparent success. Thus "two men with carcinoma of the glands of the neck were cured to such an extent with 1 to 500 solution of blue pyoktanin that they asked to be dismissed, claiming ability to resume work." * Another patient, a male also, with an enormous sarcoma which projected from the pelvic cavity up into the abdominal cavity, and which encroached on and obstructed the bowels, was remarkably reduced in size, and the general condition of the patient so far improved that he could walk about in the coldest weather, attend and give receptions, etc., and live as he did when healthy. He used in this case a solution of 1 to 500, but he now says that much more concentrated solutions may be employed.† He advises that proper antiseptic precautions be taken that the whole mass of the neoplasm be impregnated with the pigment, and that the staining must be repeated frequently, say every second or third day.

With the local applications of pyoktanin in its ordinary form, or in solution applied without using the syringe, this work is not properly occupied.

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* Merck's Bulletin, March, 1891. † Ibid.

CANTHARIDIN.

Potassii Cantharidas. [*Cantharidate of Potassium.*]
Sodii Cantharidas. [*Cantharidate of Sodium.*]
Ammonii Cantharidas. [*Cantharidate of Ammonium.*]

PREPARATION OF LIEBREICH.—The preparation used by him was the cantharidate of potassium.

Liebreich brought forward, at a recent meeting of the Berlin Medical Society, a new remedy for phthisis. When he mentioned cantharidin, there is little doubt the members might have felt some surprise, for cantharidin had been known by the ancients, and Glover had made a physiological investigation of its properties many years ago.

The special power of cantharidin which arrested Liebreich's attention is its influence over the capillaries of the system, whereby a considerable exudation of serum takes place about pathological products in various situations. He ascertained that a hypodermatic injection of cantharidin caused this flow of serum about depots of tubercular matter in cases of consumption.

The next bit of knowledge influencing this process was the fact that the serum of the blood of man and of the inferior animals had a special toxic effect on pathogenic micro-organisms, inhibiting their activity and destroying their products.

These two facts therefore constitute the basis of Liebreich's method: first, that the remedy causes an abundant exudation of serum; second, that this serum is destructive of the microbes producing pathological new formations.

He has practised the injection of cantharidate of potassium, with promising results so far. There has been much improvement in the condition of those who have undergone the treatment, especially if the cases have not advanced beyond the primary stage.

As cantharidin itself is but slightly soluble in water, it became necessary to prepare solutions of some compound of cantharidin with a base; Liebreich began with $\frac{1}{3000}$ of a grain, but he gradually increased the dose up to $\frac{1}{100}$ of a grain, and this amount produced no injurious effect either upon the tissues at the point of injection or upon other parts, except that the maximum dose caused some burning along the course of the urethra; but this soon disappeared. At the site of the injection there was no pain, no redness, or after-induration, if the solution were properly prepared and the dose not made to exceed the $\frac{1}{100}$ of a grain. If too large doses are injected, there may be local inflammation; but the troubles mostly to be apprehended are irritation of the kidneys, strangury and bloody urine, and the appearance of albumen. With proper care no trouble of any kind is to be apprehended.

The solution used by Liebreich is the following:

> Cantharidin (cryst.), 3 grains (0.2 gramme);
> Potassium hydroxide (pure), 6 grains (0.4 gramme);
> Water (cold), 5½ drachms (20 grammes).

Heat over a water-bath until clear; then add, while still on the water-bath, and very cautiously, cold water enough to make, when cooled, 1 litre (32⅞ fluidounces).

The dose of this ranges from 0.16 c.c. to 0.33 c.c., rarely to 0.66 c.c., the last mentioned *very rarely*.

The good results reported by Liebreich* have been supported by the experience of Fränkel,† Hermann,‡ Guttmann, and Lublinski.§

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* Merck's Bulletin, February and March, 1891. † Ibid. ‡ Ibid.
§ Therap. Monatshefte, April, 1891.

B. REMEDIES AFFECTING THE NERVOUS SYSTEM.

1. *Analgesics or Anodynes.*

OPIUM.

MORPHINA: MORPHINE.

Morphinæ Sulphas. [*Sulphate of Morphine.*]
Morphinæ Hydrochloras. [*Hydrochlorate of Morphine.*]

History.—Morphine was the first remedy used subcutaneously. After the inoculation experiments of Lafargue, first published about 1836, Dr. Alexander Wood, of Edinburgh, began in 1844 to insert a solution of morphine under the skin. Although this is the origin of the subcutaneous method as now practised, it is perfectly demonstrable that Magendie, in the course of his physiological experiments, was in the habit of inserting poisons under the skin, to procure their characteristic effects, long before the earliest date assigned for the origin of the hypodermatic method.

Preparations.—A solution, a "hypodermic tablet," or a powder of given weight may be used. There is no general agreement as to the salt of morphine which is best; but as the sulphate is most soluble, and, when neutral, not more irritating than any other salt, it should be preferred. The muriate is much used in Germany, and Eulenberg's formula is as follows:

℞ Morphinæ muriatis, gr. iv;
Acidi muriatici, gtt. iv;
Aquæ destillatæ, ʒi. M.

In this formula the acid serves to increase the solubility of the morphine and to prevent the development and growth of the *penicillium*. It has already been set forth that acid solutions are highly irritating, and have produced much mischief by exciting a local inflammation, followed by suppuration and sloughing. The committee appointed by the Medico-Chirurgical Society of London to examine the subject of subcutaneous medication reported in favor of a solution made with acetate of morphine, dissolved by the aid of sufficient acetic acid and afterwards carefully neutralized with liquor potassa. The committee wisely remark, "In using drugs which require an acid to render them soluble in water, it is found that very acid solutions are apt to irritate, and the solutions were, therefore, carefully neutralized. Very alkaline solutions should be avoided for the same reason."* Dr. Anstie, in his much-quoted paper on the "Hypodermic Injection of Remedies," says that "morphine should be used in the form of acetate, dissolved with a minimum of acetic acid in hot distilled water, five grains to the drachm."† Dr. Lawson recommends a solution of the muriate, in the proportion of ten grains to two drachms, so that six minims contain a half-grain of morphine.‡ "This solution," says Dr. Lawson, "is always solid at ordinary winter temperature and generally so in summer, and it must be heated before each injection." A more recent English writer, Dr. Wilson,

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* The Medico-Chirurgical Transactions, vol. l. p. 565.

† The Practitioner, July, 1868.

‡ On Sciatica, Lumbago, etc., p. 93.

after making an elaborate review of the subject, concludes "that the solvent for morphine should be distilled water without any admixture of acid."* This expression of Dr. Wilson now represents the common sentiment of practical physicians, and the use of acid as a means of increasing the solubility of morphine or of preventing change in the solution has been abandoned. Much difference of opinion yet obtains as to the degree of concentration of the solution. The formulæ above given, so concentrated as to require heat to effect a solution, are not to be commended. The precipitation which takes place on cooling, and the danger of giving an overdose, are insuperable objections. The physicians replying to Dr. Kane's queries† have, with few exceptions, resorted to rather dilute solutions, sometimes after unfortunate experiences with more concentrated. The queries were intended to bring out all the facts in regard to the dangers and accidents resulting from the use of the hypodermatic syringe. As they were despatched to all physicians of any prominence in the country, it may be supposed that little remained unanswered in regard to the mishaps that had occurred, for the personal experiences of physicians were freely drawn upon to illustrate the subject. My personal observation is in favor of a rather dilute solution. The acetate and muriate of morphine, advised by some authors and practical physicians, are really less desirable, as they are less soluble than the sulphate. On the whole, we cannot improve on the formula of Magendie, and this, which I have recommended in former editions of this manual, continues to maintain the first place in my judgment:

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* St. George's Hospital Reports, 1869, vol. iv.

† The Hypodermic Injection of Morphine, New York, 1880.

℞ Morphinæ sulphatis, gr. xvi;
Aquæ, ℥i. M.
Sig.—Fifteen (15) minims contain ½ of a grain.

The advantages of this formula are the complete solubility and sufficient concentration for the fullest effect.

As in all solutions of morphine, and indeed of the alkaloids in general, a change takes place too subtile for recognition by our present means of investigation, by reason of which solutions of some days' duration become unfit for use, the addition of an antiseptic is necessary when the preparation is intended to be kept. Besides this change of unknown character, the penicillium develops in solutions of alkaloids at the expense of the principal, not only weakening the strength, but also rendering the solution highly irritating. From 2 to 4 minims of carbolic acid may be added to the above formula, or for simple water may be substituted cherry-laurel or eucalyptus or chloroform water, as has been elsewhere suggested.

For reasons explained when solutions in general were under discussion, it is preferable to have at hand the materials for extemporaneous solutions. A "hypodermic tablet" or a morphine powder of the required strength is conveniently carried, and as regards liability to accident, is much superior to any permanent solution. Since I have adopted the method of extemporaneous solutions I have not had occur the hard nodules and the points of suppuration and sloughing, which were not infrequent when permanent solutions were employed. A number of those responding to the inquiries of Dr. Kane* report a like experience,—that the abscesses, formerly quite common when a perma-

* The Hypodermic Injection of Morphine, op. cit., p. 47, *et seq.*

nent solution was used, ceased to be produced when the preparation was made at the time of injecting.

The dose of morphine for hypodermatic injection varies from $\frac{1}{12}$ to $\frac{1}{2}$ of a grain. *In commencing, it should not exceed one-third of that ordinarily administered internally.* It is prudent in all cases to test the physiological capabilities of the patient by a small dose before resorting to the maximum amount. Patients vary in their susceptibility. Women are, as a rule, more easily affected than men. One-twelfth of a grain is a sufficient dose for many of the conditions requiring an injection. Persons habituated to the use of the drug, or those suffering pain, will bear a larger quantity. The maximum doses may be administered with safety if combined with atropine (see *post*). As Brown-Séquard has indicated, large doses of morphine, when combined with atropine, exert a more decided curative effect in obstinate neuralgias. It may be necessary in such cases to give $\frac{1}{2}$ or even 1 grain of morphine with $\frac{1}{48}$ of a grain of atropine.

In order to maintain a constant physiological effect, but slight increase of the dose is necessary. This is one of the greatest advantages of the hypodermatic method, especially in cases requiring the protracted use of morphine.

Hypodermatic injections of morphine are rarely advisable in the case of children, yet as their utility is unquestionable in certain convulsive disorders of early life, it may be necessary to employ them. From $\frac{1}{60}$ to $\frac{1}{20}$ of a grain, according to age, may be regarded as a safe quantity, but the administration of so powerful a remedy should not be undertaken without careful consideration of the dangers involved.

So many accidents have happened from the incautious or improper use of morphine hypodermatically that I must

repeat the injunction to proceed cautiously. Before deciding on the dose, ascertain if the malady requiring it be one in which a special susceptibility to the action of morphine exists. Is it a case of tumor or abscess of the brain? of chronic alcoholismus? of idiosyncrasy in respect to the cerebral effects? of weak heart? of obstructive pulmonary lesions? of deficient excretion? etc. If any of these conditions be present, the dose must be small. On the other hand, if the habit of opium-taking has been formed, if there be excessive pain, or if the case be one of uræmic convulsions, the dose may be large.

Physiological Actions.—The effects of morphine injected beneath the skin are *local* and *systemic*. At the moment the injection is practised, pain is produced by the penetration of the skin, and a sensation of smarting and burning follows as the fluid diffuses through the subcutaneous tissue. The latter sensation is the greater the larger the amount of fluid, the more concentrated the solution, and the more irritating the salt of morphine used. Under the usual circumstances it is not severe or persistent. Besides a little redness at the site of injection and some tenderness, no other local symptom appears when a few drops are inserted, and these results cease in a few hours. When, however, 10 minims or more are administered, considerable swelling is produced, a large wheal forms, and the part is tender for several hours. Repeated injection at one point will produce much irritation, tenderness, and even inflammation. The accidents resulting at the point of injection under some circumstances will be described hereafter.

The effect of morphine on the tactile and pain sense of the part into which it has been injected has been much disputed. In coming to a conclusion the various results

which may be produced by the injection must have due consideration. Frequent injections or a single irritant injection may induce such a local congestion as to exalt the functional irritability of the peripheral nerves, when, of course, the tactile and pain sense will be exalted. An unirritating morphine injection lessens the tactile and pain sense for some distance about the point of insertion, as has been affirmed by Eulenberg,* Chouppe,† and others. On the other hand, when local irritation and congestion have resulted, the opposite condition obtains, as has been stated by De Renzi,‡ Mitchell, Morehouse and Keen,§ and others. In this way may be explained the contradictory observations made on this important point. Further support to the view of the local action of morphine is given by the effects which follow the application of a solution to a nerve-trunk, for when a nerve is so treated its power to transmit impressions is lessened.

The local effects of morphine are quite subordinate to the systemic. The diffusion of morphine from the subcutaneous connective tissue is about the same in all parts of the body. Any differences that may exist are due to the number of vessels in the part, or it may be due to an accidental intravenous injection. As the round of the circulation is made within a minute, the effects become manifest within that time, into what part soever the solution may be thrown. When, unhappily, the solution enters a vein, the effect is not instantaneous, although very prompt. Under ordinary circumstances, within a minute after the injection is practised, the cerebral effects, which vary with the dose, the

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* Die hypodermatischen Injectionen, etc., *supra.*

† The British Medical Journal, April 10, 1875. (Abstract.)

‡ The New York Medical Journal, vol. xviii. p. 214. (Abstract.)

§ The American Journal of the Medical Sciences, July, 1865.

idiosyncrasies of the individual, and usage, are experienced. A feeling of giddiness, faintness, depression, and nausea, accompanied by pallor of the face and contracting pupils, is the effect experienced at the first onset of the morphine impression by those not habituated to it. A deadly faintness, anxiety and alarm, extreme pallor, cold surface, and weak circulation are not infrequently produced in susceptible subjects on being injected for the first time by even so small a dose as $\frac{1}{12}$ of a grain. Usually the preliminary depression and pallor are succeeded by a flushed face, a feeling of heat and fulness of the head, increased action of the heart, tingling and redness of the extremities, and a general sense of discomfort. Very often some pain is felt in the abdomen, due to the movements of gas, and loud borborygmi occur. The mouth grows dry and pasty; the taste loses its acuteness, and the mastication and swallowing of food become awkward and difficult. The pupil contracts, and vision is rather hazy. The sense of hearing is obscured somewhat by the *tinnitus*. A minute dose will not impair the equilibrium, although more or less dizziness occur, but a full dose will render walking uncertain, even prevent the necessary co-ordination of the muscles. There will be present, indeed, the usual symptoms and appearance of intoxication. Various odd sensations are experienced. One has an overpowering sense of muscular fatigue; another has a feeling of weight on the nape of the neck and the shoulders; a third has a splitting headache, with resounding *tinnitus* and incessant and severe vertigo; a fourth feels a sudden glow, then a sinking at the epigastrium, sudden nausea and vomiting occur, after which he is languid, exhausted, but has a sense of comfort; and a fifth is merely depressed and gloomy. There are but few who experience the traditional exhilarating effects, in which the

mind is filled with delightful visions and the body is pervaded with an exquisite sense of well-being. By him to whom there are denied the higher joys of morphine intoxication, a grateful sense of freedom from all bodily discomforts, and the added feeling of delightful existence quite independent of surrounding circumstances, seem to be experienced. It is in this sense of all-pervading present comfort that the fascination of opium apparently consists, rather than in active exhilaration of the mind. When to the sufferer not only relief but a pleasing existence is given, when from the weary fatigue is made to vanish and work becomes a pleasurable exertion, and when for the disappointments and troubles of life a peaceful calm and content are substituted, it is not surprising that those in whom these transformations have been wrought should ardently desire their continuance.

The first stimulating effect of morphine on the cerebrum is of very variable duration. In some persons a condition of somnolence follows in a few minutes, and then more or less profound sleep persists for many hours. The sleep is often accompanied by vivid—usually horrifying—dreams; there is much talking and agitation, and in some persons a somnambulistic state is induced. Other subjects, again, fall into a deep sleep, with snoring, even stertorous, respiration. A large proportion of those taking morphine have but snatches of light sleep, with long intervals of wakefulness, and many are kept wide awake in a very active mental state, but experience a profound sense of comfort and peace. Those made actively wakeful usually are very drowsy and sleep heavily after the immediate effects of the morphine have declined. When the action has begun, the circulation, respiration, and temperature are characteristically affected.

Mr. Hunter* first pointed out the effect of morphine administered subcutaneously on the pulse and respiration. "In mania," he says, "I have reduced the pulse from 120 to 80 in four minutes," and he also observed "the diminished rate of respiration." I have been most fortunate in securing the co-operation of some *internes* of the Good Samaritan Hospital, who submitted themselves to experiment in preparation for the graphical representation of the results of the morphine action.

In the accompanying diagram are represented the effects on the pulse, respiration, and temperature of Dr. Rutter, who had received, whilst in a perfectly normal state, $\frac{1}{4}$ of a grain of morphine subcutaneously. In the febrile condition of the system the temperature-curve would not contain the elevation which marks the above tracing, but a depression corresponding to those of the respiration and pulse. A considerable rise in the blood-pressure also is produced. A sphygmographic tracing may or may not have scientific value. So much depends on the adjustment of the instrument, on the amount of spring-pressure, and on the nervousness of the patient, that perfectly-accurate sphygmograms are somewhat difficult to make. Those subjoined were obtained from Dr. Drake before and after the administration of $\frac{1}{4}$ of a grain of morphine hypodermatically. The first or normal tracing was taken with a spring-pressure of 200 grammes, the sphygmograph being fitted with the modifications of Dr. Burdon-Sanderson, which permit a more accurate adjustment of the spring than is possible in Marey's instrument.

Soon after taking the normal tracing, the medicament was given and the apparatus remained *in situ*. When the

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* On the Speedy Relief of Pain, etc., p. 33.

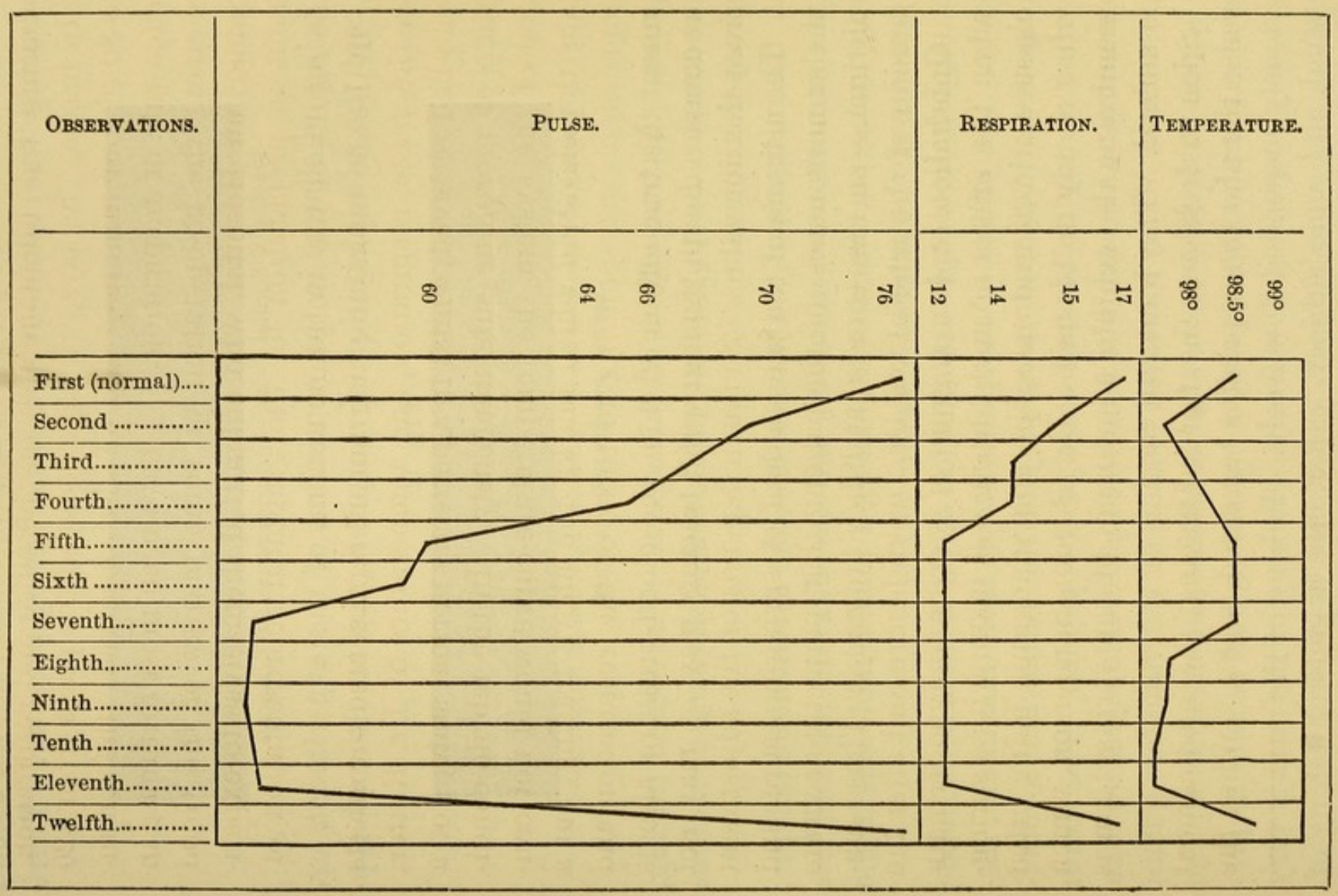
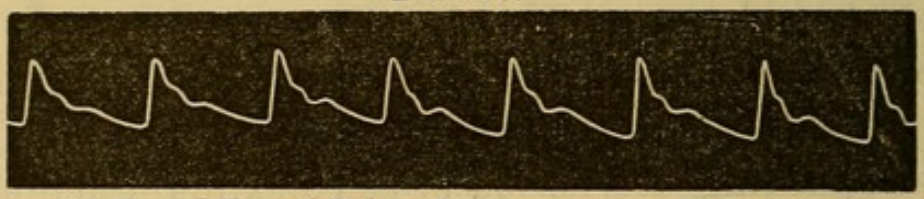

Observations.
Pulse.
Respiration.
Temperature.
60
64
66
70
76
12
14
15
17
98°
98.5°
99°
First (normal).....
Second .....
Third.....
Fourth.....
Fifth.....
Sixth .....
Seventh.....
Eighth.....
Ninth.....
Tenth .....
Eleventh.....
Twelfth.....

Fig. 9.

usual effects were produced at their maximum, the second tracing was taken at the same spring-pressure. There

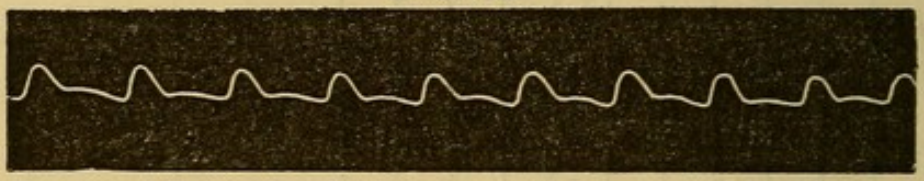
FIG. 10.



Tracing of Normal Pulse.—Spring-pressure, 200 Grammes.

being no change in the conditions of the experiment, except the administration of morphine, the result must rep-

FIG. 11.



Tracing of Pulse after the Subcutaneous Injection of Morphine.—Spring-pressure, 200 Grammes.

resent the true effects of this agent. The second tracing, as compared with the first, exhibits the following deviations from the normal:

The altitude of the wave is less, the ascent more oblique, the summit more rounded, and the dicrotic rebound less distinct,—peculiarities indicating a considerable rise in the tension of the arterial system.

Ophthalmoscopic examination of the fundus oculi, made when the effects of morphine are at their maximum, discloses an increased vascularity of the retina and a somewhat cloudy or blurred state of the papilla. The drum membrane also exhibits a more considerable injection than is normal. The increased tension of the vascular system begins to decline soon after it attains the maximum; the pulse then becomes quicker but softer, and secretions previously suspended flow freely. Itching of the nose is very usual, and some subjects experience a general itching of

the surface during the whole period of the action. Moisture appears on the skin about the time the pulse relaxes, and considerable sweating persists up to the end of the morphine influence. The tongue moistens as the skin perspires, and doubtless, also, the gastro-intestinal mucous membrane then resumes secretion and excretion. Probably, also, during the period of its maximum action, morphine suspends or enfeebles the activity of the pancreas and liver. Digestion is stopped for a time if a full dose of morphine be given after a meal, and, as a rule, constipation results; but this is by no means invariable, for in some instances the bowels continue to act regularly, and occasionally constipation has been removed by morphine injections. The diminished excretion of bile is shown by the yellowness of the conjunctiva, the muddy tint of the skin, and the lighter color of the fæces. The urine also has a higher tint than normal, due to the presence of bile-pigment and to the greater density. The rather scanty urine is referable to two factors,—to the diminished functional activity of the kidneys and to the increased diaphoresis.

With the decline in the morphine narcosis, some patients experience headache, confusion of mind, anorexia, and nausea; but these results are not so constant as after the internal use of this agent. If the injection be administered at night, the nausea and vomiting are experienced on rising in the morning. Perfect quiet, a cup of hot coffee taken before rising, an ice-bag to the cervical spine, and a full dose of bromide of sodium, may be administered for the relief of these symptoms when they are severe.

The extent and persistence of the foregoing physiological effects will depend upon the quantity of morphine injected. Very large doses excite not only immediate disturbance in the functions of the brain, but secondary

disturbances in the process of elimination of the narcotic from the blood. The occurrence of these unpleasant and depressing effects of the morphine narcosis is an additional reason for cautious tentative experiments in any case in which the physiological tolerance of this agent is unknown.

Phenomena somewhat different in character, as well as in degree, from those which I have described under this head, follow the subcutaneous injection of large doses. The following symptoms were observed by me after the injection of one grain of sulphate of morphine:

In ten minutes the patient had fallen asleep so soundly, sitting upright in bed, that he could not be aroused. At the end of an hour I found him in a state of profound narcotism, his pulse 50 and feeble; respiration 10 and labored, with stertor; skin cold and sweating; face pale and ghastly. The conjunctivæ were deeply injected; pupils minutely contracted, and insensible to the strongest gaslight. No reflex movements could be excited by touching the eyes, or by irritation of the fauces. These formidable symptoms were relieved by the subcutaneous use of atropine, the physiological antagonist of morphine.

Accidents.—Although morphine, when rightly administered subcutaneously, may be freely used, accidents do occur, and a clear conception of their causes and character becomes necessary. These accidents may be local or systemic: local, due to the site, manner of injecting, and condition of the subject; systemic, the impression of the remedy on the cerebral, respiratory, and circulatory organs.

The local irritation produced by subcutaneous injections has been briefly referred to in connection with the solution. Improperly-prepared solutions of morphine, long-

kept solutions, a rusty and dirty needle, the forcible introduction of a large quantity of fluid, are fruitful causes of local inflammation and induration or abscess. Repeated injection at the same site sets up a hyperplasia of the subcutaneous connective tissue, resulting in the formation of indurations, which may slowly suppurate, or induce such a highly-vascular state of the parts that finally injections here become very dangerous.

When a vein in the skin is perforated by the needle, a very sudden and powerful impression is produced, if, as usually happens, the morphine solution be sucked into the vessel. If the needle enter a vein and the solution be thrown directly into the blood-current, the effect produced is still more sudden and powerful. The interval between the act of injecting and the effect of the morphine is greater in the former case; in the latter, the effect may seem to be instantaneous, almost. The difference being quantitative rather than qualitative, there need be no separate consideration of the effects resulting from the two modes of the accident. There are three kinds of results: slow and feeble action of the heart, contraction of the arterioles, and therefore anæmia of the brain, causing syncope; the same conditions, associated with weakened contractile power of the cardiac muscle, resulting in failure of the heart; and profound narcotism, terminating in paralysis of the respiratory centre.

When the injection is making, the vein perforated, no difference in the operation is observed, except the escape of blood; when the injection is delivered into a vein, the fluid passes in with unusual readiness. Dizziness, oppression of breathing, singing in the ears, a fearful apprehension, intense throbbing in the head, dimness of vision, are immediately experienced; the face becomes deadly pale,

the eyesight dim, the pupils contract, the pulse is small and slow, the respiration shallow and sighing, and thus, on the instant, the patient falls unconscious in a syncopal state. After a time consciousness is slowly regained, vomiting occurs, intense headache and vertigo are felt, and on every attempt to sit up the faintness comes on again. There are great differences in the duration of these symptoms, according to individual peculiarities; they may continue from an hour or two to twelve hours or longer, and, after the subsidence of the effects directly due to the morphine, more or less indigestion, constipation, hebetude of mind, and stupor persist for several days.

If the heart muscle have undergone the changes produced by myocarditis, fatty degeneration, or fatty infiltration, or the right heart be dilated and weak in consequence of obstructive pulmonary lesions or other causes, the syncopal state induced by the injection of morphine may speedily result in death. In such cases, immediately on receiving the injection, the patient turns pale, reels, falls into unconsciousness, and, with a deep sigh, expires. Such a sudden termination is, however, not common. More frequently the fatal result is due to excessive action of the remedy,—to coma and suspension of the functions of the respiratory centre. Such cases pursue the course of opium narcosis. The patient after receiving the injection passes into a condition of stupor, presently becomes profoundly insensible, the reflexes are abolished, the pupil minutely contracted, the respiration slow and shallow, the face pale, and the skin relaxed and cold. The rapidity of the effect depends on the amount administered, the point of insertion, and the susceptibility of the individual receiving the injection.

Idiosyncrasy is an important factor in determining ill

results. There are persons, women especially, so susceptible to the action of opium and its alkaloids that the minutest quantity will produce unpleasant effects. In such subjects a small medicinal dose will cause faintness, extreme vertigo, nausea, and profound depression of the vital powers, lasting from a few hours to several days. In such cases, even on the following day, great depression, faintness, and nausea occur on attempting to assume the upright position, and a dazed, confused, and "groggy" condition of the head continues for some days longer. In the subjects of this peculiar susceptibility, a full medicinal dose may cause a fatal result by syncope.

Chronic alcoholism develops a state in which ordinary medicinal doses may cause a dangerous narcotism or sudden failure of the heart. The structural changes which occur in the brain, especially in the medulla oblongata, in the walls of the heart, and in the kidneys, explain the nature of these results.

Habit diminishes the danger of accidents. When, in the case of a morphine-taker, a strong solution is sucked or thrown directly into a vein, the following effects are observed: an intense tingling occurs over the body generally, but especially over the extremities; often extensive wheals appear; the skin is swollen and deeply red; the action of the heart becomes rapid and tumultuous, and all the arteries of the body beat vehemently; an intense headache, with strong throbbing, occasions extreme distress, and is increased by every movement. Such symptoms will persist for a half-hour or longer, and not infrequently are followed by nausea. Notwithstanding enormous doses may be taken with impunity, they may be dangerous when, after a period of reduced quantity, considerably larger doses are suddenly administered. Several deaths have been caused

in this way. Hence those reducing their daily allowance must be warned of the danger incurred by taking a dose considerably larger, although within the limits of former indulgence.

The treatment of the various accidents caused by the subcutaneous injection of morphine includes prophylactic as well as therapeutical expedients. No physician should administer a morphine injection without first assuring himself of the quantity. Deaths have been caused by the administration of approximate quantities. The rules with regard to dose, already given, should be carefully adhered to. The condition of the patient, idiosyncrasies, and existing diseases should be ascertained. Morphine is the safer if given with atropine, and this should be done unless some contra-indication of the latter exist. It has been proposed to put a ligature about the limb, in readiness to be tightened should it be found that a vessel has been entered. It need hardly be observed that such preparations are too suggestive to be made with nervous subjects, and are rather unbecoming. As the symptoms occur only when the remedy reaches the brain, a ligature may fail to be useful. The person injected should lie recumbent, and if faintness comes on, the head should be lowered below the body. The measures of chief importance for the cases of syncope are inhalation of ammonia (cautiously), artificial respiration, and stimulation of the chest muscles by the faradic current, enemata of turpentine or alcohol, the intra-venous or subcutaneous injection of ammonia, and inhalations of amyl nitrite or its subcutaneous injection. The condition of narcosis requires the subcutaneous use of atropine to counteract the respiratory and cardiac depression, and faradization of the chest muscles.

THERAPY.—The subcutaneous injection of morphine

may be used to relieve pain, to relax spasm, to subdue inflammation, to cure specific diseases, and to antagonize toxic agents. An anatomical arrangement seems best adapted to embrace all of the therapeutical facts under these several heads. Accordingly, I shall consider the uses of morphine in—

Diseases of the brain and nervous system; of the respiratory and circulatory system; of the digestive apparatus; of the genito-urinary organs, and those of constitutional or specific origin; in certain surgical diseases and operations, and as a physiological antagonist.

DISEASES OF THE BRAIN AND NERVOUS SYSTEM.

Psychical Disorders.—Mr. Hunter was the first to employ the injection of morphine in the treatment of psychical disorders, and to indicate the nature and extent of the curative effect obtained by it. He enunciated an important truth in the following observations: "For derangements of the cerebral nervous system we have in the hypodermic method a means of treatment far superseding in its immediate efficacy any other mode of medication." In another place he further remarks, "In this class of cases [mania] a single dose, administered beneath the skin, will at once break the neck of the disease. It will often at once stop the delirium, correct the mental aberration, and remove the exhaustion."* Notwithstanding the striking advantages thus shown to result from the hypodermatic treatment of mania, some years elapsed before it came to be employed. Indeed, so late as May, 1869, we find a distinguished asylum superintendent† repeating the expres-

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* On the Speedy Relief of Pain, etc., pp. 18, 19.

† C. Lockhart Robertson, in The Practitioner, May, 1869, p. 272.

sion of Dr. Anstie, "that despite the satisfactory working of the hypodermic method, and the greatly-increased power of handling remedies which it gives us, it is still very much unappreciated." Dr. Robertson believes that "this remark applies to the employment of the hypodermic injection of morphine in the treatment of mental disease." According to the same authority, Dr. Mackintosh published a paper in 1861 on "The Subcutaneous Injection of Morphine in Insanity," and the reports of the Somerset Asylum contain allusions to the advantages of this method. Lorent,* Erlenmeyer,† and Eulenberg‡ support the observations of Hunter by their individual experiences. Maudsley,§ who places opium at the head of all the remedies employed in the treatment of insanity, considers the subcutaneous injection of morphine "a valuable expedient." Reissner,‖ who has experimented largely with the hypodermatic method in the various forms of mania, comes to conclusions less favorable than those above expressed. In acute mania he had no permanent good results. Dr. Vix has, however, adduced a remarkable case in which a single injection of morphine cured a recent case of acute mania. In melancholia, Reissner's results were not more favorable than in acute mania. In chronic mania the effects were variable: some patients were calmed for weeks and months; in others large doses were without benefit. Reissner considers general paralysis unsuited for the action of morphine, and that it is contra-indicated in cases of mental disorder complicated

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* Die hypodermatischen Injectionen, etc., op. cit., p. 16.

† Die subcutanen Injectionen, etc., op. cit., p. 28.

‡ Die hypodermatische Injection, etc., op. cit., p. 154.

§ Reynolds's System of Medicine, vol. i. p. 621.

‖ Bul. Général de Thérapeutique, January 30, 1870, p. 89.

with heart- or stomach-disease, rigidity of the arteries, tuberculosis, and in certain epileptics.

More recently, Dr. O. J. B. Wolff has attempted a more accurate determination of the indications for the use of morphine subcutaneously in mental diseases. The state of the arterial tension is Wolff's guide to the use of morphine. If the sphygmograph shows a low state of the arterial tension with a slow pulse, small doses are indicated. On the other hand, as large doses of morphine, by over-excitation, cause paresis of the sympathetic, these are indicated when the pulse is quick and tension high. He advises caution in the use of large doses in the obese and the aged. He thinks the subcutaneous injection of morphine very useful in both curable and incurable cases.*

Krafft-Ebing reports excellent results from the use of morphine subcutaneously in cases of lypemania, especially when there exist at the same time neuralgic troubles. He has been equally fortunate by this method in the treatment of "moral hypochondriasis complicated with hyperæsthesia of the spinal cord," and "in forms of mental alienation determined sympathetically in the predisposed by neuralgias and neuropathies." The existence of a neuralgic element constitutes an indication for the use of morphine subcutaneously in simple mania and in hysterical mania. Krafft-Ebing considers the same mode of treatment the most efficacious for the relief of the insomnia so common in the insane.† My own experience, which has been limited, however, is also very favorable to the subcutaneous injection of morphine in the insomnia of the insane. In a case of acute melancholia, characterized by insomnia and in-

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* Archiv für Psychiatrie und Nervenkrankheiten, Band ii.

† Bul. Général de Thérapeutique, 1870, tome lxxix. p. 474.

tense restlessness, I found this method of treatment exceedingly useful. A grain of morphine reduced the pulse from 140 to 96, quieted the agitation, and procured sound and refreshing sleep.

Robertson in the paper referred to gives three typical cases of different forms of insanity—recent mania, chronic mania, and melancholia—in which the hypodermatic injection was successful. The indications for the employment of this method are the following:

Prolonged wakefulness.

Maniacal excitement.

Obstinate and persistent refusal of food, or drink, or medicine.

Destructive and suicidal tendencies.

Maudsley adds a caution here, which I transcribe for the benefit of my readers: "It will be well to have in mind that neither opium by the mouth nor morphine hypodermically injected will always quench the fury of acute mania, and that successive injections of morphine, followed by brief snatches of fitful sleep, have been followed, also, by fatal collapse."

The evidences of the beneficial effect of the injection are the following:

Prolonged and healthy sleep.

Less excitement on awakening.

Illusions or delusions less strong.

Willingness to take food.

Absence of any tendency to collapse, although pulse, temperature, and respiration are reduced.

To produce the best results, larger doses than those I have indicated as proper in general are necessary in the treatment of mania. Hunter administered $\frac{1}{2}$ and 1 grain; Robertson speaks of $\frac{1}{2}$ of a grain of the acetate of morphine

injected every four hours, and in one case of 1 grain injected night and morning. In cases which have occurred under my observation, extraordinary tolerance of the morphine was exhibited; and in that case to which I have made special reference, 1 grain was found necessary to procure sufficiently-prolonged sleep.

It is in the beginning of mania that the hypodermatic injection of morphine is most conspicuous for good. The timely use of the syringe may avert this disorder in that critical period when the occurrence of unusual excitability and sleeplessness indicates that an outbreak is imminent. This observation is especially true of puerperal mania. The introduction of chloral hydrate has modified somewhat the treatment of maniacal affections by the subcutaneous use of morphine; but, as Wolff has shown, each has its own sphere of applications.

Delirium Tremens.—We owe to Mr. Hunter the first suggestion of the hypodermatic treatment of *delirium tremens*. It was afterwards employed by Ogle, Semeleder, Lorent,* Eulenberg,† Ruppaner,‡ and others. Dr. Anstie, in an able paper on "Alcoholism,"§ thus formulates his views as to the utility of this method:

"Opium should never be administered by the stomach, but always in the form of morphine hypodermically injected, in the dose of $\frac{1}{10}$ to $\frac{1}{4}$ or $\frac{1}{2}$ of a grain."

The treatment of delirium tremens has undergone a radical change within the past few years. This is well expressed in the following observations by Dr. Anstie:

"In former times—indeed, a very few years since—the

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* Op. cit. † Op. cit.

‡ Hypodermic Injections, 2d ed., p. 132.

§ Reynolds's System of Medicine, vol. i. p. 688.

notion universally prevailed that the delirious symptoms were owing to the exhaustion which was chiefly kept up by want of sleep; and, consequently, that the production of continuous sleep for several hours was the sole and all-important means of cure. It was therefore the custom to ply the patients with larger and larger successive doses of opium, with the view of drowning the delirium in narcotic stupor. Great mischief arose from this wide-spread belief and practice. In the first place, it has often happened that the patient, without ever sleeping at all, has passed first into a condition of coma-vigil, next of stertorous breathing, and at last sunk, fairly poisoned with opium."

I have quoted these strong but just expressions to warn my readers against the abuse of the hypodermatic injection of morphine in the treatment of delirium tremens.

The following are the indications for the use of this method in this disease:

The condition of "horrors," or wakefulness, preceding delirium.

Excessive and uncontrollable vomiting of food, drink, and medicine.

Mild cases, in which there is little tendency to depression of the vital forces, in which the assimilation of food proceeds satisfactorily.

It is contra-indicated in severe and protracted cases, with great depression of the vital forces and non-assimilation of food.

In cases in which serious organic lesions of liver or kidneys have occurred.

In cases in which the delirium tremens is consecutive to traumatic or other serious lesion of the brain.

In **cerebro-spinal meningitis** opium is the best remedy, especially in the onset of that disorder, and according to

Radcliffe* the hypodermatic injection of morphine is the best method of administration. Erlenmeyer,† who appears not to have had any personal experience with the hypodermatic use of morphine in this disease, refers to the experience of Bois. According to Eulenberg,‡ Niemeyer used this method as a palliative in an epidemic at Rastadt and Carlsruhe. It relieved the pain and cramps, and quieted the extreme restlessness (*gross Unruhe*), which are marked phenomena in these cases. Dr. B. Arnold, of Donzdorf, reports favorably of its use in these cases.§ According to Stillé,‖ the opium treatment was very serviceable in the disease as he observed it in Philadelphia. The author's experience is fully confirmatory of the published observations. He has witnessed remarkable cures effected by the timely, and even heroic, use of morphine subcutaneously. It is especially serviceable in the earlier stage,—stage of irritation,—and ceases to be useful when depression of function—paresis—occurs.

In the psychical disorders *insomnia* is a prominent symptom, for the relief of which the morphine injection is especially indicated. When insomnia is the substantive disorder, a combination of morphine and atropine is better than morphine alone,—a fact which I shall develop in a future chapter.

In the treatment of **coup-de-soleil, sunstroke,** very unexpected and gratifying results have been obtained by Dr. Hutchinson at the Pennsylvania Hospital.¶ He injected

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* Reynold's System of Medicine, vol. i. p. 312.

† Die subcutanen Injectionen, op. cit., p. 31.

‡ Die hypodermatische Injection, op. cit., p. 156.

§ Schmidt's Jahrbücher, Band cxxix. p. 103.

‖ Epidemic Meningitis. Philadelphia, 1868.

¶ Pennsylvania Hospital Reports, vol. ii. p. 291.

¼ of a grain of the sulphate of morphine, which produced almost instant relief, and was followed by rapid recovery.

Hysteria.—In England Hunter,* in Germany Lander and Fronmüller,† were the first to employ the hypodermatic method with morphine in the treatment of hysterical convulsions. Lorent‡ recommends it in *hysterical melancholy*. In my own experience, no remedy has acted so promptly and satisfactorily in terminating a hysterical paroxysm as this. One-twelfth to one-eighth of a grain of sulphate of morphine is sufficient for this purpose; but in this disease, owing to the craving for narcotic stimulation, it is not proper to administer a remedy efficacious indeed, but so apt to induce appetite for its repetition.

Epilepsy.—Brown-Séquard was the first to indicate the utility of hypodermatic injections of morphine in epilepsy. He combined atropine with it. Results as important as they were unexpected have followed this method. It has been found that not only are the paroxysms in violent cases quickly relieved, but permanent benefit also has been obtained by diminishing the number, frequency, and severity of succeeding attacks. This remedy disputes with bromide of potassium the first place in the amelioration and cure of epilepsy. One may succeed when the other fails; both, of course, fail frequently. It is important, then, to have clear notions as to the kind of cases in which one or the other should be preferred.

As has been pointed out by S. W. Duckworth Williams,§ Russell Reynolds,‖ and myself,¶ bromide of potassium is

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* On the Speedy Relief of Pain, etc., loc. cit.

† Eulenberg, loc. cit. ‡ Op. cit., p. 17.

§ On the Bromide of Potassium in Epilepsy and Certain Psychical Affections. Pamphlet. ‖ The Practitioner, vol. i. p. 5.

¶ Fiske Fund Prize Essay, 1871, p. 38.

more effective in cases of *grand mal* in which the paroxysms occur frequently, with great violence, and during the daytime, and less effective in those which occur chiefly at night. The bromide is more effective in epileptoid convulsions symptomatic of "coarse organic lesion of the brain." It is less effective in the *petit mal* and in convulsive *tic*.

The hypodermatic injection of morphine is preferable in epilepsy the paroxysms of which occur at night, in the *petit mal*, and in convulsive *tic*. It is not proper, as a general rule, in cases of epileptoid character dependent upon cerebral lesion.

When the paroxysms succeed one another rapidly, and are violent, the injection may be made during an attack, and without loss of time. Ordinarily two or three times a week will suffice, and, whenever practicable, the onset of an expected attack should be anticipated. A very marked amelioration in obstinate cases may be thus induced. With the decline in number and violence of the seizures there will be witnessed under this treatment most gratifying improvement in the mental condition. For the treatment of epilepsy, 7 or 8 minims of my solution, or $\frac{1}{4}$ of a grain, will be a sufficient quantity for each injection. Notwithstanding the good effects of the practice, the certainty of inducing a morphine habit by frequent repetition of the narcotic impression is a serious objection to the method, and it is, consequently, rarely employed at the present time.

Scanzoni was the first to use the hypodermatic injection of morphine in *eclampsia*. This practice was followed by Lander, Hermann, and Lehmann, with good results.* The

* Erlenmeyer, op. cit., p. 35.

injection is much safer than the inhalation of chloroform, almost as prompt in its effects, and quite as efficient in suspending the morbid reflex excitability. In the convulsions of infancy, whether dependent upon reflex irritation of teething, worms, indigestible food, etc., the hypodermatic injection of a small quantity ($\frac{1}{30}$ to $\frac{1}{16}$ of a grain) of sulphate of morphine will promptly terminate the paroxysms. This treatment must be conducted with caution in very young subjects. It will be prudent in any case to attempt relief by the ordinary measures, especially by the removal of the cause of irritation, before resorting to so powerful an agent. The dose for this purpose should not exceed $\frac{1}{16}$ of a grain, and may be sufficiently powerful in one-half this quantity ($\frac{1}{32}$ of a grain).

One of the most important recent contributions to our therapeutical resources is the demonstration, made by Professor Loomis, of New York, of the remarkable curative power possessed by the hypodermatic injection of morphine in the *convulsions of albuminuria.* Heretofore the presence of albumen in the urine has been held to contra-indicate the use of the preparations of opium; but the observations of Loomis have established the fact of an antagonism between the action of morphine on the one hand and of that condition of the intra-cranial circulation which occurs in albuminuria on the other. In albuminuria the arterial tension is low, the perivascular lymph-spaces are distended with serum, and the brain-substance is anæmic. In this state of things Traube found a sufficient explanation of the convulsions which by others were supposed to be caused by uræmia.

In the treatment of uræmic convulsions, considerable doses of morphine are not only well borne, but are demanded by the conditions present. For an adult $\frac{1}{2}$ of a

grain may be administered at once, and this must be repeated promptly if the convulsions continue, or if they recur after having ceased for a time. As much as 2 grains may be injected within a few hours in severe cases. The author must, however, repeat the caution that such heroic medication must not be undertaken without due consideration and an accurate diagnosis.

Chorea.—Hunter* and Levick,† of Philadelphia, employed the hypodermatic injection of morphine in this disease with success. When the jactitations are incessant and violent, preventing sleep and causing injury to the soft parts, the patient wearing out at length, the use of morphine subcutaneously has undoubted value. It is useful in those cases in which Trousseau ‡ was in the habit of prescribing enormous doses of morphine internally. But over ordinary cases of chorea, as Dr. Bristowe § has shown, "specific forms of treatment have little or no real influence," and suitable hygienic means will as certainly conduct the case to a favorable termination. Nevertheless, in the very violent cases to which I have referred there is no means of treatment equal to the hypodermatic injection of morphine. Generally speaking, such cases require the maximum doses, as Trousseau's use of 10, 12, and even 14 grains of morphine daily with success sufficiently indicates. Commence with $\frac{1}{4}$ of a grain, and increase according to the effect produced; it will rarely be necessary to exceed 1 grain at a single injection.

Tetanus and Hydrophobia.—Hunter used the hypodermatic method in cases of traumatic tetanus, "giving sleep and diminishing the spasms," but without permanent re-

* Loc. cit., p. 27. † The American Journal of the Medical Sciences.
‡ Clinique Médicale de l'Hôtel-Dieu, tome ii. pp. 195, 196.
§ The Practitioner, No. 10, April, 1869, p. 195.

lief, death ensuing in each. Ruppaner* injected two cases with the liq. opii comp., which very much assuaged the sufferings of the patients, but did not retard the fatal termination. He urgently recommends further trials with this agent. More favorable results were obtained by others. Thus, Eulenberg† used it with success in a case of traumatic tetanus. In idiopathic tetanus, and in trismus neonatorum, more favorable results have been obtained, but these forms of trismus are much more amenable to treatment than the traumatic. Demarquay‡ obtained good results in the treatment of cases of tetanus during the second siege of Paris, by a new mode of using subcutaneous injections. He carried the needle deeply into the contracted muscles, and, if possible, to the point of entrance of the nerves. He thus injected the masseters, the muscles of the neck, the sterno-cleido-mastoid, the sacro-lumbar muscles, etc. He used in this way 1 to 2 grains of the hydrochlorate of morphine daily, with the effect to relax the spasms and permit the nourishment of the patient. Of three cases treated in this way, two recovered and one died; but the fatal result in this case was due not to the tetanus, which was relieved by the injections, but to pyæmia. The subcutaneous use of the extract of Calabar bean (physostigma), or of woorara, is much more effective in the treatment of tetanus.

The sufferings of the patient affected with *hydrophobia* may be much diminished by the hypodermatic injection of morphine, but I am aware of no case in which the fatal termination has been averted.

Local Muscular Cramp and Spasm.—Eulenberg has

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* Hypodermic Injections, p. 136. † Op. cit., p. 136.

‡ Bul. Général de Thérapeutique, October 15, 1871, p. 299, *et seq.*

used the subcutaneous injection of morphine in the muscle-spasm succeeding amputation of the thigh. I have obtained the greatest advantage from this method of treatment in the painful jactitations of the muscles which occur in cases of fracture of limbs long paralyzed. In a case of fracture of the femur on the paralyzed side of a hemiplegic patient, the injection procured instant relief to the very violent and persistent muscular spasms which occurred in a few hours after the injury. As is well known, Dr. Marshall Hall was the first to point out the fact that in paralysis of cerebral origin the muscular irritability is not lost, and may indeed be greater than normal; afterwards confirmed by Duchenne de Boulogne, and now universally admitted. In the patient to whom I refer the muscular irritability existed in an exaggerated degree. Besides the pain which the violent spasm produced, union of the fractured femur would have been impossible if no means had existed for terminating the muscular spasms.

Neuralgia.—The greatest triumphs of the hypodermatic method have been achieved in the treatment of neuralgia. As Dr. Anstie, in the able article already referred to, remarks, "The advantages of morphine, hypodermatically administered, over opiate medication by the stomach, are such as would be *a priori* incredible, nor can they as yet be fully explained. In particular, it is impossible to account for the far greater *permanence* of its action in relieving nerve-pain, which is so marked that its discovery has initiated quite a new era in the treatment of severe neuralgias."*

Following the classification of Valleix, the neuralgias are divisible into two classes:

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* Op. cit.

I. Superficial Neuralgias.
II. Visceral Neuralgias.
The first class is subdivisible into the following:
Trifacial.
Cervico-occipital.
Cervico-brachial.
Intercostal.
Lumbo-abdominal.
Crural.
Sciatic.

The second class will be more conveniently referred to in connection with internal diseases.

It would be unprofitable to devote space to a special consideration of nerve-pain according to its anatomical seat, for the principles of treatment are the same. I propose to make observations on the most important varieties, to illustrate the hypodermatic treatment in all.

Neuralgia of the fifth nerve, or trifacial, is the most important of the whole group. It occurs more frequently, is more painful, and is more difficult to cure. But from the lightest case of facial pain, due to irritation of decayed teeth or cold, up to the atrocious and incurable epileptiform tic, there are numerous gradations in respect to severity and curability.

In *toothache* the hypodermatic injection of morphine is often immediately curative. It is, of course, less permanently beneficial when caries exists, but even in this case it affords great relief. It may also be used to diminish the pain of extraction. The facial neuralgia of pregnancy is promptly cured by it, as I have repeatedly ascertained by trial. This fact was first pointed out, I believe, by Dr. H. R. Storer, of Boston, the eminent gynæcologist of that city. These cases, as is well known, are extremely

obstinate under the old methods of treatment, and those who have suffered from them on former occasions are exceedingly grateful for the relief so promptly and permanently afforded by the hypodermatic method.

The attacks of neuralgic pain experienced in any portion of the distribution of the fifth are readily relieved by the same means. This remark is true of *migraine*, *hemicrania*, *clavus hystericus*, and other forms of neuralgic headache. I need hardly remind the reader that this method of treatment is not proper in that form of headache which often precedes and is a symptom of cerebral hemorrhage. That severe and obstinate neuralgia of the fifth known as *tic douloureux* is generally curable by the hypodermatic injection of morphine, and if not curable, is always much ameliorated by this means. A single or two or three injections may not suffice, but the persevering use of full doses may at length be successful. In obstinate cases the dose may be raised from $\frac{1}{4}$ to 1 grain twice a day. Even that intractable form of *tic douloureux* described by Trousseau,* under the name "epileptiform neuralgia," may be much ameliorated by this means, and the existence of the patient elevated from a condition of abject misery to comparative comfort. The extent of the curative influence exerted by the hypodermatic injection in cases of *tic douloureux* will depend upon the age of the patient and upon the presence or absence of structural changes in the nerve or in the brain. Certainly the injection, properly used, will render unnecessary those severe surgical measures sometimes practised (section of the nerve) for temporary relief to the agony which the patient endures. I cannot too strongly insist that for decided relief of these severe

* Clinique Médicale, tome ii. p. 100, *et seq.*

cases very large doses are necessary,—1 grain twice a day. It is quite common to hear that hypodermatic injections have been tried in a certain case and have failed; but upon inquiry it will be found that they have not been properly made, or that a sufficient quantity of morphine has not been used. In a case of severe epileptiform tic treated by me, a hypodermatic injection had been used by another practitioner without avail, but in my hands ½ of a grain of morphine did not fail to induce sound and refreshing sleep for the whole night, and great comfort and freedom from pain for some hours on the following day. What was equally gratifying in this case, the epileptiform convulsions were rendered notably milder.

Cervico-occipital and *cervico-brachial neuralgia* are more amenable to treatment than *tic douloureux*. A few injections of morphine will generally suffice to cure them.

I have had most gratifying success in the treatment of *herpes zoster* by this means. The hypodermatic injection at once suspends the severe pain and burning (intercostal neuralgia) which accompany this disease, and cuts short the duration of the eruption.

Next to the severer forms of tic, the most troublesome neuralgic disorder with which we have to deal is *sciatica*. I may affirm with regard to this what Dr. Anstie has remarked about epileptiform tic, that the hypodermatic method has inaugurated quite a new era in its remedial management.

In severe and protracted cases, in which changes in the nerve and in the nutrition of the limb have taken place, permanent relief cannot always be guaranteed to the patient; but the injections steadily continued in the maximum doses will in a great majority of cases effect a cure finally. When morphine fails, atropine may be tried, and

vice versa; or both, as is preferable in my experience, may be employed together.

Dr. Lawson,* who has had an unfortunate personal experience with this painful and troublesome malady, and has also had a number of cases under treatment, concludes that the hypodermatic injection of morphine "*is almost the only remedy for sciatica.*" He advises the injection to be made into the thigh, four inches below the hip-joint, and over the course of the nerve. Although I can coincide in judgment with Dr. Lawson in respect to the utility of the subcutaneous injection of morphine in the treatment of acute or recent cases of sciatica, I must demur as to chronic or old cases. In these relief to pain and amelioration of the condition may be certainly effected by the morphine injections, but curative results less certainly. We have in the deep injection of chloroform a more decidedly curative agent, and to the article on this subject the reader is now referred.

Notwithstanding the exceeding utility of hypodermatic injections of morphine in the treatment of neuralgia, no judicious physician will rely on them exclusively in the management of severe cases. A suitable dietary and regimen must be enforced; constipation and other reflex sources of nervous disturbance must be corrected, and anæmia relieved by iron, cod-liver oil, the hypophosphites, etc. The part which cachexias—syphilitic, plumbic, mercurial, and paludal—may play must not be overlooked in the selection of remedies. Even where curative results are not attained, where relief to pain only is the result, the existence of the patient may be rendered tolerable.

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* The Medical Times and Gazette, November 12, 1870, p. 555, and also Sciatica, Lumbago, and Brachialgia, London, 1872.

Is it necessary to confine the injections to the "painful points," or to the site where pain is felt? I have already indicated my belief that the position of Mr. Charles Hunter is in the main correct, and that "localization" of the injection is not necessary. There is by no means unanimity of opinion on this point. Dr. Wood, the discoverer of the method, Béhier, Erlenmeyer, Lorent, Eulenberg, and Mitchell, Morehouse, and Keen, think that better results are obtained by injection into the painful spot. Dr. Anstie, although believing that remote injection is in general as effective, maintains that exceptions are occasionally met with. Eulenberg bases his opinion on the fact that tactile and pain sensibility are diminished at the site of the injection. This point is disputed. Immediately after the injection is practised, the neighborhood of the puncture is more sensitive to impressions, but after a time a decline in sensibility occurs. Repeated injection, if followed by inflammatory action, increases the local sensitiveness, but, otherwise, division of the nerves in the skin by the needle lessens the sense of pain.

When the neuralgia is seated deeply in the trunk, the injection must necessarily be practised at some remote point. When the neuralgia is superficial, the nerve accessible, it is an easy task to inject the fluid into the tissues adjacent. This practice—the injecting into the neighborhood of the nerve—is more efficient than remote injection in cases of sciatica, herpes zoster, and other superficial neuralgic affections, especially in cases of long standing, in which we may suppose the sheath of the nerve or the nerve itself has become altered. For it has been found that under such circumstances, the neuralgic pain being local and produced by lesions of the nerve, as, for example, in many cases of sciatica, the injection of various irri-

tant substances into the vicinity of the diseased nerve will often be followed by a notable diminution of the pain and sometimes by a cure. This important fact has been demonstrated by Luton,* Bertin,† and Ruppaner.‡ It is probable that in this way local injections sometimes succeed when remote injections fail.

There are various neuroses of the respiratory tract quickly relieved by the subcutaneous use of morphine, and certain inflammatory affections modified to a remarkable extent. The first named, merely functional disorders, will be considered first.

Laryngismus Stridulus.—This reflex spasm of the laryngeal muscles is quickly relieved by the hypodermatic injection of morphine. As simple attacks occurring in children are readily cured by less powerful measures, this method should be reserved for the more important cases. In adults the same condition of the laryngeal muscles may be due to the pressure of an aneurism or other tumor on the recurrent laryngeal nerve, and is quickly arrested by the morphine injection. *Hysterical aphonia* may be immediately removed by one injection, but I must urge the injunction that morphine must be given with great circumspection to hysterical and nervous subjects generally, since they quickly fall into the morphine habit.

Cough.—Cough maintained by habit—for example, the cough succeeding whooping-cough—is quickly improved by this treatment; sometimes a few injections effect a cure, but if not, decided amelioration. *Whooping-cough* in the spasmodic stage is greatly benefited by the injection of

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* Archives Générales, 1867, p. 506. † Ibid.

‡ Hypodermic Injections, op. cit.

minute quantities of morphine and atropine in combination: $\frac{1}{60}$ to $\frac{1}{20}$ of a grain of morphine and $\frac{1}{350}$ to $\frac{1}{150}$ of a grain of atropine. The cough of bronchitis, of phthisis, of aneurism, etc., is often surprisingly relieved by very small doses of morphine thus administered.

Asthma.—For the relief of an asthmatic paroxysm there is no means now known comparable to the hypodermatic injection of morphine, or of morphine and atropine. This fact I have maintained for many years—in the first and subsequent editions of this work. Within a few years past there have been frequent allusions in periodical medical literature to the good effect of morphine subcutaneously in spasmodic difficulty of breathing, notably in asthma. Professor Sée has especially been prominent in urging this method of treatment, and Professor Hirtz declares it produces "marvellous results." The following are the effects to be expected in ordinary cases:

It promptly relieves the paroxysm and enables the sufferer to lie down and sleep quietly; it lengthens the interval between the seizures and renders succeeding paroxysms milder. Usually I combine atropine with morphine, to give larger doses with safety, for in this as in some other neuroses the maximum doses are sometimes required to give relief. Although the relief afforded is most grateful and surprising, it cannot be alleged, I think, that any cases are cured, but that decided amelioration has been obtained in many who have been subjected to the treatment for some time, is a well-assured fact.

The dose necessary will vary with the susceptibility and habit. Those unaccustomed to the subcutaneous use of morphine, and susceptible, may be relieved by $\frac{1}{12}$ of a grain. This will be a sufficient dose to begin the treatment in any subject, but habit will lessen the power and

diminish the relief, so that increasing doses will be necessary. There is always danger of the morphine habit forming in these cases. The relief afforded is so prompt and grateful that patients wish to have the syringe in their own hands. The remedy is soon abused and an incurable habit formed. Moderation is the condition of benefit, for if the patient is allowed to pursue his own inclination and consume an enormous quantity of morphine, a state of the nervous system is soon reached in which the remedy is constantly necessary.

Emphysema.—The hypodermatic injection of morphine gives more relief to the paroxysmal difficulty of breathing in emphysema than any other remedy. Judiciously used, and not permitted to become a habit, it is a precious resource. Even more apt is the subcutaneous use of morphine to become a habit in emphysema than in asthma, and with even more disastrous results. Having witnessed several unfortunate examples of the morphine habit in such subjects, I desire to impress on my readers the necessity for caution in the use of this remedy.

Hiccough.—Usually the hypodermatic injection of morphine gives prompt relief in this neurosis. It is not effective when hiccough comes on in the course of abdominal —chiefly hepatic—diseases, for the treatment of which morphine has been employed. It is effective the more nearly the disease approaches the neurotic form, and is less effective the more serious the lesions of which hiccough is a symptom.

Acute Inflammatory Affections of the Respiratory Organs.—An acute catarrh of the nares, pharynx, larynx, and bronchi—*a common cold*—may be aborted by the timely administration of a minute quantity ($\frac{1}{16}$ to $\frac{1}{8}$ of a grain) of morphine subcutaneously. It is probably the most

effective treatment which we can employ in the treatment of this disease throughout its course, if the initial stage has passed. It is equally effective in the initial stage of *bronchitis*, and throughout its subsequent stages. An attack of *pneumonia* may be prevented by a full dose of morphine at the formative stage. I make this statement with full knowledge of its importance, and because I have seen cases which appeared to me to have so resulted by this treatment. It is difficult to decide on the affirmative of this proposition, for if a case supposed to be the beginning of pneumonia is stopped as it begins, how shall its true character be determined? To be successful it is essential that a full dose ($\frac{1}{4}$ to $\frac{1}{2}$ of a grain) be given just as the preliminary congestion is developing. I am the more inclined to maintain this ground since Professor A. L. Loomis has recently (1881) strongly advocated the treatment of the first stage of pneumonia by the hypodermatic injection of morphine. When so skilful a diagnostician and therapeutist as Dr. Loomis maintains the superiority of this plan of treatment I am strongly inclined to adopt it, the more especially as my own observations have in a measure prepared me for it.

There can be no two opinions in regard to the success of the treatment of *pleuritis* by the subcutaneous injection of morphine. Here, as in the maladies above referred to, it is possible by a timely use of the remedy to abort an attack of pleurisy. If the disease has passed the initial stage, the same treatment is the best up to the occurrence of exudations.

The Cardiac Neuroses.—I have had very satisfactory results from this method in the treatment of that form of *angina pectoris* which consists essentially in a neuralgic affection of the cardiac nerves. It is also recommended

by Bamberger in the same disease, and by Erlenmeyer, Lorent, Eulenberg,* and other authorities. In the so-called "restraint neuroses" of the heart, a few cases of which have fallen under my observation, the very formidable symptoms were quickly removed by the morphine injection. Whether the symptoms are dependent on irritation of the pneumogastric or reflex irritation through the sympathetic, the good effects of the injection are equally evident. As Handfield Jones† asserts,—an opinion with which my own experience coincides,—the inhibitory action is frequently exerted through the gastric nerves. Rheumatic, malarial, and saturnine affections of the nervous apparatus unquestionably exert an influence in the production of cardiac neuroses.‡ These agree in producing pain, anxiety, breathlessness, and great depression of the heart's action, and are quickly relieved by the hypodermatic injection of morphine. Of course permanent relief will be obtained from suitable treatment for the cachexia on which these neuroses are dependent.

Violent and irregular action of the heart, when a functional trouble merely, is quickly relieved by this treatment. Usually a minute dose suffices. When palpitation and irregularity are due to narrowing and obstruction at the aortic orifice, the hypodermatic injection of morphine seems to me very questionable, if not positively unsafe, practice. There is, however, a condition of the heart in which this treatment does most conspicuous good: in the case of dilated right cavities, with cough, difficult breathing, low state of the vascular tension, ischæmia of the arteries, general œdema, dry skin, and scanty urine.

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* Die hypodermatischen Injectionen, op. cit.

† Functional Nervous Disorders, p. 215, Am. ed.

‡ Ibid., p. 218.

Frequently, under these circumstances, the appetite is lost, the stomach intolerant, and the medicines used for relief, notably digitalis, increase the existing distress and are rejected by vomiting. The good effected by the injection of $\frac{1}{12}$ to $\frac{1}{6}$ of a grain of morphine is most striking: the cough lessens, the breathing becomes easy, the arterial pulse grows stronger and fuller, the skin perspires freely, the kidneys act more energetically, and the stomach becomes quiet, so that food is taken with some relish. Besides these good effects in the changed state of the functions, others are experienced from remedies, especially digitalis, which can now be taken.

The late Dr. Anstie formulated the following point of practice: Whenever opium or morphine is indicated in any case of disease, and anorexia or vomiting or obvious gastric disturbance exists, the remedy should be administered by subcutaneous injection. Although morphine, when exhibited in suitable doses by hypodermatic injection, is less apt to produce nausea and vomiting than when administered by the stomach, this rule is by no means of constant application.

Dyspepsia.—Dr. Clifford Allbutt, of Leeds, England, advocates the hypodermatic use of morphine in nervous dyspepsia with intolerance of food.* There can be no doubt of its utility. Not only is the stomach rendered more tolerant of food, but an appetite is created, and hence the effects are peculiarly grateful. Here, again, I must interpose a caution: nervous subjects are so lifted up out of the Slough of Despond by morphine that a craving is quickly established. The symptom *gastralgia* is usually quickly relieved by this remedy, as also the pain of *gastric*

* The Practitioner, 1869, vol. ii. p. 341.

ulcer; but it does more. By allaying pain and arresting vomiting waste is stopped and the strength nurtured. In the treatment of *acute gastritis* the subcutaneous use of morphine is invaluable, for it relieves the pain and vomiting, checks the inflammation, and obviates the necessity for disturbing the organ by drugs.

One-fourth of a grain is a sufficient quantity to be injected daily in cases of dyspepsia, gastralgia, and ulcer. In acute gastritis, this quantity may be necessary every four or six hours. The site of the injection is of little consequence, but patients generally prefer the epigastric region.

Scirrhus.—In cases of *scirrhus* of any portion of the digestive tract, especially of the stomach, no palliative is comparable to the hypodermatic injection of morphine. The existence of a patient afflicted with scirrhus of stomach is not only prolonged, but is rendered comparatively peaceful and calm by this treatment, for it diminishes or arrests the vomiting, enables the food to be assimilated, gives freedom from pain, promotes sleep, and thus saves the strength.

Cholera.—The most instantaneous and striking relief is afforded by the hypodermatic injection of morphine in *sporadic cholera.* It is indicated in this disorder after the irritant cause, whatever it may be, is evacuated from the intestinal canal. From $\frac{1}{6}$ to $\frac{1}{2}$ of a grain, according to the severity and violence of the attack, may be injected into the epigastrium. The subcutaneous injection is strongly indicated in *epidemic* or *Asiatic cholera.* In this disease, the gastro-intestinal mucous membrane is not in a condition to appropriate remedies; hence the subcutaneous method is eminently rational.

Dr. Patterson,* of the British Seamen's Hospital, Con-

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* The Medical Times and Gazette, January 27, 1872.

stantinople, has employed the hypodermatic injection of morphine in a recent cholera epidemic. Of ten cases "treated in the usual manner," nine died and one recovered. Of forty-two cases treated by morphine subcutaneously, twenty-two recovered and twenty died. Of these forty-two cases, eight were *in articulo mortis* when admitted, one had a severe disease of the liver, one was far advanced in consumption, one was 60 years of age, one was near her confinement, and three were intemperate. Dr. Asche * treated two cases of cholera by this method successfully. According to the author's experience, for the first symptoms in cholera, the morphine injection is the most serviceable remedy, but when cramps occur and collapse is imminent, morphine must be supplemented by chloral. A combination of these agents possesses peculiar curative power in true cholera, as the author has ascertained by actual trial.

The **vomiting of pregnancy** has been relieved by the hypodermatic injection when all other means had failed. For the milder cases this treatment is unnecessary and improper; but in those severe cases in which life is reduced to the lowest ebb by the continual vomiting, and in which forced abortion has hitherto seemed the appropriate remedy, it is eminently successful. In all severe cases in which the ordinary remedies fail to give relief, recourse should be had to the hypodermatic method. A daily morning injection ($\frac{1}{12}$ to $\frac{1}{4}$ of a grain) administered during the period of greatest difficulty, will enable gestation to proceed without danger to the mother, and without the necessity of adopting that serious alternative,—abortion.

Colic.—It is the present practice to employ this method

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* Schmidt's Jahrbücher der gesammten Medicin, Band cxxv. pp. 331–337.

for relieving the pain and spasm of colic. In most of these cases, of course, further treatment is necessary: constipation must be relieved; obstructions be overcome; the saturnine cachexia be removed; but the injection, by relieving spasm of the muscular layer of the bowel, permits these objects to be accomplished much more easily and speedily than would otherwise be possible. Cases of hepatic colic, within the range of my observation, have been quickly relieved by the hypodermatic injection of morphine, where opium internally failed to produce the least mitigation of the pain, and where the inhalation of chloroform procured only the most temporary respite. When pain is very excessive, the reader should remember small doses may not suffice, but $\frac{1}{4}$ and even $\frac{1}{2}$ of a grain may be necessary, repeated according to circumstances.

The same observations are applicable to *nephritic* and *uterine* colic.

Peritonitis.—Opium being the remedy *par excellence* for inflammation of serous membranes, the hypodermatic injection of morphine should be employed in all cases in which promptness and completeness of effect may be desired. This is especially the case in peritonitis, whether primary or secondary. Moreover, as in many cases of this disease the alimentation is of prime importance, and as nausea and vomiting are frequently present, the stomach administration should be deprecated, and the hypodermatic be preferred.

Neuralgia.—In the various forms of neuralgic pain which affect the abdominal organs, whether *gastralgia*, *enteralgia*, *hepatalgia*, *nephralgia*, etc., no remedy procures so prompt and, in many cases, complete relief as the hypodermatic injection of morphine.

Constipation.—In many cases of colic due simply to con-

stipation, the injection not only relieves the pain but overcomes the constipation. It is true that in many cases the first injection temporarily suspends the peristaltic movements, but when habitually used this effect disappears, and the normal movements are not diminished, but promoted. Cases in which constipation existed have thus been corrected during a course of hypodermatic injections. A physiological fact which I have already noted throws light upon this: in a few seconds after the injection, borborygmi and distinct intestinal movements are observed. Should constipation exist in cases in which it may be desirable to use the hypodermatic injection of morphine, the circumstance just mentioned need not be considered a contra-indication.

I have already indicated the utility of the hypodermatic injection of morphine in *nephralgia* and *nephritic colic*. Lorent * refers to its use in parenchymatous nephritis to relieve the headache of uræmic intoxication. To this experience must be added the remarkable observations of Loomis in respect to the exceptional utility of morphine injections in *uræmic convulsions*. When, however, the action of the kidneys is deficient, excretion lessened, or elimination checked, morphine is contra-indicated.

Affections of the Bladder and Urethra.—In cases of *chronic cystitis* I have given great relief by the hypodermatic injection. It suspends those violent expulsive efforts which occasion the principal suffering. In *acute cystitis* the injection, by procuring quiet to the organ and by diminishing the irritability of the mucous membrane, will directly contribute to the cure. The sufferings of the

* Die hypodermatischen Injectionen, op. cit.

patient afflicted with *calculus* may be thus prevented until operative measures can relieve him permanently. *Spasm of the bladder* is quickly relieved by the same means; as also that painful but obscure affection, "the bar," which sometimes succeeds too violent and prolonged sexual intercourse. The hypodermatic injection may also be used to relieve *spasmodic stricture*, but for this purpose it is by no means equal in my experience to chloroform or to galvanism by the method of electrolysis. It is convenient to blunt the sensibility preliminary to the operation of catheterism, and is a capital means for relieving *chordee* and prolonged and teasing erections. But to prevent unpleasant erections and nocturnal losses, the use of morphine and atropine together is preferable to morphine alone. For information on this subject I refer the reader to the chapter on "Morphine and Atropine."

The hypodermatic injection of morphine is capable of a variety of important uses in obstetric practice. It promptly arrests those *false and irregular pains* at the beginning of labor, which annoy the woman without advancing the case. In primiparæ it has been used to diminish the sufferings of labor. It is much better than morphine by the stomach to procure rest and sleep during a prolonged first stage. No remedy is equal to the hypodermatic injection of morphine for the relief of *after-pains*. In all of these circumstances no fear need be entertained that the judicious use of the injection will interfere with regular uterine contractions. The quantity to be administered will vary from $\frac{1}{6}$ to $\frac{1}{4}$ of a grain; the latter amount need rarely be exceeded. At the present time morphine has been displaced in professional esteem by the recently-discovered analgesics of the aromatic series of coal-oil derivatives.

The pain of *dysmenorrhœa* can be promptly relieved by subcutaneous injection of morphine; but for all pelvic pain, as Dr. Anstie has remarked, atropine is the best remedy. As a palliative in *scirrhus of the uterus* and of the *mammæ* the hypodermatic injection of morphine is much superior, in respect of economy and effectiveness, to the stomach administration of the same drug. Lastly, on this topic, in all cases of severe pain involving any of these organs the hypodermatic injection of morphine is indicated.

Diseases of Constitutional or Specific Origin.—Dr. William Henry Fuller writes enthusiastically of the great value of the hypodermatic injection of morphine for relieving the pain of *acute rheumatism*. I shall have some remarks to make in a succeeding chapter upon the use of morphine and atropine in that disease, and will not anticipate. I have used with great advantage the hypodermatic injection of morphine to relieve the *nocturnal pains of tertiary syphilis*. Besides the complete and permanent relief to the pain which I have procured by persistence in the injections, I have observed also remarkable improvement in the lesions of bones and muscles. Not only in syphilitic but other forms of disease in which pain precedes, and in which an altered condition of the nerves produces structural changes, I have observed that relief to the pain is followed by cessation of the morbid process in the part. This fact is well shown in *zoster*, an affection of the skin dependent upon some functional disturbance of its sensory nerves, which disappears very promptly after relief of the hyperæsthesia. Of course, in syphilitic neuralgia, the hypodermatic injection should not be used to the exclusion of the iodide of potassium. In the cases in which I have employed it the pain persisted, notwithstanding repeated use of large doses of the iodide,—a condition of

things not infrequently encountered, for long use of this remedy and to the point of saturation—to borrow a term from the chemists—induces a tolerance fatal to therapeutical efficiency.

In Certain Surgical Diseases and Operations.—To prevent shock, and to relieve pain after operations and injuries, the hypodermatic injection of morphine is not as much used as it should be. No means affords such relief as this in the first few hours after *fracture* or *dislocation*. The reduction of dislocations may be facilitated and the pain prevented by the injection, in cases where it is undesirable or impracticable to use chloroform. It has been shown* that the *reduction of strangulated hernia* is much facilitated by the same means. In all operations requiring the knife, to prevent the after-pain, to sustain the vital powers, and to maintain the necessary quietude of wounded parts, the hypodermatic injection of morphine should be used.

To aid Chloroform Narcosis.—Bernard† made the important discovery that the use of morphine subcutaneously, previously to the inhalation of chloroform, aided materially in the production of anæsthesia, and with a much smaller quantity of chloroform, and prolonged the stage of narcosis so that continued inhalation was not required. Nussbaum, the distinguished surgeon of Munich, soon after made a similar observation independently. Bernard advised the subcutaneous use of morphine before commencing the inhalation; Nussbaum, after the condition of analgesia had been commenced. Professor William Warren Greene, M.D., then of Pittsfield, Massachusetts,

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* The Practitioner, August, 1869.

† Bul. Général de Thérapeutique, tome. lxxvii. p. 241, *et seq.*

some time afterwards announced the same fact, without being aware, apparently, of the recommendation of Bernard and the practical application of the discovery to surgical practice by Nussbaum. The effect of the injection before beginning the inhalation is to diminish the irritation of the air-passages, to prevent the coughing and struggling, and doubtless, also, it removes the danger of cardiac paralysis, which in some rather rare cases takes place with the first action of the anæsthetic on the cardiac ganglia. In many subjects protracted vomiting and great depression of the vital powers occur on recovery from the anæsthetic state: a morphine injection will prevent these results. It appears in a high degree probable that the subcutaneous injection of morphine will obviate the tendency to death by cardiac or respiratory failure in the anæsthetic state. As it does prolong the anæsthetic stage with a lessened quantity of chloroform, it seems incredible that surgeons will neglect so important an addition to their resources.

As a Physiological Antagonist.—The antagonism existing between morphine and atropine has been abundantly proved by clinical facts. The nature of this antagonism and the practice based on it will be considered in the section devoted to this subject. Morphine has been used successfully as an antagonist in poisoning by *gelsemium*, and by *veratrum viride*. In a case of poisoning by gelsemium, narrated by Dr. Courtwright,* the symptoms were promptly relieved by the subcutaneous injection of morphine. Two grains of morphine sulphate were required to antagonize a tablespoonful of the saturated tincture, about equal in strength to the official fluid extract. Several cases of successful treatment of opium-poisoning by veratrum viride

* The Cincinnati Lancet and Observer, 1876, vol. xxxvii. p. 961.

have been reported, and in many cases an alarming degree of depression caused by veratrum viride has been removed by the administration of tincture of opium. The clinical experience has been confirmed by trials on animals.*

THE OPIUM OR MORPHINE HABIT AND ITS TREATMENT.

The introduction of the hypodermatic syringe has placed in the hands of man a means of intoxication more seductive than any which has heretofore contributed to his craving for narcotic stimulation. So common now are the instances of its habitual use, and so enslaving is the habit when indulged in by this mode, that a lover of his kind must regard the future of society with no little apprehension. It may well be questioned whether the world has been the gainer or the loser by the discovery of subcutaneous medication; for every remote village has its slave, and not infrequently several, to the hypodermatic syringe, and in the larger cities men in business and in the professions, women condemned to a life of constant invalidism, and ladies immersed in the gayeties of social life, are alike bound to a habit which they loathe, but whose bonds they are powerless to break. Lamentable examples are daily encountered of men and women, regardful only of the morphine intoxication and indifferent to all the duties and obligations of life, reduced to a state of mental and moral weakness most pitiable to behold.

Usually the habit of morphinism is formed in consequence of the legitimate use of the hypodermatic syringe in the treatment of disease. Employed in chronic painful

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* Cartwright Lectures for 1880, On the Antagonism between Medicines and between Remedies and Diseases. New York, 1881, p. 77.

maladies for a long period, it is discovered, when an attempt is made to discontinue the injections, that the patient cannot or will not bear the disagreeable, even painful, sensations which now occur. More frequently, when the injections are to be used for a long time, the patient is unwisely intrusted with the instrument, and taught all the mysteries of the solutions and the mode of administration. Under these circumstances, there being no restrictions on the sale of the drug, the patient rapidly increases the dose, and presently comes to use a quantity of morphine which may seem almost incredible. Twenty, forty, sixty grains of morphine daily the author has known to be consumed by persons who have come under his observation, and Levinstein* records cases in which, in a short time, 1 gramme (15 grains) was the daily allowance. To maintain a constant effect on the organism there must be a material increase in the amount administered every few days, and ultimately in most subjects a condition of the nervous system is brought about in which the new dose simply relieves the horrors and bodily depression left by the preceding quantity. Slaves to a vice beyond their control, they no longer experience the feeling of well-being, the exhilaration, the intoxication, which were produced at first. There are very obvious differences in the physical and mental effects of moderate doses used for a comparatively short period and large doses administered for years. It will conduce to a clearer conception of the subject to treat of these two classes of morphiamaniacs in separate paragraphs.

1. *Small Doses for a Short Period.*—If the injections have been administered in a moderate quantity—$\frac{1}{2}$ of a grain to 1 grain several times a day for six months—and at a

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* Die Morphiumsucht. Berlin, 1877.

fixed hour, the patient begins to experience characteristic nervous sensations as the time for the injection approaches; he becomes uneasy, restless, "fidgety;" he is wakeful, his senses are abnormally acute, and he has more or less headache and vertigo; his feelings are easily touched; a globus rises in the throat; nausea and troublesome borborygmi, with some intestinal pain, occur; general *malaise*, a sensation of fatigue, accompanied with muscular pains and decided inability for physical exertion, with depression and a cold sweat, are felt. These are the sensations, in less or greater degree, according to the time which has intervened, that inform the individual of the need of a new dose. Marvellous, indeed, is the change when the injection is practised. All the disagreeable, even painful, sensations and the dreadful unrest, which had but a moment before caused an indescribable discomfort, have now vanished, and in their stead are present a feeling of perfect comfort, and an active state of body and mind equal to any effort. How grateful is the patient for the feeling of relief, and how impossible to forego the use of a drug which so transforms his feelings and imparts a glow to the world about him!

If the injections are suspended suddenly and entirely, very severe nervous disturbances are induced. An obstinate headache, vertigo, tinnitus; wakefulness, coming on after a short period of somnolence, interspersed with snatches of sleep disturbed by horrible dreams; during the waking moments an inexpressible anxiety and gloom and depression; unappeasable restlessness, with an overpowering sense of fatigue and a deep-seated aching in the members; nausea, vomiting, repugnance to food, intestinal pain, diarrhœa, sometimes of a colliquative character; very great depression of the powers of life, a weak, small pulse,

becoming rapid and thready on exertion; coldness of the surface, a cold, clammy sweat, are the formidable symptoms developed by the sudden withdrawal of morphine, when used for some months in moderate quantity.

2. *Large Doses for a Long Period.* — The symptoms already detailed are present in these cases, but are more pronounced. The physiognomy of the morphiamaniac is peculiar: his face pallid, eyes dull and glazed, pupil small and sluggish, countenance strange and weird, expression unearthly. His skin has an earthy, sallow tint, the nutrition impaired either in the direction of an increased accumulation of fat, the tissues being soft and watery, the muscles small and wanting in contractile energy, or in the way of general emaciation. Whether gaining or losing in weight, feebleness is a characteristic of the bodily state. The least exertion causes a rapid pulse and accelerates the breathing. The appetite is poor and digestion is feeble. Great repugnance is felt to animal food, and, indeed, towards all the more substantial articles of diet, and fluids and fruits are almost wholly used. This abnormal taste is in part due to the dry mouth and cracked tongue,—physical conditions unfavorable to the sense of taste,—and in part to the poor digestion. The secretions of the intestinal canal and of its annexed organs, notably the liver, are so diminished in amount as to affect digestion seriously, hence the stools are dry, hard, scybala-like, yellow or grayish in color, and coated with tough mucus. So insensible does the mucous membrane become that the fæces are retained for lengthened periods, hemorrhoids form, and an obstinate eczematous eruption appears at the margin of the anus. After a time, the retained fæces set up a high degree of irritation, an acute gastro-intestinal catarrh is produced, and an attack of cholera morbus occurs, with

sometimes very serious depression of the powers of life. In some individuals, it is true, the hypodermatic use of morphine does not impair the appetite and the digestive power, and does not interfere with the normal and regular action of the intestines; but these cases are exceptional. Gastro-intestinal attacks, such as I have described, occur in some morphiamaniacs every few weeks; in others every few months,—several times, certainly, during the course of the year. The effect of the capricious and *bizarre goûts*, of the lessened digestive power, and of the diminished absorption, is to impair the quality of the blood,—to induce a serious kind of anæmia. None of the organs of the body can perform their functions properly under these circumstances; hence the mental and physical feebleness of the morphiamaniac. There is a function, however, which suffers especially,—the reproductive. The first effect of the use of morphine to a moderate extent is to increase the sexual feelings, but a considerable dose administered for the first time will depress or suspend the power of erection. Victims of the subcutaneous use of morphine soon lose all sexual feeling, and are deprived of the power of erection and the production of semen. During the continuance of the habit no semen whatever is secreted, and no nocturnal losses occur; when the habit ceases, the secretion of semen is resumed and involuntary evacuations again take place. Morphine suspends the function without otherwise impairing it, for we find that these subjects possess the same virility after the cessation of the morphine habit that they possessed before. The same result occurs in women. When the morphine habit is established, the menstrual function ceases and the sexual life is entirely suspended, and the woman is as absolutely without all of those feelings and instincts pertaining to her sexual relations as if they

had never existed. As in man, this suspension of the sexual life is coexistent with the morphine habit, for the natural order is restored when the vice ceases.

Levinstein emphasizes the occurrence of albuminuria and diabetes in cases of morphine habit. I have made many urinary examinations in these cases, and have as yet met with no instances of these maladies. It is true, in a few examples of considerable hepatic disturbance, I have noted the presence of sugar in the urine, but it was not permanent, and they could not, therefore, be regarded as cases of diabetes. Without presuming to call in question Levinstein's accuracy, it may be affirmed of cases met with in this country, that they are not due to the subcutaneous use of morphine.

The frequent use of the syringe, often the hasty introduction of the needle, and the use of a rusty and dirty needle, the injection of badly-prepared solutions, the repeated injection into certain localities, have a disastrous effect. Large, hard nodules form, which slowly suppurate, extensive sloughing may take place, and septicæmia and pyæmia sometimes occur with fatal result. In a considerable number of these morphiamaniacs, suppuration, abscesses of considerable size, and ulcers are produced. I have seen the arms, the abdomen, the thighs and legs, a mass of ulcers, of abscesses in various stages of formation, and of cicatrices (Levinstein).

Dujardin-Beaumetz* narrates a case in which the injuries thus produced resulted in death. M. Calvel† has collected many cases of abscesses, traumatic fever, and other accidents produced by the injections, but he rightly enough refers them to the causes above mentioned,—the

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* Bul. Général de Thérapeutique, Jan., 1879, p. 87. † Thèse de Paris.

state of the needle, improperly-prepared solutions, and the cachexia induced by the morphine habit. Braithwaite* reports a most instructive case of morphine habit of six years' duration, in which there occurred numerous abortions. In a new pregnancy at six months, a vast abscess formed in the thigh, from which erysipelas developed, and a high degree of constitutional disturbance arose. Nevertheless, delivery occurred at term, and an attempt was then made to stop the morphine suddenly, but most serious troubles resulted, the erysipelas reappeared, and the attempt had to be abandoned. On the other hand, many escape these accidents entirely. One of the most inveterate subjects I have ever encountered was a man living in the wilds of Texas, who used a glass hypodermatic syringe that had been broken many times and mended with successive deposits of sealing-wax, until only the rusty old needle remained in view, and yet escaped all accidents. Several instances have been reported—one already quoted—in which death was produced by the suppuration and the systemic condition thereby induced. That there is a special state of the tissues induced by morphine, to which the formation of abscesses is due, is hardly admissible. The causes mentioned above are quite sufficient to account for them.

After a time the repetition of the injection does not induce any pleasurable sensations. For a few minutes after the insertion of the morphine the patient experiences mental sensations of a most depressing kind, but gradually a condition of well-being follows, consisting chiefly in relief from the horrible mental and physical agony which comes on as the morphine influence declines.

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* The Lancet, 1878, p. 874.

The morphiamaniac never has sound and refreshing sleep. Although, after a period of wakefulness due to the stimulant action of the narcotic, he lapses into a condition of somnolence more or less profound, it is disturbed by dreams and visions of the most horrifying aspect, entirely without the range of human experiences. If the individual awake in the midst of these weird dreams, some time elapses before he can realize his situation, and then comes over him, like a flood, a dreadful sense of the position in which the morphine has placed him. Doubtless the visions of the English Opium-Eater, which are not realized in the experiences of those who take opium as a test experiment, were actually present during sleep or the half-waking state. It results from this condition of the brain during sleep that the organ is not adequately rested, hence the sense of fatigue of mind which is felt on awaking, and which is removed only by the narcotic. In many subjects, ultimately, sound sleep is never produced, and a certain proportion pass into that condition of obstinate wakefulness known as *coma vigil.* The action of morphine must then be supplemented by the bromides, chloral, etc., for this condition is one of imminent danger to the mind. In spite of all the means which can be used, some of these pass into a busy, active, and trembling delirium,—*delirium tremens*,—or into acute mania or acute melancholia, with strong suicidal impulses.*

In the more severe cases of morphine habit, attacks of fever similar to ordinary intermittents take place irregularly. In my experience these attacks are usually associated with an acute gastro-intestinal catarrh, and are preceded by constipation and a much overloaded colon.

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* Leidesdorf, The London Medical Record, November 15, 1876.

They occur more usually in the summer and fall, rarely in the winter, and they may appear in regular order for several days as quotidian intermittent, or assume the remittent type, terminating in two or three days in a profuse sweat. When the paroxysms are quotidian, they are identical with quotidian ague,—there is a chill, followed by fever and sweat. Although they may be regular, they are usually irregular, and are not amenable to quinine, but do readily yield to an increased quantity of morphine. Very great depression of the powers of life may occur in some of these cases when a chill is coincident with a severe attack of cholera morbus. I have known instances in which the objective phenomena of a seizure were similar to those of a "pernicious intermittent."

Besides the immediate results of the morphine habit by hypodermatic use, the unfortunate morphiamaniac is assailed by dangers accidental and contingent, but nevertheless of high importance. A sudden illness, the performance of a surgical operation, may be seriously complicated if the physician or surgeon in attendance is not aware of the existence of the habit and the extent to which it is indulged. Still more serious are cases of sudden insensibility or impairment of the language faculty, for then the patient cannot communicate the fact of the habit.

Sufficient data do not exist as yet to permit an exact statement of the anatomical changes occurring in the morphiamaniac, except the anæmia or cachexia. It is probable that no real changes take place, and that the morbid complexus is really functional in character.

When, in the old and confirmed cases of morphine habit, an attempt is made to withdraw the morphine suddenly, the most serious symptoms are produced. As soon as the effect of the last dose taken has passed off, they

describe various uneasy sensations,—of creeping and crawling in the skin; tingling in the hairy scalp, in the hands and feet, and other places; a more or less profuse, often very profuse, perspiration breaks out over the body; the nose runs freely with a watery mucus, and sneezing comes on in paroxysms; nausea is experienced, and after a time vomiting occurs; the bowels become relaxed, and soon an exhausting watery diarrhœa sets in; the pulse grows quick and the action of the heart excitable and more feeble as the waste increases by vomiting and purging; the urine may be albuminous or contain sugar, as affirmed by Levinstein, and the nervous system falls into a very unstable condition. The statement of Levinstein on this point, however, has not been confirmed by those most competent to judge, and the negative evidence is universally against him thus far. That some of the narcotics in question induce the saccharine reaction, especially cocaine, is a well-known fact. As these symptoms progress, the mind is disturbed by horrible depression during the waking moments, and by strange, fantastic, weird dreams during the brief snatches of sleep. Great depression of the vital powers comes on as the case progresses, and in old subjects of morphine addiction a condition of collapse ensues. Having had a patient who was compelled to go through such an experience, I shall not be again induced to repeat it, if for no other, for strictly humanitarian reasons, since the mental and physical sufferings are truly horrible. Levinstein advocates this method and succeeds, but one may accomplish results in an asylum not attainable in ordinary practice, where the patient possesses entire liberty of action. But Levinstein's experience is not agreeable to any humanitarian. Although the details are brief, it is obvious that his patients suffer severely. He describes two degrees of col-

lapse,—the mild and the severe,—in which the patients pass into the condition of the algid stage of cholera, and may require, to save them from death, a hypodermatic injection of morphine. The only permanent cures are, in the experience of the author, those in whom the reduction was gradual. I do not deny that by the immediate withdrawal a cure may be effected in a few days or weeks, but such cures are not permanent. The time during which they are under treatment does not suffice to relieve the system of the terrible unrest, the wakefulness, and the longing, which persist for months after the withdrawal of morphine. On the other hand, by the slow, almost insensible, diminution of the daily amount, the nervous system has the opportunity to adapt itself to the change, and hence the unrest and the longing die out.

There are, really, two classes of morphine consumers:

1. Those who take the drug as a means of intoxication.

2. Those who have had morphine prescribed as a remedy, and are forced to continue its use after the subsidence of the disease or because of the persistence of the affection for which originally given.

In accordance with the usual practice, I have stated the evils of opium-taking in the strongest colors, that what influence soever I possess may be thrown against the formation of the habit. It must be admitted, however, that there is another side to the question; that examples exist in considerable numbers of men and women who have only been benefited by the habitual use of morphine or opium; who have during many years carried on business, and have carefully performed all of the duties of life incumbent on them, and have been rather more free than their neighbors from the maladies and disabilities usual to advancing years. Dr. Price, of Burlington, New

Jersey, who is known as the unrelenting foe of alcohol and opium, has within the past year narrated several cases in which the facts were as just stated. Professor H. C. Wood has mentioned the influence of opium on his late uncle during the last years of his life. He does not hesitate to declare that the daily use of a few grains of crude opium increased the length of his uncle's life and procured immunity from many distresses he would otherwise have suffered from. He gives the opinion that no proof exists showing that opium causes structural alterations in the human body.

De Quincey died at 74. His health in early life was very precarious, but he achieved an immense amount of literary work, which seems to be increasing in reputation, and is now more read than during his lifetime. He is the author of "Confessions of an English Opium-Eater,"—a book which, although full of extraordinary writing, describes a state of things as little like the reality of ordinary experience under opium as can be conceived. It cannot be doubted, I think, that De Quincey had done no better had opium never crossed his path at all.

The case of Coleridge has, as I conceive, been misinterpreted. He suffered from acute and subacute rheumatism, and at 19 had a most severe seizure, and his physician prescribed, among other remedies, *opium*. It gave him most grateful relief, and he became what we now call an *habitué;* but "as he suffered much, much may be forgiven him." He had for many years, at least, severe pain which only opium would quiet.

The use of the anodyne began when he was 18 or 19. The "Ancient Mariner" was written while on a journey to the Lakes, or certainly was begun. My space will not permit me to go into the details of the history now told

of the poem. It must be clear, however, that Coleridge wrote the greatest of his works after beginning the use of opium!

Wilkie Collins, the English novelist, used laudanum as an aid to literary composition during his active life, and had reached the dose of one pint at the time of his death.

The New York courts have lately made the ruling that the use of opium is of itself not a bar to testamentary capacity.

I might thus multiply examples, showing that in many persons the use of opium does not impair the powers, but rather sustains and increases them. I do not wish to be understood as expressing more than that in various instances—in a limited number—opium acts thus favorably. In the great majority, however, it must be said that only disaster attends on him who becomes an habitual opium-eater.

I feel bound in justice to my work to state, as I have done, the reverse side of opium-eating; but at the same time no physician guards more jealously than I do the interests of his patients by refraining from the use of narcotics when it can properly be done.

Treatment of the Morphine Habit.—The methods of treating morphine addiction are three in number, and can be thus classed:

The slow or gradual method.

The quick method.

The immediate method.

The first of these consists in such slow diminution of the dose habitually taken that the patient is hardly conscious of the change, and a long period of time may be consumed in the process.

By the quick method the morphine is withdrawn in a few days, and by some occasional doses the condition of collapse which constantly threatens is warded off. From one to four weeks are occupied with the treatment, including the withdrawal, and very often the patient, having arrived at a state of tolerance of his sensations due to the absence of the accustomed narcotic impression, is in such a condition that he can maintain his ground and overcome those abnormal feelings which follow in the wake of stopping the morphine. My own voice is decidedly in favor of the slow method,—the withdrawal of morphine by insensible gradations,—so that when the final dose is disposed of, the peculiar sensations that arise are feeble and borne without special difficulty. Although a long period may be required to accomplish this, the time is well expended if success is assured. The point of chief difficulty is the getting rid of those abnormal sensations which come on as the morphine influences decline. Various agents have been proposed to act as substitutes for the opium or morphine, but it needs little investigation to show that any complete substitute must have the same influence on the system, and must therefore be just as difficult to recover from. To substitute one form of intoxication for another may be a loss instead of a gain. Of all other so-called substitutes than the two to be spoken of below, there is nothing favorable to be said. The two that may be considered to have genuine powers and yet have little real affinity for each other are *antipyrin* and *cocaine*. These two differ not less between themselves than they differ from morphine in the mode and character of their action. They agree in the power to remove pain, but not in the mode by which it is accomplished, except that each one has an influence upon the production of pain at the central apparatus,

in the brain, in the spinal cord, or in the peripheral nerves.

To conduct the treatment known as the "immediate method," it is necessary to be provided with the means of relief for the condition akin to the algid stage of cholera or that which comes on a few hours after the morphine is withdrawn. Antipyrin and cocaine are most effective for this purpose, and are to be used *pro re nata*. The injection of ether may be necessary when the vital powers are depressed to the danger-line. Even then, in two to four days after the morphine has been stopped, such a condition of depression, threatening lethal effects, may occur notwithstanding the use of antipyrin and cocaine, that some morphine may be necessary to restore the vital functions. No case of long-standing morphine addiction can be treated by the immediate method in its purity; some morphine must be given to save life.

As I have stated, my experience and direct observations will not admit of any other conclusion than that the slow method is the best of the three kinds of attempts to cure. If the immediate method is pursued with resolution, the results are brilliant, but by no means permanent. In the quick method—two to four weeks—the result will be excellent, but relapses are so numerous that the good accomplished at last is trivial.

On the contrary, the method of slow reduction of the amount taken is the true method, and has a large proportion of cures to its credit.

Why do relapses occur by the immediate or quick methods? Because the system of the patient has not had time to accommodate itself to the changed state of things. The abnormal sensations have not had time to disappear. If a habit has been in existence for many years, how long

does it take, *cæteris paribus*, for the abnormal conditions to be displaced entirely by the normal feelings and associations? If the individual continues to feel the need of an impression now wanting, if the terrible unrest induced by the absence of morphine is still present, how can the unfortunate individual prevent his mind flying to the mode of relief which but recently he has enjoyed?

The amount of difficulty in the treatment of any case will depend on sex, constitutional peculiarities, the length of time the habit has continued, and the *per diem* quantity which has been administered. When the physician or an attendant has administered the injections and the patient has not acquired the method, the task is comparatively easy. The following rules will be found useful, indeed, essential:

Never stop the injections suddenly.

Diminish the dose very gradually, without the knowledge of the patient, if possible.

When the amount of morphine consumed is large (say 5 grains a day) it is better to add cocaine in such proportion that a physiological balance may be secured; in other words, that the effects of both may be equal to the other, neither one preponderating. When this is effected the reduction in dose should include both, and the cocaine be reduced in quantity *pari passu* with the morphine. A distinct antagonism exists between morphine and cocaine, although it does not extend entirely through the whole range of their actions, and hence, as the experiment has not been tried, it remains doubtful whether it is sufficient to overcome the toxic action in either.

Although the first confident expectation, that in cocaine is a remedy for the opium habit, has not been realized, it nevertheless plays an important part in the management

of these cases, and it is most helpful in bringing about a better state.

But the difficulty of breaking up the morphine habit is vastly greater in the case of confirmed subjects who have used the syringe themselves for years. What method must be pursued in these cases? I am firmly of the opinion that the morphine should be very gradually diminished,—so gradually as to make but little demand on the moral strength and the self-control. If the patient is required to suffer the horrible sensations produced by the want of morphine, the treatment will fail, for he will prefer indulgence though it lead to death. The patient's co-operation must be secured, and he must decide for himself that the attempt shall be made. Strangely enough, the morphiamaniac's impatience must be held in check. When under the influence of the morphine they have great confidence in their self-control, and they demand that a large reduction shall at once be made. It is never safe to yield to these importunities, for when the flood of desire comes rolling in they are powerless to resist, and when cheating begins the attempt is a failure. It should be a fundamental rule with every practitioner to reduce the morphine by slow stages.

The patient must give up the custody and use of the syringe to some one else, and must have the quantity necessary to make him comfortable at certain regular intervals, and without failure. If the daily quantity used is not large,—say 4 grains,—the syringe should be given up at once, and the morphine be administered by the stomach in proportional quantity,—*i.e.*, about three times as much.

Thus, if 4 grains was the daily allowance subcutaneously, at least 12 grains will be needed by the stomach. The

rule may be formulated as follows: *Give by the stomach a sufficient quantity to make and keep the patient comfortable.* It is a most important advantage gained to exchange the subcutaneous mode of administration for the stomachal; for, although the effect is slower in the latter, it is better maintained, and the patient experiences less sudden and severe changes in his feelings. What is even more important, the chain of morbid associations connected with the hypodermatic syringe is broken up, and the patient feels hopeful, and anticipates release from his bondage because already freed from the necessity of puncturing his skin.

When the *per diem* allowance of morphine hypodermatically is from one scruple to a drachm, considerable reduction must take place before the syringe can be abandoned, but it should be dropped at the earliest moment.

The rate of reduction should not be more rapid than $\frac{1}{16}$ of a grain hypodermatically, and $\frac{1}{5}$ of a grain by the stomach, each three to eight days; but an arbitrary rule of that kind cannot be maintained in all instances; it must be varied somewhat according to the habits and idiosyncrasies especially. The necessary time must be given to it, though a year or more may be required. Haste on the part of the physician and impatience on the part of the subject will defeat the purpose in view.

Are there any aids to treatment? Is there not some drug which may destroy the appetite for the narcotic? These questions are constantly asked, and they may be answered in the affirmative, but not in accordance with popular notions. The success of the plan proposed may be facilitated by several expedients. It is of the first importance to correct the abnormal condition of the diges-

tive functions. One or two compound cathartic pills at night will change the character of the evacuations, and induce a more healthy state of the intestines. As a stomachic and nerve tonic, a solution of strychnine in a mineral acid is highly useful:

℞ Strychninæ, gr. i;
Acid. muriatic. dil., ℥ij. M.

Sig.—Ten minims in a tablespoonful of water three times a day, before meals.

If the stomach is irritable and the hepatic function torpid, the following prescription is serviceable:

℞ Acid. carbolic.,
Tinct. iodi, āā ℥ss. M.

Sig.—One or two drops in water three times a day, before meals.

If there is merely an atonic condition of the digestive functions, the tincture of nux vomica, in doses of 10 to 15 drops three times a day, may be very useful. Under the same circumstances, quinine is indicated, especially in solution with a mineral acid; or the quinine may be given in combination with iron, as in the elixir of phosphate of iron, quinine, and strychnine; or the tinctures of cinchona, with the other bitters, may be prescribed in combination. The fluid extract of cuca or coca (*Erythroxylon Coca*) has been used with distinct advantage in many cases as a tonic and restorative. According to some experienced observers, it has an effect on the nervous system which entitles it to be regarded as supplying the place of a need or a craving.

An important point in the management of these cases is the alimentation. If the morphiamaniac can take food and digest it, the difficulty in the treatment is reduced

one-half. It is, in fact, a useless effort to give tonics if the food-supply is wanting, or inappropriate, or undigested. Milk, egg-nog, animal broths, should be given freely, and as soon as possible steak, chops, and other substantial food. Their digestion may be aided by the simultaneous administration of pepsin, pancreatine, and mineral acids. If the stomach refuses everything else, it will probably take milk, or milk and lime-water. If but little food enters the stomach, it may be supplemented by rectal alimentation,—notably by injections of defibrinated blood, on the plan of Dr. Smith, of New York. If food can be taken in a small quantity only, it should be taken frequently,—every three hours. The supreme point is to renovate the blood, so that all the organs shall functionate properly. With an improved state of the cerebral nutrition there will come a more manly feeling, a firmer will, and a higher moral sense.

The use of alcohol is a highly-important question. When the nervous system is losing the loved morphine impression, it will take kindly to alcohol. There is a loss rather than a gain in the substitution of alcohol for morphine, and, unfortunately, this is an exchange which has not infrequently been made. Levinstein refers to cases, and I have known the exchange to be made in both ways. Although alcohol in any of its forms must be used with caution, it is undeniably serviceable. A whiskey toddy at bed-hour may induce quiet and refreshing sleep; wine at dinner in moderation will promote digestion. But I especially warn the practitioner against a procedure which the patient will be inclined to adopt,—that is, to take sufficient alcohol to cause a distinct impression on the nervous system, in place of the morphine impression. This must result disastrously, for when the alcohol influence expires

there will occur such a condition of depression that more alcohol or morphine will be necessary.

To procure quiet and refreshing sleep is essential in these cases. When the morphine is very gradually diminished, the function of sleep may not be disturbed, and if proper care is used, will not be. When, however, the morphine is decreased rapidly, or is suddenly stopped, the most agonizing feeling of unrest is felt all over the body, but especially in the members, conjoined with the most absolute wakefulness. Under these circumstances chloralamide may be extremely useful, indispensable, indeed, for by procuring sound and refreshing sleep, life even may be saved. During the course of treatment chloral or chloralamide will be necessary now and then, but the utmost circumspection is required to prevent the substitution of a chloral for a morphine habit. The patient is always clamorous for some agent as a substitute.

Occupation is an important adjunct to the treatment, for every disagreeable sensation increases with the attention given to it. The occupation should give employment to both mind and body, and should be engrossing but not harassing. Depressing news, the ordinary annoyances of life, and especially anxiety of every kind and degree, should be removed from these patients, that there may be no excuse for the smallest departure from the prescribed course. Travel may be serviceable, but there are so many contingencies as to involve risk of failure in the treatment. Furthermore, there are the fewest number in a pecuniary condition to justify the attendance and the largely-increased expenditure. But change of scene, in so far that the individual is removed from the associations connected with his habit, is always desirable.

CODEINUM: CODEINE.

Codeinæ Sulphas. [*Sulphate of Codeine.*]
Codeinæ Hydrochloras. [*Hydrochlorate of Codeine.*]

As the strength of this alkaloid is barely one-half that of morphine, the dose for hypodermatic injection is from ¼ to ½—even to 1 grain. As, however, commercial codeine is apt to contain morphine, large doses ought not to be given until the strength of the specimen used is ascertained. Extemporaneous solutions should be prepared from powders of the strength required.

Physiological Effects.—The actions of codeine are similar to those of morphine. It is less nauseant and more hypnotic. It probably, also, has less effect in restraining the intestinal movements, and in lessening the irritability of the bladder. The various secretions and excretions are less affected by codeine than by morphine. Codeine has also less pain-relieving power. While thus, in the whole range of the action, codeine is less powerful than morphine, it has more distinctly a hypnotic action and less nauseating and constipating effects. When the usual medicinal dose—¼ to ½ of a grain—is administered subcutaneously, the same local effects are produced by codeine as by morphine. The systemic action is as prompt, but is less decided; the stage of stimulation is less pronounced and shorter in duration, and the action of the heart and the arterial tension are less elevated than is the case with morphine. From these actions it may be inferred that codeine is possessed of valuable qualities which might be utilized in preference to morphine in various morbid states.

Therapy.—Codeine may be used in the various maladies in which morphine is now administered hypodermatically,

but it presents no advantages, except in those cases in which a special hypnotic action is desired,—in *mania*, *hypochondria*, and *delirium tremens*, with the limitations already enjoined in the case of morphine. In *diabetes* it has been employed with distinct advantage. Whether crude opium, morphine, or codeine is best in the treatment of diabetes has been much discussed. Sometimes one is used, sometimes another; but it is now conceded by those best acquainted with the subject that morphine is more reliable and effective. Dr. Pavy has declared himself as holding the opinion that morphine is the first of remedies, and Dr. Bruce maintains that so long as the patient takes morphine he is safe. In the *neuroses of the respiratory organs* it is probable that codeine would prove more advantageous than morphine.

Codeine is one of the remedies much in vogue now in the treatment of *chronic morphinism*. It acts as a substitute for the more powerful medicament, the narcotic influence of the codeine taking the place of the morphine influence. As codeine possesses only about one-half of the power exerted by morphine, it is clear that if codeine fill the place of morphine in equal measure, the patient has gained one-half against the influence that has been habitually exercised over him.

In the plan of immediate withdrawal of morphine, codeine can be employed to prevent or to remove that low state of the mind that comes on, and that depression of the vital forces which leads on to collapse.

According to the plan of quick withdrawal, in which morphine is given a few times to obviate the tendency to death, codeine can be substituted for the morphine when the narcotic is demanded by the system. Also, in the gradual withdrawal codeine can be given for the mor-

phine entirely, when the patient is able to bear the substitution. It is evident that codeine can be made to take a useful place in an unpromising condition.

Under many circumstances codeine, hypodermatically, can be utilized for morphine to prevent the formation of a habit and to give the same relief for the same condition more safely.

ATROPINUM: ATROPINE.

Active Principle of Atropa Belladonna.
Atropinæ Sulphas. [*Sulphate of Atropine.*]
Atropinæ Hydrochloras. [*Hydrochlorate of Atropine.*]

The sulphate is the salt chiefly employed for hypodermatic use. This supplies all the conditions: it is readily soluble in water; the solution is free from irritating qualities. The formula which I employ is the following:

℞ Atropinæ sulphat., gr. i;
Aquæ destillatæ, ℥i. M.

Five minims of this solution represent $\frac{1}{96}$ of a grain. A much stronger solution may be used, as the following:

℞ Atropinæ sulphat., gr. i;
Aquæ destillatæ, ʒi. M.

A minim of this represents $\frac{1}{60}$ of a grain. Or the following may be preferred:

℞ Atropinæ sulphat., gr. i;
Aquæ destillatæ, ʒii. M.

A minim of this contains $\frac{1}{120}$ of a grain. I prefer the first solution for these reasons:

It is sometimes desirable to inject very minute quantities in susceptible subjects, and this cannot be done when the solution is very concentrated.

The dose may be more easily varied in a weak solution.

I have elsewhere stated the general objections to strong solutions, which apply to atropine.

A *penicillium* develops very rapidly in an atropine solution, and at the expense of the alkaloid; the more concentrated the solution the greater the loss.

On account of the rapid growth of the *penicillium*, the solution of atropine should not be kept too long, but should be prepared in small quantity frequently during warm weather. Filtration will, of course, free the solution from visible impurities, but considerable loss of strength will occur each time.

Extraordinary discrepancies are to be found in the statements of the various authorities as to the quantity of atropine which may be used subcutaneously. Dr. Anstie* notes with surprise the large quantity advised by Trousseau,—$\frac{1}{12}$ to $\frac{1}{6}$ of a grain,—a quantity sufficient to produce most serious toxic symptoms. Dr. Ruppaner† gives the dose at $\frac{1}{60}$ to $\frac{1}{30}$ of a grain, Lorent‡ at $\frac{1}{25}$ of a grain, and Courty employed as much as $\frac{1}{6}$ of a grain at a single operation. Five minims of the solution which I recommend to the reader, or $\frac{1}{96}$ of a grain, is a sufficient amount with which to begin the injection in any case except when used as an antagonist. Very great differences in the susceptibility to the atropine influence are found to exist. Children bear a much larger proportional amount than adults. Women are much more susceptible than men. Persons having a light complexion are much more easily influenced by it than those having a dark complexion. A delicate female, having light-blue eyes and flaxen hair, possesses,

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* The Practitioner, op. cit.

† Hypodermic Injections, op. cit.

‡ Die hypodermatischen Injectionen, loc. cit.

according to my observation, the maximum susceptibility. For such subjects 1 minim of my solution, or $\frac{1}{250}$ of a grain, is a sufficient dose to commence with, and even this amount will occasion decided symptoms in many subjects. To produce a curative effect in many severe cases of neuralgia,—*e.g.*, sciatica,—much larger doses than I have recommended may be necessary. It will rarely be required, however, to inject more than $\frac{1}{60}$ of a grain at one time.

Physiological Effects.—The local symptoms at the point of puncture are the same as those I have described for morphine.

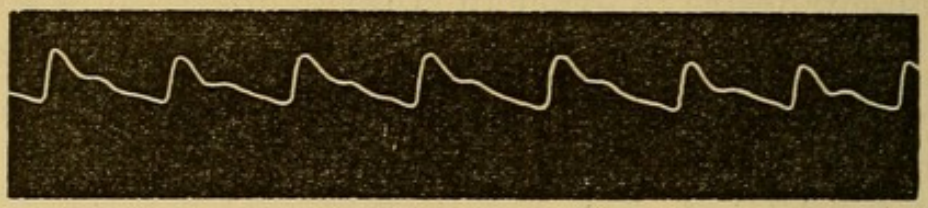
A peculiar dryness and pallor of the lower lip is the first systemic effect to be observed. The dryness quickly invades the mucous membrane of the mouth, fauces, and larynx, rendering deglutition somewhat difficult, and the voice husky. At the same time the pupil begins to dilate, reaching its maximum dilatation in about thirty minutes. With the dilatation of the pupil there occur also deranged accommodation—the vision being presbyopic—and dimness of vision, the outlines of objects being blurred and indistinct. Flushing of the face, more or less deep according to the temperament of the patient, fulness of the head with supra-orbital pain and sense of distention, and giddiness, are now experienced. With the development of these effects we observe increased action of the heart and rise in the bodily temperature. The pulse rises in a few minutes to nearly twice the normal number of beats, and the thermometer exhibits elevation of temperature; but the correspondence between pulse-rate and temperature characteristic of fever does not exist. In the diagram, Fig. 12, the influence of atropine on the pulse and respiration movements, and upon the temperature, is exhibited. I subjoin also a sphygmographic tracing showing the influence of

FIG. 12.

OBSERVATIONS ON DR. DE C.
PULSE.
RESPIRATION.
TEMPERATURE.
70
80
90
100
105
20
24
30
98°
99°
100°
101°
102°
Normal.....
First hour.....
Second hour.....
Third hour.....
Fourth hour.....
Fifth hour.....
Sixth hour.....
Seventh hour.....
Eighth hour.....
Ninth hour.....
Tenth hour.....
Eleventh hour...
Twelfth hour.....

atropine on the arterial tension. This must be compared with the first tracing on page 212, which is the normal tracing of Dr. Drake, upon whom the observation was made.

FIG. 13.



At this period the subjective sensations of the patient, as well as the objective phenomena, are those of fever; the skin is hot and burning, and dry; the pulse full and bounding; the face flushed; the eyes injected; the head aches; the ears ring; the mouth is dry and hot; the voluntary movements are disordered in consequence of the vertigo and of the impairment of the muscular sensibility; objects appear confused, and distances cannot be correctly appreciated; hallucinations and illusions occur; when sleep takes place it is disturbed by vivid dreams, sometimes frightful, sometimes pleasing, the patient awaking and holding conversation with imaginary persons. Sometimes a somnambulistic state is produced, in which the patient walks about as if engaged in his usual avocations, talks with the objects of his visions, and quarrels and struggles with those who would oppose and restrain him.

Sometimes the face and forehead are of a vivid red hue, resembling in color the eruption of scarlatina; the fauces are also red and injected, and, to complete the resemblance to this eruptive fever, a whitish fur covers the tongue, through which the red and enlarged papillæ project.

The dryness of the mouth, after some hours, is replaced by a moist condition, in which a viscid, sticky, and somewhat odorous secretion makes its appearance. Corre-

sponding to this change in the mucous membrane of the mouth some increase in the peristaltic movements of the intestines is to be observed, the evacuations being somewhat loose.

Frequent desire to evacuate the bladder is now experienced, with diminished power, the emission of urine taking place slowly and with difficulty, and sometimes, indeed, only after repeated efforts does the flow occur.

The mental effects, generally such as I have described, are sometimes of a character to awaken grave anxiety. Great depression of mind, a melancholic state, with a suicidal tendency, at night horrible dreams and visions, leading to acts of violence, have been noted by me in some exceptional cases. I mention this that the practitioner may avoid repeating the atropine injection, if such results follow its use in any patient.

Such, in general, are the effects produced by the hypodermatic injection of a full medicinal dose. These effects continue about twenty hours; the dilatation of the pupil, the disorders of vision, and the slowness and difficulty of micturition being the last symptoms to disappear and may continue three or four days.

Atropine cannot be considered very actively toxic. The symptoms which it produces afford ample warning of danger before the life of the individual is really placed in jeopardy. The sensations which accompany the full manifestation of its physiological effects are so unpleasant that the patient early seeks relief, and the symptoms are so characteristic that a mistaken diagnosis is hardly possible.

When a fatal dose is received, all the effects which I have described exist in an exaggerated degree. The pulse finally becomes small and thready, the action of the heart

weak, and coldness of the surface succeeds to the unnatural warmth. This change in the symptoms indicates that the "irritability" of the organic muscular fibre is exhausted.

In order to a thorough comprehension of its therapeutical action, we must form some exact notions of the mode in which these physiological effects are produced.*

The facts to be investigated are these:

The dilatation of the pupil.

The dryness of the mouth (arrest of secretion).

The increased action of the heart and lungs.

The rise of body-heat.

The influence on sensibility and motility.

Several opinions have prevailed as to the mechanism by which the dilatation of the pupil is accomplished.

This effect, as well as the presbyopia, is now known to be produced through the influence of atropine on the organic muscular fibre. By contraction of the radiating fibres of the iris, which are innervated by the sympathetic, the pupil dilates; by contraction of the circular fibres, innervated by the third nerve (motor oculi), the pupil grows smaller (myotic); by contraction of the muscle of accommodation, the lens is elongated, its diameter diminished, and the subject becomes presbyopic. It is probable, also, that this effect is facilitated by the paralyzing action of atropine on the oculo-motor nerve.

A number of experiments have been made to determine the character of the influence exerted by atropine upon the heart and lungs. The part that paralysis of the pneumogastric plays; the part that direct stimulation of the cardiac portion of the sympathetic takes in the production

* I have examined this whole question in my Prize Essay of the American Medical Association for 1868, on "Atropine, its Physiological Effects and Therapeutical Uses," to which the reader is referred for full information.

of the phenomena, have been earnestly discussed. The inhibiting influence of the pneumogastric on the action of the heart is well understood: if the terminal filaments of this nerve are paralyzed, the action of the heart increases. It has been found, however, by Lemattre,* that the action of the heart is increased by atropine, notwithstanding division of the pneumogastric: this agent must, therefore, exert an immediate stimulant action on the cardiac ganglia of the sympathetic. This same effect is produced on the organic muscular fibre of the arterioles, as demonstrated by Lemattre in the vessels of the frog's foot and confirmed by myself. I have demonstrated another fact: the contraction of the vessels after a time ceases, and relaxation takes place. This change is coincident with a weakened action of the heart; in other words, the atropine finally exhausts the irritability of the organic muscular fibre. This is a capital fact, which must not be forgotten in our therapeutical employment of atropine.

The rise in body-heat is a product of increased oxidation, the result of a greater activity of the circulation. The redness of the skin and mucous membrane is due to the larger amount of blood pumped into the capillaries and the increased arterial tension. The increased oxidation finds expression in a much greater excretion of urea and the urates.

There are several physiological facts which explain the action of atropine in arresting secretion of the pulmonary and intestinal mucous membrane. Prevost† has demonstrated that ablation of the spheno-palatine ganglion is followed by greatly-increased secretion from the Schnei-

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* Archives Générales, 1864.

† Archives de Physiologie Normale et Pathologique, tome i.

derian mucous membrane. The action which atropine exerts on the ganglia of the sympathetic must be the opposite of this.

Patients brought fully under the influence of atropine generally experience considerable disorder of voluntary movement. This effect is compounded of vertigo, diminished sensibility of the sensory nerves, loss of co-ordinating power, and paresis of the muscular system of animal life.

A very curious phenomenon was observed by Fraser* in frogs paralyzed by atropine many hours. When they lay limp and motionless, completely paralyzed and apparently dead, it was found that cutaneous irritation immediately excited tetanic spasms. I had noted previously (Prize Essay) that during the combined action of atropine and physostigmine these convulsant and tetanic spasms could be excited at once. This remarkable fact serves to show the close relationship in action of those agents which belong to the two groups respectively of paralyzers and tetanizers.

THERAPY.—It will be convenient to arrange the subjects under this head in the same way as in the section on the therapeutical applications of morphine.

Cerebral Diseases.—The subcutaneous injection of atropine is contra-indicated in inflammatory affections of the brain and meninges, for a constant result of the toxic effect of this remedy is hyperæmia of these organs. I have seemed to produce some good results, and certainly have

* Previously Undescribed Tetanic Symptoms produced by Atropine in Cold-blooded Animals. From Transactions of the Royal Society of Edinburgh. Edinburgh, 1869.

relieved the referred pains of the extremities in cases of general paralysis by injection of atropine. The "*late rigidity*" which comes on in many cases of hemiplegia, and which is often accompanied by severe pain in the affected limbs, has been much benefited by the hypodermatic injection of atropine. The pains of *progressive locomotor ataxia*, and that annoying disturbance of the sensory nerves, "*the fidgets*," which so constantly attends upon this disorder, may be relieved by this means. It has seemed to me that the subcutaneous injection of atropine exercised some influence also in retarding the progress of this disorder. Lorent has used the injection of atropine with advantage for relieving the pains which accompany *chronic meningitis* and *myelitis*. According to the views of Brown-Séquard, who holds that belladonna, by producing contraction of the arterioles, diminishes the supply of blood to the cord, the hypodermatic injection of atropine ought to be very serviceable in myelitis. But it is now known that the increased action of the heart, and the greater arterial tension produced by atropine, favor hyperæmia of these parts.

The hypodermatic injection of atropine is serviceable in certain cases of *delirium tremens*. The indications for its use are these:

Obstinate insomnia with great restlessness.

Weakened action of the heart; coldness of the surface; clammy sweat.

Failure of nutrients, bromide of potassium, chloral, and hypodermatic injections of morphine, to quiet the delirium and induce sleep.

In similar conditions in the *psychical disorders* the subcutaneous injection of atropine is serviceable. This method of treating these disorders has the sanction of the eminent

authority of Graefe. My own observation entitles me to insist on this caution: the use of atropine is unsuited to cases in which there is hyperæmia of the nervous centres, or in cases of excitement with power. Moreover, it is not suited to cases of melancholia, for the reason already stated, that in many persons it produces great despondency of mind.

Certain cases of *mania*, characterized by restlessness, motor activity, and mental as well, with hallucinations and incoherent rambling, the physical state being that of weakness and relaxation, are sometimes remarkably benefited by atropine. Ringer* describes such a case, and shows that atropine is nearly if not quite as useful as hyoscyamine has been in analogous cases.

In *puerperal mania*, the general system being in the condition of weakness and depression, atropine is often successful in securing sleep and improving the mental state.

Atropine cannot be considered a *hypnotic* in the true sense of that term. It is sometimes said to produce this effect indirectly; by allaying pain, it is believed to render sleep possible. This, in the opinion of the author, is not a correct statement of the ground of its utility in certain cases. It is sometimes very useful as a hypnotic in cases of wakefulness and coma-vigil, dependent upon cerebral anæmia and intense motor activity.

Neuralgia.—The subcutaneous injection of atropine is not as effective in the treatment of the neuralgias in general as morphine by the same method. The systemic effects of atropine are also more unpleasant. For these reasons morphine is generally preferred. Nevertheless, when morphine fails to produce the desired result, or dis-

* The Practitioner, vol. xviii. p. 166.

agrees with the patient, as is sometimes the case, atropine may be used. In certain neuralgias, it must be admitted also, atropine is said to be preferable to morphine,—*e.g.*, in pelvic pain, in which Dr. Anstie considers it superior to morphine, in sciatica, and in certain cases of *tic douloureux*. In the pain of the various forms of *dysmenorrhœa*, in *ovarian neuralgia*, and in the pelvic pain experienced a few days after delivery, and due to the pressure of the womb on certain nerves, atropine by subcutaneous injection is most serviceable.

The principal triumphs of atropine over neuralgia have been in cases of *sciatica*. It is now admitted that atropine is one of the best remedies for this disease. First proposed and used by Mr. Hunter, it was afterwards employed by Béhier, Courty, Oppolzer, Lorent, and others. It has been found, however, that distant injection, and even injection into the subcutaneous tissue of the affected thigh, do not produce such good results as throwing the fluid deeply into the neighborhood of the affected nerve. More frequently, indeed, than in any other form of neuralgia, except the most obstinate and protracted cases of tic douloureux, the nerve itself, or its sheath, has undergone structural alteration; the limb is diminished in size, its temperature and sensibility lowered, and the power of its muscles impaired. In the condition of neuritis more advantage is to be derived from local than from distant injection, just as Luton, Bertin, and Ruppaner have cured such cases by the injection of irritants into the affected parts.

In severe cases of sciatica and tic douloureux $\frac{1}{40}$ of a grain of sulphate of atropine may be injected; but it should not be forgotten that this quantity will excite very severe symptoms in susceptible subjects. Generally, 5 minims of my solution, or $\frac{1}{48}$ of a grain, will produce de-

cided atropinism. Cessation of pain is not immediate upon the systemic effects, as Mr. Hunter originally pointed out; indeed, the pain is often at first increased, but improvement takes place after a variable interval, and is often more permanent than after the morphine injection.

Tetanus and Hydrophobia.—In tetanus, atropine has been used in numerous cases, but without success. Recovery has undoubtedly occurred in certain chronic cases, and in idiopathic tetanus; but it does not appear that the result was fairly attributable to the subcutaneous injection of atropine. Within the sphere of my observation, it has been freely used in cases of tetanus and hydrophobia, but without permanent benefit.

Epilepsy.—Brown-Séquard proposed the subcutaneous use of atropine in epilepsy, but he combined it with morphine. Erlenmeyer used it, but with a negative result. My own experience with atropine in this disease is as combined with morphine. The subcutaneous injection of atropine may be employed, instead of the internal use of belladonna, on the method of Trousseau.* Recent experience at Leidesdorf's clinic has demonstrated that atropine has remarkable curative power in epilepsy. Its administration was based on the property possessed by it of reducing the reflex function in small doses. Large doses, as is well known, have the opposite effect on the reflex faculty. A number of cases have been reported cured. The daily use of $\frac{1}{120}$ of a grain subcutaneously is probably a suitable amount.

The subcutaneous injection of atropine is applicable to the treatment of certain neuroses of the thoracic viscera.

Asthma.—Courty was the first to employ atropine sub-

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* Clinique Médicale, tome ii.

cutaneously for the relief of asthma. He injected the solution over the pneumogastric nerve. Belladonna, in large doses, is now held to be the best remedy by Hyde Salter, Professor Sée, and others.* Professor Sée recommends belladonna because it is a "vascular and cardiac" agent, and "because the means of modifying respiration is to be found in the power to alter the pulmonary circulation." The hypodermatic injection of atropine is preferable to the internal use of belladonna for the following reasons:

The effect is more speedy and certain.

The relief which it affords is greater and more lasting.

In my experience cases of emphysema and spasmodic breathing, due to dilatation of the right cavities of the heart, are not so much benefited by atropine as is asthma. I think it prudent to add a caution here: as atropine exhausts the irritability of the sympathetic ganglia, it is not proper to push the use of this agent in cases in which the muscular tissue of the heart is weakened by dilatation or fatty degeneration.

In order to procure the greatest relief to the asthmatic paroxysm, the injection should be made promptly at the beginning of the attack. The dose will vary from $\frac{1}{96}$ to $\frac{1}{60}$ of a grain. It may be inserted at any convenient situation. Succeeding attacks should be anticipated if possible, the injection being made when the first warnings are felt by the patient. As the effect of the atropine injection reaches its maximum in about a half-hour, it will at this time be perceived whether a sufficient quantity has been administered.

This method of administering belladonna is much to be

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* The Practitioner, July, 1869.

preferred to the stomach administration, or to the methods of fumigation, pulverization, or inhalation, notwithstanding fumigation is strongly urged by Professor Sée* in some lectures on the subject of asthma.

The administration of atropine may occasion much distress in the case of those asthmatics who suffer from dryness of the bronchial mucous membrane, and who experience relief when the secretion of mucus becomes abundant. I have known most alarming dyspnœa produced by the use of atropine, in such subjects, and I therefore record a warning for the benefit of the inexperienced.

Harley†—influenced by the fact that great increase of the heart's action follows the administration of atropine, a fact, indeed, previously much insisted on by V. Bezold—recommends this agent as a cardiac stimulant in conditions of great depression of this organ. It is certainly exceedingly useful in those restraint neuroses in which the inhibitive action is exerted through the pneumogastric, for by paralyzing the terminal filaments of this nerve and stimulating the cardiac ganglia of the sympathetic, the action of the heart is quickly improved and the depression overcome. It is in this action, according to Professor Sée, that we have an explanation of the utility of atropine in asthma.

Atropine, it will be remembered, first arrests the secretions of the intestinal mucous membrane, but in the reaction which ensues, increased secretion takes place. It promotes peristaltic movements by its action on the circular fibres of the intestinal tube.

Vomiting.—Sea-sickness and the vomiting of pregnancy

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* Bul. Général de Thérapeutique, 15 Août, 1869.

† Gulstonian Lectures, also Vegetable Neurotics.

are both relieved by subcutaneous injection of a small quantity—$\frac{1}{200}$ to $\frac{1}{120}$ of a grain—of atropine. But the good effects are not constant, and, when successful, diminished by repetition.

Colic.—The various forms of colic may be relieved by this agent, but it is not so effective in most of them as morphine. It is adapted to cases of colic dependent upon constipation or upon lead-poisoning, but the most desirable results are obtained by the conjoined administration of morphine and atropine.

Cholera.—In the algid stage of cholera, during the last epidemic in the South-west, the subcutaneous use of atropine appeared to bring on reaction in some very unfavorable cases. It was seen in that epidemic, as in other cases abroad of which the main indication was sudden failure of the heart, that atropine has great power to restore the heart's action when suddenly depressed by reflex causes. The subcutaneous injection of $\frac{1}{200}$ to $\frac{1}{60}$ of a grain may be practised; but there is always the danger of that subsequent failure of the circulation which comes of the reaction from overstimulation, whence follows the rule to use no more of the remedy than is necessary to restore the circulation.

Bladder Diseases.—In *dysuria* and *enuresis* it is often most effectual. Belladonna has long had a deserved preeminence in the treatment of nocturnal incontinence of urine. Atropine by subcutaneous injection is the most effective way of administering it.

Irritation of the bladder, when arising from a nervous erethism, may be relieved in the same way. That troublesome disorder, *spermatorrhœa*, is most successfully treated by the hypodermatic injection of atropine. Two indications are to be supplied in many of these cases: the erotic

sensations which originate during the sleeping state are to be suppressed; the reflex act of emission to be prevented.

No agent accomplishes this more successfully than the subcutaneous injection of atropine at bedtime and at such intervals as observation has shown to be necessary.

Constitutional Diseases.—Remarkable relief to the pain and soreness of *acute rheumatism* has been obtained by Lorent from the subcutaneous injection of atropine. This treatment has been suggested by Harley as if it were an original idea with himself. He recommends that the atropine be injected in the neighborhood of the inflamed joint. I have followed this practice with great relief to the patient. One or two injections of $\frac{1}{100}$ of a grain daily will generally be sufficient to quiet the pain; but morphine may be combined with it advantageously, if the patient be wakeful. At the present time antipyrin injected into the limb or given by the stomach is preferred.

As a Physiological Antagonist.—The subject of the antagonism of morphine and atropine will be discussed hereafter.

The subcutaneous injection of atropine may be used against the toxic symptoms of certain vascular agents, as aconite, veratrum viride, tartar emetic, digitalis, which produce great depression of the heart's action. It has been proposed, also on insufficient grounds, for relief of poisoning by hydrocyanic acid. In my prize essay on atropine I have shown that hydrocyanic acid in toxic doses acts too speedily for atropine to influence the result, and that animals fully under the effects of atropine are quickly poisoned by an ordinary toxic dose of the acid.

Atropine is an antagonist to pilocarpine, muscarine, and

physostigmine (eserine), and may be used to overcome and remove the lethal symptoms caused by either of these agents.

ANTAGONISM OF ATROPINE AND PHYSOSTIGMINE OR ESERINE.

HISTORY.—For the first time, in 1864, Kleinwächter treated a case of poisoning by atropine by the internal administration of physostigmine, the symptoms being relieved to a great extent. In 1867, Bourneville, in a thesis on the treatment of tetanus by physostigmine, related a single experiment in which the effects produced by a quantity of the powdered kernel, introduced into the stomach of a cabiai, were overcome by the subcutaneous injection of atropine. In 1868 I made a number of experiments proving the existence of the antagonism. The most important research was that of Professor Thomas R. Fraser, of Edinburgh, in 1869, who performed a great variety of experiments, and introduced new principles for the guidance of future researches of the same kind.* This investigation is followed by the report of the Committee of the British Medical Association, Dr. J. Hughes Bennett, Chairman.†

ANTAGONISM.—Before proceeding to the analysis of the published facts and experiments, we must have a definite conception of the actions of the two agents. In what respect do atropine and physostigmine differ? I have already described the delirant effect of atropine, its power to dilate the pupil, to stimulate the heart and the respiration, to arrest secretion, to flush and at the same time dry the

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* On the Antagonism between the Actions of Physostigmine and Atropine. From the Transactions of the Royal Society of Edinburgh, vol. xxvi.

† The British Medical Journal, 1874.

skin. Physostigmine does not affect the cerebral functions; it contracts the pupil, paralyzes the voluntary muscles, but does not impair sensibility, increases secretion, energizes the heart-beats and raises the arterial tension, and causes death by paralysis of the respiratory muscles. Placed in opposition, we find that the points of difference are: on the brain, atropine causing delirious excitement, with hallucinations and illusions,—physostigmine not affecting this organ at all; on the pupil, atropine causing dilatation by stimulating the radiating fibres innervated by the sympathetic,—physostigmine causing contraction by paralyzing the radiating fibres, thus leaving the third nerve unopposed; on the respiration, atropine stimulating the respiratory centre,—physostigmine paralyzing the muscles of respiration; on the heart, atropine increasing the rate of movement without adding to the power,—physostigmine increasing the power without hastening the movements of the heart; on secretion, atropine drying the mouth and the secretions of the intestinal tube,—physostigmine increasing the salivary flow and the secretions of the whole intestinal canal; on the voluntary muscular system, atropine causing paralysis of the motor nerves,—physostigmine producing spinal paralysis. As regards the lethal effects, the tendency to death by paralysis of the respiratory muscles, produced by physostigmine, is overcome by atropine. Or, as it is expressed by Professor Fraser, "atropine prevents the fatal effect of a lethal dose of physostigmine by so influencing the functions of certain structures as to prevent such modifications from being produced in them by physostigmine as would result in death. The one substance counteracts the action of the other, and the result is a physiological antagonism so remarkable and decided that the fatal effects, even of three

and a half times the minimum lethal dose of physostigmine, may be prevented by atropine."

The first reported example of atropine-poisoning treated by physostigmine proved a success. The first experiment made with the definite purpose of ascertaining whether an antagonism existed, also, apparently proved the point. But the first sustained and sufficiently-extended experiments made to test the antagonism were those undertaken by myself in 1868, before the published observation of Bourneville. While acknowledging the superiority in every way of the research undertaken by Fraser, I respectfully submit that my investigations, as published in my prize essay* of the American Medical Association, clearly preceded his by a year. Claims of priority are, however, ungracious, and I do not therefore urge mine. In his historical review, Professor Fraser has not sufficiently, I think, put my claim on its proper basis. Quoting from my essay, he takes a sentence or two from the general conclusions, which do not adequately convey the whole meaning of my researches. Thus, he says, "Dr. Bartholow deduces a number of general conclusions regarding the mutual counteraction of the two substances on several of the structures and functions modified by them. The following quotation contains an epitome of his views: 'Atropine is not a physiological antagonist to physostigmine, except in regard to their action on the organic nervous system. It would be improper, then, to use atropine against poisoning by Calabar bean.'" As I shall presently show, my conclusions have been confirmed by subsequent investigations, —the antagonism existing in the actions on the nervous system of organic life, as I had demonstrated. After the

* Transactions of the American Medical Association, 1869.

detail of some typical cases, out of a large number of similar experiments, I came to the following conclusions:

"Atropine and physostigmine are antagonistic as to their influence over the respiratory movements,—atropine increasing and physostigmine retarding them.

"They are antagonistic in their action on the heart,—atropine producing excitation of the cardiac ganglia, and physostigmine paralyzing them.

"They are opposed in respect to their action on the sympathetic,—atropine causing increased action, and physostigmine paralyzing the system.

"They have opposite effects on the pupil in virtue of opposite effects on the sympathetic,—atropine dilating the pupil by its action on the radiating fibres of the iris, and physostigmine contracting the pupil by paralyzing the radiating fibres."

My conclusions of 1868 have not been invalidated by the subsequent investigations, and hence the experimental data must have been accurate. I therefore venture to submit that Professor Fraser's quotation from my essay does not adequately represent my opinions. Apparently without investigating on his own account, and accepting a very restricted excerpt from my paper, Dr. H. C. Wood* says, "In 1869, Professor Roberts Bartholow, of Cincinnati, on the strength of a few really indecisive experiments, arrived at a conclusion opposite to that of Bourneville." Dr. Wood has absolutely no warrant for this positive assertion. So far from coming to a conclusion opposed to that of Bourneville, it was to the same purport, and based on a number of really decisive experiments. I have dwelt on my own

* Therapeutics, Materia Medica, and Toxicology, 3d ed., p. 320.

views longer, probably, than they deserve, but historical accuracy is of some moment, and every man wishes that his opinions be properly interpreted.

The quotation I have made from Fraser's paper indicates his belief in the existence of an antagonism in the lethal effects of atropine and physostigmine of wide range, and his experiments, which were very numerous and carefully made, certainly support his opinion. The Committee of the British Medical Association hold this antagonism in less favor; although they admit its existence, they find it is more limited in range than Dr. Fraser had supposed. Their general conclusion is: "sulphate of atropine antagonizes to a certain extent the fatal action of Calabar bean," yet they maintain that, "for all practical purposes, atropine as an antidote to Calabar bean is useless, and not to be compared with the effects of chloral hydrate." In the first part of this strong statement, the Committee confirm the conclusion to which I had come, several years before, in respect to the use of atropine as an antagonist to the toxic effects of physostigmine.

The special points of antagonism have been elaborately studied by various observers. As respects the heart, atropine first causes a rise of the blood-pressure, but this is followed by the opposite condition, or diminution of blood-pressure, while the action of the heart continues accelerated. Physostigmine slows the movement by lengthening the diastolic pause, and increases the vigor of the contraction, and also raises the arterial tension. By Arnstein and Sustschinsky,* the excitability of the cardiac branches of the vagi was found to be increased by physostigmine, and lessened by atropine. The experiments of Rossbach and

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* Centralblatt für die Med. Wissenschaft, No. 40, 1867.

Fröhlich, in all respects remarkable and novel,* seem not to confirm these observations. Köhler† and Harnack and Wilkowski‡ found that physostigmine lessened the pulse-rate, after the peripheral filaments of the vagi were completely paralyzed by atropine. Harnack,§ in a polemical paper strongly characterized by the *fortiter in re*, controverts the views put forth by Rossbach and Fröhlich, and by Rossbach alone, in respect to the action of atropine on the heart and on the pupil. Köhler holds that physostigmine slows the heart by paralyzing the accelerator nerve. It had already been shown that atropine stimulated the accelerator nerve (Bezold and Bloebaum). Tachau‖ and Roeber¶ maintain that the retardation of the heart is due to a paralyzing action of physostigmine on the cardiac ganglia, but Laschkewich** shows that this retardation is due to stimulation of the inhibitory apparatus. The rise of arterial tension produced by physostigmine is probably due to contraction of the constrictor fibres of the arterioles, since strong local contractions of the intestine are produced by this agent when it is thrown into an artery supplying a small part of the bowel (Bauer).†† How much soever the explanations differ, the fact remains that atropine and physostigmine act in an opposed manner on the heart. As respects the respiration, there are fewer differences of opinion. That physostigmine causes death by paralysis of respiration, the heart continuing in action after

* Pharmacol. Untersuchungen, Würzburg, 1873, p. 77.

† Archiv für exper. Pathol. und Pharmacol., Band i. p. 277.

‡ Ibid., Band v. p. 204. § Ibid., 1875, Band iv. p. 146.

‖ Archiv d. Heilkunde, Band vi. 69.

¶ Hermann's Lehrbuch der experiment. Toxicologie, p. 339.

** Beobachtungen über die physiol. Wirkungen der Calabarbohne, Virchow's Archiv, Band xxxv. p. 291.

†† Hermann, op cit.

respiration has ceased, seems abundantly established.* On the other hand, it is generally conceded that atropine stimulates the respiratory function. Physostigmine suspends, ultimately, reflex excitability, and is a spinal paralyzer; hence the function of respiration is only affected (Laschkewich, Tachau). On the other hand, the respiratory centre is stimulated by atropine; an acceleration of breathing takes place when the vagi have been divided (Bezold and Bloebaum). It is, therefore, clear that these agents are opposed in their actions on the function of respiration.

The point of opposition most conspicuous, and that which first suggested the existence of the antagonism, is the effect on the pupil,—eserine causing contraction, and atropine dilatation of the pupil. Marked differences of opinion exist as to the mechanism of the antagonism. By some the contraction of the pupil caused by eserine is referred to a paralyzing action on the dilator fibres (Fraser, Hirschmann),† and by others to a spasm of the sphincter fibres (Grünhagen and Rogow,‡ Bezold and Goetz). That the latter view is correct seems supported by the fact that the effect of physostigmine on the muscular layer of the intestine is to induce tetanic contraction or spasm. Further, when the pupil is contracted by eserine the contraction is readily overcome by atropine, but the atropinized pupil resists the action of eserine.

The delirium, hallucinations, and illusions caused by atropine are in no respect affected by physostigmine. In all of the instances of poisoning by Calabar bean reported,

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* Hermann, op. cit., p. 341.

† Archiv für Anat. und Physiol., 1863, p. 309.

‡ Centralblatt für die Med. Wissenschaft, 1863, p. 577.

the mind remained unaffected until near the end, when, carbonic-acid poisoning coming on, stupor and drowsiness supervened. All respiratory poisons, pure and simple, are accompanied at the close of life by the carbonic narcosis due merely to the suspension of hæmatosis. Carbonic-acid narcosis is an important element in the morbid complexus of atropine-poisoning. These agents do not, therefore, have an antagonistic action on the cerebrum.

In the spinal effects of atropine and physostigmine there are obvious differences. They are both paralyzers, but atropine causes, in cold-blooded animals, a subsequent tetanic condition. When atropine and physostigmine are administered simultaneously, this tetanic condition occurs at once,—a fact which I was the first to demonstrate; and so exalted is the reflex function of the spinal cord, that a slight tap on the surface of the body causes a tetanic spasm, the condition in the intervals being that of relaxation. In several of the cases of atropine-poisoning, trismus was a marked symptom. Atropine affects the spinal cord, as Ringer and Murrell have shown;* and the paralysis induced by it, they maintain, is largely spinal, although it does impair the irritability of the motor-nerve trunks. According to the experiments of Dr. Mary Putnam Jacobi, the sensibility of the sensory nerves is impaired by atropine. Physostigmine, on the other hand, increases the irritability of the sensory nerves and is a spinal paralyzer, leaving the motor nerves and the muscles intact. These agents, therefore, agree on more points than they differ in their action on the spinal cord.

As respects the function of secretion, there is an obvious difference in action between physostigmine and atropine.

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* The Journal of Anatomy and Physiology, xi., Part xi.

An increased flow of saliva, of the intestinal juices, of the tears, and of the sweat, is a constant result of the action of physostigmine, and is due, according to Heidenhain,* to a central excitation of the secretory nerves. This conclusion seems established by the fact that the increased secretion of saliva failed to occur when the chorda tympani was divided near the submaxillary gland. The action of atropine is the opposite of this: it suspends secretion, most probably by paralyzing the end organs of the nerves in the gland, for, as Schiff has shown, arrest of the secretion of the submaxillary gland follows division of the chorda tympani. Increased outpouring of saliva takes place when the divided extremity of the nerve is galvanized; whence it may be concluded that physostigmine stimulates the secretory centres.

On the motor functions, and on the muscles, atropine and physostigmine act differently. I have already emphasized the tetanizing action of atropine on cold-blooded animals, and the trismus which occurs in so many cases of poisoning. Botkin † was the first to show that atropine paralyzed the motor-nerve trunks, and Laschkewich ‡ and Fraser proved that, in poisoning by Calabar bean, the irritability of the motor nerves and the contractility of the muscles were unaffected. The action on the motor functions is therefore different and not opposed.

In summing up the results of the various researches, it may be regarded as established: 1. That physostigmine, or eserine, and atropine are antagonistic in their effects on the pupil. 2. That they act differently, but probably not antagonistically, on the heart, unless we accept the

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* Arch. für die ges. Physiol., Band v. p. 40. Quoted by Hermann.

† Virchow's Archiv, Band xxiv. p. 85. ‡ Ibid., loc. cit.

views of Köhler and Bezold and Bloebaum,—the former maintaining that physostigmine paralyzes the accelerator nerves of the heart, and the latter that atropine stimulates these nerves. 3. That they are opposed in their action on respiration, physostigmine paralyzing, and atropine stimulating the respiratory function. 4. That they are not opposed in their action on the cerebrum, atropine producing delirium, and physostigmine having no effect on the cerebral functions, while both cause more or less carbonic-acid narcosis. 5. That they act differently and not in an opposed manner on the spinal cord and nerves, both producing paralysis, but atropine does, and physostigmine does not impair the irritability of motor nerves. As regards the sensory nerves, physostigmine augments their irritability, while atropine seems rather to lessen it, if any effect is produced. 6. That they act oppositely on secretion, physostigmine stimulating and atropine arresting the secretions in general.

It follows from these considerations that the lethal effects of physostigmine, due to paralysis of respiration, are overcome by atropine by sustaining the respiratory function. The Committee of the British Medical Association assert that "the antagonism exists within very narrow limits," but this happens to be sufficient to avert death when doses little more than lethal have been administered; still, the use of physostigmine against the lethal effects of atropine is of doubtful propriety. The paralyzing effect of physostigmine on respiration may, doubtless, be successfully overcome by the suitable application of atropine.

ATROPINE AND PILOCARPINE.

The antagonism of action between belladonna and pilocarpus, or atropine and pilocarpine, is one of the most

interesting, as it is one of the most exact, in the whole series of antagonisms of medicinal agents. The functional disturbance produced by atropine has been sufficiently elaborated in the preceding sections. Our task is now chiefly concerned with the peculiar powers and attributes of pilocarpine. The history of jaborandi affords us a capital illustration of the benefit of physiological research as applied to the study of remedies. When it was first introduced, a great many observers in all parts of the world set about the study of its actions. In an almost incredibly short time we were put in possession of its actions, and the range of its uses was at once indicated. All has been abundantly confirmed by trials on man, and the first conclusions arrived at have only been supported by subsequent investigations. The literature of pilocarpus is already vast. I will call your attention only to the subject of its antagonistic action. We must first form a definite conception of what pilocarpine does.

In a few minutes after the alkaloid pilocarpine has been injected subcutaneously, or taken into the stomach, the action of the heart increases, the face flushes, and a subjective sense of heat is felt throughout the body, but especially about the face. The increased action of the heart does not take place when very large doses are administered, and the increase from small doses is not maintained after the characteristic sweating. The pupil contracts, spasm of the accommodation occurs, and recession of the near point takes place. More or less headache is experienced, and there are present a feeling of frontal tension and transient vertigo. Soon after the flushing of the face and the subjective sense of heat are experienced, perspiration begins, first on the forehead usually, and then over the whole body, and presently the

sweating is enormous, the skin literally pouring out water. Simultaneously with, or often before, the sweating, the salivary glands become active, and presently mouthful after mouthful of saliva is discharged, so that the quantity may be measured by ounces, even pints. In some instances the one secretion seems to be substituted for the other. Thus, when the salivary flow is great, the sweat is less, and *vice versa*, but the usual experience is that both secretions are enormously increased. With the full development of the salivary and sudoral discharge, the pulse declines in force, in volume, and in the number of beats, the face becomes pale, the strength diminishes, and a feeling of exhaustion is experienced. The temperature, which was slightly or not at all increased during the stage of excitement, descends somewhat below normal after the sweating. The secretion of urine is rather less than normal, but the bladder is irritable and the desire to micturate is frequent. The surface of the body is cool, and a sense of chilliness is experienced. Drowsiness comes on, as a result of the exhaustion, and is not a direct effect of the remedy on the brain. When the preparations of pilocarpus are taken into the stomach, and, to a much less extent, when the active principle is thrown under the skin, more or less nausea, even vomiting, is produced, and not infrequently a watery diarrhœa.

The opposition of actions, between an agent causing such functional disturbances as I have just described and atropine, is apparent at a glance. Let me briefly indicate the main points as a preliminary to the study of the mechanism of the antagonism. The first increase in the cardiac movements caused by pilocarpine is of very short duration, and is followed by feebleness of the heart and diminished arterial tension; atropine induces and maintains a

quickened heart-beat and a high arterial tension during at least the whole duration of the action of pilocarpine. A subjective sensation of heat and flushing of the face is caused by both, but is very transient in the case of pilocarpine. Contraction of the pupil is produced by pilocarpine, dilatation by atropine. Dryness of the mouth and of the skin results from atropine, profuse secretion from pilocarpine. Both of these agents tend to cause nausea and vomiting, and a watery diarrhœa. Both render the bladder more or less irritable, and atropine increases the urinary secretion a little, while pilocarpine diminishes it. As regards the nervous system of animal life, no antagonism exists. Pilocarpine does not affect the cerebral functions directly, while atropine causes delirium. Pilocarpine induces weakness of the muscular system, but atropine brings on a tetanic condition by stimulation of the cord, and paralysis by an action both on the cord and on the peripheral motor nerves. In all those actions involving the functions of the organic nervous system there is very complete antagonism, but in respect to the nervous system of animal life no antagonism is possible.

The only examples of application of the antagonism to the treatment of poisoning, which I have been able to find, are two cases of poisoning by belladonna liniment, received into University College Hospital in charge of Dr. Sydney Ringer,* but many have occurred since. Pilocarpine was injected subcutaneously in both, without any obvious influence over either. The experience in the more important of the two cases demonstrated that $1\frac{1}{3}$ grains of pilocarpine failed to excite perspiration, when $\frac{1}{3}$ of a grain of the same sample caused in healthy persons most profuse

* The Lancet, March 4, 1876.

sweating. It is obvious that belladonna is relatively more intense, as it is more prolonged, in its effects.

The first experiments to determine the antagonism of atropine and pilocarpine were those of Vulpian,* and were confined to the salivary and sweat secretions. When the saliva and sweat are pouring out in a stream from the action of pilocarpine, the flow of secretion is almost instantly arrested by the administration of atropine. The mechanism of this antagonism has been thoroughly investigated by Vulpian,† Langley,‡ Marmé,§ Petrina,‖ and numerous other investigators. Pilocarpine stimulates the nerve ends in the glands, and, as Heidenhain long ago proved, atropine paralyzes the end organs of these nerves. The chorda tympani and the sympathetic filaments distributed to the submaxillary gland being divided, pilocarpine still has power to cause increased secretion, as Langley has shown, thus proving that this agent also stimulates the gland-cells. In this respect, also, it is probable that atropine has an antagonistic action. The experiments of Langley on this point have been confirmed by Nawrocki,¶ Fuchsinger,** and the other observers just named.

The increase of secretion caused by pilocarpine is not limited to the skin and salivary glands, but extends to the mucous membrane of the nose, bronchi, and intestinal canal, although to a less extent. The arrest of these secretions by atropine is not less prompt and decided. The increased secretion caused by the subcutaneous injection

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* Gazette Hebdom., 1875–76, p. 81. † Loc. cit.

‡ Journal of Anatomy and Physiology, vol. xi., Part i. pp. 173, *et seq.*

§ Virchow und Hirsch's Jahresbericht, 1878, p. 173.

‖ Deutsch. Archiv für klinische Med., Band xxi. p. 258.

¶ Centralblatt für die Med. Wissenschaft, Band vi. p. 97.

** Pflüger's Archiv, Band xv. p. 483.

of $\frac{1}{4}$ of a grain of pilocarpine muriate or sulphate is arrested by $\frac{1}{100}$ of a grain of atropine. In a personal trial of this quantity of pilocarpine, already described, I found that the salivary flow began in three minutes, and in five minutes I was drenched by perspiration, the flush of the face and sense of warmth had ceased, the surface felt cold, and a condition of extreme bodily depression came on. A marvellous change was wrought by the subcutaneous injection of $\frac{1}{100}$ of a grain of atropine. In three minutes the sense of depression began to decline, in five minutes the surface grew warm again and the flow of sweat and saliva ceased, so that by the end of ten minutes the disturbances caused by each had disappeared and I was in the same condition as if neither had been taken.

The first effect of pilocarpine on the heart is to increase its action. This is coincident with flushing of the face. Belladonna, after a very brief preliminary slowing, greatly increases the action of the heart, and also flushes the face. The increased action due to pilocarpine is brief, and is followed by slowing and feebleness of movement. The resemblance in action is only apparent. The increased movement produced by atropine may be explained, as we have seen, in either of two modes,—by paralysis of inhibition, or by stimulation of the accelerator fibres. The increased action due to pilocarpine is a result of the dilatation of the arterioles. It is just here that the antagonism exists. The manometric observations of Kahler and Soyka,* the experiments of Langley, Hardenhewer,† and Robin,‡

* Kymographische Versuche über Jaborandi, Archiv für exper. Pathol. und Pharmacol., Band vii. p. 435.

† Berliner klinische Wochenschrift, No. 10, 1877.

‡ Étude Physiologique et Thérapeutique sur la Jaborandi, Journal de Thérapeutique, various numbers for 1875.

alike demonstrate that pilocarpine lowers the vascular tension by a paralyzing action, causing dilatation of the arterioles. The sudden withdrawal of the blood to the peripheral vessels necessarily causes increased action of the heart. Belladonna exactly antagonizes these effects: it raises the arterial tension by inducing contraction of the arterioles. The depression in the heart's action, and irregularity of rhythm, due to the action of pilocarpine on the motor apparatus, and which succeed to the preliminary increased movement, are antagonized by atropine (Service).*

The temperature variations observed by all who have carefully investigated this point are explained by the circulatory disturbance. According to Robin, just before sweating begins, and when it is going on actively, the temperature rises, but this does not appear to be a constant result. When the sweating has reached its maximum the temperature begins to fall, the decline reaching from 0.5° to 2° Fahr., and this reduction of body-heat persists for several hours,—it may be for twenty-four hours (Robin, Curschmann,† Weber,‡ Ringer and Gould,§ *et al.*). The decline of temperature caused by pilocarpine is antagonized and prevented by atropine. By raising the vascular tonus, and arresting or preventing the profuse discharge of saliva and sweat, atropine restores the normal equilibrium, and consequently the fall of temperature is prevented.

Extending our investigation now to the eye, we find that the most exact opposition of actions exists in the effects of pilocarpine and atropine on this organ. Myosis, spasm

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* Journal of Anatomy and Physiology, April, 1879.

† Berliner klinische Wochenschrift, June 18, 1877.

‡ Centralblatt für die Med. Wissenschaft, No. 44, 1877.

§ The Lancet, January 30, 1875.

of accommodation, and recession of the near point are produced by pilocarpine; and the exactly opposite effects —dilatation of the pupil, paralysis of the accommodation, and removal of the distant point—are produced by belladonna (Königshofer, Tweedy,* Galezowski,† *et al.*).

That pilocarpine directly affects the brain is doubtful. It is true, headache, vertigo, tinnitus aurium, etc., have been observed from considerable doses; and drowsiness, even sleep, accompanies the state of languor and depression caused by the profuse salivary and sudoral discharge and the lowered vascular tonus. These secondary results of the action of pilocarpine are not antagonistic to the delirium, hallucinations, and illusions of atropine. In the cases narrated by Dr. Ringer the delirious excitement of belladonna-poisoning was not modified by the action of pilocarpine,—so that, viewed from either the theoretical or the practical stand-point, the existence of an antagonism on the brain must be denied.

The nausea and vomiting caused by pilocarpine are probably not affected, or are increased, by atropine. When the action of the drug ceases, the stomachal distress occasioned by it ceases also,—hence, in this indirect mode, atropine may prevent or arrest it.

I have already indicated some points of similarity of action between pilocarpine and atropine,—the quickened heart and flushed face,—but these, as has been shown, are apparent, and not real. They both agree, however, in the insusceptibility of children to their action. The observations of Ringer and Gould are very precise in regard to this insusceptibility of children to the action of

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* The Lancet, January 30, 1875.

† The Medical Times and Gazette, 1877, vol. ii. p. 358.

jaborandi. They found that the quantity which sufficed to produce profuse sweating in adults affected children very slightly or not at all. Children are equally insusceptible to the effects of belladonna.

To sum up the results of the investigation, we find that belladonna and pilocarpus are antagonistic in their action: 1. On the secretions, especially of sweat and saliva, pilocarpus promoting and belladonna arresting them. 2. On the heart and arterial system, pilocarpus slowing and enfeebling the heart and depressing the vascular tonus, belladonna stimulating the cardiac movements and raising the arterial tension. 3. On the eye, pilocarpus contracting the pupil, inducing spasm of accommodation, and approximating the nearest and most remote points of vision, belladonna dilating the pupil, paralyzing accommodation, and making the vision presbyopic.

On the brain there is no real antagonism. The excitement, the delirium with hallucinations and illusions, and the subsequent coma, caused by atropine, are not affected by any of the actions of pilocarpine. The soporose state brought on by the latter, as I have pointed out, is a secondary effect, the result of exhaustion and cerebral anæmia.

Continuing the subject of the antagonistic relations of atropine, we have next to consider the mutual interactions of

ATROPINE AND MUSCARINE OR AGARICINE.

As muscaria, or muscarine, is comparatively little known, it may be useful to make a preliminary statement of its history and characteristics. It is obtained from amanita muscaria, the fly fungus. We owe to Schmiedeberg and Koppe the discovery of the alkaloid, and to Schmiedeberg

and his pupils the full and accurate information now in our possession in regard to its physiological actions.* Muscarine has strong alkaline and basic properties, uniting with acids to form salts. It is a colorless substance having the consistence of syrup, is readily soluble in water, and its salts deliquesce rapidly on exposure to air. It seems to be actively toxic,—$\frac{1}{30}$ of a grain producing in the human subject very decided symptoms. The effects, taking a general view, are as follows: Considerable gastro-intestinal disturbance, nausea, vomiting, and diarrhœa, and violent colic, due to a tetanic contraction of the muscular layer of the bowel, are produced by it. An active and rather pleasurable delirium, rambling, and incoherence, not unlike that of alcohol, are caused by the fungus, so that it is used as an intoxicant by some of the inhabitants of Eastern Asia. In toxic doses the excitement is followed by more or less profound stupor, epileptiform attacks, trismus, and abolition of all reflex movements. During the stage of pleasurable intoxication the pupil is contracted, vision is dim, objects are seen as through a mist, and also probably double. The action of the heart is weakened and finally arrested in the diastole, the respiration is labored and stertorous, the salivary secretion is increased, the surface of the body becomes cold, and death ensues from failure of the heart.

On the brain, it is probable that muscarine acts in two modes, directly and indirectly; it first excites the cells of the gray matter, and ultimately paralyzes them; the heart being weakened, less blood passes to the brain, and hence this organ is in a condition of anæmia. On the eye mus-

* Das Muscarin, das giftige Alkaloid des Fliegenpilzes, etc., Leipzig, 1869; also, Archiv für exper. Pathol. und Pharmacol., Bde. iv. u. vi. Hermann, op. cit.

carine produces peculiar effects. It causes spasm of the accommodation and a marked degree of myosis, by stimulation of the motor oculi. The vision is disturbed, therefore, by the spasm of the accommodative apparatus and by the myosis, which limits the amount of light admitted to the retina.

The secretions generally are increased by muscarine, but it especially stimulates the salivary secretion. According to Prévost,* the bile and the pancreatic and urinary secretions are increased. It promotes the salivary secretion by stimulating the end organs of the nerves, and this is independent of a centric influence, for it takes place after the trunks of the nerves have been divided.† It is probable, if Prévost's view is correct, that the increase of the other secretions is due to the same mode of action.

A slight and momentary increase in the cardiac movements is first produced by muscarine, but this is followed by retardation. Direct application of this agent arrests the heart in the diastole, but mechanical, chemical, or electrical irritation will induce contraction. Section of the vagi does not prevent this effect. It may therefore be concluded that muscarine acts on the motor ganglia in the substance of the heart, and not on the muscle, nor on the apparatus of inhibition. A very considerable decline in the blood-pressure is a constant result, after a short preliminary rise. The walls of the vessels relax, as Bogosslowsky‡ has shown, and, as the action of the heart is at the same time depressed, it is obvious that the vascular tension must be reduced. During the stage of delirious

* Gaz. Méd. de Paris, 1870, tome iii. p. 243.

† F. A. Falck, Der Antagonismus d. Gifte. Volkmann's Samml. klin. Vortr., No. 159, 1879.

‡ Centralblatt für die Med. Wissenschaft, 97, 1870.

excitement, the respiration is rather hurried, but when the subsequent depression comes on, the respiration becomes slower and shallower, this result being due to a paralyzing action of muscarine on the respiratory centres.

When we come to compare these disturbances of function caused by muscarine with those produced by atropine, we must admit, with Schmiedeberg, that no example of physiological antagonism could be more exact. On the brain, the intoxication, with cerebral anæmia, of muscarine is opposed by the active delirium and cerebral hyperæmia of atropine. On the eye, the contracted pupil of muscarine, due to stimulation of the circular fibres innervated by the third nerve, is opposed by the dilated pupil of atropine, produced by stimulation of the radiating fibres, innervated by the sympathetic. The effect of atropine on the eye is relatively more powerful, for, when the pupil is contracted by muscarine, it can be dilated by atropine, but, when dilated by atropine, it cannot then be contracted by muscarine. On the function of secretion the antagonism is not less striking. Muscarine promotes the salivary secretion by stimulating the end organs of the nerves in the gland, and atropine arrests this secretion by paralyzing these nerves.* But atropine is relatively more powerful here, also, for, when the salivary secretion is arrested by atropine, muscarine cannot re-establish it, yet the secretion caused by the latter is promptly arrested by the former. This opposing mechanism probably extends to the hepatic and pancreatic secretions as well. The intestinal cramp caused by muscarine is removed by atropine. On the heart, nothing can be more perfect than the opposing actions of

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* Luchsinger, Die Wirkungen von Muscarin u. Atropin auf d. Schweissdrüsen d. Katze, etc., Archiv für die ges. Phys., 18, 1878, p. 501.

these agents. This fact is frequently adduced by physiologists as a striking exemplification of the doctrine of antagonism. If the heart is arrested in the diastole by muscarine, it is started again by atropine. If an animal is first brought under the influence of atropine, the heart is not stopped by muscarine, notwithstanding it is so readily poisoned by this agent. The antagonism is equally exerted on the respiratory function: muscarine lessens the respiratory movements and finally arrests them, while atropine stimulates this function.

Thus, viewed from all sides, these agents are exactly antagonistic. Is a function disturbed by one agent in a particular mode, it is also disturbed by the other agent in an opposite mode. In fact, we should search in vain for an illustration of the law of antagonisms more perfect than that subsisting between atropine and muscarine.

ATROPINE AND QUININE.

The only systematic experimental investigation of the antagonism between atropine and quinine which I have been able to find is that of Pantelejeff.* Clinical experience on this point is abundant enough, but we are not now concerned with this aspect of the question. Pantelejeff has ascertained that quinine arrests the heart in diastole, and that the subsequent administration of atropine causes the heart to resume its contractions. This result was observed both in frogs and in rabbits. In the latter animals, when the action of the heart was resumed after the suspension of its movements, the auricles began to contract before the ventricles. Examination of the web of the frog's foot disclosed the interesting fact that,

* The Lancet, July 31, 1880, p. 176.

after the subcutaneous injection of quinine, the calibre of the arterioles was lessened by contraction of their walls, while the opposite effect, or dilatation, followed the administration of atropine. Quinine causes a rise in the blood-pressure, after a brief preliminary fall, and atropine retards it.

BROMAL HYDRATE AND ATROPINE.

One of the subjects undertaken by the Committee of the British Medical Association, to whose important labors I have so often to refer, was the investigation of the antagonism of bromal hydrate and atropine. This research was especially in charge of Professor McKendrick, and the scope of it was limited to the lethal effects. All of the facts are comprehended in the conclusions to which he was conducted by his experiments, as follows:

"1. There is a distinct physiological antagonism between bromal hydrate and atropine. 2. After a fatal dose of bromal hydrate, the introduction of atropine arrests excessive secretion from the salivary glands and mucous surfaces of the lungs, and thus obviates the tendency to death from asphyxia, caused by the accumulation of fluids in the air-passages. Atropine also causes contraction of the blood-vessels, and thus antagonizes the action of bromal hydrate, which causes dilatation of these vessels by paralysis of the sympathetic nerve. 3. While atropine may save life after a fatal dose of bromal hydrate, the converse apparently does not hold good, as we never have succeeded in saving life after a fatal dose of atropine by the subsequent injection of bromal hydrate."

ATROPINE AND ACONITINE.

The last application of the physiological antagonism of atropine is that with aconitine, for which we are indebted

to Dr. J. Milner Fothergill.* These researches are not extensive, but they probably represent the actual state of the antagonism. *A priori*, a very perfect and extended opposition of actions would be presumed to exist. Aconitine, a respiratory and cardiac depressant, ought to be neutralized by atropine, a respiratory and cardiac stimulant. The facts, in the main, support this supposition. "Thus, to a rabbit weighing two pounds six ounces, I gave," says Dr. Fothergill, "3 grains of atropine, and six minutes afterwards $\frac{1}{300}$ grain of aconitine; the animal survived. A week afterwards the same rabbit had the aconitine alone, and died in two hours and a half." Small doses of atropine he found had very striking effects on animals to which lethal doses of aconitine had previously been administered. The animals all recovered from doses of aconitine, which subsequently killed them all when administered without the atropine. "It was found, however, that if the administration of the atropine was delayed beyond sixteen minutes, it was powerless to arrest the lethal action of aconitine."

MORPHINE AND ATROPINE.

So numerous and important are the uses of these agents when administered together that separate and independent consideration of the combination seems necessary and desirable. The two agents are used together in varying proportions, and much depends on an accurate adjustment of the quantities to the powers respectively.

A permanent solution may be prepared as follows:

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* The Antagonism of Therapeutic Agents. Philadelphia, 1878, p. 41.

℞ Morphinæ sulphatis, gr. xvi ;
Atropinæ sulphatis, gr. ss ;
Acidi carbolici, gr. viij ;
Aquæ lauro-cerasi *vel* chloroformi, ℥i. M.

Sig.—Five (5) minims contain $\frac{1}{6}$ of a grain of morphine and $\frac{1}{192}$ of a grain of atropine.

A *penicillium* develops in the solution, and slowly diminishes its activity by growing at the expense of the alkaloids.

Powders for extemporaneous solutions may be prepared as follows :

℞ Morphinæ sulphatis, ℈i ;
Atropinæ sulphatis, gr. ss.
M. Fiat pulv. No. cxx. (120).

Sig.—Each powder contains $\frac{1}{6}$ of a grain of morphine and $\frac{1}{240}$ of a grain of atropine.

On the whole, these are to be preferred : they are convenient to handle, readily soluble, accurate, and therefore satisfactory. The relative proportions of morphine and atropine in the solutions, as in the powders of the mixed alkaloids, will be governed by the character of the cases for which they are administered.

History.—By the year 1810 considerable experience of an empirical kind had accumulated in regard to the antagonism of opium and belladonna ; for we find that in this year Joseph Lipp published an inaugural thesis on the toxic effects of belladonna berries, and on the curative powers of opium. We owe to Graves, the great Dublin clinician, the first really scientific suggestion of an antagonism. He supposed that the state of the pupil would afford an indication in fevers of the need of opium or belladonna—the former to be given when the pupil was dilated, the latter when it was contracted. Acting on this

suggestion, Dr. Thomas Anderson,* of Edinburgh, employed belladonna against opium-poisoning—a mydriatic against a myositic—with success. Two years subsequently, Dr. William H. Mussey,† of Cincinnati, seeing the account of Dr. Anderson's cases, tried the same expedient successfully in a case of attempted suicide with laudanum. In July, 1859, Mr. Benjamin Bell,‡ of Edinburgh, published an account of two cases, in which symptoms of poisoning produced by the subcutaneous injection of atropine were removed by considerable doses of morphine. Influenced by these results of Mr. Bell, in December of the same year Mr. Seaton,§ of Leeds, treated eight cases of poisoning by belladonna berries with opium,—seven of the eight cases recovering. In January, 1862, Dr. C. C. Lee,‖ of Philadelphia, reported two cases, one of opium-poisoning treated by belladonna, and one of belladonna-poisoning treated by opium, the result a success in each case. Dr. Lee also entered into some detail on the literature of the subject, referring to the experiences of Anderson, Mussey, and Seaton, and to the adverse experiments of Brown-Séquard. During the same year (1862), the most important paper which had hitherto been published made its appearance from the pen of Dr. William F. Norris.¶ In this paper the cases illustrating an antagonism of action between opium and belladonna, which had been previously published, were tabulated; and a full historical

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* Braithwaite's Retrospect, 1855, Part xxx. p. 301.

† The Cincinnati Medical Observer, 1856, vol. i. p. 70. There were but two volumes issued of this periodical, when it was united with The Lancet.

‡ The Edinburgh Medical Journal, 1859, vol. iv. p. 1.

§ The Medical Times and Gazette, December, 3, 1859, p. 551.

‖ The American Journal of the Medical Sciences, vol. xlii.

¶ Ibid., vol. xliv.

account of the subject, from which subsequent writers have drawn their information, and to which I am much indebted, is there given. In 1865 an admirable paper, based on clinical and experimental observations made at the military hospital for wounds and injuries of the nerves, and embodying the results of an immense experience, was published by Drs. Mitchell, Morehouse, and Keen.* In the following year (1866) Dr. Constantin Paul † published a monograph, supporting the view of the existence of such antagonism. Since this time the cases, papers, and monographs have so greatly multiplied that it would be impracticable to name them all in this historical review. I have collected all the published cases for statistical study, and will refer to the more important papers and monographs hereafter. The cases thus far collected by me number one hundred and sixty of opium- and belladonna-poisoning, in which the one drug was used to counterbalance the effects of the other.

The history of this subject would not be complete without some reference to the opinions of those who doubt the existence of the antagonism, or disbelieve in it utterly. The opposition to the generally-accepted view is based chiefly upon researches on animals. The most influential of these experimentalists is Brown-Séquard.‡ His observations have been made for the most part on guinea-pigs and rabbits. Bois § studied the effects of these agents on

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* The American Journal of the Medical Sciences, July, 1865, vol. l. p. 67. On the Antagonism of Atropine and Morphine. Founded on Observations and Experiments made at the United States Hospital for Injuries and Diseases of the Nervous System.

† De l'Antagonisme en Pathologie et en Thérapeutique, 1866, pp. 92–115.

‡ Jour. de la Physiol., etc., 1860, tome iii. p. 726.

§ Gaz. des Hôp., 71, 1865.

cats. He regards the following experiments as conclusive against the view that an antagonism exists. To a cat he gave a dose of morphine just less than sufficient to cause death; when entirely recovered from the effects of this quantity, he gave to the same cat a dose of atropine having effects just short of lethal. When a sufficient time had elapsed to insure complete recovery from that dose, he administered those quantities together, when the result was fatal. Camus * investigated the action of the alkaloids of opium, and the antagonism of atropine and morphine, using cats and pigeons, while Onsum † conducted his researches on frogs. In what mode soever, or on what animals, the investigations were conducted, the results were uniformly opposed to the existence of an antagonism. I may now anticipate so far as to say that the methods of investigation pursued were not free from sources of fallacy, and that the results obtained were largely vitiated. The most elaborate series of experiments on this topic, embracing animals and men, were those of Harley,‡ but his facts admit of a different interpretation from that which he has given them. His fundamental error consists in regarding as examples of antagonism only those in which the opposition of actions exists throughout the whole range of effects, which, as I have already stated, is hardly true of any known examples.

In 1870, Dr. Köning § published a dissertation on the supposed antagonism of morphine and atropine, his research being conducted on animals. As had his prede-

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* Gaz. Hebdom., 2 sér., 1865, tome xii. p. 32.

† Schmidt's Jahrbücher, Band cxxviii. p. 288. (Abstract.)

‡ The Old Vegetable Neurotics, pp. 280 and 291.

§ Schmidt's Jahrbücher, Band cxlix. p. 18.

cessors in this inquiry, Köning decided adversely to the existence of this antagonism, although he noted the antagonizing influence of these agents on the pupil, the respiration, and the action of the heart. In 1873, Fröhlich,* of Würzburg, experimented with these agents on frogs and cats. His experiments rather indicated the existence of points of opposition, but not sufficient to prevent death from a lethal dose of both agents. In 1874 † appeared the report of the committee appointed by the British Medical Association, Professor J. Hughes Bennett, M.D., of Edinburgh, chairman. In making the report on this division of the subject—the antagonism of morphine and atropine—the reporter says, "Extraordinary pains were taken to determine the question whether or not morphine and atropine were antagonistic of one another; and the researches now to be described will be found to add largely to our precise and exact knowledge as compared with the unfounded and contradictory opinions which have hitherto prevailed. The conclusions at which they arrived, after experiments on the rabbit chiefly, are as follows:

"1. Sulphate of atropine is physiologically antagonistic to the meconate of morphine within a limited area. 2. Meconate of morphine does not act beneficially after a large dose of sulphate of atropine, for in these cases the tendency to death is greater than if a large dose of either substance had been given alone. 3. Meconate of morphine is not specifically antagonistic to the action of sulphate of atropine on the vaso-inhibitory nerves of the heart; and, 4, the beneficial effect of sulphate of atropine

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* Pharmakologische Untersuchungen, 1873, pp. 224 and 231.

† The British Medical Journal, 1874, vol. ii., various numbers.

after the administration of large doses of meconate of morphine is probably due to the action sulphate of atropine exercises on the blood-vessels. . . . It may also assist up to a certain point, not precisely fixed in these experiments, by stimulating the action of the heart through the sympathetic, and obviating the tendency to death from deficient respiration observed after large doses of morphine."

In 1876 the same investigation was undertaken by Corona, dogs and cats being the animals employed. He arrived at the singular conclusion that a partial physiological antagonism existed between morphine and atropine, but not a therapeutical antagonism,—for whilst morphine is useful in atropine-poisoning, in poisoning by morphine, the effects are not removed by atropine. In this opinion Corona stands quite alone. In the following year (1877), Dr. Hans Heubach reviewed the literature of the subject, and undertook a new investigation of the supposed antagonism, confining his experimental research to animals. These investigations, carried on at Binz's laboratory at Bonn, support the view of a limited antagonism in the cardiac and respiratory organs but not in general.

Physiological Effects.—Although much has been said in the preceding pages upon the physiological effects of morphine and atropine, when separately administered, it is necessary now to show the influence which they reciprocally exert when administered together. Their so-called "physiological antagonism" may be most conspicuously exhibited by a comparison of their individual with their combined action on the different parts of the body.

1. *On the Nervous System.*—Both act upon the brain,—atropine producing delirium, hallucinations, and disturbed sleep; morphine causing, generally, somnolence. Both

relieve pain, but this effect is much more decidedly the property of morphine. Both produce disorders of motility, staggering, difficulty of co-ordinating muscular movements, vertigo, confusion of mind, and headache. When given together, these effects are curiously modified.

Morphine corrects the hallucinations and phantasms of atropine.

Atropine in small doses—$\frac{1}{96}$ of a grain—increases the hypnotic power of morphine; but if the quantity of atropine be sufficient, it overpowers the effects of morphine on the cerebrum, causing wakefulness or disturbed sleep, phantasms, and illusions.

The pain-relieving power of morphine is increased by atropine.

The disorders of motility, and the vertigo, are not diminished when the two agents are used together, but the after-headache and confusion of mind are much less.

When toxic doses are used, the narcotism of morphine is overcome by atropine, and *vice versa*. In a case which occurred to myself, and which I have already referred to, serious symptoms produced by 1 grain of morphine were relieved by $\frac{1}{24}$ of a grain of atropine. As, however, the effects of atropine are much more prolonged than those of morphine, it is not easy to exactly counterbalance the effects of one by the other. The cases of morphine-poisoning, in which atropine was used as an antidote, that have fallen under my observation, received too much atropine, the toxic symptoms of the latter remaining long after the narcotism of the morphine had disappeared.

Upon the organic nervous system these agents seem exactly to antagonize each other.

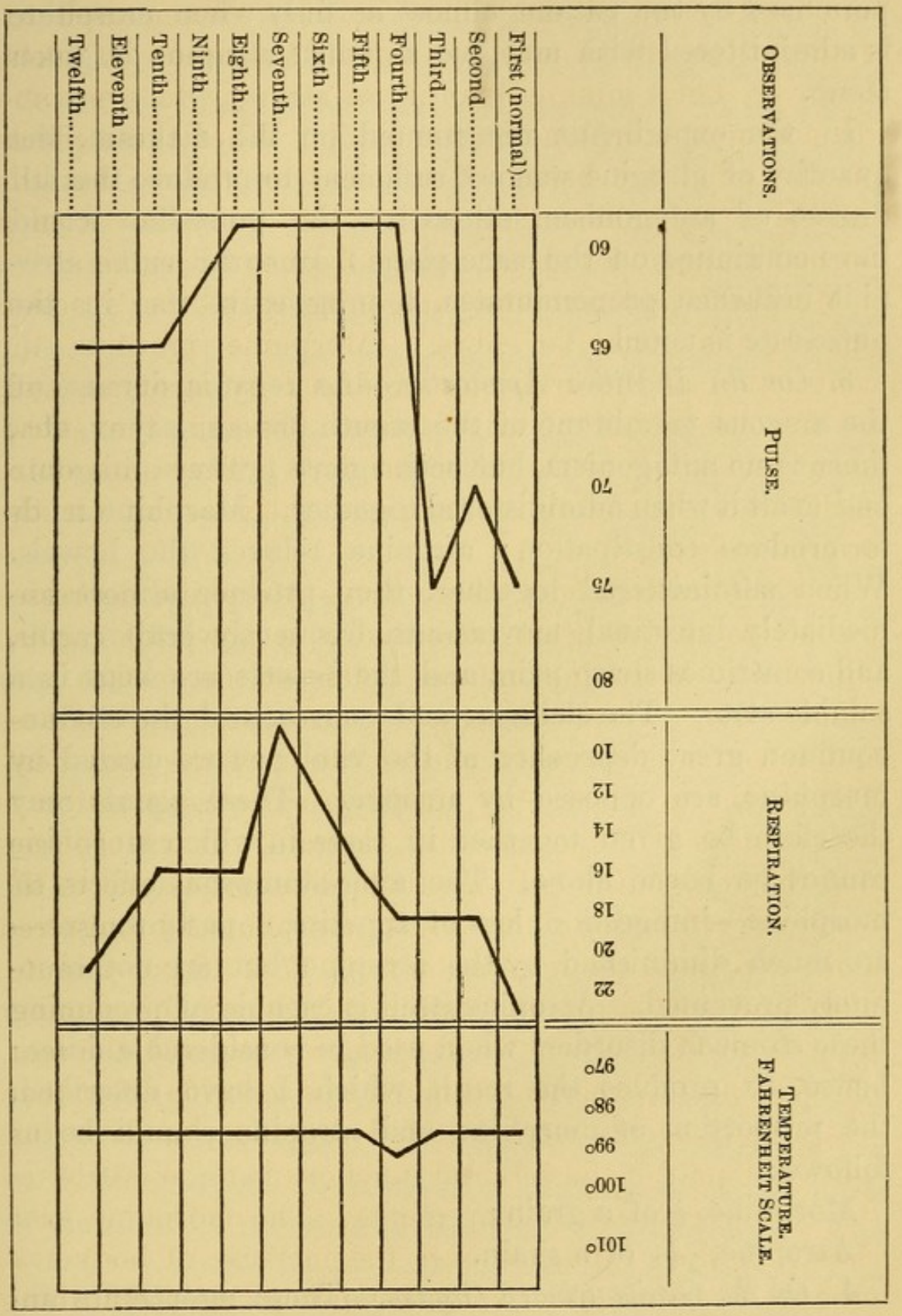
Morphine causes contraction of the pupil, and a tetanic condition, according to Graefe, of the muscle of

accommodation; atropine causes dilatation of the pupil, and contraction of the ciliary muscle. When used together, these effects may be precisely balanced. It takes, however, but a minute quantity of atropine to overcome the action of morphine on the pupil. When these effects on the pupil are balanced, it does not follow that the muscle of accommodation is in a condition to act in a normal manner, for visual defects frequently remain.

Morphine and atropine antagonize each other's action on organic muscular fibre. Morphine prevents the contraction of the arterioles produced by atropine, and, as a consequence of this action, prevents the subsequent relaxation of the muscular fibre. They antagonize each other, therefore, as respects their action on the arterial tension.

2. *On Circulation and Respiration.*—Morphine depresses the action of the heart; atropine is a powerful cardiac stimulant. Morphine induces pallor of the surface, and reduces the external temperature; atropine causes redness and injection of the skin and elevation of the body-heat. The extent to which they modify each other's action is well exhibited in the annexed diagram. It will be seen that the antagonism between them does not extend to the respiratory function; for, whilst morphine administered alone depressed the respiration from 17 to 12 per minute, morphine and atropine combined reduced the number from 18 to 10. When Dr. De Courcey received the morphine alone, he experienced much less soporific effect than when both agents were injected together; and to this quiescent state of the cerebral functions is to be attributed the slower respiratory movements. The morphine exercises a marked influence over the increase of body-heat produced by atropine. Notwithstanding this, the flushing

FIG. 14.


OBSERVATIONS.
PULSE.
60
65
70
75
80
RESPIRATION.
10
12
14
16
18
20
22
TEMPERATURE. FAHRENHEIT SCALE.
97°
98°
99°
100°
101°
First (normal).....
Second.....
Third.....
Fourth.....
Fifth .....
Sixth .....
Seventh.....
Eighth.....
Ninth .....
Tenth.....
Eleventh .....
Twelfth.....

of the face and the strong subjective sense of heat are experienced by the patient almost as fully when morphine is administered with atropine as when atropine is given alone.

In the experiment represented on the diagram, the quantity of atropine was not sufficient to produce the full degree of antagonism, otherwise the pulse-line would have continued on the same plane. In so far as the atropine influence preponderates, a progressive rise in the pulse-rate is noted.

3. *On the Digestive Apparatus.*—As regards dryness of the mucous membrane of the mouth, fauces, larynx, etc., there is no antagonism, but both agents produce this state and exalt it when administered together. Morphine tends to produce constipation; atropine relaxes the bowels. When administered together, they produce almost immediately intestinal movements, frequently borborygmi, and sometimes sharp pain, and the bowels are kept in a soluble state. The sickness and nausea, and the not uncommon great depression of the vital powers caused by morphine, are opposed by atropine. These agents may therefore be given together in cases in which morphine cannot be borne alone. The after-stomachal effects of morphine—indigestion, loss of appetite, a pasty tongue—are much diminished by the atropine, but are not absolutely prevented. Atropine itself is capable of producing these stomach disorders when used in considerable doses; hence, to produce the result which I have described, the proportion of morphine and atropine should be as follows:

Morphine, $\frac{1}{4}$ of a grain;
Atropine, $\frac{1}{120}$ of a grain.

4. *On the Genito-urinary Organs.*—These agents are an-

tagonistic as to their effects on the kidneys and the urinary excretion. Morphine suspends and atropine promotes the functional activity of the kidneys. By inducing congestion of the Malpighian tufts, and increasing the *vis a tergo*, atropine acts as a diuretic, and with the additional water there strains off from the blood the larger amount of urates produced in the more rapid metamorphosis of tissue. Morphine increases the action of the sudoriparous glands, and atropine diminishes it, thereby in the one case lowering, in the other case exalting, the functional activity of the kidneys.

Both produce dysuria, but this result comes of a different action in each case. Morphine impairs the contractile power of the muscular coat of the bladder, so that it contracts with difficulty, the emission of urine taking place slowly; atropine maintains steady tonic contraction of the sphincter, so that it dilates slowly under the voluntary effort, when the desire to micturate is experienced.

Both morphine and atropine impair the sexual appetite; atropine at once, and morphine when long used.

A comparison of the actions on man shows that opium and belladonna act oppositely, or in an opposite manner, *on the brain*, *on the pupil*, *on the circulation*, *on the lungs*, *on the stomach*, and *on the skin*. Opium, with the exceptions named, causes somnolence and stupor; belladonna, excitement, hallucinations, and delirium. When administered jointly and in the proper proportions, sopor, closely approximating natural sleep, is the result. This was well exhibited in the case of Dr. Legg,* whose patient, a boy of 5 years, drank by mistake a mixture of equal parts of liniment of opium and liniment of belladonna. The

* The Medical Times and Gazette, November 3, 1866, p. 474.

effects of the belladonna, owing to its more rapid action, first dominated the situation, when there was delirium with hallucinations, the boy driving sheep and picking up money from the bed; but then drowsiness supervened and heavy sleep, when he was not forced awake and kept walking. The violence of this ambulatory treatment was wholly unnecessary, and indeed injurious, for, if he had been permitted to sleep, the antagonism on the respiration and circulation would have sufficed to save life. Facts of the same kind were observed in a case jointly cared for by Dr. Mussey, of Cincinnati, and myself. A boy of 8 years, the son of a physician of Cincinnati, was given internally by mistake an anodyne application for earache, containing 2 grains of morphine and 1½ grains of atropine. When the toxic symptoms were well advanced the mistake was discovered, and Dr. Mussey and myself were summoned. We found the pupils fully dilated, the face flushed, and an active delirium, in which the boy fought and struggled violently against imaginary enemies. After an hour or two of this excitement, a soporose state came on, and was very profound for a number of hours. As, however, the respiration was full, strong, and rhythmical, the pulse regular and of good volume, we decided to await the result of the antagonism. Dr. Mussey had published one of the first cases of opium-poisoning illustrating the antagonistic action of belladonna, and I had seen several cases, so that we were perfectly agreed as to the proper course, and the result justified our decision. Another case in which the simultaneous administration of opium and belladonna was due to accident was reported by Dr. Cotter.* A young lady swallowed a liniment composed

* The American Journal of the Medical Sciences, vol. l. p. 67, *et seq.*

of opium and belladonna, the amount taken being equivalent to 25 grains of the extract of belladonna and 12 grains of opium. At first the symptoms of belladonna-poisoning were largely in excess; after some hours she appeared like one helplessly drunk, and was so drowsy as to be kept awake with great difficulty; then another period of excitement came on, and this was followed by a period of profound sleep, from which she awoke relieved. Such are the facts as taught us by these accidental experiments on man. What is the clinical experience available for further study of the problem?

As a result of large observation and experience of the effects of these agents on man, Drs. Mitchell, Morehouse, and Keen conclude that "the headache and phantasms of atropine are certainly thus controlled [*i.e.*, by morphine], as well as the partial deafness and visual defects which in high doses it occasions. On the other hand, when morphine has been fully used, the drowsiness and stupor, which are the best tests of its power, disappear before the influence of atropine. . . . Perhaps the most peculiar cerebral symptom of atropine is its tendency to cause phantasms and illusions. We found under doses of $\frac{1}{25}$ of a grain these were common, and in some men could always be brought on. Usually they were absent so long as the eyes remained open, but arose at once on closing them. This condition was singularly subdued by morphine. Drowsiness caused by morphine was as surely lessened or destroyed by the counter agency of atropine; and, in fact, atropine given alone and in full doses is very apt to cause a restless night to follow, so that it is assuredly in no sense a hypnotic."

Harley strongly insists on the modifying influence of morphine over the cerebral effects of atropine. "The in-

fluence of opium in converting the insomnia of belladonna into sleep, and the influence of belladonna in determining not only sleep, but narcotism in individuals under the influence of opium, are illustrated in several examples. Some of the cases," he further says, "serve to give greater force to these observations, and teach us that we must be careful how we employ opium as a means of converting the restlessness and insomnia following excessive doses of belladonna into quiet sleep." Harley, strangely enough, does not regard these different cerebral effects as due to an antagonistic action, but as synergistic. It is, nevertheless, evident enough that his observations are confirmatory of those of Mitchell, Morehouse, and Keen, who state with more precision the exact features of the reciprocal influence. In fact, at the present time, professional opinion is no longer divided on this point, and morphine and atropine, and opium and belladonna, are constantly prescribed together to secure an hypnotic effect, not attainable by the exhibition of either remedy alone. Clinical experience on man has been confirmed by observations on animals, so far as the facts are applicable. Thus, Erlenmeyer* shows that the exciting effect of atropine on the brain is lessened by the narcosis of morphine. Harley's experiments on dogs were similar in results: "The cerebral effects of atropine are," he says, "intensified and prolonged,—the insomnia which results from excessive doses is converted into narcotism, or a mixture of narcotism and delirium." Heubach,† whose researches were carried on in Binz's laboratory, was led to similar conclusions.

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* Berliner klinische Wochenschrift, loc. cit.

† Arch. für experiment. Pathol. u. Pharmakol., 1878, Band viii. p. 31. Antagonismus zwischen Morphin u. Atropin.

Obviously, the actions of such agents on the brains of animals can be compared only according to the extent of development, for, the brain of man being more complex in structure and more highly specialized, must be affected both with less severity and in a greater variety of manifestations. In animals the effect of the narcotic is necessarily limited to the cephalic organs possessed by them, whereas in man, not only to those, but to the higher special organs he is possessed of, is the influence distributed. In animals the narcotic more affects the motor centres and the centres of respiration and circulation, while in man its effects are exerted not only upon these centres, but upon the higher centres and upon the mental sphere. Do we not have in this difference in development the reason of the much greater toxic power in animals of morphine and atropine when administered simultaneously? Bernard* has signalized this important point in his introduction to the study of experimental medicine. After declaring that observations on animals, in respect to the functions of the cerebro-spinal nerves, and the vaso-motors and secretors of the sympathetic, and on circulation and digestion, hygiene and toxicology, are perfectly and at all points applicable to man, he indicates conditions under which the observations on animals are not thus applicable. For example: "From the physiological point of view, the experimental study of the organs of sense and of the cerebral functions must be made on man necessarily, because on the one hand man is above the animals in respect to those faculties of which they are not possessed, and, on the other, animals are unable to indicate the nature of those sensations of which they may become conscious."

* Introduction à l'Étude de la Médecine Expérimentelle. Paris, 1865, p. 219.

My conclusion, after the examination of the experimental and clinical evidence, therefore, is, that, as respects the brain, opium and belladonna exert opposing actions. The illusions, hallucinations, and busy delirium caused by belladonna are counteracted by opium. The result of their conjoined action is sopor, deepening into coma when the quantity of both is large. When administered simultaneously, if the effects of atropine preponderate, there will occur periods of excitement and delirium, interspersed with relatively shorter periods of sopor and coma. The more decidedly opium preponderates, the less there will be of delirium, and the more of sopor. When opium is in excess, the tendency is to coma and stertorous breathing, after a period of sopor.

There are some highly-important points in regard to the antagonistic action of morphine and atropine on the pupil. Graves, as is well known, first proposed to make use of this antagonism as a guide to treatment. There can be no doubt that this antagonism exists,—that opium contracts and belladonna dilates the pupil; opium weakening and belladonna stimulating the radiating fibres of the iris. There are, however, occasional exceptions. As the state of the pupil is usually regarded as a guide to the use of the antagonist in cases of poisoning, it becomes in a high degree important to know if this indication can or can not be depended on, and to what extent. In Case XIV. of a list of unsuccessful cases, we find that a very large quantity of morphine was given to counteract the effects of some belladonna liniment taken by accident, and that, notwithstanding the apparent preponderance in the action of the morphine, the pupil continued dilated. In one of the successful cases of joint administration of opium and belladonna, in which the symptoms produced

by the latter much preponderated, the pupil was minutely contracted. It has been observed occasionally, in cases of opium-poisoning, that at a certain stage in the narcosis the pupil dilated. On the other hand, in profound belladonna narcosis, the largely-dilated pupil has suddenly contracted in some occasional cases. These are exceptional manifestations, it is true, but, as there are two examples in one hundred and twenty cases, the value of the indication afforded by the state of the pupil is correspondingly weakened. The antagonism between morphine and atropine may be exerted without the contraction caused by the former, or the dilatation by the latter, being entirely overcome. No fewer than twenty cases illustrate this proposition. The rate at which these agents act on the pupil varies greatly. Atropine acts both more promptly and for a much longer time. Atropine has, also, a more powerful action; for, of the twenty cases which show that the size of the pupil may not be much affected by the antagonist, sixteen were examples of preponderating dilatation. From these facts it must be concluded that the state of the pupil cannot always serve as a guide for the further administration of the antagonist.

The next point for consideration is—the antagonistic influence of opium and belladonna on the heart. That opium, in full doses, acting alone, slows the heart, and that belladonna quickens it, are unquestionable facts. Observers are by no means agreed as to the influence reciprocally exerted by these agents when administered simultaneously. Mitchell, Morehouse, and Keen find that "morphine has no power to prevent atropine thus influencing the pulse, so that as regards the circulation they do not counteract one another." Harley maintains that morphine, here as elsewhere, increases the effect of

atropine. "If, however," he says, "the dose of atropine is small, and the morphine produce considerable derangement of the vagus, the rapidity of pulse is not greater than when the atropine is administered alone. In my own observations I have invariably seen that the acceleration of pulse produced by atropine is lessened by morphine, and *vice versa*, and this is the conclusion derived from a study of the reported cases of poisoning. The effect of the atropine, however, preponderates. The result of the combined effect is not the mean of the two, but is nearer the standard of atropine than of morphine. As wakefulness and active delirium increase the pulse-rate, and stupor with absolute repose lessens it, these factors must also be considered in estimating the relative share of opium and belladonna in the result. The experiments on animals have usually demonstrated an antagonistic action as regards the heart." Harley's experiments on dogs certainly show that the accelerating effect of atropine on the heart is remarkably lessened by combination with morphine. In the careful experiments of Heubach, the same result is shown; the increased pulsations caused by atropine are diminished by morphine, but the general level of effect is above the mean considerably. We must, therefore, conclude that the effects of morphine are antagonistic to those of atropine on the heart to a limited extent, but that the effects of atropine preponderate, and, hence, the result of the combined effects is a rate of movement greater than the mean.

Without doubt, the most important point in the whole range of the antagonism of morphine and atropine is the opposed action on the respiratory function. Less difference of opinion exists on this than on any other point connected with the subject. In general terms, it may be

said that opium is a respiratory depressant, and atropine a respiratory stimulant. The cause of death in opium narcosis is failure of respiration, the action of the heart ceasing after respiration. Atropine counteracts this tendency, and maintains the activity of the respiratory function. All the cases of poisoning teach this lesson. As the opium narcosis deepens, the respiratory acts become less and less frequent and more and more shallow; the quantity of oxygen admitted to the blood lessens, and the oxidation processes decline; the surface becomes cold, and, carbonic acid accumulating, carbonic-acid narcosis is added to the toxic coma. Atropine counterbalances these effects by raising the number and increasing the depth of the respiratory acts, hence more oxygen is admitted to the blood, the chemical interchanges are more extensive and speedy, and excretion is facilitated. The improvement is represented by a flushed face, a warm and dry skin, and a more active circulation generally.

Atropine proves fatal by exhausting the irritability of the motor ganglia of the heart and of the general vasomotor system, and also of the respiratory centres. Morphine, by lessening the work of the heart and of the lungs, opposes these effects of atropine. The facts presented in the one hundred and twenty cases of poisoning generally support this view of the antagonism. In some of the cases, it is true, the narcosis was too profound to permit any new impression to be made; but, in those suitable for the action of the antagonist, nothing could be more striking than its favorable influence on the respiration. Dr. Johnston, of Shanghai, whose experience of opium-poisoning has reached to hundreds of cases, says that the effect of the atropine is simply marvellous in stimulating the respiratory function and removing the

carbonic-acid narcosis. In the fatal case of atropine-poisoning narrated by Dr. Gross, the injection of morphine induced stertor. I have already suggested that the more gradual introduction of the morphine influence would have prevented this accident, which seems to have been an idiosyncrasy, rather. In a case narrated by Dr. Fothergill,* the influence of the antagonist on the respiratory function is most conspicuous. A woman had taken, at 11 A.M., laudanum containing from 12 to 17 grains of opium. At 2 P.M. the respiration was almost gone, but the pulse, though small, was rhythmical and regular. One grain of sulphate of atropine was then injected subcutaneously. In a half-hour the respiration was becoming well established, and, in an hour and a half after the injection, was going on steadily, 13 to the minute, and long and deep. No further use of the antagonist was necessary to overcome the effects of the poison. It is probable, indeed, that the quantity of atropine used was rather in excess, as an emetic had caused the discharge of some opium, and the subsequent account shows a preponderating action of atropine. An equally instructive case, as showing the power of atropine to overcome the respiratory depression caused by morphine, is narrated by Dr. McGee.† A stout, muscular man of 40 years swallowed 30 grains of opium in 10 or 12 ounces of whiskey. He became profoundly comatose. In two hours $\frac{1}{8}$ of a grain of atropine was injected, and, this having no effect, in half an hour the same quantity was repeated. The respirations were then nearly suspended, the face being livid,

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* The Antagonism of Therapeutic Agents. Philadelphia, H. C. Lea, 1878, p. 132.

† The American Journal of the Medical Sciences, July, 1869, p. 282.

but under the influence of the atropine the respirations increased greatly; the pulse rose to 140, the pupils became widely dilated, and consciousness was so far restored that the patient could be roused. He then slept profoundly for a number of hours, but his pulse continued at 81, with the respirations full and deep, and Dr. McGee, wisely trusting to the antagonistic action, did not exhaust his patient by ambulation, flagellation, artificial respiration, and other ingenious devices for keeping awake those who need the restorative effects of sleep and quiet. I might narrate many examples from the collection of cases made for this study, showing the importance of the antagonism exerted on the respiratory functions. There is no difference in the lesson taught us in the cases of opium narcosis. The cases of atropine-poisoning treated by morphine are not less instructive. Various examples come to us with the authority of such names as Graefe,* Schmidt,† Fronmüller,‡ Cohn,§ and others, occurring in ophthalmic practice. Some of these were probably not lethal, although characteristic and violent symptoms were produced; yet the antagonistic action of the morphine was not less conspicuously displayed.

If we now pass from the clinical evidence to the results of experimental research on man and on animals, we are greatly surprised with the differences in the conclusions drawn. Mitchell, Morehouse, and Keen conclude that "the influence of atropine on the pulse and respiration is in no way altered by the use of full doses of morphine, so that in this particular their supposed antagonism does not

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* Schmidt's Jahrbücher, Band cxxv. p. 350.

† Ibid., Band cxxiv. p. 167. ‡ Ibid., Band cxxvi. p. 282.

§ Berliner klinische Wochenschrift, 11, 16, 1865.

exist." In some experiments of my own, made on a medical student, I found that morphine modified to a considerable extent the effects of atropine on the pulse and respiration,—a fact clearly exhibited in the graphic representation of the results.* Harley expresses himself with decision against the supposed antagonism of these agents on the respiratory function, but he indicates conditions under which they may be used in opposition with advantage,—a singular contradiction between his facts and his opinions. "Belladonna is powerless to obviate the chief danger in opium-poisoning,—viz., the depression in the respiratory function." But, in another place, he says, "in the treatment of belladonna-poisoning, our efforts must be directed to sustain the breathing. Opium must be used, not as an antidote, but as a means of calming the nervous agitation when it is excessive," etc. It is impossible to find any meaning in such explanations. Again, he says, "when the heart shows indications of failing power, the subcutaneous injection of $\frac{1}{96}$ of a grain of sulphate of atropine, at intervals of two hours, must be practised." The facts of Dr. Harley admit of very different interpretation from those which he has advanced; they prove that atropine exerts a distinct stimulant action on the respiratory organs, and are in conformity with clinical experience. We may now regard it as settled that atropine antagonizes the depression caused by morphine on the respiratory function, notwithstanding the adverse opinions just quoted.

The antagonistic action of atropine and morphine is further exhibited in the control of the former over the nausea, depression, and actual syncope caused by the latter. This antagonism is exhibited in ordinary medicinal doses,

* See the tracings on another page.

and clinical experience justifies the remark of Harley, that morphine should not be administered alone unless its action on the subject is known, but always with atropine. The explanation of the utility of atropine in preventing the nausea and depression caused by morphine consists in the counterbalancing action of these agents on the cerebrum. While the depression—ofttimes the syncope—is thus prevented, the nausea may occur, for atropine also excites nausea in some subjects. The coldness of the surface and the clammy sweat caused by morphine are removed by atropine. The importance of this fact is considerable. The first effect of morphine is to raise the arterial tension and to energize the cardiac movements, but this is followed by decline in the tension and by slowing of the movements. The peripheral vessels become relaxed, and the blood-current becomes slow; the sweat-glands act freely, and the functional interchanges between the blood and tissues are suspended. The action of atropine brings about an important change; the peripheral vessels contracting in their vermicular manner, and more blood being received from the heart, the surface grows warm and dry, and the function of metamorphosis of tissue is resumed. The effect of this resumption of activity at the periphery on the condition of the cerebrum is only less important than the renewal of hæmatosis at the lungs.

Atropine stimulates the action of the kidneys somewhat, and morphine checks the flow of urine. They both act to render the emission of urine more difficult, but it is an error to suppose that they act in the same way. Morphine dulls the sensibility of the mucous membrane and diminishes the contractile energy of the muscular coat of the bladder; atropine stimulates the sphincter to more energetic contraction, so that the voluntary efforts at relaxation are opposed.

Having now indicated the points of antagonism, and examined into the opinions for and against the belief in its existence, we are prepared to ascertain how a lethal dose of the one can overcome the effects of a corresponding dose of the other agent. It is evident that very rarely is a lethal dose of one agent counterbalanced by the other in animals. The reason apparently is the difference in the extent and variety of the cerebral structures in man, as compared with the inferior animals. The physiological actions are the same in animals as in man, except the difference in degree, to employ the words of the illustrious Bernard, but when we reach the brain, we find that in animals the force of the poison is expended on a few comparatively simple organs, whereas in man it is diffused over much more extensive and complicated structures.

Experience has demonstrated that the quantity of poison which can be antagonized successfully and a fatal result averted is comparatively limited. Very considerable quantities, as we have seen, were taken in some of the successful cases, but they did not exceed a certain limit, and the stomach-pump and emetics were freely used, so that the actual amount entering the blood was far less than that taken into the stomach. What disposition of the poison is effected? There is no chemical union of the antagonist, to destroy the toxic power. It is simply opposed until elimination is accomplished. The tendency to destroy life by overwhelming the functions of particular organs is opposed and held in check, and gradually the poison is eliminated. Furthermore, the separation of the poison from the blood and its excretion by the usual channels are greatly promoted by the action of the antagonist in maintaining the functional activity of the organs depressed by the poison. The rate of elimination and the means of promoting

it become, therefore, important elements in the management of these cases, and, I may also add, are usually wholly neglected. The principal route of excretion is by the kidney, but the skin and intestinal canal also convey off some of the poison. In a few minutes after the alkaloids are swallowed, traces of them are discoverable in the urine. Free action of the kidneys should therefore be maintained by the use of diluents. Another practical point of high importance is the removal of the urine as fast as it accumulates in the bladder. Brown-Séquard has shown that absorption of alkaloids takes place from the mucous membrane of the bladder, and he proposes to make use of this fact by injecting morphine solutions into this viscus. It is probable that alkaloids contained in the urine may diffuse into the blood again from the bladder. The action of the bowels should be free, and the skin should be stimulated, —in fact, all the channels of excretion should be kept freely at work.

No absolute rule can be laid down as to the quantity of the antagonist to be used. Taking morphine-poisoning as a type, the quantity of atropine must be determined by the effects. What are the guides? The pupils? No. For, although they may react in the usual way to the antagonist, it must be remembered that the action of atropine preponderates, and in some instances they do not react normally. The true guides are the state of the respiration and that of the circulation. If the breathing is deep and rhythmical, and the pulse is full and strong, the state of the pupil and the depth of the narcotism are of little moment. When the amount of the antagonist administered suffices to establish the respiration and circulation in their proper condition, the quantity is sufficient, whether or not it may be theoretically. As a rule, it is better to give the antagonist

in small quantity, frequently repeated, until the amount required has been given. Large doses, as is evident in some of the cases, produce unpleasant effects, and may be in excess of the real requirements. In some actual trials, I found that $\frac{1}{20}$ of a grain of atropine was about equal in toxic power to 1 grain of morphine. In deciding on the dose of the antagonist, the amount of the poison probably eliminated must be taken into consideration.

THERAPY.—It would be a waste of space to repeat the therapeutical applications of morphine and atropine already given with considerable fulness in the preceding sections. Nevertheless, it is necessary to indicate the circumstances requiring or permitting their conjoined administration. A general rule may be formulated as follows:

Whenever the hypodermatic injection of morphine is proper and necessary, atropine should be combined with it unless contra-indicated.

In the *psychical disorders*, in which power is in excess, the conjunctivæ injected, the temperature high, morphine should be used alone. When power is deficient, the tendency being to depression, atropine should be combined with it. This is the rule, also, for other *affections of the brain* in which the subcutaneous injection is indicated.

For the relief of *insomnia*, or to procure sleep, the combination of morphine and atropine is to be preferred. The reader should not forget that an excess of atropine, or an amount of atropine sufficient to antagonize the cerebral effects of the morphine, will prevent sleep. They should be used in the proportion of $\frac{1}{120}$ to $\frac{1}{96}$ of a grain of atropine to $\frac{1}{4}$ or $\frac{1}{2}$ of a grain of morphine. As the susceptibility to atropine varies immensely, the precise quantity to be employed in any case must be regulated accordingly.

In the treatment hypodermatically of the *various convulsive disorders*, morphine and atropine should be combined.

The *neuralgias* are best treated by the combined morphine and atropine solution. There are several reasons for this:

Much larger doses of morphine may in this way be injected without danger to the patient; and the larger the quantity, as Brown-Séquard has shown, the greater the curative power.

Morphine and atropine combined are more effective than either singly.

The systemic effects during the time of maximum narcosis, and also after the narcosis has disappeared, are much less unpleasant and depressing when the two agents are combined than when morphine is used alone.

Sometimes atropine is better borne than morphine, and *vice versa:* in this case the agent whose effects are least unpleasant should be in excess.

In *sciatica* atropine is sometimes more effective than morphine: the proportions in which they should be used are as follows: $\frac{1}{48}$ to $\frac{1}{120}$ of a grain of atropine, $\frac{1}{4}$ to $\frac{1}{2}$ of a grain of morphine; here the physiological effects of atropine predominate, but the toxic effects are guarded by the morphine.

In *neuroses of the respiratory and circulatory organs* morphine and atropine should be used together. This is especially the case in *angina pectoris* and *asthma*, with the caution I have already given as to the use of atropine in certain diseases of the heart. Morphine alone is to be preferred in *pleuritis*.

In the *diseases of the digestive apparatus*, requiring hypodermatic medication, morphine and atropine should be used together.

As a general rule, in *diseases of the urinary and genital organs*, the two agents should be combined. For some purposes atropine should be in excess, as in *spermatorrhœa*, when the more decided anaphrodisiac effect of this agent is indicated. In cases of *pelvic* and *uterine pain*, atropine should be proportionally in larger amount than morphine.

Acute rheumatism, *rheumatic gout*, *muscular rheumatism*, and *myalgia* are best relieved by a combination of morphine and atropine, the latter being in excess, as respects its physiological action, of the former. The injection of atropine, thus guarded by morphine, exerts in these diseases an action beyond the relief of pain, how desirable soever that may be: it modifies, in a way not now understood, the morbid process. The progress of research renders it more and more probable that rheumatism is an expression of disorder in the nervous system, rather than an affection *per se* of the fibrous structures. Besides relieving in some way this centric disturbance, atropine favors the excretion from the blood of products (the urates) representing the active but imperfect tissue-change occurring in these diseases.

In surgical disorders of various kinds, the combined use of morphine and atropine has most important and varied applications: *to prevent and relieve shock; to cure pain; to relax spasm; to facilitate surgical operations.* Whenever, in surgical practice, the hypodermatic injection of morphine and atropine is indicated, the following rule should regulate the relative proportion in which they are employed:

If the action of the heart be feeble, the surface cold, and the vital powers depressed, atropine should be in excess as respects the physiological effects.

TREATMENT OF TOXIC SYMPTOMS CAUSED BY MORPHINE OR

ATROPINE.—I may assume, notwithstanding the objections of Harley and the results of experiments on animals by Brown-Séquard, that the physiological antagonism of morphine and atropine has been amply demonstrated by cases of poisoning occurring in man.

In treating cases, the difficulty of precisely regulating the amount necessary to overcome the toxic symptoms is not easily surmountable. I ascertained, in the case which occurred to myself, that $\frac{1}{24}$ of a grain of atropine was equal in toxic power to 1 grain of morphine. The state of the pupil affords valuable but not unerring indications; atropine possesses more power, relatively, over the movements of the iris than morphine.

In a case of morphine-poisoning, subcutaneous injections of atropine should produce the following results:

Dilatation of the pupil.

Flushing of the face succeeding to pallor.

Dryness and warmth of the skin succeeding to a cold and clammy sweat.

Rise in the pulse-rate and temperature.

Return of reflex movements of eyelids and fauces.

The dilatation of the pupil should be slightly maintained, and should not be carried to the exaggerated degree sometimes thought necessary. The mistake should not be made of confounding the sopor produced by morphine and atropine with morphine coma. This caution is the more necessary because this sleep is often considered a condition of danger requiring renewed administration of the antidote, and the patient is at length poisoned by atropine. Sufficient atropine should be administered to maintain the action of the heart and the respiration. So long as these continue good, no danger is to be apprehended from *sleep* merely.

Atropine, relatively considered, does not equal morphine in toxic activity. Severe physiological effects do not necessarily imply a condition in which life is endangered. It is to be remembered that the toxic effects of atropine endure much longer than those of morphine, and hence repeated applications of the physiological antidote may be required.

HOMATROPINUM: HOMATROPINE.

A Synthetical Product obtained by the Combination of Tropine with Amygdalic Acid.

We owe to Professor Ladenburg, of Kiel, the discovery that atropine, the active principle of atropa belladonna, is a compound alkaloid, a product of the union of tropine with tropic acid. If tropine is combined with amygdalic acid, the resulting product is oxytoluyl-tropeïne, and to this Ladenburg has given the name *homatropine.* If homatropine is combined with hydrochloric, bromhydratic, or sulphuric acid, the resulting salt is hydrochlorate, bromhydrate, or sulphate of homatropine, respectively. Of these the favorite salt is hydrobromate of homatropine, but the most satisfactory, according to Galezowski,* of the various salts is the chlorhydrate.

Actions and Uses.—There is a close correspondence between *atropine* and *homatropine;* but the latter is the weaker. The dryness of the mouth, the dilatation of the pupil, the paralysis of the cord, etc., are common to both.

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* Journal de Thérapeutique, February 25, 1881, p. 121.

Galezowski, who has made comparative observations on both, formulates his conclusions as follows:

1. Homatropine dilates the pupil very strongly, but the dilation does not continue longer than eighteen or twenty hours.

2. It paralyzes the accommodation but in a slight degree, and the paralysis does not last longer than two or three hours.

3. It has no irritant local action, and hence it may be used with advantage when atropine and duboisine would cause local disturbances.

By reason of the fact that homatropine affects the accommodation so little, it can be usefully employed in making ophthalmoscopic observations, and in the case of eye-trouble in a child, it is the better because of the early disappearance of the pupillary dilatation.

Schläfer* has also made comparative observation on the effects of atropine, duboisine, and homatropine on the eye, with the following result:

The beginning of mydriasis—dilatation of the pupil—is in the case of atropine fourteen minutes, in that of duboisine eight minutes, in that of homatropine nine minutes.

As respects the maximum, atropine reaches it in thirty to forty-five minutes, duboisine in fifteen to twenty-five minutes, homatropine in thirty to forty minutes.

The maximum continues with atropine twenty-six hours, with duboisine twenty-four hours, with homatropine three hours.

The return to the normal with atropine is four days, with duboisine four days, with homatropine one day.

According to Schläfer, the effects of eserine neutralize

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* Journal de Thérapeutique, 1881, p. 121.

those of homatropine permanently; but only temporarily atropine and duboisine.

The action of the heart, when atropine is given, differs from that caused by homatropine; the former, after a very brief stage of slowing the heart's action, much accelerates it, whereas homatropine slows the heart and lowers the tension of the peripheral vessels; the number of pulsations per minute may fall as low as 20. Homatropine, according to Berteau,* has little or no action on the skin, but it dries the mouth very decidedly.

When a sufficient dose of homatropine is taken the effect on the nervous system of animal life is exhibited in increasing weakness of the lower extremities, inco-ordination of muscular movements, vertigo, numbness, and tingling and lessened sensibility of the sensory nerve apparatus. With the onset, for a brief period, the symptoms are rather tetanic in character; but these phenomena are not pronounced in man, but rather obscure, whilst they are distinct in rabbits and guinea-pigs. With the first appearance of characteristic symptoms in the muscular and nervous systems of animal life, corresponding conditions occur in the vascular system: the heart is slowed in movement and the tension of the vascular system rises. These symptoms are brief in duration, and are quickly succeeded by increasing weakness of the muscular system; paralysis follows paresis, and presently, if the dose has been sufficient, complete muscular resolution occurs. The mouth and throat become excessively dry and parched and difficulty in swallowing increased.

If the dose of homatropine be large the pupils dilate,

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* Berliner klinische Wochenschrift, October 11, 1880. Quoted by Journal de Thérapeutique, 1881, p. 562.

the pulse lessens in force and in number of beats, and becomes irregular. The larger the dose the more quickly the paralytic symptoms come on and the shorter the tetanic stage.

Homatropine is chiefly used in ophthalmic practice because of the readiness with which dilatation of the pupil and change in the accommodative apparatus are effected and recovered from. It can be employed in the treatment of the *sweating of phthisis*, but it is inferior to atropine (Berteau*) for this purpose. Murrell finds that it does have an effect on the secretion of sweat, but that "it is decidedly inferior to atropine" and to picrotoxin, and some others.

At present we believe that homatropine is not utilized for the several disorders outside of ophthalmic practice, in which the other mydriatics are now employed successfully.

HYOSCYAMINE: HYOSCINE.

Alkaloids of Hyoscyamus Niger.

Salts of Hyoscyamine:
- **Hyoscyaminæ Hydrobromas.**
- **Hyoscyaminæ Hydrochloras.**
- **Hyoscyaminæ Sulphas.**

Salts of Hyoscine:
- **Hyoscinæ Hydrobromas.**
- **Hyoscinæ Hydrochloras.**

PROPERTIES.—Hyoscyamine and hyoscine bear the same relation to the group of mydriatics as their position here

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* Op. cit.

denotes: they come after or second to the chief member of the group, atropine, but hardly in respect to their clinical uses. Since the discovery of hyoscine it has advanced greatly in professional opinion. It is easily applied to the treatment of disease; being soluble in water, its salts can be employed efficiently by the hypodermatic method.

A suitable solution for this manner of using hyoscyamine is the following:

℞ Hyoscyaminæ hydrochloratis *vel*
Hyoscyaminæ hydrobromatis, gr. i;
Aquæ destillatæ, ℥i. M.

Sig.—Four (4) minims contain $\frac{1}{120}$ of a grain, nearly, of the hydrochlorate of hyoscyamine or the hydrobromate.

The amount in 4 minims of this solution is that which an adult can take with readiness. Much larger doses have been prescribed, down to $\frac{1}{20}$ of a grain in some instances, but such doses are not safe, although the danger is not very near.

The following is a suitable formula* for the hypodermatic injection of hyoscine:

℞ Hyoscinæ hydrochloratis, gr. i;
Aquæ destillatæ, ℥i. M.

Sig.—Two (2) minims contain $\frac{1}{240}$ of a grain.

In commenting on the dose of hyoscine to be given, Bruce† affirms that $\frac{1}{200}$ of a grain is a sufficient amount in many of the cases in which this alkaloid is administered. It is characteristic of the mydriatic group of remedies that they give notice of danger to come long before the danger is actual.

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* The Therapeutic Gazette. Claussen, Zeitschrift für Therapie, September 1, 1886.

† The Practitioner, November, 1886.

The antagonists of hyoscyamine are opium, physostigmine, and others less near in action and power.

PHYSIOLOGICAL EFFECTS.—Hyoscyamine exists in two forms: as a crystalline and as an amorphous body. The latter is the more powerful of the two. The salts of the alkaloids agree closely in their actions with what acids soever they may be combined, and hence it may be concluded that the mineral acid does not affect the result in any way. Although hyoscine is isomeric with hyoscyamine and atropine, there are distinctive differences between them chemically and also, in a still greater degree, physiologically. They agree more frequently than they differ, and as mydriatics there are no qualitative differences between them.

Hyoscyamine and hyoscine dilate the pupil in the same manner as atropine; but hyoscine acts more promptly and its effects are both greater and of longer duration than those of atropine (Tweedy*). Hyoscyamine and hyoscine and their salts act on the cerebrum and spinal cord, lowering sensibility and inducing a calm mental condition, allaying spasm, and bringing on sleep. Also the motor functions are disordered, co-ordination is impaired, and muscular weakness results. The eyelids droop, the pupils are dilated, and the vision is affected for near objects.† Hyoscine dilates the pupil strongly, as is the effect of all the mydriatics in varying degrees. As compared with atropine, it acts more promptly on the pupil, and the effect is more powerful and more prolonged, the impairment of the accommodation being more prolonged also. Both hyoscyamine and hyoscine dry the mouth, stop the flow of saliva, and cause more or

* Sohrt, under Professor Kobert, at Dorpat. Virchow und Hirsch's Jahresbericht, 1887, p. 418.

† The London Lancet, December 4, 1886.

less difficulty in swallowing, and they also diminish the sweat secretion, inducing dryness of the skin. They also oppose the action of pilocarpine on the sudoriparous and salivary glands, and check entirely the flow of sweat and saliva brought on by pilocarpine when at its highest effects. In some excitable subjects, sometimes in a neurasthenic subject, hyoscine causes delirium, nausea and vomiting, hallucinations, etc. It is rather a matter of idiosyncrasy than of the real action of the medicament when such symptoms appear prominently as elements in the morbid complexus. In this instance, as in the cases of many other narcotic remedies, peculiarities of the individual endowment have much to do with variation in the mode of action; hence, when such variations occur, the nature and results of the action should be referred to their proper sources. In this way only can the real powers of the medicament be ascertained. These deviations from the normal—idiosyncrasies—should be carefully studied, whether they be physiological or pathological, if the true characteristics of the drug's actions are to be brought out. In respect to hyoscyamine and hyoscine, they are apt to produce in certain types of individuals sudden weakness and faintness, prostration and nausea, and great depression of the circulation. Such alarming symptoms may be brought on by the minutest doses when the idiosyncrasy above referred to is in operation.

In respect to the functions of circulation and respiration, the effects of these alkaloids are less powerful than is atropine; but hyoscyamine, again, has more effect on these functions than hyoscine.

A slight rise in arterial tension, with *quickened* action of the heart, are the first effects of hyoscine on the vascular system, but these are soon followed by lowered tension and less rapid action of the heart. Great dryness of the

mouth, succeeded by a viscid, tenacious mucus, accumulating in the fauces, seem to be constant phenomena in all of the atropine group.

Hyoscine, like atropine, antagonizes muscarine and other agents acting similarly. Hyoscine is excreted by the kidneys, and when a few drops of the urine of an animal receiving a full dose of the medicament is put into the eye of another animal strictly normal, dilatation of the pupil follows, and thus for several succeeding animals, also, the same result may be produced by the successive urine specimens.

The actions of hyoscyamine and hyoscine most useful in practical therapeutics are those affecting the nervous system. These actions are the sedative, calmative, and to some extent the sleep-producing or hypnotic. It has long been known that hyoscyamus (containing hyoscyamine and hyoscine) has decided effects on the brain, and these actions were often utilized in the diseases of children affecting the cerebral structures, whether in function only or by reason of changes in the organic substratum.

As regards the power of this alkaloid to lessen cerebral activity and promote sleep, there is a nearly general belief, but qualified by adverse opinions. Many foreign authorities hold to its value as a hypnotic. Among those who may be classed with the affirmative are Kraus,* Kobert,† and Kobert and Sohrt,‡ Kny,§ Salgo,‖ and J. Mitchell Bruce, of England; on the negative side are Erb,¶ Serger, Näcke,** and others. In this country

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* Therap. Monatshefte, 1888, p. 250.

† Kobert, Archiv für experimentelle Pathol. u. Pharm., Band xxii. p. 419.

‡ Ibid. § Therap. Monatshefte. ‖ Ibid., 1888, p. 298.

¶ The Practitioner, November, 1886, and Wien. Med. Wochenschrift.

** Therap. Monatshefte, March, 1891.

opinions are quite as discordant; for example, Francis L. and John R. Haynes ascertained that of fifty-seven persons to whom it was administered in three hundred and thirty-eight doses, in fifteen only was it followed by sleep, whilst in twenty-nine cases the symptoms produced by it were various, or were negative. They concluded that hyoscine, in their experience, was "extremely unreliable as a hypnotic." Dr. Wetherill* has given a much more favorable opinion of its action, regarding it as a useful hypnotic, and his opinion is seconded by Dr. Schaeffer,† whose experience was gained in the Maryland Hospital for the Insane. He asserts that for the relief of "ordinary insomnia," in "doses of $\frac{1}{120}$ of a grain it will give very satisfactory results."

Specimens of hyoscine must vary considerably in purity and strength, or these discordant views would not exist. At the same time not all observers are equal in the capacity of seeing. However, the discrepancies may be due to a cause suggested by Dr. Kny, that when insomnia is accompanied by motor excitement, hyoscine succeeds in bringing about sleep; but in cases characterized by depression, inaction, and lack of movement, it has no such effect. It is stated by most observers that the delirium and the wakefulness that are present are accompanied by high excitement and constant irregular movements of the muscles. Indeed, the state of present opinion is, for the most part, that agitation and active delirium and incessant movements are the indications for the administration of hyoscine. A further reason for discrepant opinions is idiosyncrasy; but the principal cause of varying judgments is the dose in which hyoscine is administered. It is clear that

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* The Therapeutic Gazette, 1886, p. 98. † Schaeffer, ibid., p. 170.

to induce sleep which shall be quiet and refreshing small doses are necessary, and those which experience has found to be most serviceable range from $\frac{1}{100}$ to $\frac{1}{200}$ of a grain, and even below these figures. Indeed, it is probable that those having a special impressionability to its influence should take the smallest doses,—say from 1 minim of a solution containing 1 grain to 1 ounce of water; consequently, the amount given would be $\frac{1}{432}$ of a grain. This small dose can then be given more frequently than the maximum dose, and an increase in the daily quantity may be thus cautiously secured.

The larger doses, even when sound sleep is obtained, cause considerable murmuring, jactitations, and motor excitement when the action of the medicament is at its maximum, and on the following morning some headache, a pasty tongue, and a general feeling of narcotic stimulation, unduly active, operating during the night. But when sleep is secured by minimum doses, it is quiet, refreshing, and not followed by any untoward circumstances (Fischer,* Kobert,† J. Mitchell Bruce,‡ and others).

One of the uncertainties in the administration of narcotics is the behavior of the renal function. There is danger in giving remedies when the kidneys are so damaged that elimination is hindered. Tirard§ has shown, however, that hyoscine can be given when albumen is present in the urine. As a rule, when poisons are eliminated promptly, the excretion takes place by the kidneys.

It is a remarkable fact that Erb saw no cases in which

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* Ueber die Wirkung des Hyoscins. Therap. Monatshefte, June, 1888.

† Archiv für experimentelle Pathologie und Pharmakologie, 1886, Band xxii.

‡ The Practitioner, November, 1888.

§ Tirard, The London Medical Record, 1887, p. 105.

hyoscine, given in medicinal doses, caused sleep accompanied by much restlessness, muttering, delirious excitement, etc., and he attributes this to the administration of doses much too large. No doubt this is true in many instances (Fischer). Removing the source of the discrepancies above described, it becomes clear that these are the circumstances that compel differences of opinion.

To declare the judgment from a consideration of all the evidence, the action of hyoscine on the brain and nervous system is that of an agent having the power to quiet, to lessen the sensibility of the sensory nerves, and to calm the agitation of the motor nerves and the abnormal activity of the muscular system.

THERAPY.—The first and most important point is the application of these alkaloids to the treatment of cerebral maladies. The testimony of those who have had most experience with these remedies in disease is, that the cases to which they are specially adapted agree in having great motor excitability and active muscular movements. In asylum practice the same rule obtains: in the cases of acute mania, melancholia, and other mental maladies, characterized by incessant activity of the muscles, constant excitement, and insomnia of the most persistent character, hyoscine has been used with conspicuous advantage.* On the other hand, when the condition is one of torpor, melancholia with depression, or any form of mental disease characterized by inaction and indisposition to any kind of exertion, Kraus,† of the Buda-Pesth Lunatic Asylum, strongly commends the use of hyoscine, and affirms its special utility as a sleep-producer in all irritative conditions, even

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* Prideaux, The Lancet, September 27 and October 4 and 11, 1879.

† The London Medical Record, December 29, 1887.

in acute maniacal attacks, in hallucinatory irritability, and in paralytic restlessness. In the exacerbations of dementia paralytica it has acted well. Kraus found it useful in cases where morphine, chloral, and paraldehyde had been given in vain.

In asylum practice we thus learn that hyoscine is very successful as a hypnotic. If we compare the observations of Kraus and of the English observer, Dr. Pitcairn,* who finds that $\frac{1}{150}$ up to $\frac{1}{70}$ of a grain is a sufficient quantity to develop the state of sleep, whilst larger doses are apt to produce alarming symptoms, we learn that their views are in accord. Referring again to Dr. Salgo, it is seen that his practice among the insane leads to precisely the same results as those of Kraus, whilst the results obtained by Dr. Pitcairn are correspondent to those of Haynes.† Again, Dr. George Thompson,‡ of the Bristol Asylum, after some preliminary trials of hyoscine, made a report, in the main, of the same character as Kraus's.

Dr. C. Reinhard has used hyoscyamine in fifteen insane and twelve epileptics. In eight of the insane it produced calmative effects and did good, and in five epileptics with maniacal attacks it diminished their number and severity. Mendel§ has also used hyoscyamine in various psychoses with advantage, those improved being characterized by high motor excitement. In *active delirium* the crystallized alkaloid prepared by Merck has been used by Fronmüller‖ with good results. To these observations showing the value of this remedy in disorders of the mind may be

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* The British Medical Journal, June, 1888.

† The Therapeutic Gazette, op. cit.

‡ Ibid.

§ Allg. Zeitsch. f. Psych., xxxvi., 1879.

‖ Memorabilien. Quoted in Virchow u. Hirsch's Jahresbericht, 1877.

added the reports of Pearse,* Gill,† and Lawson,‡—all confirming the utility of hyoscyamine in mania with high motor activity. More recently, Seguin§ has made an exhaustive study of the actions and uses of this agent. He finds that in mania it produces sleep more certainly even than chloral, and without bad after-effects. It has produced a positive cure in a case of delusions of persecution, and has done more than any other remedy in *paralysis agitans*, as respects relief to the trembling. In *chorea*, *mercurial trembling*, *senile trembling*, etc., in *spasmodic cough*, *laryngismus*, *hiccough*, etc., hyoscyamine has been used with success as a palliative in numerous instances, occasionally with curative results.‖ Prideaux¶ makes the important observation that it acts differently as respects promptness and efficiency under varying conditions of insanity. Thus, in *acute mania* characterized by depression, $\frac{1}{16}$ of a grain will have a decided effect, whilst in the condition of excitement of *chronic mania* larger doses are necessary, reaching as high as $\frac{1}{10}$ of a grain subcutaneously, which he regards the preferable mode of administration. In mania with intense motor excitement and destructive tendencies, Prideaux regards hyoscyamine as "the most rapid and reliable narcotic we possess." In *epileptic mania*, *delusional insanity*, and in *chronic dementia*, it does good in many cases.

Some observers assert that no after-morning troubles came to vex the patient who received the medicament the night before,—such troubles as nausea, vomiting, and

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* The Lancet, September, 1876, p. 319.

† The Practitioner, February, 1878, p. 84.

‡ Ibid., August, 1878.

§ The Archives of Medicine, June, 1881.

‖ Oulment, Bul. Général de Thérapeutique, tome lxxxiii. p. 481.

¶ The Lancet, September 27 and October 4 and 11, 1879.

headache. When large doses had been administered, it was not unusual to have such experiences.

In spasmodic nervous diseases hyoscine has been used with good results; also in *whooping-cough*, *asthma*, *hiccough*, etc., but not permanently, since a tolerance of the remedy is quickly established, when its effects become uncertain and are soon lost. In the graver spasmodic affections, such as hydrophobia, tetanus, eclampsia, hepatic and renal colic, the action of hyoscine is inferior to other remedies now in use.

DUBOISINE.

An Alkaloid derived from Duboisia Myoporoides, which belongs to the Solanaceæ.

PROPERTIES.—*Duboisine* occurs in small crystals soluble in water to nearly fifty per cent. It is isomeric with atropine, hyoscyamine, and daturine, and, although of the same molecular constitution, they differ somewhat in chemical and physiological properties. They do not react in the same way to tests for atropine, and they differ in respect to the functions of the eye. Duboisine paralyzes the accommodation more quickly and more thoroughly than does atropine, and the effects pass off in half the time, but it is rather more irritating to the conjunctiva than any of the other mydriatics.* They act in the same manner and to the same extent in causing dryness of the mucous membrane and of the skin. Duboisine, in acting on

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* On the other hand, it is asserted by Schoeler (Berliner klinische Wochenschrift, No. 13, p. 186) that he had seen in several cases just as much from atropine.

the iris, paralyzes the constrictor muscle, but separately from the accommodation, the former persisting long after the latter. This view is also maintained by some of our American ophthalmologists,—Dr. W. F. Norris and Dr. Risley.* Duboisine does not remain so long in action on the accommodation as atropine,—about half as long (Risley),—and for this reason may be preferred to the latter. Very singular effects have been caused by duboisine soon after it was instilled into the eye, but not a shorter time than is required for making the round of the circulation. The writer had an opportunity to see the first case in which these untoward effects had occurred. It was in the case of a young woman, a patient of Professor W. W. Seely, of the Medical College of Ohio, Cincinnati, who had just obtained the alkaloid, and made the first instillation in this country. She experienced very alarming sensations (to her), grew faint, was pale, and the pulse slow but not irregular. She felt greatly more anxiety as to the sensations which she experienced than the symptoms seemed to call for. These effects passed off, for the most part, in a half-hour, but strange feelings, with a sense of unreality in all things about her, persisted several days. Duboisine acts on the brain and mind in a manner similar to atropine, but toxic effects are not so readily produced by absorption from a solution instilled into the eye. The usual effects of duboisine, to take a comprehensive view, are expressed in the following paragraph:

Dryness of the mouth and fauces, difficulty of deglutition, and a husky voice are experienced in a few minutes; simultaneously there is a sense of fulness in the head, tinnitus, and vertigo; the action of the heart is accelerated,

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† The American Journal of the Medical Sciences, 1880.

the pulse gains in tension, the face flushes, the pupils dilate, and the vision for near objects is blurred and indistinct; the sense of fulness in the head is followed by headache, especially of the frontal region, the vertigo impairs the locomotion, and the voluntary muscles, especially of the lower limbs, become paretic. During the time of the maximum effect of a full medicinal dose there is considerable excitement of mind, an intense restlessness, but apparently no sensations of a pleasurable kind, but rather anxiety and dread. With the subsidence of the more active symptoms, notably the decline in the circulation and the diminished excitement, a more quiet condition of the mind, a feeling of somnolence, comes on, followed by sound sleep. Dreams and visions disturb the sleep somewhat. In animals (dogs) large doses produce a high degree of excitement, apparently hallucinations and delirium. No corresponding experiences have thus far occurred or been noted in man, but Dr. Chisolm, of Baltimore, reports a case of "temporary insanity" resulting from an instillation of solution of duboisine.

Thus the effects of duboisine are very nearly the same as those of atropine. Instilled into the eye, the pupil dilates, but more readily than from atropine, and the dilatation ceases earlier. Duboisine is more irritating to the mucous membrane. On the heart and circulatory system duboisine acts in a manner quite similar to atropine:* they both increase action by a paralyzing effect which they both exert on the vagus, and, probably, by stimulation of the accelerator apparatus also. The tension of the arterial system is raised by moderate doses, but large medicinal or lethal doses cause paresis of the organic muscular fibre, or paresis

* Ringer and Tweedy, The London Lancet, 1880.

of the constrictor fibres and consequent dilatation of the vessels. The respiration is affected in a similar manner: it is accelerated; at first stronger in force and deeper in volume, and afterwards becoming weaker and irregular.

The character of the actions of atropine and duboisine is well exhibited in their influence respectively on the organic nervous system and on the vagus. Duboisine first stimulates the vagus and then paralyzes it, and the effect of these influences are again shown by the resulting changes in the sympathetic nervous system and the organs innervated by it, as, for example, the rise in tension and slower movement of the vascular system, followed by greatly-increased movement with lessened tension. Both act in the same way on the apparatus in question; but with the greatly-increased action of the heart and blood-vessels, the temperature rises, the skin reddens, and very frequently a punctated redness presents itself, which has the appearance and the characteristics of the scarlet-fever eruption.

As respects the action of the mydriatics, the following comparative statement will show the position of duboisine in the group:

When dilatation of the pupil is required for some brief examination of the inner parts of the eye, homatropine is preferable, for it brings on the dilatation in five to ten minutes, but it lasts only three hours. When the pupil is dilated by duboisine or by atropine, eserine removes the mydriasis in about five minutes if it is caused by atropine, and in twenty minutes if it is caused by duboisine. This fact, *cæteris paribus*, proves the greater strength of *duboisine* as compared with atropine. To sum up: mydriasis is produced more rapidly and lasts longer with atropine; homatropine, while it acts quickly, is less powerful, the dilatation not being complete, even with the maximum doses.

Further, paralysis of the ciliary and motor filaments of the circular muscle occur more rapidly when induced by atropine or duboisine than by homatropine, and the effects of the two former continue much longer. Such are the conclusions of Dr. Herman Schaeffer,* and they agree for the most part with the conclusions of other American and foreign ophthalmologists.

One of the antagonisms of duboisine especially serves to illustrate the nature of its physiological actions, and should therefore receive some attention here. The finest example of physiological antagonism is that exerted by atropine or duboisine against pilocarpine. The sweating and salivation, the lowered temperature, the depression of the heart's action, and other symptoms caused by pilocarpine are completely neutralized and the normal restored by duboisine or atropine.

THERAPY.—It is obvious that duboisine agreeing so closely with atropine in the whole range of its powers, almost, must agree also in the therapeutic effects and applications. Besides the domain of ophthalmology, in which it is useful, duboisine is a remedy of great value in certain disorders of the mind. Especially is it applied in those eye-diseases in which the accommodation must be paralyzed, but in which it is desirable to have this function restored to the normal as quickly as possible. For examinations of the eye it becomes very useful. It is said to be more irritating to the mucous membrane than is any other of the mydriatics.

Duboisine is a remedy of the highest value in the treatment of *mental disorders* accompanied by much restlessness and an irritable motor activity. I have had admirable results from its use in cases of *puerperal insanity*. In my

* The Archives of Ophthalmology, New York, No. 10, p. 197.

judgment it is competent to cure cases of puerperal mania whenever the conditions present are of the kind just mentioned,—that is, cases distinguished by incessant muscular movements, wakefulness, and an irritable and active mental disturbance of a kind corresponding to the motor activity in the muscular system. When these conditions coexist, no other remedy, or remedies, is so useful and, as my own experience justifies me in saying, curative. I have given hypodermatically from $\frac{1}{120}$ to $\frac{1}{60}$ of a grain of the sulphate of duboisine. As rapidly as the state of the patient will warrant the dose should be increased to $\frac{1}{60}$ of a grain.

Not only puerperal mania, but other kinds of *mania* characterized by restlessness and incessant activity in the motor sphere are greatly benefited or, if organic changes have not occurred, cured by duboisine. As respects the quantity to be given, my experience is that one dose a day is quite sufficient, for the action is so prolonged that accumulation of the remedy must occur if taken more frequently.

Remarkable improvement has taken place in some cases of exophthalmic goitre by the administration of duboisine in the hands of Dujardin-Beaumetz* and his pupil, Desnos.† The nature of the impression is plainly exhibited in the reports.

The solution most useful for the exhibition of duboisine by hypodermatic injection is the following:

℞ Duboisine sulphat., gr. i;
Aquæ destillatæ *vel*
Aquæ chloroformi *vel*
Aquæ lauro-cerasi, ℥ss. M.
Sig.—Five (5) minims contain nearly $\frac{1}{50}$ of a grain.

Should any accident occur, the most efficient antagonists are morphine, atropine, chloral, etc.

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* Dictionnaire Mat. Méd., Paris. † Ibid.

SOLANINE.

An Alkaloid or Glucoside obtained from Several Varieties of the Solanaceæ.

THE SOLUTION.—Solanine is not soluble in water, and hence Geneuil has proposed the addition of a mineral acid to make the solution clear; but mineral acids in the minutest quantity, unneutralized, are highly irritating, and will almost always produce an eschar, and are also highly painful when injected. Solanine is itself an irritating substance, and will often cause a local inflammation of considerable severity.

As regards the nature of this active principle there are contradictory opinions. Gaignard * holds, on the authority of M. Adrian, that solanine is a glucoside, and therefore it does not combine with acids to form salts. On the other hand, M. Geneuil † says that it is a glucoside-alkaloid that combines with acids to form salts, and he makes mention of the hydrochlorate of solanine as the preparation employed by him in making his investigations.

The field of the actions of solanine is the nervous system. The effects begin at the periphery; the terminal nerves—sensory first and then the motor—decline in functional activity, and finally cease to react to stimuli peripheral and central, and from paretic become paralyzed. Then the spinal cord and medulla oblongata cease finally to functionate, and the reflexes are no longer excitable. In accordance with their notions, Bardet and Gaignard, who have examined its physiological actions, conclude that its toxic actions are of two kinds: first, apathy; secondly,

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* Bul. Général de Thérapeutique, tome cxiii. p. 12.

† Ibid., tome cxi. p. 265.

convulsions. The stage of apathy is the condition assumed with the paralysis above sketched. When large toxic doses are administered, the paralyzing action does not appear, but the excitability of the cord (excito-motor) is enhanced, convulsions of a corresponding tetanic character soon come on, and death quickly follows.

The results of the physiological study indicate that solanine must be useful in painful and spasmodic affections, and the rather small clinical experiences justify the conclusions. It is in the smaller doses that the most favorable results are obtained, and whilst the larger doses have effects that approach the danger-line, they exert an irritant action on the spinal cord that opposes the sedative effects desired. It is evident, therefore, that cerebral and spinal maladies of a kind suited to the action of solanine can only be favorably influenced by small or medium doses.

As respects the hypodermatic injection of solanine, it is evident that this mode of administration has some very objectionable features. It is apt to cause a considerable local swelling and sloughing of the tissues at the point of contact, and it is, besides this, painful. There can be no question respecting the powers now ascribed to it, but it is more useful when given by way of the stomach than by the hypodermatic method.

CHLOROFORMUM: CHLOROFORM.

(*For the hypodermatic injection only pure chloroform should be made use of.*)

Chloroformum Purificatum.

Dose: From 5 to 15 or more minims.

The Deep Injection of Chloroform.—The injection of chloroform is not adapted to the treatment of internal maladies,

and is only useful in external neuralgiæ so situated that the injected chloroform may act on the nerve-trunk or on the peripheral distribution of the nerve. I have entitled the method "The Deep Injection of Chloroform," in the articles I have written calling attention to the efficiency of this plan in the class of cases to which it is adapted.*

To illustrate: In the case of neuralgia of the infra-orbital division of the fifth, the needle is inserted deeply underneath the lip, passing up so that its point is in the neighborhood of the nerve where it emerges; in the case of the sciatic, the needle should be passed near the trunk of the nerve at its exit from the pelvis. In the case of any superficial neuralgia the same plan is pursued,—the needle inserted deeply, so that its point rests in the neighborhood of the affected nerve. I am the more disposed to reiterate this instruction because it is too often supposed that the treatment consists in the subcutaneous injection of chloroform. This practice was long ago condemned or regarded as improper, owing to the violent local inflammation which follows its introduction into the subcutaneous areolar tissue. Thus, the late Dr. Anstie,† in an article on the "Hypodermic Injection of Remedies," says of chloroform, that it is "an agent entirely unfit to be used in that way." Hunter, after some trials with it, had made a similar declaration: "The injection of chloroform is not to be recommended for the human subject." This remark is all the more noteworthy because Hunter was one of the earliest and most enthusiastic advocates of the hypodermatic method. Eulenberg‡ simply repeats the remark of Hunter, and

* The Clinic, 1873, vol. v. p. 145; The Practitioner (London), 1874, vol. xiii. p. 288.

† The Practitioner, vol. i., op. cit.

‡ Die hypodermatischen Injectionen, *supra*.

mentions an experience of Sandras, in which 10 drops of chloroform were injected.

Physiological Effects.—The effects produced by the injection of chloroform into the areolar tissue are these: vaporization of the chloroform, and consequent gaseous distention of the surrounding parts, painful swelling, inflammation, and, occasionally, the formation of an abscess; but in my experience, never. The pain experienced by the patient at the moment of injection is also considerable, and as the needle is withdrawn the chloroform acts energetically on the wounded skin. These are very serious objections to the *hypodermatic injection* of chloroform. They are, to a large extent, obviated in the method of *deep injection.* It is true, in the latter method, considerable pain is felt and swelling arises, but the pain soon subsides and the inflammation rarely proceeds to suppuration. The pain is felt at the moment of injection and for some minutes subsequently, but this disappears and is succeeded by a feeling of numbness and anæsthesia of the parts into which the chloroform diffuses. A puffy swelling quickly forms at the site of the injection, and an induration of variable size is left, but it afterwards is slowly absorbed. The numbness persists for a week or more. Systemic, or rather cerebral, sensations are felt usually only when the injection is inserted into the deeper parts of the face, and then are very transient, consisting of a little giddiness followed by drowsiness. Indeed, the results, so far as systemic effects are concerned, may be regarded as absolutely free from danger. So much swelling and induration occurring at the site of an injection must occasion apprehension of the formation of an abscess. Thus far this untoward result has not happened in any of my cases or in any of the reported cases, with one exception. This was a man suffering from *tic*

douloureux, in whom repeated injections were made about the supra- and infra-orbital foramina, a locality unsuited for *repeated injections*.

To ascertain more satisfactorily than is possible from patients the degree of suffering which attends the deep injection of chloroform, and the extent and duration of the resulting numbness, I practised an experiment on myself by injecting 10 minims of Squibb's chloroform deeply in the calf of the leg. The pain was by no means so severe as I had anticipated, and could easily, indeed, be borne. Considerable swelling resulted, and an induration as large as a filbert continued for two weeks, when it was absorbed entirely. Immediately after the injection numbness was experienced about the site of the injection; it then extended downward, and on the following day had reached the bottom of the foot. A space in which the sense of touch and the appreciation of pain and temperature were decidedly diminished existed from the point at which the chloroform was inserted to the hollow of the foot, although somewhat irregular in shape, at least two inches in transverse diameter at any point. This condition of altered sensibility persisted for several weeks.

It is obvious, from the foregoing considerations, that chloroform injected into a part modifies the conductivity of the nerves. As *pain* means an irritation of a nerve or nerves, being dependent upon the perception by the centres of consciousness of this impression, and its reference outwardly to the end organs of the affected nerve, we may assume, with some confidence, that chloroform causes an interruption in the route or circuit of transmission. It has long been known that swelling of a part, the seat of a neuralgia, is a signal of the cessation of the pain.

When the chloroform is injected into the deeper parts

of the face, it comes into relation to vessels having an intimate connection with the intra-cranial circulation. It is, of course, perfectly well known that the facial vein communicates with the pterygoid plexus and the cavernous sinus. This anatomical fact explains the greater cerebral effect of an injection of chloroform in the deeper parts of the face as compared with the same injection elsewhere.

THERAPY.—Since the publication of my original cases of *tic douloureux*,—the first ever treated by the "deep injection of chloroform,"—various cases of *neuralgia*—of the *fifth*, *cervico-brachial*, *sciatic*—have been treated by me successfully by the chloroform injection. This method is especially adapted to the treatment of sciatica. I have had under my personal care, from 1874 to 1884, twelve cases of sciatica, all of great severity and all chronic, in which I used the chloroform injections, and of these eight were cured, two improved, and two received no benefit. I do not include in this summary those cases of sciatica which were symptomatic of spinal or cerebral disease. Other cases have been reported in this country and abroad in which this method succeeded after other approved methods had failed.* One of the most remarkable cases demonstrating its utility is that reported by Dr. J. B. Mattison,† in which not only was the neuralgia cured, but also the opium habit with which it was complicated.

Strictly localized *spinal pain* and *coccygodynia* have been cured by me by injecting the chloroform deeply near to the point of emergence of the sensory nerve branches, or, in case of the pain in the coccyx, as deeply as possible about the point of greatest pain.

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* Dr. de Cérenville, La Tribune Médicale, August 20, 1876; Dr. Collins, The Clinic, 1875.

† The Medical Record, New York, May, 1874.

The official spiritus chloroformi, U. S. P., has been substituted for pure chloroform in cases of chronic sciatica coming to the Jefferson Medical College clinic, and with success, although not so complete.

It may be well to state here that *aqua chloroformi* (*chloroform water*)—that is, the small amount of chloroform taken up by water—possesses energetic antiseptic power. Owing to this, and also to the permanence of such a solution, Salkowski recommends it as the vehicle for hypodermatic injections, having sufficient solvent action for the remedies used, and preventing all change in the solutions of alkaloids by reason of its germicide action. It prevents the development of the penicillium, or of micro-organisms, in the solution.

ÆTHER: ETHER.

Æther Fortior. [*Stronger Ether.*]

Æther fortior is the form used for inhalation and for hypodermatic injection. It contains ninety-five per cent. of ethyl oxide and has the specific gravity of 0.725. It dissolves in eight times its volume of cold water at 70° Fahr.

The ordinary commercial ether contains impurities too active not to interfere with the development of the normal physiological action, and is so irritant as to set up a morbid process in the tissues where injected.

The usual dose is a syringeful,—that is, sufficient to fill an ordinary hypodermatic syringe having a capacity of 20 to 30 minims.

Actions and Uses.—When ether is injected beneath the skin it causes an emphysematous swelling and burning

pain, more especially along the needle-track. The systemic effects are at once felt, the pulse becomes stronger and fuller, the face flushes, and the skin grows warm and perspiring. In two or three minutes (probably in ten to twenty seconds) the odor of ether is observable in the breath. A sense of exhilaration, disordered gait, inco-ordination of muscular movements, and torpor follow in the order just given when full doses are directed.

Among our French colleagues ethyl bromide has been proposed, and has been utilized to some extent as a substitute for ether administered in this way, and, on the other hand, ether has been employed as a substitute for chloroform in the process of deep injection, and it has been successful in a great many cases,—I suppose quite as successful as chloroform when exhibited in cases appropriate to this kind of treatment.

When ether is injected for the relief of pain in cases of adynamic pneumonia, a grateful stimulation is felt as the pain subsides, the respiration becomes easier, the pulse grows fuller and stronger, the face gains in color, and the tongue, which before was dry and cracked, now becomes moist and smooth. Such is the grateful change occurring in cases of pneumonia having the so-called typhoid character.

Dr. Barth reports on fourteen severe cases of adynamic pneumonia and broncho-pneumonia treated by ether injections, which were employed as the condition of depression increased in severity. Of these fourteen cases treated thus, eleven recovered and three died, an astonishing result when we compare these statistics with those of to-day. The amount used at each injection is about 15 minims, and the number of injections from two to four a day, according to the amount of depression in each case. The mortality

from pneumonia, at least in the pneumonia succeeding to the epidemic of influenza, has been much greater than that in Barth's cases.

M. du Castrel has pursued the same plan of treatment in cases of *variola* of an adynamic type in his charge. He gave the ether injections to tide over the times of greatest depression. The result was a corroboration in every particular of the truth of Dr. Barth's statements as to the effects of the ether injections. In maladies *hemorrhagic* in character, hitherto requiring transfusion of blood, and in *post-partum hemorrhage*, the injections of ether have been sufficient in themselves to prevent the death that was impending.

In cases of arterial thrombosis and in sudden failure of the heart, typical examples of which are afforded us in thrombosis of the pulmonary artery, in the bites of venomous snakes, in the algid stage of cholera, and in surgical shock, the injection of ether has proved to be a resource at once satisfactory and safe. Whenever, indeed, from any condition to which remedial measures can be applied, there is at the same time a state of things in which, from various influences, the system is in a feeble state and the heart depressed suddenly by extrinsic causes,—under these circumstances the timely injection of ether may save life or tide over successfully a dangerous condition of affairs, although it may be but temporary in duration.

It is not necessary to confine the amount of ether administered to one syringeful, for successive doses of this quantity may be administered as frequently as the state of affairs requires, without serious risk.

Very often in cases of chloroform narcosis the use of ether has been advocated, or attempted, or actually performed. In none of these has a fatal result been averted.

So far as the injection of ether is concerned, there is not one single point in a case of chloroform narcosis which justifies such practice; for the relationship of the two agents, and the correspondence in their actions and in their mode of causing death, are so complete that they are mutually synergistic and not in any sense antagonistic.

The general observations made on the therapeutical applications of ether must suffice: all those uses applicable by inhalation do not come within the purview of this work, and hence I beg to refer the reader to the books treating of such topics.*

Alcohol, Whiskey, and Brandy.—Alcohol, in its several forms in use, has not infrequently been injected in a time of emergency. Very often is such injection practised in cases of chloroform or ether narcosis, in threatened failure of the heart from any cause, or in sudden and powerful pain, inhibiting the nerve-centres both of conscious impressions and of respiration and circulation in the medulla oblongata. Although it may be well to derive such aid from this source, yet it is clear that, instead of spirituous liquors, spirit itself should be used. The alcohol strength of the spirituous liquors is about fifty per cent. or at proof. As it is the alcohol and ethers, and not the other ingredients of the spirit, that accomplish the purpose, it were far better to prescribe a definite dilution of alcohol. Equal parts of pure alcohol and water is a formula which should be preferred. It very often happens that an induration, or an inflammatory swelling terminating in an abscess, is the final outcome of such a procedure as the depositing under the skin of whiskey or brandy.

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* See Bartholow's Treatise on Materia Medica and Therapeutics, 7th ed., 1888.

CHLORALAMIDE.

Chloral Hydrate and Formamide.

PROPERTIES.—The name, as is quite obvious, is a combination of the names of the two substances entering into its composition, but it is not correctly so, since *formamide* differs from *amide*, although closely allied to it. As the name is a trade designation, and has thus far been used universally, it will no doubt continue to represent the medicament.

Chloralamide, as it appears in commerce, is a whitish crystalline substance having a slightly bitter taste, although not caustic. It is little soluble in cold water, and in hot water quickly decomposes. The rate of solubility in cold water is as 14 to 100, and it is less soluble in hot water. At a temperature above 140° Fahr. it is said to become less soluble than in cold water, and, also, it then begins to decompose.

The dose of chloralamide ranges between 10 grains and 1 drachm, but the latter should not be exceeded under any circumstances. The dose which, by common consent, is considered effective as a hypnotic for an adult is 45 grains. Smaller doses than this will rather rarely cause sound and refreshing sleep, except in the case of children. For hypodermatic injection, as remedies administered in that way act more powerfully, the dose most suitable under all the circumstances for an adult is 30 grains. Locally it appears to be unirritating to the tissues. It causes no disorder of the stomach, and it is said that no part of the system is acted on unduly. Formulæ in harmony with the facts above given can be constructed in accordance with the purposes intended to be subserved by its administration.

The place most suitable for the injection is the thigh behind the trochanter or buttocks, where the connective tissue is most abundant. As a considerable quantity of fluid is necessary to convey enough of the medicament into the tissues, a suitable space must be found to contain it, and at the points named it is better to deliver the fluid, and gently displace it by pressure and manipulation from the point of entrance into all the surrounding parts.

Physiological Actions.—The proprietors of chloralamide are very pronounced in their opinions of its innocuousness under all circumstances. It is true that it causes but trifling irritation when injected beneath the skin, but it is not entirely free from all injurious action. One reason why it does sometimes cause irritation is the length of time the solution remains unabsorbed. The action does not begin for a half-hour to two hours after the injection is practised, so slow is its diffusion into the blood. Chloralamide dissolves but slowly in the juices of the body. When given by the stomach or by the rectum, the rate at which it moves to affect the system is also slow, but rather more rapidly by the rectum than by the stomach; the appearance of characteristic effects occupies from one to two, even three, hours, and never less than a half-hour; but by the hypodermatic method the time is reduced about one-half. Because of the delay in the development of its actions, the hypnotic dose is directed to be administered an hour or two before the accustomed time of going to sleep. The duration of the sleep produced by chloralamide ranges from one to eight hours. The usual disturbances following the taking of a dose of a sleep-producing narcotic are wanting after the administration of this remedy: no headache, no nausea, no general *malaise;* only the usual cloudi-

ness after a night of sound slumber. In other words, only such sensations as normal sleep gives to every possessor of such an organism as will fall into quiet sleep whenever the time comes. As compared with the sleep obtained by the administration of chloral, that from chloralamide is less prompt but longer in duration, and the after-conditions somewhat better; indeed, more like normal sleep, if that were possible.*

How chloralamide causes sleep is not well understood. It is probable, as Kny† states, that it is split up in the blood into chloral and formamide, and that the sleep is due to chloral and formamide acting simultaneously on the cerebral cells; but of this there is no real proof. It also, at first, lowers somewhat the arterial tension, but this presently yields to the opposite action and the tension rises.

Chloralamide lowers the reflex excitability‡ when in action by disease, as in chorea, but it has little or no effect, in the normal state, upon the spinal cord. At first, when the owners of the patent gave it out as free from any danger, too large doses were administered, and then it was seen the action was not unlike all the other members of the aromatic series, in that there ensued a profuse sweat, weak and irregular action of the heart, and shallow and irregular respiratory movements. It is not essential under any circumstances that a dose exceeding 60 grains or 1 drachm should be given; but, misled by the first reports and by the commercial enthusiasm, the safe point was often passed to the detriment of the patient.

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* Peiper, Deutsche Med. Wochenschrift, August 8, 1889. Quoted by The Therapeutic Gazette, 1889, vol. xiii. p. 612.

† Therap. Monatshefte, August, 1889.

‡ Malackowski, The London Medical Recorder, June 20, 1890, p. 216.

In common with all the members of this group of analgesics, chloralamide causes a measles-like eruption to appear on the skin. Pye Smith encountered a case in which the skin exfoliated as in scarlatina.

THERAPY.—As a hypnotic, or sleep-producing medicament, chloralamide ranks highly and is hardly surpassed by any one agent; but it is not so effective when pain is present and the case is one in which insomnia is an outcome of the inflammatory state, as in pneumonia, where the use of chloral is often so effective. Nevertheless, cases have been reported in which severe pain caused the insomnia, and yet chloralamide promptly cured them. It is the general consensus of professional opinion that this remedy, like its progenitor, chloral, is more effective in relieving *insomnia* when the conditions are simple and no complications of pain and inflammation have arisen (Kny,* Reichmann†).

In *chorea* it has proved very efficient. Alt‡ was the first to prescribe it in this malady, and he reports rather remarkable cures in instances where arsenic and other approved remedies had failed. Five days of treatment with 15 grains three times a day effected a "nearly absolute cure" of a boy 11 years of age. Since the publication of Alt's observations others have appeared, the general opinion being that chloralamide is a valuable remedy in chorea and free from local injurious action. Alt also regards it as among the best hypnotics. Dr. Umpfenbach, an alienist, reports in the *Therapeutische Monatshefte*, February, 1890, p. 66, *et seq.*, on the use of chloralamide as a hypnotic remedy in various cases of nervous diseases accompanied by mental

* Therap. Monatshefte, August, 1889.

† Deutsche Med. Wochenschrift, August, 1889.

‡ The Therapeutic Gazette, 1889, vol. xiii. p. 745.

disorder in the asylum, and he concludes his paper with the statement that he finds this new agent not any better than other sleep-producing medicines already in use, for example, chloral hydrate. It seems to the author that this is a just estimate of the value of chloralamide as a remedy. Strahan,* in the asylum at Northampton, England, has prescribed chloralamide in two hundred cases, and he finds it an excellent hypnotic, but not better than paraldehyde, except in the matter of odor and of taste, and not any better than chloral, only that it does not affect the pulse, the respiration, or the action of the heart, and is free from danger. As these are very important differences, it may be concluded that the alienists think more highly of chloralamide than of chloral hydrate, as a rule.

In *paralysis agitans*, *sclerosis*, and other nervous affections characterized by clonic convulsive movements, chloralamide has acted favorably in inducing rest and sleep, and thus, it is probable, modifying the morbid process of which insomnia is a symptom.

Dr. Hagemann, two years later, reports on a great variety of cases in which chloralamide has maintained its superiority as a *sleep-producer*, having no injurious effect on the actions of the heart and lungs or on the mucous membrane of the intestinal canal.

For hypodermatic injection the amount of fluid must be large, as already explained, for the solubility of chloralamide does not exceed 10 to 14 parts per 100 parts. However, when a less abundant solution is required, the amount of water needed can be lessened by adding about one-eighth of alcohol. In the alcoholic menstruum, although the amount of the alcoholic constituent is not large, a consid-

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* The London Lancet, August, 1889.

erably greater proportion of chloralamide is soluble. For example:

℞ Chloralamide, ʒij;
Alcoholis, ʒij;
Aquæ chloroformi, ʒvi. M.
Sig.—A syringeful at a dose.

Chloralamide is rarely used by hypodermatic injection. When the stomach is rebellious, rectal injections act well, and indeed by some that is considered the better mode, because diffusion into the blood occurs promptly.

CHLORAL HYDRATE.

The Solution.—Crystallized chloral only is suitable for the preparation of solutions for hypodermatic use. A saturated solution in water contains fifty per cent. of chloral. Although this is rather irritating to the tissues, a weak solution may be more objectionable, as two punctures will be necessary to introduce the required amount.

℞ Chloral hydrat., ʒss;
Aquæ destillatæ, ʒi. M.
Sig.—Thirty (30) minims contain 15 grains of chloral.

As chloral diffuses into the blood more rapidly from the subcutaneous areolar tissue than from the stomach under ordinary circumstances, 10 grains will be a sufficient quantity for an adult; but special conditions may require more.

Physiological Effects.—Very great pain and smarting are felt at the point of puncture, and it persists, unfortunately, for a half-hour or longer. Considerable swelling, an erythematous blush, and urticaria-like eruption take place about the puncture. A hard nodule, very prone to suppurate, usually forms. Especial pains are necessary to

avoid penetrating a vein, for, although Oré has proposed the intra-venous injection of chloral for the purpose of inducing anæsthesia, the direct admission of chloral to a vein is considered so hazardous that the proposed expedient is almost universally condemned. The production of sleep is the result of the chloral injection, and this follows promptly, usually without any disturbance of function. In some subjects, however, just as when taken into the stomach, a period of excitement, with headache, precedes sleep, or, it may be, prevents it altogether. If the dose be sufficient, sleep is very sure to follow, and the drowsiness comes on within five minutes after the injection is practised. The sleep of chloral is very like that of natural sleep, and there are no after-disturbances,—no headache, nausea, nor constipation.

Administered subcutaneously, chloral possesses distinct pain-relieving power, differing in this respect from the effects of its stomach absorption.

A weak heart, especially a fatty heart, is an important contra-indication to the hypodermatic injection of chloral, still more than to its administration by the stomach. Numerous deaths have resulted from its incautious use in cases of weak heart when taken by the stomach; the danger is greater, of course, when it is thrown under the skin.

THERAPY.—So unpleasant is the local action of chloral that its use by the hypodermatic injection is restricted, usually, to cases in which the stomachal administration is prevented by the condition of that organ, or by the inability or the unwillingness of the patient to swallow.

Vomiting, not controlled by the ordinary means, may sometimes, frequently indeed, be arrested by the injection of 5 to 10 grains of chloral in the epigastric region. Obstinate *hiccough*, not amenable to the usual treatment, may

also be stopped in the same way. In violent *cholera morbus* and in true *cholera* excellent results are obtained from the chloral treatment, better, in the author's experience, than from any other. In the cholera epidemic at Riga, in 1871, the injections were remarkably successful.* Similar successes attended the practice of Mr. Hall, an English army surgeon, at Kheri, Oudh, India,† of Nepven,‡ and others. During a short epidemic of cholera in Cincinnati in 1873, I had the most convincing proofs of the efficiency of chloral injection. When the cramps are severe and the algid state well advanced, very considerable doses must be used. In one very formidable case, in which there seemed but little hope, 60 grains were administered hypodermatically in two hours, with the effect to stop the cramps, restore warmth, and to remove, indeed, all unfavorable symptoms.

In *asthma* decided relief is produced by the injection of chloral. Other *neuroses* of the chest organs are equally benefited; but the utmost circumspection is needed lest a fatal result follow, by paralysis of a weak heart.

The hypodermatic injection of chloral is indicated and may be employed in all *cerebral disorders* in which chloral is so much prescribed by the stomach: to procure sleep, to allay the excitement of mania, and to prevent convulsive attacks. The remedy is employed in this group of cases hypodermatically, when the patient cannot or will not swallow it in the usual way. In superficial *neuralgiæ* the local use of chloral may be substituted for the deep injection of chloroform.

Chloral and Morphine.—In most of the cases for which

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* O. Liebreich, Berliner klinische Wochenschrift, 1871, p. 408. Letter from Dr. v. Reichard.

† The Practitioner, July, 1875.

‡ Gaz. Méd. de Paris, September 13, 1873.

chloral is directed in the preceding paragraphs the combination with morphine is to be preferred, generally speaking, to the chloral alone. As is perfectly well known, the pain-relieving power of chloral is greatly inferior to that possessed by morphine. A combination of the two makes an anodyne and hypnotic of the highest order of excellence; that which is wanting in one is supplied by the other, and in respect to their special properties each adds to the power of the other. In a paper read before the New York Neurological Society, I showed that whilst morphine increased the physiological effects of chloral in all other respects, it prevented the depression of the heart's action caused by the latter, and thus obviated the chief danger from its administration. The combination is rendered still more efficient by the addition of atropine or cocaine. The following formulæ are intended to illustrate and embody the above principles, and may be employed for the hypodermatic injection of these remedies:

℞ Chloral hydrat., ʒiij;
Morphinæ sulph., gr. iv;
Aquæ destillatæ, ℥i. M.

Sig.—Twenty (20) minims contain 7½ grains of chloral and $\frac{1}{6}$ of a grain of morphine.

℞ Chloral hydrat., ʒiij;
Morphinæ sulph., gr. iv;
Atropinæ sulph., gr. $\frac{1}{5}$;
Aquæ destillatæ, ℥i. M.

Sig.—Twenty (20) minims contain 7½ grains of chloral, $\frac{1}{6}$ of a grain of morphine, and $\frac{1}{120}$ of a grain of atropine.

℞ Chloral hydrat., ʒiij;
Morphinæ sulph., gr. iv;
Atropinæ sulph., gr. $\frac{1}{8}$;
Cocainæ sulph., gr. vi;
Aquæ chloroformi, ℥i. M.

Sig.—Twenty (20) to forty (40) minims.

BROMOFORM.

Bromoform is a liquid, oily in consistence, colorless when pure, or brownish after keeping, when the separation of bromine may be suspected. If kept in the light, or especially when the sunlight is permitted to fall on the vial, decomposition ensues, and the liquid becomes brownish and unfit to use. It must be kept in tightly-stoppered bottles, as it is extremely volatile. It can be administered by the stomach, given in a tablespoonful of water, on which it is dropped, or inhaled, which is a good mode of procuring its effects, or administered subcutaneously in its undiluted form, as it is not irritating to the tissues. The dose for hypodermatic injection ranges from 2 to 10 minims, and the time every two to four hours.

Actions and Uses.—Bromoform is a hypnotic and depresso-motor. It inhibits the actions of the reflex system, lowers the rate and the fulness of breathing, and tends to arrest the respiratory and cardiac movements by causing paralysis of the centres supplying these organs with the necessary force to carry on their working. It acts on the reflex centres and diminishes the response to peripheral irritations.

Bromoform is very mildly toxic. It is not a dangerous agent if used judiciously, and can be given to the youngest children without risk. The dose for children ranges from 1 to 4 minims.

Obviously, bromoform is a remedy to allay spasmodic action and to cure diseases of a spasmodic character. Stepp,* Löwenthal,† assistant in Senator's clinic, and

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* Deutsche Med. Wochenschrift, Nos. 31 and 44, 1889. Quoted by Therap. Monatshefte.

† Berliner klinische Wochenschrift, No. 23, 1890. Quoted ibid.

Dr. Fischer,* of New York, who has read a valuable paper on its use in *whooping-cough*, published favorable reports. From these data we learn that it is a remedy of exceptional value in this troublesome disease. According to Löwenthal, the good effects of the remedy are seen on the second or third day, the vomiting arrested in a week, the number of paroxysms of coughing greatly reduced in the course of ten days, and the convalescence established at once, so that the average duration may be comprehended in two to four weeks. According to Dr. Fischer, the appetite was not destroyed, and the usual complications, as *bronchitis*, *pneumonia*, *measles*, etc., were not so frequent, and when the pneumonia did appear, it was much more easily and successfully treated than had been the case before. It was found necessary to continue the remedy for a short time after the disappearance of the symptoms, lest a relapse occur. It was ascertained to be better, also, to increase the dose by a drop at a time, if required.

Dr. Fischer concludes that of all the remedies hitherto known for whooping-cough, *bromoform is the best.*

Other spasmodic diseases are also benefited or cured by the administration of bromoform, such as *asthma*, *emphysema*, *hiccough*, and *laryngismus stridulus*. In severe attacks of asthma, 5 drops of bromoform may be injected subcutaneously at once, and every half to one hour subsequently, as the case may require; but if no impression is made after two doses, the remedy is unsuited to the case. In severe cases of hiccough in adults a single dose will often cure at once. The passage of calculi, hepatic and renal, will be promoted, no doubt, and the pain alleviated by the timely use of bromoform. The uses of bromoform are, indeed,

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* The New York Medical Record, September 6, 1890.

not sufficiently understood as yet to permit a final statement to be made. The extent of the therapeutical influence remains to be demonstrated. And this fact is equally true of other remedies of a similar kind. For example:

Auri Bromidum.

Auri et Sodii Bromidum.

The last named is only considered here because of its relationship to the other agents of this particular group.

The bromide of gold has been brought forward as a remedy for *epilepsy* by Goubert, and the reports on its efficiency are rather remarkably uniform testimony to its success. It is said by its original promoter that the bromide of gold is far more prompt in action and greatly more curative than are the other bromides, and the doses are at the same time far less in amount. Compare $\frac{1}{20}$ of a grain of bromide of gold with 10 to 30 grains of bromide of potassium or sodium. Besides its effects in epilepsy, it will be found, probably, to be useful in corresponding nervous maladies. It is asserted of it that it causes no depression of the mental or sexual functions.

In addition to these properties, the various remedies mentioned above are, at the same time, very powerful as antiseptics.

URETHAN.

Urethan is a carbonate of ethyl, a derivative of the aromatic series of hydrocarbons. It occurs in the form of rhomboidal crystals, and as a crystalloid it dissolves freely in water, in alcoholic solutions, and in ether. Rubbed up

with chloral hydrate and camphor, it forms a transparent fluid, and this solution is a solvent of considerable power, taking within itself the alkaloids in general, including morphine, atropine, strychnine, etc. The taste of urethan is not disagreeable, rather fresh and cooling.

The following formula is a suitable one for hypodermatic injections:

℞ Urethan, ℥ss;
Aquæ destillatæ *vel* aquæ chloroformi, ℥i. M.
Sig.—Twenty (20) minims is a suitable dose for an adult.

Urethan is not irritating to the tissues or to the stomach, and when injected beneath the skin it does not cause any unpleasant after-effects, such as dizziness, headache, nausea, arrest of secretions, etc.

The first to give a full account of the source, chemical characteristics, and physiological actions of urethan was Schmiedeberg,* the great professor of pharmacology at Strasburg. He demonstrated its apparent freedom from ill qualities, and its action on the system. He proved that it possesses hypnotic qualities of a valuable kind, and that it lowers the sensibility of the sensory nerves and the motility of the motor nerve. Hence it is anodyne as well as hypnotic. Rottenbiller† has also studied its actions on the human subject, using the remedy subcutaneously, and found that it is a reliable hypnotic, but loses its effects by repetition, and the duration of the action in individual cases varies from two to four or six hours. The most certain effect as a hypnotic is obtained from the larger doses, —from 30 to 60 grains. He advises against the giving

* Archiv für experimentelle Pathologie und Pharmakologie, Band xx. p. 206.

† Centralblatt für Nervenkrankheiten, No. 10, 1886.

of doses above the safe limit of 60 grains. Schmiedeberg* also states that it is better, when maximum doses are to be administered, that they be divided up and taken at shorter intervals to avoid the sudden impression of so great a quantity. Although observers have agreed that ill results do not occur under 60 grains, it is quite certain that beyond that point headache, hebetude of mind, nausea, and vomiting may be expected,—again asserting the law that remedies both of the fatty and aromatic series, given in maximum quantity, may surprise both physician and patient with untoward actions. It is wise in administering urethan to avoid large doses; yet Huchard† advises that the amount necessary to cause sleep—3 or 4 grammes (45 to 60 grains)—be given at one time!

Besides the hypnotic action which urethan exerts, it also has the power to stimulate the respiration. Contradictory opinions have been given in respect to the action of urethan on the circulatory system. Schmiedeberg maintains, as against Huchard and Eloy, that it has no influence on the heart, whereas these latter hold that the action of the heart is accelerated. The temperature is unaffected by it, says Schmiedeberg; the temperature falls, says Huchard. A mode of determining the temperature by the effect of urethan on the rectal heat of the rabbit is altogether fallacious. The author has conclusively shown‡ that such a mode of arriving at a fall of temperature in the rabbit is not at all to be depended on, for when a rabbit is kept immobile, within a half-hour its temperature begins to decline, and the fall goes on rapidly until

* Op. cit.

† Bul. Général de Thérapeutique, tome cx. p. 103.

‡ The American Journal of the Medical Sciences, 1878.

the amount of reduction reaches from 2° to 5° Fahr. This occurs without any other interference with the functions of the animal, and is therefore explanatory of Huchard's* observation, without resorting to the action of some medicament. That my observations were correct has been abundantly confirmed; yet these fallacies have been often perpetrated since, and the results of many an observer have been fatally weakened or destroyed thereby. It is probable that Schmiedeberg was correct and his opposers wrong as respects the effect of urethan on the body-heat. Equally so, no doubt, when he states that urethan has no positive action on the mechanism of the heart's movements, and that it rather slows than increases the heart-beats. Coze,† of the faculty of Nancy, France, has published an excellent account of his researches on the actions of urethan. His conclusions, given at the end of the article, are as follows: "Urethan has a manifest hypnotic action, induces muscular resolution, and in large doses causes anæsthesia. It slows the pulse and lowers the temperature. Its local action is so little irritating that it can be used subcutaneously. It does not affect the humors of the body nor the nutrition. It is functionally antagonistic to strychnine."

Unquestionably urethan has an antagonistic action against convulsive disorders of a tetanic character. Aurep‡ states in a few words the law of its powers: Small doses augment the excitability of the motor centres; large doses impair the reflex faculty and ultimately destroy it. He agrees with other observers, that urethan opposes the

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* Bul. Général de Thérapeutique, tome cx. p. 103.

† Ibid., p. 327.

‡ Wratsch, Nos. 31 and 32, 1886. Quoted by Bul. Général de Thérapeutique, tome cxii. p. 120.

tetanizing action of strychnine and other convulsants; but whilst these phenomena are overcome in the case of strychnine-poisoning, the paralyzing action goes on and death ensues the more quickly when they are administered together in lethal dose than when used to oppose the toxic qualities of each. When, however, consecutive doses of urethan are given against the convulsive and toxic action of strychnine, the opposing action of the urethan becomes predominant, and at length the strychnine tetanus is overcome. The same fact is true of picrotoxin, resorcin, and nicotine. Thus in poisoning by convulsant agents, especially by strychnine, this action of urethan becomes an important fact, for it renders the use of chloral under such circumstances unnecessary; and whilst chloral is dangerous to life, urethan can be given in suitable doses without in any way causing untoward results.

A case of strychnine-poisoning has been reported lately as cured by urethan without the intervention of any other remedy. Dr. Ferreira,* of Brazil, has published a series of cases in which convulsions were the chief phenomena, urethan having been prescribed with success, either modifying or curing them in all instances. The formula proposed by Huchard,† which Ferreira followed, is as follows:

> Distilled water, 100 grammes (1550 grains);
> Urethan, 20 grammes (310 grains).

As a hypnotic urethan has been placed between paraldehyde and chloral,—*i.e.*, not so powerful and far safer than chloral, and stronger and more certain in action than paraldehyde.

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* Bul. Général de Thérapeutique, tome cxii. p. 275.

† Ibid., tome cx. p. 103.

There has been not a little disappointment over the failure of urethan to maintain the position to which it was assigned when it was brought forward by Schmiedeberg. It was as a hypnotic that its place in the esteem of the medical profession was to be assured. Probably the uncertainties of its action in respect to insomnia were due to insufficiency of the dose. The bulk of the medicament is considerable when a full dose is given, and hence 15 to 20 grains were prescribed when 45 to 60 grains were really necessary. Whether this be the cause or not, the fact remains that urethan is now but little prescribed.

AMYLEN HYDRATE.

Dimethylethylcarbinol.

This recent contribution to the antiseptic, antipyretic, and hypnotic groups of medicaments, now being brought out with such extraordinary profusion, is one of the most promising of the recent products. Amylen hydrate is a tertiary alcohol with the formula $C_5H_{12}O$. It is soluble in water in the proportion of one to eight,—1 minim of amylen hydrate to 8 minims of water. It is a clear, colorless liquid, with a warm camphoraceous taste and a pungent, disagreeable odor, recalling paraldehyde. The best vehicle for internal (stomachal) administration is water with some extract of licorice, which successfully disguises the taste. For hypodermatic use the proportion of one to ten is probably the most generally useful. Instead of water it may be dissolved in oil of vaseline or, better, chloroform water. The dose ranges from 5 to 60 minims; but although the latter amount has been exceeded, it is now

regarded as the limit of safety on the maximum side of the dosage, whereas 5 minims should be considered as the limit of utility on the minimum side.

The first to make a proper physiological and clinical investigation of amylen hydrate was Von Mering, whose reports were made from studies in the clinic of Professor Jolly.* The results were highly favorable to the new remedy, and subsequent investigations confirmed and strengthened them, at the same time adding new facts. Dr. Scharschmidt † soon after published a paper based on his observations made at the clinic of psychiatry, the doses administered ranging between 45 and 60 grains. According to Dr. Scharschmidt, amylen hydrate was successful as a hypnotic in eighty per cent. of his cases, the remedy procuring sound sleep of five to seven hours, and this result was due to doses of 20 to 45 grains. In comparison with paraldehyde this effect may be stated thus: it required 75 grains of paraldehyde to produce the effect of 22 grains of amylen hydrate, and as to chloral, 15 to 20 grains acted less favorably than 30 to 50 grains of amylen hydrate. Considered with reference to the time required for symptoms to appear, it was often noted that the time of somnolence was not later in quiet cases than five to fifteen minutes after the stomach received the medicament, and was never postponed later than one-half of an hour to one hour, and these cases were such perturbed and violent ones as mania produced.

One of the observations of greatest importance is the absence of any change in the rhythm, form, or volume of the cardiac or respiratory movements. There did not

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* Therap. Monatshefte, July, 1887, and Merck's Bulletin, July, 1889.

† Ibid., September, 1887.

occur any sweats, or chills or rigors, such as had been witnessed in the course of the actions of other hypnotics that have been brought forward recently.

The first experiences with amylen hydrate have been supported by the investigations of the same remedy made after the expiration of two or more years. Thus Dr. Wildermuth, writing in 1889, records his treatment of *epilepsy* with this remedy. He finds that the more severe the case the more efficient the remedy. When the attacks are of the variety known as the *grand mal*, when they are nocturnal, when, in addition to the disease, there is also considerable bromism, this combination of pathological conditions is rapidly relieved by amylen hydrate. Also, if the bromides, by long-continued use, have become necessary to the patient, they can be withdrawn when the effects of amylen hydrate are fully produced, and in the course of six to eight weeks the convulsions are suspended. The only after-effects noticed from the action of amylen have been somnolence and occasionally nausea, due to the large doses administered. Here again is the proof that amylen hydrate is free from the unpleasant consequences caused by the antiseptic, antipyretic, and hypnotic agents belonging to the aromatic and fatty series; none of the severe symptoms occurring during its action,—no severe rigors, threatening, even terminating in, collapse, no depression of the heart-movement, and no threatenings of heart-failure.

No dangerous symptoms have been witnessed as yet. In some cases at the Leipsic clinic, a mistake occurred in the administration, by which such large doses as 5 grammes (82 grains) were given to three patients, and to a fourth 3½ grammes (54 grains). The result was they all slept deeply and on the following day could not be roused;

the reflexes were suspended, and both sensibility and motility were abolished; the pulse was small and the temperature was reduced two to three degrees below normal. All slept through the second night, but on the third day all had recovered and presented no points of difference from their usual appearance and condition. In this accident we have a typical representation of the full effects of amylen hydrate on the human body.

The accumulated testimony proves that amylen hydrate is a hypnotic, that it allays cerebral excitement, and lowers the reflex excitability of the medulla and spine and lessens the impressionability of the sensory nerves and the sensory part of the cord. It is generally conceded that it causes death by paralysis of respiration.

As respects its therapeutical applications, amylen hydrate has been successfully used as a hypnotic in various affections requiring such a remedy. It has been employed by Mering in *delirium tremens* with entire success. In other kinds of *mental disorder*, in which insomnia is a prominent feature, it has been useful in a high degree, in asylum practice, and in clinics of psychiatry (Krafft-Ebing).

In the various maladies characterized by the condition of spasm, as in *asthma*, *whooping-cough*, *singultus*, *chorea*, *tetanus*, *strychnine-poisoning*, etc., it occupies an important place as a remedy.

It has also proved effective in certain painful affections of the abdominal cavity, characterized by paroxysmal pain and spasm. It is asserted that in *catarrhal jaundice* and in the bilious state succeeding to *biliary colic* it is especially useful, not only relieving pain, but removing the local trouble giving rise to pain.

As compared with other hypnotics, such as chloral, chloralamide, paraldehyde, exalgin, and urethan, amylen

hydrate comes next to chloral in efficiency, and is far less dangerous in the tendency to cardiac failure. It is more active than paraldehyde, and no doubt as safe or nearly so.

METHYLAL.

PROPERTIES.—Methylal is an oily liquid, having an ethereal odor and a taste rather pungent. Its composition is represented by the formula $C_3,H_8.O_2$, and it belongs to the group of *acitals*. It is freely soluble in water, alcohol, and the fixed oils, and may be administered in solution in water, also by inhalation, and by subcutaneous injections.

The first proper study of methylal was made by Dr. Richardson,* of London, in 1868, although it was discovered so long ago as 1839 by Malaguti. After Richardson's results were made known, its actions were observed by Nicol, Personali, and Krafft-Ebing. Its special functions have been shown to be the relief of pain and the production of sleep. It does not cause anæsthesia, except by very prolonged and excessive inhalation, and in some animals, but not in man, except the dose be lethal.

As a hypnotic it has been used with some success by Mairet and Combemale,† who ascertained that it acted thus in doses of $3\frac{1}{2}$ to $7\frac{1}{2}$ grains for every two pounds of body-weight. It causes hyperæmia of the mucous membrane, and profuse lachrymation, nasal and faucial and salivary discharge, when inhaled, and during the state of toxæmia. The effects are more sustained and are also more powerful

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* The Medical Times and Gazette, London.

† Le Progrès Méd., No. 17, 1887. Quoted by Therap. Monatshefte, 1887, p. 270.

when methylal is given hypodermatically. The sole objection to this mode of administration is the irritating quality of the medicament, for not a little pain is always felt, and sometimes after-local inflammation followed by ulceration. It should not be understood that such injections will invariably result in abscesses and ulcerations, but only when frequently injected in the same part, or when done without care or attention to cleanliness.

As respects the effects of methylal on individual functions: it increases a little the action of the heart, but lowers somewhat the vascular tension, lessens the number of respirations but increases their volume. On the brain the action is hypnotic and antispasmodic. When a sufficient dose is given in any of the modes of administration, a deep and prolonged sleep follows. In ordinary doses it is difficult to anæsthetize by inhalation, and it causes such a free discharge from the mucous membrane and so much irritation that this mode of administration is of doubtful propriety.

Methylal abates the sensibility of the sensory nerves, and is therefore an analgesic. Pain is more surely relieved when so superficially placed that the affected nerve can be reached by the injection. It has an effect on the reflex centres, lessening their sensibility, and this property in turn gives to the remedy a function which is styled antispasmodic.

Methylal antagonizes agents having the tetanizing action,—for example, strychnine;* but it is not equal to urethan in this respect, nor indeed can it be depended on in a case of poisoning. If it were equal to the task of antagonizing strychnine in the whole range of its actions,

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* Personali, The Therapeutic Gazette, 1887, vol. ii. p. 317.

it must be a medicament of far greater powers than it is now supposed to be. Motrokhin * finds that it causes more or less deep anæsthesia, but of very transient duration, and when a moderate dose is administered, the strychnic convulsions are lessened in violence but not arrested; and when, with a view to stop them, a massive dose is given, a fatal result quickly follows, more quickly than if strychnine alone were given. The same facts are true of another convulsant,—picrotoxin.

Dr. B. W. Richardson, of London, who has given methylal much attention, concludes that it resembles methylic alcohol in action. The attempts made by Richardson to convert methylal into an anæsthetic agent proved abortive. Others engaging in the same design have been defeated, equally, so that now it is not regarded as an anæsthetic agent. That it produces, when massive doses are given, a state of complete insensibility is admitted, but this is not, properly speaking, an anæsthetic action; it is a mere insensibility with a state of muscular resolution, both due to an overpowering effect on the centres of conscious impressions, such as any other narcotic may produce.

EXALGIN.

Methylacetanilid.

The name exalgin—a trade designation—is far more easily managed by an ordinary vocal apparatus than the chemical title methylacetanilid. Acetanilid—known generally as *antifebrin*—has different properties from its con-

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* The Therapeutic Gazette, 1887, p. 411.

gener, the *methyl*acetanilid, although there are many points of resemblance between them, many of identity. They are representatives of the aromatic group, all of which have antiseptic, hypnotic, and analgesic actions. The addition of *methyl* adds to the analgesic and hypnotic properties of the acetanilid, methyl being an alcohol having similar powers.

The name exalgin describes the supposed chief action, and as it is now in common use, it were better to retain it, rather than adopt the German designation, which is better only so far as chemical consistency may be regarded as important.

Exalgin occurs in needles and long tablets. It is indifferently soluble in cold water, but is specially soluble in water containing some alcohol. However, as alcohol smarts not a little when thrown under the skin, it were wise to use as little as will effect the desired solution.

It is a derivative of acetanilid, being one of the three isomeric modifications of that preparation. By the stomach, the dose is from 2 to 6 grains a day; but for hypodermatic injection it is better not to exceed two-thirds of the amount given by the stomach,—that is, from 1 to 4 grains a day. If no idiosyncrasy exists, or if there are peculiarities in the case, or if the state of the system is against its action, the dose may range from 6 to 12 grains.

Exalgin was discovered by Briggonet, and the first physiological investigation into its mode of action was made by Dujardin-Beaumetz * and Bardet. They demonstrated its powers, in respect to the correspondence of its action to the other members of the aromatic series, and ascertained the predominance of the analgesic effects over

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* Bul. Général de Thérapeutique, tome cxviii. p. 206, *et seq.*

the other and usual attributes of this group. Whilst apparently first as an analgesic, it was supposed to be inferior to antipyrin and many others in the antiseptic and hypnotic effects. Subsequent experiences, however, have not supported the view of its one-sided powers, but, rather, have shown its efficiency as an antipyretic and as an antiseptic.

A medicinal dose raises the arterial tension for a short time and it then falls to the original standard, and very little variation in the circulation is observed, the usual change being some slowing of the heart-beat, without alteration of its force or tension. As the condition of the patient is one closely approximating normal sleep, the circulation and respiration are also in harmony with the other vital acts. From these data it must be concluded that the proper medicinal doses do not approach the danger-line.

When a lethal or toxic dose is taken, the arterial tension falls, the breathing soon begins to labor and quickly is deeply oppressed, and sleep comes on, rapidly growing into coma; then the reflexes disappear, and finally, in respect to these points, heavy sweats, rigors, and other toxic phenomena appear. Death ensues rather by paralysis of the respiratory muscles, and it is probable that the cardiac muscular tissue participates in these changes, and as a necessary consequence the heart dies with or soon after the respiration. When a full dose, but still medicinal, is given to a warm-blooded animal, general clonic convulsions come on, and when injected into a group of muscles, they becomes paralyzed. The action of exalgin is on the centres of the medulla oblongata and spine, and not on the peripheral nerves and muscles unless it is applied directly to these parts. The most important change

induced by exalgin is that in the blood,—the separation of hæmoglobin,—whereby the oxygen-carrying function is either damaged to a great extent or entirely destroyed. According to the extent of the mischief done must the function of oxidation, heat-production, and all other vital acts be impaired.

When the actions of exalgin and antipyrin are compared, the first difference to attract attention is the small amount of exalgin necessary to obtain a result for which massive doses of antipyrin are required. A dose of exalgin of 6 to 12 grains in twenty-four hours will have as much effect on a morbid process for which 60 to 120 grains of antipyrin will be needed. As respects the phenomena which attend on the close of the functional performances when given for a febrile attack, there are marked differences; any considerable doses of antipyrin cause chilliness or chills or rigors, a profuse sweat, and more or less depression of the vital forces; sometimes, indeed, the heart's action becomes exceedingly weak, on the verge of failure. None of these signs and symptoms are present with the effects of exalgin. Throughout the whole course of their actions it is certain that exalgin is superior in respect to the amount of material used to procure certain definite results.

When a lethal dose is taken, characteristic effects follow, the drug resembling in the manner of its actions the other members of the aromatic series; for when deep somnolence approaches there is more or less stimulation of the nerve-centres with the usual effects of pain and spasm, followed very soon by paresis, paralysis, and muscular resolution, sweats, chills, and great depression of the vital powers, approximating in all ways to the effects of antipyrin, antifebrin, and others of the same group.

Exalgin is excreted by the kidneys within twelve hours after being taken, and can be found in the urine. Although not actively toxic, it is capable of causing death when—as it is said—7½ grains for every two pounds of body-weight are administered.*

THERAPY.—The therapeutical uses of exalgin were at first confined to cases of *pain* and cases of pain accompanied by *insomnia*. It was supposed, indeed, that exalgin was chiefly endowed with the attributes of sleep-producing and pain-relieving, differing from the other members of the same group in a superior power in these directions, and compensating thus for its inferiority as regards the other powers of which it is the possessor in a minor degree in common with the rest of this group. When given for the hypnotic action, somnolence begins in fifteen to thirty minutes, and sound sleep soon follows very like the quiet, tranquil breathing of an adult in good health. It is less useful than antipyrin or antifebrin in cases of wakefulness due to injuries or high excitement; quiet cases of mania without motor excitement is its special field. In the instances of severe pain—of neuralgia *per se*—and the condition of pain arising from inflammatory states and from trauma and cancer, collected by Professor Fraser,† of Edinburgh, the results of the treatment by exalgin were as follows: There were eighty-eight cases, and of these sixty-seven proved to be successes by the treatment and twenty-one were failures. These statistics are significant of the power of the remedy in affections characterized by severe pain. Moreover, the source of the pain must be

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* Bul. Général de Thérapeutique, September 15, 1889. Quoted by The Therapeutic Gazette, vol. xiii. p. 746.

† Professor Thomas R. Fraser, University of Edinburgh, Bul. Général de Thérapeutique, tome cxviii. p. 206, *et seq.*

taken into account in making up the judgment. There were in the list of causes of the pain cases of cancer, which of course offer little opportunity for the relief of pain permanently. If there had been selected cases of neuralgia *per se*, no doubt the results had been more striking. So far as they go, there can be no doubt of the significance of these figures.

As a remedy for the febrile state, exalgin is effective according to the amount given. If the rule that 7½ grains for every two pounds is the lethal quantity, for a man weighing one hundred and fifty pounds it would require somewhat more than 1 ounce to kill him. This proportion is accepted by Gaudineau ;* but so much depends on idiosyncrasy that no hard-and-fast rule can be applicable to man. As, however, the medicinal doses are so far inferior in strength to the merely lethal, dangerous symptoms can hardly be caused by any medicinal quantity. Therefore in the treatment of insomnia and pain the full amount required can be given without apprehension.

Exalgin has a good effect in cases characterized by spasm or by irregular muscular action. In *chorea* its success has been striking. The first account published by Moncarvo † was highly satisfactory in that it demonstrated the powers of exalgin as compared with antipyrin. Previously, Moncarvo had used antipyrin with success, but he was induced to make a change in his remedy because of the quantity of antipyrin required, and the cost. He decided to try exalgin, probably because of its pronounced action on the reflexes, which it depresses and ultimately suspends when a sufficient dose is given. His experience with the new remedy was in a high degree fortunate and successful.

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* Bul. Général de Thérapeutique, September 15, 1889.

† Ibid., November 30, 1890.

2. *Excito-motors.*

STRYCHNINA: STRYCHNINE.

BRUCINA: BRUCINE.

Alkaloids of the Strychnos Nux Vomica.

Both alkaloids dissolve to a slight extent in water, yet not sufficiently so for use hypodermatically; but as salts they dissolve freely.

Strychninæ Sulphas: Brucinæ Sulphas.

Strychninæ Hydrochloras: Brucinæ Hydrochloras.

HISTORY.—Strychnine was no doubt the first agent submitted to systematic examination by the physiological method. Magendie, having ascertained its properties, suggested that "medicine would perhaps derive great advantage from the knowledge of a substance whose property is to act on the spinal cord, for we know that many severe diseases have their seat in this part of the nervous system." Causing muscular rigidity, he supposed it might be used with good effects in the condition of paralysis, and it was not long before Fouquier subjected the suggestion to the test of experiment, and treated cases of paralysis successfully. The first application of strychnine hypodermatically in the treatment of disease was made by Dr. Béhier, of Paris, but the observations of Mr. Charles Hunter really initiated the clinical experience since continued so successfully.

THE SOLUTION.—The following solution is convenient:

℞ Strychninæ sulphatis, gr. i;
Acid. carbolic., gr. i;
Aquæ *vel* aquæ lauro-cerasi *vel* aquæ chloroformi, ℥i. M.
Sig.—Ten (10) minims contain $\frac{1}{48}$ of a grain.

As a solution of strychnine will long remain free from a penicillium, the addition of carbolic acid is necessary only when the solution is intended to be kept several months. Although one grain will dissolve in an ounce of water entirely, at the ordinary temperature, it tends to crystallize out; hence before taking out the required amount the bottle should be placed in a vessel containing some hot water. The sulphate, in larger relative proportion, and other salts, as the nitrate, have been proposed, but from a mistaken notion of the solubility. The sulphate is the most soluble of the salts of strychnine, but not more freely than in the proportion of the above formula. By the aid of heat, two or more grains will dissolve in an ounce of water, but on cooling the surplus will crystallize out. On the other hand, the solution containing one grain to the ounce will remain a perfect solution for some time, and not until after several months will some minute crystals form on the glass.

The dose of strychnine subcutaneously has been variously given. Lorent employed from $\frac{1}{25}$ to $\frac{1}{10}$ of a grain, and Eulenberg has given up to $\frac{1}{8}$. Hunter administered from $\frac{1}{90}$ to $\frac{1}{24}$ of a grain. Echeverria produced toxic symptoms in a boy—which, however, were readily recovered from—by $\frac{1}{30}$ of a grain. From 5 to 10 minims of the solution recommended will be suitable quantities under the varying circumstances of cases. Half a grain is the smallest fatal dose recorded.

It is important to note the effects produced by the hypodermatic injection of medicinal doses. Unfortunately, until toxic symptoms are excited, the disturbance is too vague for characteristic description. Some facts can be stated, however, from clinical observation.

When a solution of strychnine of the usual strength is

injected under the skin, a sensation of heat and smarting persists for some time in the part. The skin also becomes red in the neighborhood of the puncture; a subjective sensation of warmth is perceived in the limb, and an actual rise in temperature may be noted. At the same time erection of the hair-follicles (*cutis anserina*) takes place.

In a few seconds, pain or distention is felt in the abdomen, intestinal movements and loud borborygmi occur, just as is the case so frequently after the hypodermatic injection of the narcotic alkaloids. Next the pupils dilate, deep-seated pain and throbbing are felt in the brain, and an unpleasant giddiness renders the erect posture painful, and standing or walking uncertain. Ringing in the ears, detonation, anxiety, a feeling of dread, and flashes of light before the eyes are also quite commonly experienced. The countenance of the patient affords some indication of the cerebral disturbance, it wearing an expression of anxiety and distress as the effects of the drug increase.

The foregoing symptoms are more severe if larger doses be administered, and in addition there occur some stiffness of the jaws, jerking of the extensor muscles, and sharp pains like electric shocks shooting through the limbs. Dr. Echeverria has so well described these severe symptoms that I transcribe his account. My own observations supply no further experiences than those I have just detailed, of cases receiving the hypodermatic treatment with the ordinary medicinal doses.

"I injected first the right thigh, and about two minutes after the left. In two minutes more the boy commenced to sigh, and have a meaningless smile, with stiffness in the jaws, soon passing into real trismus. The pupils were largely dilated, the face congested, and tetanic spasms of the respiratory and cervical muscles followed. Every

attempt to articulate a word awoke a spasm. He could neither speak nor be touched without being seized with a jerk, and the whole surface of the body was in a perspiration." * In another case Dr. Echeverria had similar experiences. He thus describes them: "In about eight minutes she complained of giddiness, and was soon seized with trismus and opisthotonos. The tetanic spasms were not violent, and were accompanied by general perspiration, congestion of the face, and enlargement of the pupil." Other important observations were made by Dr. Echeverria. "The temperature of the limbs was always raised after the injection. The frequency of the pulse was also augmented. The capillary circulation was rendered more active in the limbs, exhibiting large red patches, more intense in the vicinity of the punctured region. This condition would last three and even four days after the operation. The injections were attended with perspiration of the head and limbs, more profuse with the girl than with the boy. The pupils were always dilated, and gurgling of the bowels would persist some minutes after the puncture. Another very perceptible result was the fibrillar contractions, or twitching of the muscles of the limbs, lasting for a minute or two, and which I have found prolonged for more than an hour in other similar cases."

When we come to analyze the symptoms produced by the subcutaneous injection of strychnine in full medicinal doses, we observe that the effects are exerted on the nervous system of animal life, and to some extent on the sympathetic system.

In small quantity it does not affect the irritability of the

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* Treatment of Paralysis by Hypodermic Injections of Strychnine. Medical Communications of the Connecticut State Medical Society, 1868.

motor and sensory nerves, as Klapp * and Spitzka † have shown, but in large doses it does appear to have this effect, as Vulpian ‡ and others have demonstrated. The opposing observations on this point are reconciled by the fact, discovered by Martin-Magron et Buisson, that the action of strychnine on the nerves is local, and therefore greatly influenced by the quantity reaching them.

Strychnine causes a rise in pressure of the blood by stimulating the vaso-motor centre in the medulla, and by inducing contraction of the arterioles, as has been experimentally demonstrated by Mayer, § Spitzka, || and others. It also, in medicinal doses, stimulates the intra-cardiac ganglia, thus increasing the heart's rate of movement. Clinical observation has seemed to be conclusive as to the power of strychnine to stimulate the respiratory organs and to increase the depth and force of inspiration.

In a lethal dose the effect follows almost immediately on the administration of the poison. The head feels powerfully distended; a shudder passes over the body, with a catch in the breathing; a pain deep in the epigastrium shooting to the spine occurs at the same time; the jaws are clinched; electric-like shocks fly through the limbs; the muscles of extension of the extremities and the muscles of the abdomen become rigid and start up in sudden strong contraction; the face is pale and distorted by a grim smile (*risus sardonicus*); the pupils are dilated; the pulse is quick; the breathing jerking. With the progress of the action the sensibility of the reflex centre be-

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* The Journal of Nervous and Mental Diseases, 1878, vol. v. p. 619.

† Ibid., 1879, vol. vi.

‡ Archives de Physiologie Norm. et Path., 1870, p. 116, *et seq.*

§ Archiv für experiment. Pathologie u. Pharmakol., Band xi. p. 458.

|| *Supra.*

comes so acute that the minutest peripheral impression—a breath of air, a touch, a gleam from a mirror—will excite a spasm, in which general extension of the voluntary muscles takes place, the breathing is suspended, the hands are clinched, the toes incurvated, the head bent backward, and the body so arched that the heels and the occiput are the only points of support. During the paroxysm the face grows dusky, and the skin generally dark and perspiring. Death ensues by the fixation of the respiratory muscles, but rarely occurs in the first paroxysm, and may be delayed to the third or later. The mind is unaffected until carbonic-acid narcosis comes on. Much soreness is felt in the muscles after the paroxysm, but they are not rigid. The paroxysms increase in number and violence to the end, which occurs usually within two hours.

THERAPY.—The original suggestion of the use of strychnine in the treatment of *paralysis* was made, as has been shown, by Magendie, after his course of experiment demonstrating the nature of its actions. Dr. Béhier, of Paris, was, it appears, the first physician to employ strychnine by the hypodermatic method, and afterwards Professor Courty, of Montpellier, used it with complete success in three cases of *facial paralysis*. Notwithstanding these, and some other authoritative statements regarding the curative effects of strychnine thus administered, it was not until Mr. Charles Hunter's paper—"On Strychnia Hypodermically administered in Paralytic Affections"*—appeared that professional attention was strongly directed to this subject. Echeverria's paper also revived interest in this country, continued by cases occurring in the practice of Dr. Hammond, of New York, which were reported by

* The British and Foreign Medico-Chirurgical Review, April, 1868.

Dr. Reuben A. Vance.* These were cases of hemiplegia, paraplegia, and local paralysis. As might have been expected, the local paralyses were most decidedly benefited, but all were improved in a marked degree. The forms of paralysis which have been treated in this way are the following:

Hemiplegia.	Infantile paralysis.
Paraplegia.	Local paralyses.
Progressive muscular atrophy.	
Progressive locomotor ataxia.	

Mr. Hunter reports three out of four cases of *hemiplegia* cured by injections of strychnine. Two of the cases were respectively of six and two and a half years' duration. This statistical statement should not mislead the reader. Success like this cannot be expected in the treatment of paralysis of cerebral origin; the cases of Mr. Hunter were evidently very favorable cases for treatment by this method. Nevertheless, the hypodermatic injection of strychnine, in many cases, is decidedly curative. As Dr. Echeverria has well remarked, "the effects of strychnine are widely different when administered hypodermatically or by the mouth. By the latter method the quantity may be repeated and increased, unsuccessfully, as manifested in the cases of Hunter, and in those here related; and yet a smaller dose of the substance, exhibited hypodermatically, be capable of regenerating at once the lost muscular power."

We should possess clear notions, then, as to the circumstances in which it may be proper to use the hypodermatic injection of strychnine in hemiplegia, for, manifestly, a remedy of such power may prove to be as harmful when

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* The Journal of Psychological Medicine, vol. iv. p. 367, *et seq.*

indiscreetly employed as it is unquestionably useful in suitable cases.

It is contra-indicated in recent hemiplegia.

In my own experience it has not been useful in old cases characterized by contractions of the palsied limbs.

It has been exceedingly useful in old cases of hemiplegia in subjects not very advanced in life, the paralysis being partial as to motility, and the limbs not wasted.

The hypodermatic injection of strychnine has been used in *spinal paraplegia* by Béhier, Courty, Ruppaner, Hunter, Echeverria, and others, with success. The rules for its administration are similar to those I have given for hemiplegia.

It is not proper in acute cases involving structural alterations of the spinal cord.

In cases of paraplegia due to softening or tumor in the spinal canal it will do harm.

It will be beneficial in cases of reflex paraplegia, in paraplegia due to anæmia of the cord, in hysterical paraplegia, and in those cases of paresis of the muscles of the inferior extremities due to concussion of the cord, but after the acute symptoms have subsided.

It is certainly true, however, that Mr. Hunter obtained advantage from it in a case the symptoms of which indicated myelitis. Dr. Echeverria's Case I. may be classed in the same category,—the patient complaining of formication and numbness, and being paralyzed both as to motion and sensation.

The hypodermatic injection of strychnine has proved an exceedingly valuable adjunct to the treatment of *infantile paralysis*. If the electro-muscular contractility to the continuous or induced current be not lost, very beneficial results may be expected from this treatment. The injec-

tion promotes the capillary circulation, and increases the growth and power of the muscles.

In various *local paralyses* the hypodermatic injection of strychnine is even more decidedly curative. Courty* cured *facial paralysis* by injecting strychnine over the course of the facial nerve. Pletzer, Lorent, Sacmann, and Eulenberg had good results from the same treatment.† In a case of paralysis of the vocal cords with aphonia, Neudörfer failed, but in a similar case Waldenburg succeeded with the strychnine injection.

In the "drop-wrist" of lead-poisoning—*paralysis of the extensors*—it is a very important addition to the other means of treatment of this very obstinate affection. It is more successful than any other agent in *writer's cramp.* Palsy of single muscles or groups of muscles, following cold or rheumatism, is generally curable by this means. The injection also increases much the contractile power in cases of palsy following injury of nerve-trunks.

Paralysis of the bladder, with dribbling of urine, and *paralysis of the sphincter ani* not due to myelitis, are much benefited and frequently cured by this means.

In *progressive muscular atrophy* it has been used with great advantage in cases in which the electro-muscular contractility was not lost.

In paralysis of cerebral or spinal origin, without wasting of the muscles, the injection may be made under the skin. The dose of strychnine will vary with the age of the subject, from $\frac{1}{60}$ to $\frac{1}{10}$ of a grain. In local paralyses, in infantile paralysis, in progressive muscular atrophy, the injection must be made into the affected muscles. If the electro-contractility be not lost, the following effects may be expected:

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* Eulenberg, p. 243. † Ibid.

Rise in the temperature of the limb, and increase of capillary circulation.

Increase in muscular power with improvement in the nutritive condition of the muscles.

Cure of the paralysis.

If, however, the electro-muscular contractility to the galvanic current is lost, fatty degeneration may have so far proceeded that the injection of strychnine will be useless.

The method of practising the injection into the muscles is as follows:

The affected muscle or group of muscles is grasped with the left hand and made prominent, and with the right the needle is plunged quickly and boldly into the muscular tissue. When inserted as far as necessary, the needle is withdrawn a short distance to clear any vessel it may have penetrated, at the same time moving the point about, and then the fluid is slowly injected. It is important, of course, to avoid the blood-vessels, and to insert the needle into the paralyzed muscles. The pain of this operation is not greater than the subcutaneous injection, and little danger of deep-seated abscess is to be feared. Muscular tissue, as is well known, does not readily take on the morbid action called inflammatory.

The systemic effects do not follow so quickly nor are they as powerful after injection into the muscular tissue as after the subcutaneous injection. Both local and systemic effects are produced; but the local effects are largely desired in cases of local paralysis. Some cases of local paralysis of the bladder cannot be reached in this way. In paralysis of the sphincter ani the needle may readily be thrust into this muscle.

The subcutaneous injection of strychnine has been used

in *progressive locomotor ataxia*, but with a negative result. In my own experience I have observed no decided influence for good or evil.

Neuralgia.—The hypodermatic injection of strychnine has been used by Dr. Anstie in *gastralgia* and *cardiac neuralgia*, with advantage. "My decided opinion is, at present," says Dr. Anstie, "that there is no such remedy for gastralgia as strychnine subcutaneously injected in doses of $\frac{1}{120}$ to $\frac{1}{60}$ of a grain." Although I cannot speak so positively as Dr. Anstie on this subject, I can say that I have observed good effects from the strychnine injection in the class of cases to which he refers.

Amaurosis and Amblyopia.—According to Eulenberg, Fremineau was the first to employ the hypodermatic injection of strychnine for the cure of a case of amaurosis following typhus. Sacmann soon after reported a cure of amaurosis by the same means, and Spaeth one of amblyopia,—"functional paralysis of the retina." Dr. Lacerda,* of Lisbon, employed the hypodermatic injection of strychnine with success in a case of "amaurotic amblyopia." Talko, of Tiflis,† also succeeded in curing amblyopia by repeated injections, ranging in strength from $\frac{1}{40}$ to $\frac{1}{4}$ of a grain. The most important contributions to our knowledge of this subject have been made by Professor Nagel, of Tübingen, who reports cures of amblyopia and amaurosis, and even cases of the latter in which there was white atrophy of the optic disks.‡

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* Gazette de Lisboa, 1867, xi., and Schmidt's Jahrbücher der gesammten Medicin, Band cxliii. p. 67.

† Ibid., Band cxlv. p. 74.

‡ Berliner klinische Wochenschrift, 1871, Band viii. p. 6. Also, Dr. Nagel's special treatise, which, however, I have not had the opportunity to consult.

Weinow* employs the nitrate, $\frac{1}{50}$ of a grain, injected into the temple every two or four days. If no improvement occur after three injections, he discontinues the practice. In an excellent paper on the subject, Bull† gives a *résumé* of Nagel's observations, and follows with an account of twenty-four cases. He concludes that in functional amblyopia we may expect good and permanent results from strychnine; and even in some cases of organic origin, provided there be no extensive atrophy of the nerve structures, some improvement is obtained from the use of the remedy. If actual atrophy of the nerve exists, he thinks strychnine useless. All authorities are agreed that it is in alcohol and tobacco amaurosis, especially the latter, that the injection of strychnine renders such important service. It is conceded that the remedy will do no good if no improvement has occurred after three or four injections.

Strychnine has been used successfully in the treatment of all forms of *alcoholic toxæmia*, and is strongly urged by Popoff, Menassein, and Tolwinsky.‡ Dr. Stadler, of New Orleans, reports a case of opium-poisoning in which the weak heart was powerfully sustained by injections of strychnine.§

To these must be added the amblyopia of disuse, of hysteria, and allied states.‖

The Antagonisms of Strychnine.—The discovery of chloral hydrate and the subsequent announcement of

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* Quoted in The London Medical Record, vol. i. p. 156.

† The American Journal of the Medical Sciences, 1872.

‡ Therap. Monatshefte, 1888.

§ The New Orleans Medical and Surgical Therapeutic Gazette, vol. xiii. p. 90.

‖ L. De Wecker, Thérapeutique Oculaire, p. 640.

strychnine as its physiological antagonist, made by Liebreich, have been followed by numerous researches, monographs, and clinical reports. Liebreich demonstrated that animals in a deep stupor from chloral intoxication, the dose administered being lethal, were aroused, and death was averted by strychnine. If, for example, two rabbits of equal weight—say three pounds—receive $\frac{1}{96}$ of a grain of strychnine sulphate, a fatal dose, and to one of them 15 grains of chloral be also given, the former will die in tetanic convulsions in ten minutes, while the latter will sleep two hours or more quietly, and will wake up in a normal state. Such a striking exhibition would seem to be conclusive, but other observations are necessary. The most important and elaborate research undertaken to determine the supposed antagonism of chloral and strychnine is that of the Committee of the British Medical Association, Dr. J. Hughes Bennett, Chairman.* The Committee first, rightly, settled the lethal dose of each agent; they next ascertained the result of the simultaneous administration of chloral and strychnine; and then the result of the administration, at varying intervals, of one subsequently to the lethal dose of the other agent. Their general conclusions are as follows: "1. That, after a fatal dose of strychnine, life may be saved by bringing the animal under the influence of chloral hydrate. 2. That chloral hydrate is more likely to save life after a fatal dose of strychnine than strychnine is to save life after a fatal dose of chloral hydrate. 3. That, after a dose of strychnine producing severe tetanic convulsions, these convulsions may be much reduced, both in force and frequency, by the use of chloral hydrate, and consequently

* The British Medical Journal, October 3, 1874, p. 437, *et seq.*

much suffering saved. 4. That the extent of physiological antagonism between the two substances is so far limited that (1) a very large fatal dose of strychnine may kill before the chloral has had time to act; or (2) so large must be the dose of chloral hydrate to antagonize an excessive dose of strychnine that there is danger of death from the effects of the chloral hydrate. 5. Chloral hydrate mitigates the effects of a fatal dose of strychnine by depressing the excess of reflex activity excited by that substance, while strychnine may mitigate the effects of a fatal dose of chloral hydrate by rousing the activity of the spinal cord; but it does not appear capable of removing the coma produced by the action of chloral hydrate on the brain."

A careful investigation of the supposed antagonism of chloral and strychnine has been undertaken by Husemann.* He holds that chloral is an antidote to strychnine, prevents spasms, and averts death, and that it has a corresponding effect in the case of the strychnine base sold under the name of brucine. One of the earliest attempts to ascertain whether the antagonism existed was that of Rajewski,† who found that chloral prevented or relieved the cramps caused by strychnine, and also to a certain extent the cardiac depression, but that strychnine was not in the same degree an antagonist to chloral. In a memoir on the treatment of poisoning by chloral, Erlenmeyer‡ holds that, while chloral is useful to oppose some of the effects of strychnine, the converse does not hold good, and strychnine is not useful in chloral-poisoning. The

* Antagonistische und antidotarische Studien, Arch. für exp. Pathol. und Pharmakol., Band vi. p. 345.

† Centralblatt für die Med. Wissenschaft, 17, 1870, p. 261.

‡ Prakt. Arzt, Band xiv. p. 11. Quoted in The Practitioner.

influence which Erlenmeyer's opinion might otherwise have is decidedly weakened by a statement made in this connection, intended to illustrate and enforce his views, that while morphine is an antagonist to atropine in poisoning by the latter, atropine is not an antagonist in poisoning by morphine. Arnould,* who has also investigated this question experimentally, regards the antagonism as more limited in scope than Liebreich has maintained. This question has also been studied by Professor Oré, of Bordeaux,† who concludes that strychnine rather promotes than prevents the poisonous action of chloral.

What is the teaching of clinical experience? I have found recorded seven cases of strychnine-poisoning, in which chloral was the chief or only means of treatment employed. An equal number of cases I find in which chloroform inhalations were practised successfully. Although the latter do not come within the range of the present subject, yet, as the effects of chloral are attributed by Liebreich to the disengagement of chloroform in the blood, they may serve to illustrate and confirm the former. Of the seven cases of strychnine-poisoning, in which chloral was the chief or only agent used, all proved successful. No facts could be stronger. I am unable to find any cases of chloral-poisoning in which strychnine was properly and adequately used, as it is in animals.

If we now sum up the evidence, we cannot fail to be convinced of the antagonistic action of chloral and strychnine; but chloral is an antagonist to strychnine-poisoning, rather than strychnine is an antagonist to chloral-poisoning. The experience on rabbits shows that $\frac{1}{96}$ of a grain of strychnine is equivalent to 15 grains of chloral. In

* Presse Méd. Belge, 1870, No. 9, p. 69. Quoted by Husemann.

† Bul. Général de Thérapeutique, tome lxxxiii. p. 403, *et seq.*

the cases of poisoning in man, 30 grains of chloral subcutaneously was sufficient to allay the spasms and avert death from 4 grains of strychnine. But no absolute rule can be laid down, since the susceptibility to the action of these poisons varies greatly in different individuals. As in the published cases emetics were used, and in many instances the quantity of strychnine was merely estimated, no positive conclusions can be drawn from them. Artificial respiration materially retards the action of strychnine, and warmth, as Brunton* has shown, exercises a remarkable influence in lessening the effect of chloral. Thus, "Dr. Brunton found that an animal wrapped in cotton-wool may recover perfectly from a dose of chloral which is sufficient to kill it when exposed to the cooling action of the air, and that recovery from the narcotic action is much quicker when the temperature is maintained in this way, and still more rapid when the animal is placed in a warm bath, provided this is not excessive." Heat would therefore seem to be an antagonist to chloral, and for an obvious reason, for heat increases the action of the heart, and thus opposes the depression of the heart, which is a main factor in the toxic effects of chloral. In the treatment of the toxic effects of strychnine by chloral, the amount of the latter administered should be determined by the symptoms. Sufficient chloral should be given to suspend the strychnine spasms, for the danger consists in the stoppage of respiration by tetanic fixation of the respiratory muscles. The amount required for this will, doubtless, vary within considerable limits, as I have already intimated. In the case of the Sioux Indian, treated by Dr. Turner,† the quantity of strychnine was not known, but the

* The Journal of Anatomy and Physiology, May, 1874, No. 14.

† The Medical and Surgical Reporter, June 15, 1872.

return of the spasms from time to time required repeated doses of chloral, 105 grains in all being given within five hours. When strychnine is used against chloral-poisoning, the objects to be accomplished are different. By stimulating the cardiac and respiratory centres with strychnine, the tendency to cardiac and respiratory failure is prevented. The quantity required will be determined by the effects; but it is probably much less than theory indicates. The initial dose may be $\frac{1}{60}$ of a grain, and each succeeding dose $\frac{1}{120}$ of a grain, which may be repeated every half-hour, or more frequently, until an approximation to the maximum is reached. Gray reports a case of recovery from 22 grains of strychnine, chloral being the antagonist used.

Chloral and strychnine can hardly be regarded as antagonistic in their actions on the mental functions, since chloral suspends them, and strychnine does not affect them in any way. In one respect they have opposite effects,—chloral producing cerebral anæmia and strychnine rather increasing the intra-cranial circulation. On the spinal cord the antagonism is very complete,—chloral suspending the reflex and motor functions of the cord and strychnine exalting both. Strychnine stimulates the respiratory and vaso-motor centres in the cord, and thus opposes and counteracts the most dangerous tendency of chloral narcosis. The chief danger from strychnine—the tetanic fixation of the muscles of respiration due to the exalted reflex function—is removed by the action of chloral. This antagonism is more certain and effective than the opposite one, or the stimulation of the chloralized spinal cord by strychnine; whence it follows that chloral is a more useful antagonist in strychnine-poisoning than is strychnine in chloral-poisoning.

An antagonism has been demonstrated between strychnine and *bromide of potassium*. Notwithstanding the difference in the rate with which they act, bromide of potassium has been used successfully in several instances to counteract the toxic effects of strychnine. The doses administered must be large and must be frequently repeated. One drachm may be given every half-hour, sufficiently diluted in water. The limitation of the doses will be determined by the effect on the spasms. Bromide may also be used in conjunction with other remedies,—with those more prompt, but evanescent in effect, as ether or chloroform inhalations.

To the antagonists already referred to paraldehyde must be added, this being, next to urethan, an efficient remedy. Gelsemine on theoretical grounds has also been proposed.

Among the newer remedies that have the power to antagonize strychnine is urethan. Although this medicament is not one of the most powerful antispasmodics, yet it has a phenomenal influence over the strychnine convulsions. If an animal is well charged with urethan in advance of the giving a merely lethal dose of strychnine, the effects of the latter will not be manifest. As urethan is far less dangerous than chloral or other antagonists of strychnine, it has a manifest advantage.

Strychnine as a Stimulant of the Respiratory Function.—The importance of atropine as a special stimulant of the respiratory function has been frequently alluded to. The resemblance in the spinal actions of atropine and of strychnine has been manifest in the study of these agents. Atropine, in therapeutical works, is sometimes suggested as an opponent and antagonist of strychnine; it is so placed in Gubler's "Commentary on the French Codex."

Hardly any statement could be more fallacious. In some experimental investigations made some years ago, I found that atropine intensified the effects of strychnine, and hastened death by contributing to the tetanic fixation of the muscles of respiration. We find that strychnine stands next to atropine as a stimulant to the respiratory function. Through the heightened reflex activity of the spinal cord and of the respiratory centres in the medulla, strychnine causes death by spasm of the respiratory muscles and asphyxia. It must therefore antagonize those agents which, like aconite, cause death by paralysis of the respiratory muscles. This supposition is confirmed by experiment. In an interesting series of experiments to test this antagonism, Dr. Fothergill found that a lethal dose of aconitine was entirely overcome by a quantity of strychnine twice as great as the lethal. The animals given the aconitine alone died; the same animals receiving the aconitine with the strychnine, in previous experiments, recovered. The existence of the antagonism is, therefore, undoubted.

An opposition of actions has been determined to exist between *strychnine and nitrite of amyl.* These substances act in an opposite manner on the nervous system of animal life and on the sympathetic system. Amyl nitrite suspends the reflex function of the spinal cord and causes paralysis of the muscular system, and death ensues from paralysis of the respiratory muscles. The most characteristic effects are those on the heart and the arterial system. It depresses the arterial tension to the lowest point, and increases greatly the action of the heart, a necessary result of the enormous dilatation of the peripheral vessels. The reflex and spinal effects, the cardiac and arterial disturbance, are the opposite of those produced by strychnine. From the physiological stand-point, then, an antag-

onism must be presumed to exist between them. An experimental research by Dr. Gray,* of Glasgow, strongly supports this view. Thus he found that $\frac{1}{4}$ of a grain of strychnine proved fatal usually to the rabbits which he used for experiment. He was able to administer $\frac{1}{2}$ of a grain of strychnine and 10 drops of the nitrite of amyl simultaneously, by subcutaneous injection, without any marked disturbance following. Of course, further investigations are necessary, but sufficient is now known to justify the inhalation of nitrite of amyl in cases of strychnine-poisoning.

PICROTOXINUM: PICROTOXIN.

A Neutral Principle obtained from the Anamirta Cocculus, or Cocculus Indicus.

Picrotoxin is found in the fruit of the cocculus, and is a crystallizable bitter principle which occurs in the form of prisms and needle-shaped stellar or foliaceous crystals. It is soluble in one hundred and fifty parts of cold water and in twenty-five parts of boiling water, and dissolves freely in alkaline solutions. This fact affords the opportunity for preparing more concentrated solutions, should they be desired. The following is a suitable solution for hypodermatic injections:

℞ Picrotoxini, gr. i;
Aquæ destillatæ, ℥i. M.
Sig.—Five (5) minims contain $\frac{1}{90}$ of a grain.

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* The Glasgow Medical Journal, 1871, p. 188.

The dose of picrotoxin ranges from $\frac{1}{100}$ to $\frac{1}{20}$ of a grain. It sometimes happens that a nodule is left at the site of the injection, but it disappears in a few days without suppuration, as a rule.

Physiological Actions.—Picrotoxin belongs to the excito-motor group of remedial agents: it tetanizes when the dose is sufficient to act on the nervous system. Although not irritant to the gastro-intestinal mucous membrane, it excites nausea, and this appears to be a natural endowment, for the nausea occurs at what point soever the medicament may be introduced into the system. It increases secretion of the salivary and intestinal glandular apparatus, and there is reason to believe, also, of the liver and pancreas. It acts on the sudoriparous glands of the skin, and increases the amount of perspiration as a constant symptom. So great is the action of the sudoriparous glands that picrotoxin ranks next to pilocarpine as a sudorific. The glandular apparatus of the gastro-intestinal mucous membrane also pours out a more abundant secretion, and consequently the number of the alvine discharges is increased and their consistence lessened. The color of the evacuations becomes more nearly normal, if before they had assumed a leaden hue, and provided no lesions had occurred before.

The circulation is at first increased in the force, number, and volume of the heart-beats, but as the effects continue, the power of the heart declines and the tension of the arterial system falls somewhat, whilst before it had been higher than the strictly normal. When the tetanic stage comes on, followed by clonic convulsions, trembling of the muscles, and general agitation, the temperature rises and the body-heat assumes a febrile form, the circulation increases in action strictly in harmony with the in-

creased capillary circulation and the consequent more rapid oxidation.

Picrotoxin acts on the spinal cord, especially on its reflex centres, and on the centres of respiration and circulation in the medulla oblongata. The action is, however, not restricted to the cord,—it includes the brain also. As respects the whole of its complexus of symptoms, they are comparable to strychnine unless the cerebral effects differ. This has been made a strong point of differentiation, because, as was at one time alleged, there are no disturbances of the cerebral functions in the whole course of the actions of strychnine. Subsequent experiences have demonstrated that strychnine does affect the brain in various ways, and through the vaso-motor system modifies the blood-supply to the organ. But this is by no means the whole of the effect. Whilst it is true that strychnine acts on the brain, it is equally true that the manner in which it affects the brain is widely different from that of picrotoxin. This difference can be the better demonstrated when the effects of picrotoxin are being studied.

It is asserted that the toxic complexus of picrotoxin is a repetition of the epileptic paroxysm. It is known that the several stages in the course of the poisoning and in the course of the epileptic state are practically the same.

With the onset, a strange, staring, unearthly expression accompanied by extreme pallor comes on, and immediately after the tetanic stage, in the course of which the muscles of respiration are fixed by the tonic spasm; air is excluded because of the closure by muscular action of the chink of the glottis, and tetanic fixation of the muscles of respiration and a deep cyanosis with stertorous breathing appear, and then these phenomena are followed by clonic convulsions of an irregular character, making up with

some minor symptoms the full outline of a clinical picture in which both conditions are repeated with fidelity.

When a toxic or a lethal dose of picrotoxin is given, the first effect on the organs of circulation is a stimulation of the heart and arteries. The blood-pressure rises a little, and the heart-beat is for a brief period slowed, but this is followed by more rapid action and lowered tension until the tetanic stage is reached, when slow action for a time occurs; but again the convulsions increase the rate of movement, the blood is rapidly distributed through the periphery, and the temperature of the whole body rises. Sweating in great profusion comes on with the rapid muscular action. The effect it has on the sudoriparous glands is no doubt due to the hyperæmia of the skin, and it may be, also, to a direct action of the medicament on the nerve-supply to the gland in question.

In full medicinal doses picrotoxin causes contraction of the pupil and hyperæmia of the base of the eye. The irritability of the sensory nerves is diminished and, on local application to the mucous membrane, some abatement of the local sensibility is induced, but not complete anæsthesia. In the absence of other local anæsthetics, picrotoxin may be used to lower the local sensibility with some certainty of success.

The cerebrum is distinctly affected. Hebetude of mind, inco-ordination of the muscles, and increasing stupor leading into coma are the characteristic symptoms. Stupor is a constant result in the case of animals. Formerly the berries of cocculus Indicus were used to stupefy fish and thus render them an easy prey; no kinds of fish were exempt from the operation of the poison; small and great, edible and non-edible, turned up on the surface of the water so stupefied as to be unable to escape.

Cocculus Indicus berries are also utilized in the making of a sophisticated beer. This agent has the bitterness of beer and the intoxicating quality of alcohol, so that it can be utilized to save hops, and to be very efficient in giving the stimulating and stupefying effects so much desired by beer-drinkers. It has a brutalizing effect on those who indulge in the drinking of such beer, and its use for these purposes should be mentioned as throwing light on some cases of poisoning.

THERAPY.—The applications of picrotoxin hypodermatically to the treatment of disease are not numerous, and it seems to the author not nearly so much as the merits of the remedy would seem to demand.

In certain spasmodic diseases it has been employed with apparent benefit in suitable cases. *Epilepsy* in subjects of a depressed and anæmic kind, especially if nocturnal in time of seizure, is not infrequently much improved by the persistent use of picrotoxin. The affinity of the morbid process set up by picrotoxin with the symptomatology of the epileptic and epileptiform paroxysms is such as to indicate the existence of an antagonism between them, and on this basis Cherone and Tasta * have made trials of this remedy with apparent benefit.† Gubler ‡ advises the use of the remedy by hypodermatic injection.

He also reports a case of *alcoholic epilepsy* cured in this way. Cases of *chorea* having certain special features are much improved by the use of picrotoxin; those most benefited are characterized by violent jactitations and great

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* Quoted from Annali Univ. di Med. e Chirurg. by The London Medical Record, October, 1880.

† Planat, Bul. Général de Thérapeutique, 1876.

‡ Gubler, ibid., 1875. Hammond, The St. Louis Medical Journal, October, 1876. Dr. William Murrell, The Practitioner, October, 1879, vol. xxiii.

irregularity as well as strength of the muscular contractions. Also, cases of *local chorea*, or *histrionic spasm*, where the movements are frequent and involved and rather widely distributed, at the same time acting with considerable force, forming a morbid complexus not amenable to ordinary medication. In such cases the injections should be made into the muscular groups most affected, visiting each in turn in inserting the medicament.

Affections involving the *vaso-motor centre* in the medulla and the ganglia of the sympathetic seem to be improved to a less or greater degree by the use of picrotoxin when all other remedies prove inefficient. *Exophthalmic goitre, glosso-labio-laryngeal paralysis*, the initial stage of *locomotor ataxia*, are affections in which, by the persistent use of picrotoxin, much benefit is sometimes experienced.

In *tetanus* and *hydrophobia* some good has resulted in the few cases in which it has been made use of. It well deserves further investigations in respect to these maladies. *Senile trembling* and *paralysis agitans* have been benefited; but in all of these instances, whilst the results have been promising, no cures have been reported as yet. In chronic myelitis affecting the gray matter, it may have a manifestly retarding effect in the progress of the case.

Among the more important conditions for which picrotoxin is given are catarrhal *affections of the gastro-intestinal canal. Jaundice* due to catarrh of the bile-ducts, insufficient secretion of the glands of the canal, and dry and ill-colored stools resulting therefrom, *chronic diarrhœa* and *dysentery* accompanied by these conditions, are all benefited by picrotoxin.

The sweats of phthisis are sometimes much relieved by the use of this remedy and also in combination with other remedies. Thus Murrell relates that a single dose of $\frac{1}{100}$

of a grain has arrested the sweats and kept them absent for three or four days. My own experience has not been so favorable as this. In fact, the remedy has usually quite disappointed me.

HYDRASTIS.

The Root of Hydrastis Canadensis.

Hydrastine. [*An Alkaloid of Hydrastis Canadensis.*]
Berberine. [*An Alkaloid of Hydrastis Canadensis.*]

Berberine possesses but little interest for legitimate practice, and is a medicament valued chiefly by eclectics, who prescribe a so-called "hydrochlorate of yellow hydrastine," this agent being little else than berberine.

Hydrastine, the white alkaloid, is the most important constituent of hydrastis, and to this must be referred the chief effects of the fluid extract. Hydrastine is the source of a new medicament—an oxidation product—obtained by Dr. Freund, who gave it the name, *hydrastinine*, now in common use.

Dr. Falck has made a careful study of this alkaloid, and finds it possessed of valuable properties that render it superior to hydrastine. As *hydrastinine* is a basis substance, and combines with acids to form salts that are soluble in water, it can be readily utilized, in hypodermatic practice, as hydrochlorate, sulphate, tartrate, etc., the alkaloid itself being insoluble.

It is now employed in medical practice both by the experimental and clinical methods, and it has already displayed valuable properties as a therapeutical agent.

Actions and Uses.—In the course of some physiological studies of hydrastis, several years ago,* I soon learned that the special powers of this agent are vested in the alkaloid hydrastine. The fluid extract and the alkaloid acted very much alike; both at first cause rigidity and startings of the muscles, and then follow tetanic spasms in which, if the dose be toxic, death often ensues by tetanic fixation of the respiratory muscles. When the spine of a frog was pithed (*i.e.*, destroyed), no action of a similar or of the same kind occurred as the tetanic muscular spasms; on the contrary, with toxic doses the muscles lay limp and without any power of motion. This experiment also shows that the spasms are spinal and not peripheral. When, however, the voluntary muscles or the heart-muscle were immersed in the fluid extract, they quickly lost their power of response to all forms of irritation, mechanical, chemical, or electrical.

As respects the vascular system, hydrastine slows the heart somewhat, increases the force of its contractions, and raises the arterial tension by contracting the calibre of the vessels. Falck makes the singular statement, that hydrastis slows and weakens the heart and at the same time raises the tension of the vessels. Now, no fact in physiology is better understood than that, with weakened cardiac contractions, the walls of the vessels are relaxed for the very necessary purpose of aiding the heart in propelling the blood through the arteries. If the arterioles are contracted the work of the heart is much increased and necessarily slowed.

The tetanizing action of hydrastis is succeeded by paralysis. When very large doses of hydrastis are given,

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* The Drugs and Medicines of North America.

the stage of tonic contraction may not develop; but, as is the case when strychnine is administered in massive doses, paralysis supervenes without any apparent stage of tonic spasm, so when hydrastine is given in very large doses, paralysis may supervene at once. Also, when hydrastine is given in a smaller quantity, the first stage of tonic spasm is succeeded by a paralysis in which all the voluntary muscles and the cardiac muscles participate.

The heart is arrested in the diastole, and its cavities are distended with blood.

There are certain differences in the actions of hydrastine and hydrastinine, but more points of identity. Falck * asserts that hydrastinine is the more valuable therapeutically, whereas Marfori † maintains the opposite thesis,—that hydrastine is the more valuable. They agree with regard to the action of both alkaloids in raising the blood-pressure and in causing paralysis after the first tonic spasms. Falck also maintains that hydrastinine is a paralyzer and is not a tetanizer, and that it increases the contractile power of the heart. Because of an irritation of the vagus, it raises the blood-pressure. It seems to me that the views of Marfori are more true to nature, and they are more in harmony with my own experimental work. Some of Falck's observations seem contradictory, as I have already intimated. The active constituents of hydrastis are eliminated by the kidneys.

The therapeutical applications of hydrastine and hydrastinine are directly deducible from their physiological actions. As they both cause active contraction of the

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* Quoted by The Therapeutic Gazette, February 15, 1890.

† Archiv für experimentelle Pathologie und Pharmakologie, 1890.

arterioles, and slow the heart, they are *a priori* suitable remedies in hemorrhage, in aneurism, and especially in *uterine hemorrhage.* A large measure of success has attended their use in these affections in the hands of Schatz * and other gynæcologists. In cases of *fibroma* of the uterus attended with large *hemorrhage*, it has succeeded admirably. Fuchs has cured a case of this kind, and Rutherford has had the same results in the treatment of five cases of fibro-myoma. Dr. Schmidt, of Prague, has also reported a remarkable case of uterine myoma, in which the effects of hydrastis seemed almost marvellous. Under its action the hemorrhage ceased, the myoma greatly lessened in size and ultimately disappeared, and the appetite and digestion were completely restored to normal.

Dr. Jinopistzeff, house physician of the Emperor Paul's Hospital, Moscow, relates experiences based on twenty cases of uterine hemorrhage of various kinds, in which the best results were obtained. Schlavatinsky strongly advocates its use under like conditions,—in uterine disorders accompanied by hemorrhage.

Some of those mentioned above, who maintain the power of hydrastine or hydrastinine to stop uterine hemorrhage, draw nice distinctions in the cases where it may be used with or without the usual success, holding that when the uterus is flabby in texture, or when the hemorrhage is a sign of malignant disease, hydrastis is not so successful as in other states of the organ. As, however, the curative effect of this agent is due to the action on the vessels,—to the contraction of the organic muscular fibre, whereby the calibre of the arterioles is so narrowed that

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* Therap. Monatshefte, 1890, p. 19.

escape of blood is much lessened,—it is idle to discuss differences in the form of diseases that probably have no existence.

It may be well to remark here that Fellner * has shown that the mode of action is by contraction of the arterioles, and that the amount given has much to do with the character of the initial effect, the smaller medicinal doses acting more to raise the tension of the vessels and to move the organic muscular fibre of the uterus than the larger, which earlier bring on a paretic effect.

In other forms of hemorrhage, as *epistaxis*, "*hysterical pulmonary hemorrhage*," Batlich has succeeded with hydrastis, and Königer, in *tubercular hemorrhage*, has been equally fortunate with the same remedy.

It is remarkable that the success with which hydrastis has been studied physiologically and utilized in practice abroad has not been imitated in the country of its origin. The eclectics or botanical or herb doctors in this country have monopolized the agent for years, and only within the last decade has it taken a place in legitimate therapeutics, but chiefly as a topical agent, with which, however, this work is not concerned.

THE DIGITALIS GROUP.

By this term is meant a group of medicinal agents having many points of similarity of action to the princi-

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* Wien. Med. Blätter. (Abstract of, in Virchow u. Hirsch's Jahresbericht, 1885, p. 448.

pal member—digitalis—and agreeing among themselves in the range and character of their effects, although having minor points of difference.

DIGITALIS.

The Second Year's Growth of the Leaves of Digitalis Purpurea.

Various principles—alkaloids and glucosides—have been discovered in digitalis, and much difference of opinion still exists as to their nature and composition. As respects the use of these agents hypodermatically, as the subject now stands, the choice is narrowed to two articles:

Digitaline. { Crystallized, insoluble in water.
Amorphous, soluble in water.
German Digitaline. Soluble in water.
French Digitaline. Insoluble in water.

For injection:

German digitaline, gr. ij;
Water, ʒiv. M.

S.—Each minim contains $\frac{1}{120}$ of a grain. Five (5) minims contain $\frac{1}{24}$ of a grain.

The crystallized digitaline (Nativelle's) is not soluble in water.

Schmiedeberg* makes the assertion that Nativelle's crystallized digitaline is a mixture of several principles, but Arnaud, in a recent investigation, has proved that this opinion is incorrect, and that, if prepared with sufficient care, it is a distinct chemical product and not a mere mixture. As it cannot be utilized for subcutaneous

* Archiv für experimentelle Pathologie und Pharmakologie, Band iii. p. 17.

injection, we may dismiss it from consideration, having said enough to prevent the reader falling into error in regard to its position as an agent for use in the human body in some form.

The German digitaline is a mixture, and is composed for the most part of digitaleïn, a neutral principle of a high degree of activity, approaching Nativelle's digitaline in its effects on the organism. A solution of this may be prepared for a hypodermatic solution, some carbolic acid—2 to 3 drops to the ounce of fluid—being added to prevent change.

In the reports of serious cases in which "heart-failure" is threatened and the life of the patient put in imminent jeopardy, it is said that the tincture of digitalis was injected subcutaneously with the view to stimulate and support the jaded heart. So much unwisdom has been put forth on the subject of "heart-tonics," and the deaths that come from "heart-failure," that the ordinary intelligence is only able to grasp the opinion that digitalis is the great heart-tonic, and only enough being given, the heart is safe and cannot fail. This mischievous error leads to the most injudicious treatment of cardiac affection.

It seems to me in a high degree important that he who would inject digitalis tincture should have some accurate knowledge of the mode in which this remedy acts on the organism, and how it becomes a "heart-tonic," if we admit the existence of such a remedy.

The first point is that digitalis often disorders the digestive tract, and may excite vomiting at what place soever it is introduced into the economy; and when the bulk of the crude preparations—such as the infusion—increases, by mere distention, the tendency inherent in the remedy to cause nausea and vomiting.

Digitalis acts slowly. It is a fact which should be well known that it requires about twelve hours to affect the organs on which it acts, and this means the retention of the active constituents in the tissues and their slow diffusion into the blood.

Digitalis raises the arterial tension by stimulating the tonic state of the vaso-motor system, and slows the heart by increasing the inhibition coming from the pneumogastric. It lengthens the interval between the systole and diastole, and increases the force of the cardiac contractions. It is a physiological law that, the arterial tension being raised, the heart must beat more slowly and with more energy to overcome the *vis-à-front*—the resistance in front—caused by the narrowed calibre of the arterioles.

That digitalis acts on the kidneys, increasing the urinary flow and to some extent the urinary solids, but chiefly the amount of water, are facts now universally admitted by all competent authorities. It was therefore, and still is, entitled a diuretic, without any attempt to explain the character of the action. We owe to Dr. Brunton the demonstration of the fact, that it is not wholly the rise in the arterial tension and the increased blood-pressure that causes the diuretic effect, but an inherent diuretic property which is exerted on the secretory elements of the kidneys, most probably in the passage through of the digitalis constituents.

Such is a brief sketch of the actions of digitalis, the most important member of this group. We must compare the other agents with the chief, and then come to a conclusion as to their proper relations, and determine when one may be substituted for the other in the treatment of cardiac and other diseases.

SPARTEINE.

An Alkaloid obtained from Scoparius.

Sparteine is a liquid and, when fresh, colorless oily substance, and contains no oxygen, in which respects it agrees with nicotine. It has active basic properties and readily combines with acids to form salts, of which the sulphate is the most useful and important.

The alkaloid is insoluble, but its salts dissolve freely in water, the ordinary menstruum (Hondé*). The following formula will prove suitable for hypodermatic injection:

℞ Sparteinæ sulphat., gr. x;
Aquæ destillatæ *vel* aquæ chloroformi, ℥i. M.
Sig.—Five (5) minims of this solution contain about $\frac{1}{10}$ of a grain.

As the dose of sparteine ranges between $\frac{1}{4}$ of a grain and 1 grain, the formula just given will permit of all necessary gradation in the amount necessary to administer.

Physiological Actions.—This remedy is rather more like digitalis than any other of the group. It acts especially on the circulatory organs. The first effect is slowing of the pulse and increase of vascular tension. A reaction from this state takes place for a brief period, and then this condition is succeeded by cardiac depression and failure. These effects, as Gluzinski† pointed out, are due to the action of sparteine on the pneumogastric nerve and on the intra-muscular ganglia of the heart, or on the muscular tissue of the organ; probably on both.

These actions of the so-called third stage are no doubt of a lethal character and are not the effects which are

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* Bul. Général de Thérapeutique, tome cix. p. 510.

† The London Medical Record, 1887, p. 154.

utilized when sparteine is applied to the treatment of cardiac diseases. The spinal cord is correspondingly affected; at first the reflex excitability is increased, and this, in turn, exhausts the irritability and paralysis ensues (Fick*). Tetanic rigidity of the respiratory muscles is succeeded by relaxation and paresis, the action of the heart continuing after respiration has ceased. From these facts it is clear that sparteine increases the power of the heart, and is in some proper sense, therefore, a "heart-tonic."

As respects the effects of this remedy on the muscular system, it has no decided action except through the spinal cord, causing some irregularity of movement and incoordination, but it does not act on the peripheral motor nerves.

The excretion of sparteine takes place through the kidneys. Broom has long been known to have active diuretic properties, for which purpose it was prescribed chiefly in the form of infusion. It increases the flow of urine, and this action is irrespective of its effect on the vascular tension; so that it must be regarded as a diuretic pure and simple.

CONVALLARIA.

Lily of the Valley. All parts of Convallaria Majalis.

The actions of convallaria are due to the presence in it of two glucosides, named, respectively, convallarin and convallamarin. *Convallarin* is found chiefly in the root

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* Archiv für experimentelle Pathologie und Pharmakologie, Band i. p. 397.

and leaves, whilst *convallamarin* is obtained from the flowers. These glucosides differ materially in properties,—the former being an emeto-cathartic, and the latter a cardiac remedy having a mode of action similar to, but not the same as, that of digitalis, and it is this similarity which assigns it to this group.

The chief action of convallaria, and for which it is employed in medicine, is its effect on the heart, in which it is said to resemble digitalis. That part of it which is the cardiac remedy need only to be considered here. The emeto-cathartic effects are of a kind to require notice in another division of the subject.

Convallaria, although not unknown to many practitioners, was not understood or its properties investigated with precision until Professor Sée took up the study and demonstrated the nature of its powers. He showed that it possessed properties not unlike those of digitalis. His enthusiastic advocacy, however, was not long sustained.

Convallamarin, the cardiac glucoside of convallaria, acts similarly to digitalis in that it slows the heart by lengthening the interval between the beats, energizes the muscular contractions, and raises somewhat the arterial tension. It does not affect the stomach if convallamarin is the form administered or if the infusion of the leaves is given. It was this form of the medicament that was used by Professor Sée* in his first investigations. Hence the decision with which he made his statements on this point. According to his experience, no nausea, no vomiting, or other disturbance of the stomach came on. Others have insisted on its disagreeable effects on the gastro-intestinal mucous membrane,—on the nausea, the prolonged vomiting, and purging in-

* Bul. Général de Thérapeutique, tome ciii. p. 49.

duced by it. Among these I may mention Bogoiavlensky,* Troitzky,† and Botkin,‡ of St. Petersburg, and Lourie,§ who says that in his cases diarrhœa was a frequent symptom. When the extract or infusion of the flowers is used none of the gastro-intestinal irritation occurs, but rather the appetite is promoted and the digestion improved.

The three stages into which the action of convallaria is divided really consist, first, of the effects already described; second, of a stage of paresis, fall of arterial tension, and irregularity and lack of rhythm of the various movements, followed by a final stage, if the dose be lethal, of an extraordinary rise in the arterial tension with irregular action of the heart, increasing feebleness of its beats, etc.

Next to the cardiac effects of convallaria is the renal action,—the diuresis,—which is a most constant symptom. In cardiac valvular incompetency with general œdema, it acts most efficiently, as a rule.

It must be admitted by the most ardent advocate of the utility of convallaria that it is a rather uncertain medicament. It is this uncertainty which has led to so much disappointment in its applications, and hence, in part, the decline in its popularity.

STROPHANTHIN.

A Glucoside obtained from Strophanthus Hispidus: the Kombe Arrow-Poison.

A specimen of strophanthus sent to Professor Fraser, M.D., of the University of Edinburgh, for investigation, is the beginning of our knowledge of this medicament. Dr.

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* The London Medical Record, July 15, 1887. † Ibid. ‡ Ibid.
§ Ibid., July 15, 1885. Quoted from La Medicina Contemp., 1885.

Fraser examined into the physiological actions and therapeutical applications of this substance, and with characteristic fidelity arrived at some conclusions regarding its real utility.

The paper of Fraser attracted wide attention, and strophanthus and strophanthin, the glucoside, received investigation at the hands of many eminent pharmacologists, and, for the most part, the results arrived at by Fraser were confirmed by the general voice of the medical profession.

The strophanthus arrow-poison is no doubt a vegetable extract in which strophanthus is the chief ingredient, but it is usual for the tribes using poisoned arrows to add some noxious animal matters. Thus Stanley tells us that the arrow-poisoners of equatorial Africa add to the vegetable extract used by them the juice of a red ant of a highly-irritating character.

Strophanthin does not affect the stomach injuriously in moderate doses, as a rule; but when long continued in considerable doses it sets up a catarrh of the mucous membrane. It diffuses into the blood promptly when given by the stomach,—even more promptly by subcutaneous injection. Bucquoy* asserts that it is so irritating to the tissues as to be unfit for hypodermatic use; but Rothziegel,† of Vienna, and others find it well adapted to this mode of administration, and assert that it is unirritating to the tissues, acts quickly and energetically, and is "without any local deleterious effects."

Gley was the first to observe that local anæsthetic effects followed the application of a solution of strophanthin to

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* Comptes-Rendus de la Société de Thérapeutique, 1890, p. 204.

† Annuaire de Thérapeutique, 1890, p. 211.

the cornea; but this fact has led to no practical adaptation of the remedy in ophthalmic practice. It causes in dogs not only anæsthesia of the cornea, but it also contracts the pupil to the point of myosis.

Strophanthus has an effect on the heart comparable to digitalis, but its physiological powers are in many respects very different. It has but little effect on the blood-pressure. Large doses rather lower the blood-pressure than increase it, according to Langgaard,* an opinion in which Fränkel† shares. It slows the pulse a little and strengthens the cardiac contractions, but not as much as digitalis does (Zerner‡). It lengthens the diastole also, and in Basedow's disease for a time lessens the pulse-rate. Kazam§ finds that strophanthin is not a muscle-poison, and that it acts on the terminal filaments of the vagus and on the cardiac ganglia. It follows that in these impressions on the nervous apparatus of the circulation, an explanation is afforded of the results of the administration.

Langgaard‖ differs from his contemporaries in respect to the effect of strophanthin on the circulation. He finds that it lowers the blood-pressure somewhat when given in large doses, but admits that he had seen a rise of the pressure at times in some of his experiments. Fraser, in whose accuracy and honesty of judgment I have the fullest confidence, says, on the other hand, that strophanthin raises the blood-pressure. This is, certainly, the stage of the action which is utilized in treatment.

Strophanthus also has decided diuretic effects, and, ac-

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* Therap. Monatshefte, 1887, p. 183.

† Ibid., 1888, p. 76.

‡ Centralblatt für die gesammte Therapie, 1887, p. 618.

§ The London Lancet, 1887, p. 1136.

‖ Therap. Monatshefte, 1887, p. 183.

cording to Csatáry,* this impression on the kidney is due to the increased blood-pressure. The diuretic action is exhibited more especially in the cases of valvular disease, incompetent or obstructive.

ADONIDIN: ADONIN.

Adonidin. [*A Glucoside obtained from Adonis Vernalis.*]
Adonin. [*A Glucoside obtained from Adonis Amurensis.*]

These glucosides have points of resemblance and some of identity. They act on the same parts, and cause effects that are analogous in action but different in power. Quantitatively, adonidin is much superior to adonin † in strength. Both slow the pulse, and that is almost the only effect adonin has on the healthy adult.

According to Cervello ‡ adonidin has an action in all respects like digitaline, but is more powerful (?). Large doses raise the blood-pressure, and small doses strengthen the heart's action, but do not affect the vascular tension to any considerable extent.

Adonidin and adonin lessen the muscular power and impair co-ordination, the former to a much greater extent than the latter.

After a time, the quantity given being lethal, adonidin causes an irregularity of the heart's action and feebleness, and being a muscle-poison, the muscles of respiration fail before the heart's movements are arrested.

Adonidin is an active diuretic and has been very suc-

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* Therap. Monatshefte, 1887, p. 451.

† Inoko, Archiv für experimentelle Pathologie und Pharmakologie, Band xxviii. p. 302, *et seq.*

‡ Ibid., Band xv. p. 235.

cessful in the treatment of cardiac dropsy. As its action closely resembles that of digitalis, and as the effects begin promptly,—usually within an hour,—it can be utilized as a substitute for digitalis when immediate action is necessary or when digitalis disagrees.

BLATTIC ACID.

Obtained from the Cockroach, Blatta Orientalis.

For a long time the cockroach has been used in Russia as a remedy for cardiac dropsy. It has proved its efficacy in many cases of the kind. Recent chemical research has separated an acid known as blattic acid,* to which the property residing in this insect is supposed to be due.

Blattic acid presents nothing disagreeable in its name, and the source of it would probably be heard with resignation by any patient if it were proved to be curative in such a formidable ailment as cardiac dropsy.

It is, as are the other members of this group, a cardiac tonic, so called, and also a diuretic. It must be admitted, I think, that we have other remedies superior to this in the affections in question.

COMPARATIVE THERAPEUTICS OF THE MEMBERS OF THE DIGITALIS GROUP.—It is necessary now to consider the mutual interdependence or synergism of the various agents composing the group. In what circumstances, or in what condition of the morbid complexus, is digitalis, in what convallaria, in what sparteine, etc., most useful? In what way may they be combined to give the best results?

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* Dictionnaire de Thérapeutique, tome i. p. 527.

Digitalis occupies the first place, it must be admitted, in those states of the heart considered atonic, as a so-called "heart-tonic." Medicines cannot influence the heart in any other than two modes: to improve its action, or the performance of its functions; to impair its action, or lessen its functions. With what critical judgment soever we bring to this task, it is impossible to designate any other mode in which the heart can be acted on by remedies.

Digitalis has long occupied the position of a cumulative poison,—that is, a poisonous medicament having the peculiarity of gradually accumulating until in amount sufficient to cause sudden and profound cardiac failure, exploding, as it were, in the organism. The only way in which ordinary medicinal doses can thus accumulate is the following: Owing to the exceeding slowness with which digitalis diffuses into the blood, there is a period during which an accumulation takes place, because the administration being generally two or three times a day, the admission to the blood does not go on at a sufficient rate, so that one dose is not disposed of when others are coming into action. This is the only sense in which digitalis is a cumulative poison. Various remedies may be considered "cumulative" in the same sense. It is important to bear in mind this peculiarity of digitalis, twelve hours at the least being required, under normal conditions, to procure an effect from it. It is important also to note that the rise of arterial tension is followed by a corresponding fall. A case of death from digitalis, narrated by Böhm, is peculiarly interesting in this connection: A girl who had taken a lethal dose of digitalis died on the fifth day on getting out of bed. None other had been given, and no other cause of death being found, it was held to be due to the single dose of digitalis,—to the reaction following or succeeding to

the action. It is often said, and truly, no doubt, that the secondary effect is due to loss of the irritability of the muscular and nervous tissues concerned.

The action of digitalis as a cumulative poison being thus cleared up, as I view it, the manner in which it may be supplemented in the performance of its special work can now be the better understood.

Being slow to act, in cases of emergency the question arises whether some remedy can be used that will speedily affect the cardiac system and maintain the action until digitalis can fill the place. There are several that can be employed as substitutes during the slow diffusion of digitalis. Of these sparteine is the best, but convallaria or strophanthin may be used. In my judgment sparteine is that remedy that may be most properly applied under these circumstances. One to two hours—even less—will suffice to procure its full action, and digitalis at once begun will have asserted itself in accordance with its own law of diffusion at its usual time. The substitute can then be withdrawn.

When digitalis causes nausea and vomiting, or sets up a troublesome diarrhœa, one of those cardiac remedies having stomachic properties should supplant it. The cases of mitral disease with general dropsy are those in which the action of digitalis is most beneficial. Strophanthin is the most directly useful of these remedies in cases of obstruction of the aortic orifice, with mitral lesions and dropsy, and in cases where the tension of the vessels is abnormally high.

In a case of weak heart with a low state of the circulation, atheroma of the vessels, and general feebleness, nowadays, digitalis is supposed to be the remedy most efficient in its capacity of "heart-tonic," and it is given in the ex-

pectation that the organ concerned will be toned up, rejuvenated, or regenerated by its peculiar impression. Nothing can be more illusory than this. When digitalis comes to act under the conditions just described, the vascular tonus is raised and the heart made to beat more energetically. To put on the brake, as it were, in some cases of this kind, in this fashion, is to endanger the anatomical elements. The fatty heart or the lesions of myocarditis may not be able to bear the strain thus suddenly imposed on them, and the high tension increases materially the work of the heart in keeping up the circulation.

The remedy for the weak heart, *cæteris paribus*, is strophanthin, which strengthens the heart and imposes no additional labor by raising the vascular tonus, which, according to some, it does not do at all, and, according to others, it exerts this power to a very slight extent.

In the conditions of pulmonary œdema, asthma, and bronchitis the most useful of these remedies* is strophanthin, and it is more appropriate as a remedy for renal or cardiac dropsy than digitalis, sparteine, or adonidin, when the tension of the vascular system is already high.

It has been used successfully in the treatment of dyspnœa, bronchial and cardiac asthma (Coulder). Pleurisy also has been successfully treated by it.

Strophanthin has considerable diuretic property, but it is somewhat uncertain in its action. As it affects the blood-pressure so little, and by many authorities is considered to have no influence over it, whatever power it has as a diuretic, we conclude that it stimulates renal action by virtue of an inherent property. That such an influence on the renal structures is inherent is rendered more probable by

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* Budd, The London Lancet, September, 1887, p. 123.

the instance related by Hutchinson, in which a cure of renal colic was speedily effected, and in this case, also, the diuresis was prompt and copious. Increased diuresis is so slowly brought on after the first exhibition of digitalis, that when quickly-acting measures are necessary, such remedies as strophanthin, sparteine, adonidin, or convallamarin should be prescribed to induce the action and maintain it until the power of digitalis is exerted.

Strophanthin seems to have an anæsthetic or analgesic and hypnotic action which are not possessed by the other members of the group, except it may be by convallamarin.

The diuretic property of sparteine is a *vexata quæstio*. As, however, there is another alkaloid in scoparius, which was isolated by Stenhouse at the same time that sparteine was found, the diuretic property may be due to the *scoparin*, whilst sparteine exerts its chief efforts on the circulatory system. Some deny the possession of the diuretic property, and by those most strongly urging their belief in its power in this respect it cannot be regarded a certain and effective one, although in some instances it is reported that it acted freely as a diuretic.

As *scoparin*, the glucoside contained in the plant with the other alkaloid, sparteine, is an active stimulant of the kidneys, and sparteine is a remedy for cardiac derangements, the combination seems a natural arrangement for giving relief to maladies in which both heart and kidneys are involved.

Adonidin, although not so prominent a remedy as the others, is growing in favor. It has effects on the heart in every way comparable to those of digitalis, but it is free from the local irritating qualities and the after-effects which render the use of digitalis offensive to many patients. Besides these points of superiority, it should be

mentioned that adonidin has no cumulative action, and promptly diffuses into the blood, its physiological effects being manifest within an hour.

The diuretic effect of digitalis, of sparteine, convallamarin, adonidin, etc., it is generally held, is a result of the increased blood-pressure, in consequence of which a physiological congestion is kept up in the renal vessels, especially of the vessels of the glomeruli. However, it has been shown by Brunton that digitalis increases diuresis by virtue of an action quite independent of the blood-pressure: it is an inherent quality.

As regards the dosage of the several members of the digitalis group, the following may be considered accurate for adults:

Digitaline, German and soluble, $\frac{1}{60}$ to $\frac{1}{20}$ of a grain.
Sparteine sulphate, $\frac{1}{100}$ to $\frac{1}{40}$ of a grain.
Convallamarin, $\frac{1}{20}$ to $\frac{1}{10}$ of a grain.
Strophanthin, $\frac{1}{150}$ to $\frac{1}{80}$ of a grain.
Adonidin, $\frac{1}{20}$ to $\frac{1}{10}$ of a grain.

COCAINUM: COCAINE.

An Alkaloid obtained from Erythroxylon Coca.

HISTORY AND PROPERTIES.—No remedy in modern times —probably in any age of the world—has become so famous in so short a time as cocaine,* and no remedy has so soon been subjected to the tests of physiological experiment and clinical observation. The preparations of coca have been used more or less for several years, but the alkaloid, co-

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* Neumann, of Vienna, in Dujardin-Beaumetz, Dict., tome ii. p. 46.

caine, received but little attention, and it was not until Koller,* of Vienna, demonstrated the nature of its action before the Ophthalmological Congress that the world came to know of its local anæsthetic power; and it was on the eye that the first experiments were made to demonstrate its action, and the eye has been the seat of most of the improvements subsequently arrived at.

Cocaine has a decided basic property and readily combines with acids to form salts, as the hydrochlorate, the sulphate, etc. Hydrochlorate occurs in two forms: small rhomboid and large crystal plates, and rhombic needles. It has a bitter taste, and is freely soluble in water and still more soluble in ether. After a few minutes a sense of numbness comes on, and the tongue and lips have a swollen feeling, are stiff, and are not readily moved to execute the movements of voice and speech.

The hydrochlorate is the salt usually prescribed now, but what part the hydrochloric acid contributes to the combination, except a somewhat higher proportion of the alkaloid than the other mineral acids, is not evident, but that is no doubt a sufficient reason. The dose varies with the age, weight, and general bodily vigor, and especially with the idiosyncrasies of the subject. Some persons are so exceedingly susceptible that the minimum dose will cause the most serious depression of the vital powers; others take an enormous quantity without a sensible disturbance of any function.

The dose of cocaine ranges between $\frac{1}{12}$ and $\frac{1}{4}$ of a grain for hypodermatic injections, and these may be considered as suitable for an adult as the minimum amount when prescribed for administration by the stomach.

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* Ophthalmological Congress Reports. Letter in The Medical Record.

The following formula is suitable for hypodermatic injection:

℞ Cocainæ hydrochlorat., gr. ij;
Aquæ destillatæ *vel*
Aquæ chloroformi, ℥ss. M.
Sig.—Ten (10) minims contain $\frac{1}{12}$ of a grain.

An excellent preparation for hypodermatic use is the solution of cocaine in oil of vaseline. It is perfectly dissolved, is limpid, clear, and remains unchanged in any climate. No organisms develop in it. The solution thus made is rather more energetic as an anæsthetic than the aqueous solution. The following is a suitable proportion:

℞ Cocainæ hydrochlorat., gr. i;
Vaselin. olei, ℥iss. M.
Sig.—Fifteen (15) minims contain $\frac{1}{6}$ of a grain.

Dr. Isidor Gluck finds that the addition of phenol (carbolic acid) removes some of the most serious objections made to the use of cocaine. Phenol prevents the local irritation, the sudden depression of the circulation and of the respiration, and the faintness, and indeed prevents all of the toxic effects when applied in ophthalmic practice. The carbolic acid prevents the changes which take place in a cocaine solution prepared for injection. It is well known that cocaine in solution rapidly undergoes deterioration. These are remarkable facts which should be subjected to the crucial test of clinical observation.

Actions and Uses.—The first analysis of coca that yielded results was that by Neumann, of Vienna, who designated the alkaloid he had discovered—*Cocaine.* Although much had been ascertained by physiological study and clinical investigation, the most important point was overlooked. It was reserved for Dr. Koller, of Vienna,

to demonstrate the anæsthetic property of cocaine when applied to the mucous membrane. When the members of the Ophthalmological Congress witnessed the result attained by Dr. Koller their enthusiasm knew no bounds, and in an incredibly short time the knowledge of the wonderful anæsthetic agent spread all over the world.

The agency of coca leaves in maintaining the vital forces under circumstances of great demand upon them, when the distance traversed or the absence of food renders some support of the kind necessary, are powers long known to be its special property. Those inhabitants of Peru who were compelled to undergo special or extraordinary exertion were in the habit of resorting to coca to support them under these circumstances. Weston, the pedestrian, whilst going through one of his great feats of walking in London, was detected chewing coca leaves for the purpose, as he supposed, of "keeping him up" whilst going through his fatiguing, indeed, rather exhausting, enterprise. The notion that this agent somehow supplied the place of food in keeping up nutrition, and in furnishing needed force for muscular effort, has been for the most part quite disproved. Coca does not take the place of food in supplying the needs of the organism; it lulls or prevents the demands of the various organs and functions, and satisfies the mental attitude, removing the feelings of hunger and fatigue. The necessary force not being produced from the immediate supply of food, is evolved from stored-up materials,—fat especially,—and thus whilst power is maintained, waste goes on in larger measure. The notion for a long time held so fancifully, that coca is a food, cannot now be considered a proper hypothesis; the explanation above given is more in consonance with the facts of to-day.

The loss of flesh in the case of those who take coca in

any appreciable quantity is due largely to the poor appetite and the enfeebled digestion, the latter due in large measure to the action of the cocaine on the mucous membrane causing an ensanguined state and lessened, if not abolished, sensibility; for when the coca is taken into the stomach, or swallowed with the saliva, more or less local effect is inevitable.

The action of cocaine on the heart and great vessels is again representative of that dual action which obtains so largely in the movements of the physiological and therapeutical remedies. Cocaine at first increases action, raises the tension of the arterial system, and increases the work of the respiratory organs. Presently this is followed by its opposite: the pulse becomes slower, the vessels relaxed, and the breathing less frequent and also more shallow. This decline in the force and volume of the reverse movements is coincident with a change in the secretions. The skin, which was warm, becomes cooler as an abundant perspiration appears on the surface; the mouth, before dry, gets to be moist, and an increase in the saliva becomes quite considerable. We may suppose that the secretions of the gastro-intestinal canal likewise change from a restrained and lessened supply to a more abundant production. It has been shown by Reichert that cocaine raises the temperature of normal animals when curarized, but curara raises the temperature of normal animals.

In the case of the action of cocaine on the nervous system of animal life, we find that it is affected in a manner similar to the nervous system of organic life: at first the nerve-centres are stimulated to increase the rate of movement; the actions of the muscles become quick, tetanic, and strong, but not sustained. The movements occur with surprising energy and promptness, but they are inco-

ordinate and suddenly arrested. They are tonic in respect to the first movement and clonic at the end. In consequence of these conditions, walking is difficult, and as vertigo is decided, the maintenance of the erect posture is difficult or impossible. The eyes are open more widely than normal; vision is hazy, and objects at a distance are confused in outline, and not infrequently illusions are created. The pupils are dilated somewhat, and the vision for near objects is moved outwardly. There occurs, also, more or less headache, dizziness, and drowsiness. The intelligence seems to be unaffected, unless illusions and hallucinations of sight and sound are developed by the disordered vision on the objects in view; in that case the ideas associated with such illusions and hallucinations may be in disorder, but no fixed delusions are present, nor, indeed, are delusions of any kind a feature of the mental state unless the action be toxic.

After a time, drowsiness, coma, and muscular resolution appear in the order mentioned. Before the period of coma is reached the mind becomes cloudy and confused; there is much roaring in the ears, but the hearing is greatly sharpened, as also the acuity of vision. In a few minutes the mouth becomes more or less anæsthetized and has a swollen feeling, and a nearly total loss of the normal sensibility of the mucous membrane occurs. Soon after a full dose is taken a feeling of nausea comes on and vomiting may occur with great suddenness, and presently be stopped, and the nausea disappears with equal celerity. Cocaine also exerts a stimulant action on the intestines, and soon after a full medicinal dose is getting into action a feeling of tenesmus is experienced and also some uneasiness of the bladder.

Cocaine is eliminated by the kidneys. It appears in the

urine in from five to twenty minutes after it enters the blood, and can be detected by the proper test. In passing out through the kidneys, cocaine exerts a stimulant action at the points of contact with the tissues, as proved by Professor Da Costa and Dr. Penrose,* and it has also, it is probable, a diuretic property of some value, but this is not wholly reliable, and could not be depended on in many diseases. When the doses are large, considerable irritability of the bladder comes on, and an increase of sexual appetite is also manifested, but the power does not seem to be increased.

I now submit a *résumé* of the actions of cocaine: It is crystalloidal in structure, and therefore is rapidly diffusible; in a lethal dose it causes vertigo and headache. At first there is no diminution of intelligence, but presently hebetude of mind, confusion, somnolence and coma, clonic after tonic spasms, or clonic and tonic spasms, hallucinations and delusions, inco-ordination, irregular and spasmodic muscular actions, especially when voluntary muscular movements are attempted, followed by muscular relaxation, paralysis, and resolution. Cocaine is found in the urine, and is eliminated almost entirely by the kidneys.

In cases of poisoning by cocaine the following may be used with success to check the tendency to death: morphine, pilocarpine, atropine, chloral, and probably picrotoxin.

THERAPY.—When the remarkable anæsthetic property of cocaine was first demonstrated, it was immediately used in all parts of the world, and numerous papers and theses were put forth descriptive of its powers. It is no

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* The American Journal of the Medical Sciences, 1889.

small task to collate these and present a satisfactory outline of the subject. I shall call the attention of the reader to those works of a phenomenal or epoch-making character illustrating any point or marking the onset of special events.

Cocaine is chiefly useful because of its topical anæsthetic action. In operations on the eye its utility is great. As it dilates the pupil, exsanguines the mucous membrane and inhibits its function of pain-sense, it is very efficient as an agent for removing the sensibility to pain in smaller operations as performed on the eye, and indeed for the larger operations of the surgeon in general surgery. As it began in ophthalmic practice, it has continued, and yet remains the most important and available anæsthetic for the operations in that field of special practice. As respects its use in eye surgery, it is to be noted that some untoward results have happened within the past few years. It was first observed by Mr. Nettleship at St. Thomas's Hospital, London, that after his operations for iridectomy and cataract there occurred, during a certain season and under some unknown conditions, inflammatory troubles involving the cornea and other parts of the eye. Among these accidents were *panophthalmitis* and two forms of disease affecting the cornea. Cloudiness of the cornea due to interstitial inflammation and a superficial state leading to the formation of ulcers were the forms taken by these accidental seizures, and were suspected, at first, to be due to climatic causes. Other observers have witnessed the same results from (it was supposed) the instillation of cocaine, but Mr. Nettleship * finally came to the conclusion that these untoward results were due to the contemporary

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* Ophthalmological Society's Report, 1885.

use of a saturated solution of boric acid, and not wholly to cocaine.

On the Continent, Schmidt, Rank, Obersteiner, and others had observed various forms of mental disorder brought on by the use of cocaine in applications to the eyes and to the nares and throat.* Also, among the more serious phenomena arising from the use of cocaine were the two forms of eye-diseases referred to above—*panophthalmitis* and *interstitial inflammation*—and external ulcerations of the cornea; but it has been discovered that these results have happened because of the simultaneous application of corrosive-sublimate solution, 1 to 1000.

Paul Bunge† seems to have been the first to ascertain the occurrence of changes in the cornea supposed to be due to cocaine, including *detachment of the retina* and *exfoliation of the external layer of the cornea.*

It should be noted that the changes in the eye due to cocaine arose from its topical application, and no mention is made of the same or similar results arising from the hypodermatic injection. The topical effects are, of course, not the same, but caution is necessary when the subcutaneous injection is practised.

In *neuralgia* of the fifth nerve (ophthalmic division), cocaine, injected as near as is possible without the needle penetrating the nerve, is a remedy of high utility.

Not only as an anæsthetic in minor operations, or in the operations of ophthalmic surgery, has cocaine proved to be a useful anæsthetic, but an amputation of the thigh has recently been made successfully by the local use of cocaine, and without a general anæsthetic agent being given; but

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* Bul. Général de Thérapeutique, tome cx. p. 95.

† The London Medical Record.

an operation involving so much tissue is hardly suitable for such an agent. Phimosis, stricture of the urethra, *abscesses*, *small tumors*, the *passage of a catheter*, *hemorrhoids*, *fistula*, and *irrigation of the bladder* in their treatment involve minor operations, for which cocaine is an anæsthetic of sufficient power. The amount to be given is an important question. As many persons—a point already discussed—have a special susceptibility to its action, no large amount should ever be given at any age until the idiosyncrasy of the individual has been ascertained by the tentative administration of a small quantity. From 2 to 5 grains have been administered during a small operation, and, as Obersteiner narrates, such an amount is only justifiable by the favorable condition of the patient during the several stages of the anæsthesia. In a small operation half a grain may suffice. Instead of delivering the whole amount at one point, it is better to inject part of the solution in one position and in another place the other part. The area of insensibility to pain depends on the amount of medicament made use of and the number of points into which it has been inserted. One grain will benumb two to four inches in extent; but not, of course, of the outer layer of the integument unless inserted beneath it; but acting on the mucous membrane, no injection beneath is required. The fluid, when thrown under the skin, acts on the sensory nerves and filaments beneath, thus inhibiting them and, as it is called, benumbing them. According to the hypodermatic method, only this mode of procuring the necessary inhibition is possible, for no amount of local application to the skin will suffice. Dr. Corning, of New York, has proposed to make use of Baunscheidt's famous needle-pointed counter-irritant machine. In this ordinary needles are arranged in a circle and are fastened to a heavy metallic

base. When the spring by which the needles are operated is drawn back and suddenly released, the dozen or less needles are precipitated into the skin, each making a puncture of a depth regulated before. Through these minute orifices a solution of cocaine will diffuse, anæsthetizing the parts, including the nerves supplying the skin. The diffusion of the cocaine through the orifices just mentioned will be effected the more readily by using the galvanic current. That is another mode of treatment, and is called the cataphoric, in which, without any preliminary making of orifices in the skin, the cocaine in solution is applied to one pole, the other being situated quite near (three or four inches), and it is said that the intervening portion of skin is benumbed. So little faith have I in this apparently scientific method, that I have hitherto refrained from the use of it under any circumstances, but have employed another mode of using galvanism and cocaine that has yielded far better results. For example, in *sciatica* I have applied the galvanic current in the usual way, and have then, at the site of the negative pole (cathode), injected $\frac{1}{8}$ or $\frac{1}{6}$ of a grain of cocaine, and relief that seemed almost marvellous has been obtained. The pain caused by the application of a blister has been promptly relieved by brushing a four-per-cent. solution of cocaine over the blistered surface.

Some of the largest operations, in which it was found impracticable or dangerous to use ether or chloroform, have been performed successfully with the aid of cocaine,—successfully, in having been done without pain. The method consisted in the injection of cocaine in advance of the surgeon's knife. As the amount injected must be large, obviously such a proceeding is extremely hazardous, and several deaths are known to have occurred

because of the injection of as much as 6 to 15 or 20 grains.

Outside the domain of surgery there are various uses of cocaine of considerable importance. In affections of the nose, throat, pharynx, larynx, and adjacent parts cocaine is applied for the relief of inflammatory and painful states, and injected subcutaneously for pain and spasm, beyond the reach of local means, in such maladies as *influenza*, in *asthma* of the spasmodic form, in *singultus*, *whooping-cough*, etc. Some excellent results have been obtained by its use recently in *pseudo-angina pectoris*. Noorden* has prescribed cocaine in two cases of the last-mentioned malady, with "results truly marvellous." The affection ceased immediately on exhibition of a single dose, and in one the cure persisted for four months and in the other for six weeks. In such cases it may be that the tension of the arterial system was low, otherwise such a surprising result could hardly have taken place. Mosler,† of Greifswald, finds it a most effective remedy in *asthma*, especially the salicylate of cocaine.

It has been proposed by Dr. Jones, of Brooklyn, New York, to alleviate the pain and disgust (gagging) necessarily belonging to the use of the stomach-tube. This disagreeable operation, and the practice associated with it, is now, fortunately, on the wane, although some specialists continue to be enthusiastic about its curative capabilities. The operation of passage of the tube is so repulsive to the patient that every resource should be utilized in making it as little disagreeable as possible. Brushing over the inner surface of the mouth, the fauces, and the

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* Berliner klinische Wochenschrift, 1886.

† The Therapeutic Gazette, vol. x. p. 623.

pharynx with a four-per-cent. solution of cocaine affords immense comfort. It is, however, in the author's judgment, preferable to throw beneath the mucous membrane some doses of the anæsthetic at various points. A much less quantity is required to induce the necessary numbness, and hence it is a much safer proceeding.

Various neuroses of the respiratory organs are greatly benefited or cured by the timely use of cocaine. In *hay-fever* (so called) no remedy gives so much relief as cocaine. A five-per-cent. solution sprayed over the mucous membrane of the nares, the fauces, and the chink of the glottis is one mode of making the application, but by no means so effective a method as some of the other plans of treatment. The most effective mode of using the remedy is by subcutaneous injection, the injection being applied under the mucous membrane, at some point nearest the main disturbance of function, or under the angle of the scapula. The more nearly the symptomatology corresponds with the asthmatic paroxysm the more decidedly does this treatment prove curative, or at least beneficial.

Among the numerous cases reported is that of Mr. Watson, surgeon of Westminster Hospital, who suffered in an extreme degree. The cocaine arrested the malady promptly, and soon effected a cure.* When the catarrhal process is limited to the nares, the injection can be made near the angle of the nose. In such cases it is not necessary to give more than $\frac{1}{6}$ of a grain twice a day. In bleeding from the nose, whether due to the catarrhal process or coming on spontaneously, the action of cocaine is more effective than the better hæmostatics.† It is also,

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* The Medical News (Philadelphia), 1885, vol. xlvii. p. 265.

† Ruault, ibid., vol. lii. p. 16.

according to the same authority, an effective agent for the arrest of hemorrhage due to trauma. The explanation of this property is not far to seek: when cocaine is applied to an abraded surface it causes an anæmia,—a contraction of the arterioles,—whereby an exsanguine state results.

Before quitting the maladies of the respiratory tract some reference should be made to the use of cocaine for repressing the pain and loss of blood in cases of removal of tumors from the larynx. Lennox Browne* has had forty cases of this kind in which the use of cocaine proved eminently successful, but the application was merely topical, and was restricted to the part occupied by the new growths.

In *painful stomachal affections* of the neuralgic character, in *irritable stomach* from reflex causes, or the pain and other distresses accompanying the *passage of gall-stones*, no remedy is more efficient, if as efficient, as cocaine by hypodermatic injection. Various reports favor its use in *dysentery*. Dr. R. L. Hinton,† of Arkansas, and Dr. Joseph Winters, of New York, recommend its use, based on personal experiences.

Professor Manassein‡ urges the application of cocaine to prevent sea-sickness. It has proved to be a most useful remedy. It should be begun before going on shipboard,—the day before. From $\frac{1}{20}$ to $\frac{1}{12}$ of a grain should be injected after the exhibition of 1 grain of calomel. When the vessel gets under weigh, and before the ground-swell of the ocean is reached, another dose—somewhat larger if well borne—should be injected.

Some combinations with cocaine deserve attentive con-

* The Lancet, November 14, 1886.

† The Therapeutic Gazette, vol. x. p. 636.

‡ The London Lancet, November 14, 1886.

sideration. A mixture of cocaine and atropine has been proposed for the treatment of *iritis*, and will, probably, prove useful in many kinds of *inflammation*. Such a combination was made use of by the authors of "*stenocardine*" to float a fraud on professional credulity, and although this false enterprise was quickly discovered and proved abortive, the attempt was not without utility in demonstrating the superiority of the two drugs, acting in unison, over the actions of either one alone.

It has been proposed to combine cocaine with antipyrin in the treatment of toothache and neuralgic pains of the jaw. M. Martin* has utilized this combination, and has had much success with it as injected beneath the mucous membrane. The formula employed by him is as follows: Hydrochlorate of cocaine 1 grain, antipyrin 8 grains, and water 20 minims. A point of considerable practical value is suggested here: It has been ascertained that this combination is more effective as a local anæsthetic than the cocaine by itself, and the anæsthetic effect is also more prolonged. It is not an antagonistic action that procures this result; on the contrary, the action is synergistic, or mutually promotive.

Mosso,† in the course of his discussion of the cocaines, gives the following as the antagonists: ether, chloroform, chloral, and morphine; but he finds that the agents known as depresso-motor remedies are, in theory and many in practice, efficient antagonists. In this country and in England the remedy most frequently used in cases of poisoning is amyl nitrite. This has the conspicuous advan-

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* Therap. Monatshefte, 1888, p. 185. Quoted from the Lyon Méd., No. 7, 1888.

† Archiv für experimentelle Pathologie und Pharmakologie, Band xxiii p. 153, *et seq.*

tage that it can be used by inhalation or subcutaneously. The congener of amyl nitrite—nitro-glycerin—can also be administered subcutaneously.

The mode of dying from cocaine-poisoning consists in spastic or clonic muscular movements, and arrest of the respiratory movements either by tetanus or by paralysis. The continued action of the motor centres and of the muscles, which are kept in constant agitation, explain how the paralysis is brought about.

CAFFEINE.

Caffeine is an alkaloid contained in various beverages made use of by the human family,—from coffee, on the one hand, to the tea of China and to the maté of Paraguay, etc.

It is isomeric with the alkaloid *theine*, and reacts to the same tests; so that when caffeine is called for, caffeine is furnished, and when theine is called for, caffeine is furnished alike. They are also identical in physiological effects.

Caffeine is not soluble in water, and cannot, therefore, be used hypodermatically. The best salt of caffeine for this purpose is the *phthalate*, as this dissolves in water in the proportion of 1 to 5, as follows:

℞ Caffeinæ phthalate *vel*
Hydrochlor. *vel*
Hydrobromat., ʒss;
Aquæ destillatæ, ʒiij. M.

Sig.—Each minim contains one-sixth ($\frac{1}{6}$) of a grain. A syringeful, which may be 20 to 30 minims, should contain 4 to 5 grains.

The dose of caffeine necessary to procure curative effects has been variously estimated. Formerly, from ½ of a grain to 1 grain* was held to be the largest that could be given with safety; but at present the dose may be considered safe that ranges from 1 to 15 grains. Huchard† has given 1 gramme (15½ grains) several times in the twenty-four hours, in adynamic states, and with fortunate results.

Actions and Uses.—Caffeine causes locally similar effects to those observed in the case of other alkaloids or glucosides,—*i.e.*, some pain, swelling, urticaria-like, and rarely an indurated nodule which is slowly absorbed or suppurates. If suitable precautions are taken, there need be no local troubles, however, and the only indication of the injection, after a day or two has passed, is a small red point.

A medium dose of caffeine produces no observable effect on a healthy adult, and only massive doses (15 grains) make a recognizable impression in headache, vertiginous sensations, trembling of the voluntary muscles, photophobia, insomnia, and even hallucinations and delirium. Generally some nausea and vomiting occur when the dose is large, especially when administered by the stomach. The disturbance produced by it in the cerebral circulation may be the cause of the vomiting also.

The most important of the effects of caffeine are those on the heart and lungs and on the organic nervous system. There can be little doubt that caffeine stimulates the brain to increased activity; but there is no evidence that the cells of the gray matter undergo changes in their protoplasm, as has been alleged (Binz).‡ Large doses of caffeine

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* This amount—or from ½ of a grain to 1 grain—is stated as the dose in the last edition of this work.

† Revue de Thérapeutique, June, 1889.

‡ Archiv für experimentelle Pathologie und Pharmakol., Band x. p. 31.

impair the conductivity of the sensory nerves and thus prevent the transference of those impulses supposed to induce the sense of pain in the centre of conscious impressions. When the nerves are placed in a solution of caffeine, they become paralyzed. Large doses by the stomach increase muscular action and heighten the reflexes.

Caffeine causes a rise in the blood-pressure, and increases the force and number of the heart-beats.

Schmiedeberg* holds the extraordinary view that the differences of opinion in regard to the action of caffeine on the nervous system are due to the fact that two varieties of frogs had been used in the experiments,—namely, *Rana temporaria* and *Rana esculenta*,—and that, in consequence, the results have varied. Binz,† who has examined into this question with great care, finds that caffeine raises the blood-pressure, but it presently declines, and this rise is accompanied by a considerable excitation of the nerve-centres.

Schmiedeberg's explanation will hardly satisfy those who hold to the rise of blood-pressure any more than those who deny this view. According to Binz the blood-pressure rises when moderate doses are given. Leven says that caffeine increases the blood-pressure and the number of cardiac pulsations. Aubert noticed an increase in the number of pulsations, without any rise of blood-pressure. Again, Dr. te Gempt‡ maintains that caffeine exerts a stimulating action on the respiratory centre and on the heart. He holds that caffeine is indicated when

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* Archiv für experimentelle Pathologie und Pharmakologie, Band ii. p. 62.

† Ibid., Band xxviii. p. 197.

‡ Berliner klinische Wochenschrift, 1888, Nos. 25 and 26. Quoted by Therap. Monatshefte, 1888, p. 516.

the pulse is frequent and weak and arhythmical, and when atelectasis, following bronchitis, is present, and in emphysema because of its action on the respiratory and cardiac apparatus. Judging these differences of opinion according to the ordinary rules, it must be said, I think, that there is little difference in the blood-pressure, whether increased or diminished, and that the weight of evidence is distinctly in favor of the affirmative view.

Binz has shown that caffeine influences the temperature, which rises according to the quantity of the agent given. Whilst medium doses increase the temperature to 0.6° C., large doses cause a rise of from 1° to 1.5° C. Medium doses bring about in a short time a rise of temperature of 0.6° C. These effects are induced without the appearance of paralysis or the production of any lethal symptoms.

It can hardly be doubted that the rise in temperature, as well as the increased cardiac and respiratory action and the greater muscular mobility with heightened reflexes, are the result of stimulation of the various nerve-centres presiding over these functions. It must therefore be regarded as a cerebro-spinal stimulant. For, besides the effects on the cerebro-spinal axis, above referred to, it is a well-known fact that coffee has at the same time a soothing and a stimulating action, which all drinkers of the beverage well know.

The discrepant views of those who have studied the effects of caffeine, mentioned above, have been analyzed, and an attempt made to arrive at truer conclusions by Professor Edward T. Reichert, M.D.,* of the University of Pennsylvania, in a paper published one year ago. After

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* Professor of Physiology. "The Action of Caffeine on the Circulation." The Therapeutic Gazette, May 15, 1890.

an elaborate investigation, he arrived at the following conclusions (abbreviated):

"The pulse-rate may be diminished during the first and second stages of the poisoning, but is usually decidedly increased. According to Hare* this is the usual result of the administration of the empyreumatic oil.

"Arterial pressure during the first stages of the poisoning is generally unaffected or diminished; occasionally a trifling increase is noted; during the subsequent stages it is diminished.

"The acceleration of the heart-beats may be accompanied by no appreciable alteration in the blood-pressure.

"Caffeine diminishes the heart's efficiency for work, arrests it in the diastole, sometimes induces sudden paralysis, and is therefore a cardiac depressant."

There can be no doubt that caffeine has a considerable diuretic property, but the constituents of the urine are altered. Urea and uric acid are both lessened in amount. Thence arises the question as to the part which caffeine has in the nutrition of the body. Does it lessen waste, whilst at the same time the process of oxidation is hindered? The support which caffeine gives in the condition of fatigue, and the removal of the sense of weariness after the work causing fatigue is ended, substituting therefor a feeling of pleasing calm, must be a condition of the nervous system rather than the result of force-production adequate to the needs of the organism in the course of the nutritive interchanges. As urea and uric acid are products of the oxidation of nitrogenous constituents, and are excreted in excess during the action of caffeine, it is certainly an erroneous assertion that remedies of the same source

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* The Medical News, No. 13, 1888.

and character act in any way to prevent waste. Caffeine is essentially stimulating, and whilst it increases the action of the heart and lungs, it also elevates the temperature. It must be concluded, therefore, that it hastens waste by increasing oxidation and movement of the organic functions; that it lessens the sense of fatigue, and apparently removes the effects of increased waste. It can hardly be doubted that such results are the indirect effect of an impression made on the central apparatus of the nervous system.

The diuretic effect of caffeine is, according to Schroeder,* not due to increased blood-pressure, but to a direct stimulation of the epithelium of the tubules of the kidneys. He has ascertained that the diuretic effect is irrespective of the arterial or vascular tension, since the greatest urinary flow has occurred when the pressure was below normal. According to Dr. S. Fränkel,† the diuresis precedes, usually, the rise of intra-vascular pressure and continues after the heightened tension declines.

Caffeine has been supposed to pass out of the system unchanged (Maly and Andreasch‡). Dragendorff,§ on the contrary, maintains that it is for the most part decomposed in its passage through the body, and that it increases the excretion of nitrogen. The increased amount of urinary water dilutes correspondingly the nitrogenous constituents, but at no time is the excretion of nitrogen lessened.

In a case of poisoning by caffeine narrated by Mr. T. Geraty,‖ a lady having an attack of migraine took, on an

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* Archiv für experimentelle Pathologie und Pharmakologie, Band xxii. p. 39.

† Bul. Général de Thérapeutique, tome cxix. p. 470.

‡ Schroeder, op. cit. § Ibid.

‖ The London Lancet, February 2, 1889.

empty stomach, before breakfast, 200 grains of "pure citrate of caffeine." Emetics were given, and the usual means resorted to in such case were zealously applied; but "in a quarter of an hour there had ensued partial unconsciousness, extreme pallor, great depression of the powers of life; the muscles were relaxed, drowsiness supervened; the pulse was slow, soft, and compressible, and the respiration was slow and sighing." A rigor occurred in an hour after the poison was taken. The symptoms disappeared in a few hours.

THERAPY.—The more accurate and extended investigations of the day have had the effect of enlarging the boundaries of caffeine's therapeutical utility.

Its original uses were chiefly as a remedy for *neuralgia*, *insomnia*, *migraine*, *opium narcosis*, etc. More recently it has been successfully used in cases of non-compensated cardiac disease with or without the complication of dropsy. It is also a valuable remedy in *adynamic states*, in such a condition as *croupous pneumonia* which has passed the period of crisis, and when the resolution is postponed; also in typhoid fever, when failure of the heart is imminent from profuse hemorrhage, or the algid condition due to profuse watery evacuations corresponding to that stage of cholera, or arising from any unknown accident.

Caffeine is the more useful remedy because it is not followed by any of the after-troubles belonging to digitalis, nor is it a cumulative poison.

In cardiac diseases the curative actions of caffeine correspond closely to digitalis, and as it does not cause, properly speaking, a distinct rise of tension, it is far safer than digitalis. Again, caffeine has a stimulant effect on the centres of animal and organic life without imposing additional work on the laboring heart by an increase of the

tension due to contraction of the calibre of the peripheral vessels. In my own experience, caffeine has acted admirably in doses of 5 to 10 grains twice each day. The weak and arhythmical heart has taken on tone and regularity. Besides the beneficial stimulating action of caffeine, there are the added advantages of an active diuretic effect, which contributes materially to the curative results in a case of cardiac dropsy.

Caffeine is also made use of in adynamic states with great advantage. Dr. Henri Huchard reports a case of pneumonia in which, after the right, the left side was also invaded; the depression was profound; syncope was constantly threatened, so feeble was the action of the heart; and added to this serious complexus of symptoms was an attack of dysentery of severe type. The patient recovered. Dr. Huchard administered during the space of thirty days ninety-five injections of caffeine of 4 grains each. Other cases of pneumonia, less formidable, received the same injection with evident advantage. In typhoid fever it proved to be highly effective in the adynamia of various sources. It must be regarded therefore as a cardiac and respiratory stimulant of great power and of practical value.

Fränkel* concludes that caffeine should be administered subcutaneously in cases of *collapse* from local disease of the heart. There can be no two opinions on this point if the question is examined into without prejudice.

Caffeine is also a remedy of decided utility in *opium narcosis*. It antagonizes those depressing conditions of the heart and lungs upon which the danger in these cases depends.

It has been ascertained by Carello that caffeine associated

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* Op. cit.

with hypnotics in diseases of the heart greatly increases the quantity of urine discharged, and it is alleged that at the same time the characteristic effects are increased in respect to the functions of the heart and great vessels. The narcotics most useful are chloral and paraldehyde. It must be said that this use of chloral is more than doubtful owing to its depressing effects on the organ in question.

ERGOTA: ERGOT.

The Sclerotium of Claviceps Purpurea.

PREPARATIONS:

℞ Extracti ergotæ fluidi, ℥ss.
Sig.—From five (5) drops to thirty (30) drops, according to necessity.

℞ Extracti ergotæ (Aq.), Squibb, Bonjean, ℥ij;
Aquæ destillatæ *vel*
Aquæ chloroformi *vel*
Aquæ lauro-cerasi, ℥ss;
Acidi carbol., ℥ss. M.

Sig.—Each minim contains ½ of a grain of extract of ergot. It should be rubbed up until the ergotin is suspended, but must not be so thick that it will not flow through the needle of the syringe.

Squibb's instructions for preparing a solution are as follows:

Squibb's Extract of Ergot.—"Extract of ergot is almost entirely soluble in cold water, and represents good rye ergot in the proportion of 1 grain of extract for 5 grains of ergot. Sixty grains of this extract dissolved in 250 minims of water—the solution filtered and made up to 300 minims by passing water through the filter to wash it and the residue upon it—makes a solution which represents

ergot in the proportion of minim for grain, and is of the same strength as the fluid extract of ergot, but is free from alcohol or other irritant substance."

By the same process a much stronger solution can be prepared; for the mere rubbing up to make a solution, it is required only to limit the amount to that quantity which will not leave the solution too thick to pass through the syringe.

In preparing a formula for the prescription of "ergotin" the following solution will be found useful:

℞ Ergotin., ʒij;
Aquæ destillatæ, ℥i. M.

Sig.—Each minim contains ¼ of a grain. The addition of one per cent. of carbolic acid will prevent change for some time.

Aufrecht* reports that he finds the injection of ergot nearly or quite painless, and in his hands no abscesses have followed in ten thousand injections. Also, he advises against the use of alcohol or glycerin in preparing solutions, and recommends distilled water as the only menstruum.

The ergotin of Bonjean is an aqueous extract which contains all the matters soluble in water, and is therefore possessed of the powers for which ergot is prescribed; but not to their fullest extent, it is probable. Soon after Dragendorff and Podwissotzky published their chemical examination and added two new words to the nomenclature of ergot, by naming the new substances *sclerotinic acid* and *scleromucin*, respectively. Tanret, the French chemist, also discovered a crystalline active principle, which he called *ergotinine*, the term ergotin having been appropriated before this by Bonjean.

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* Therap. Monatshefte, May, 1891.

The views of Dragendorff and Podwissotzky had been before the medical public a short time when Kobert's study of the subject appeared, and other new terms were then introduced. To the crystallized active principle found by him he gave the name *cornutine;* to the acids associated with it, *sphacelic acid*, ergotinic acid.

Kobert* finds that Tanret's ergotinine is, of itself, an inert substance, or at least if a given specimen not specially prepared is made use of. Whenever it exhibits active properties, the probability is that it contains cornutine. On the other hand, Tanret makes the statement that whenever cornutine is active, it must contain ergotinine. These eminent men are at cross purposes. It is probable that ergotinine has no action on the uterus, but does affect decidedly the nervous system of animal life. Cornutine exerts a vigorous action on the uterus and is distinctly abortifacient. Sphacelic acid also acts on the uterus, but has a special and destructive action on the walls of the arterioles, and causes exudates from the vessels. This substance is the chief source of the gangrenous action of ergot and other characteristic changes. Recklinghausen examined the pathological alterations caused by sphacelic acid, and his authority must be considered as final on any histological subject. Whilst Recklinghausen saw and described the structural changes caused by sphacelic acid, Grunfeld† found no changes in the vessels and spinal cord, and was therefore at variance with his predecessor in the inquiry.

Subsequent use of cornutine (Kobert) has confirmed the

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* Archiv für experimentelle Pathologie und Pharmakologie, Band xvii. p. 316.

† Virchow und Hirsch's Jahresbericht, 1890, p. 414.

claims of its discoverer, and hence it is well to add to the other formulæ one for this new remedy: *

℞ Cornutin., 0.05 gramme = nearly $\frac{1}{3}$ of a grain;
Aquæ destillatæ, 15 grammes = 231 grains;
Acid. hydrochlor., 4 drops. M.

Sig.—The medium is about 10 milligrammes, the small dose 3 to 6 milligrammes.

In a careful review of the researches above alluded to Langgaard † makes an effort to show the true relations of the various newly-discovered principles of ergot. Kobert finds in ergot two acids and one alkaloid, as already stated: *ergotic* and *sphacelic acids*, and *cornutine*. The sclerotinic acid of Dragendorff and Podwissotzky is an impure ergotic acid. The latter has very powerful effects of a narcotic character, but does not affect the uterus at all. Langgaard holds that the so-called ergotins are merely mixtures in uncertain quantity of the active ingredients of ergot, but the most constant and most powerful ingredient is ergotic acid. The ergotinine of Tanret is found in ergotin as well as cornutine, but it has no action on the uterus, and is not poisonous.

Kobert's sphacelic acid and cornutine both strongly stimulate uterine action and are effective in treating uterine troubles; but the most efficient and the most stable is cornutine in that it acts more powerfully on the uterus than any other agent, and can be preserved for years without change.

These conclusions of Langgaard are in the main warranted by the existing state of knowledge, and it seems to me that they are correct, if I may express an opinion after a limited personal experience.

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* Thomson, Annuaire de Thérap., 1889, p. 245.

† Therap. Monatshefte, 1887, 1888.

Physiological Effects.—Considerable pain, lasting for several minutes, attends the injection of ergotin, and a tumefaction, subsequently sometimes hardening into a firm nodule, may form at the site of the puncture. It is rare, however, for suppuration to occur, if proper care is exercised in the preparation of the solution, and in injecting.

If a moderate dose is injected, there may be no symptoms whatever produced. Frontal headache, transient giddiness, more or less dilated pupils, are produced by full doses in from fifteen minutes to a half-hour. In a somewhat longer time,—an hour or two after the injection,—sometimes quite severe rhythmical pains come on, referrible to the region of the uterus, and undoubtedly uterine in seat. Women experienced in the sensation, spontaneously, liken the pains to those of the first stage of labor. In a case of uterine fibroid expelled from the cavity by the action of ergotin hypodermatically used, severe rhythmical pain always came on in a half-hour after the injection. That these pains are uterine seems highly probable, not only in respect to the example cited above, but because of the unquestionable action of ergot on the parturient uterus. The cases are parallel, for when subinvolution exists, or when a fibroid is contained in the uterine cavity, the muscular development of the organ is sufficient to permit the action of ergotin to take place. On the other hand, ergot unquestionably affects the muscular fibre of the intestine, but in the examples of pain above referred to there was no increased intestinal action.

When considerable daily doses of ergotin are injected, the patients complain of a sense of pressure, with pain and numbness in the muscles of the thighs and legs. They also complain of fatigue on slight exertion, of a sense of

coldness of the limbs at night, especially, and muscular cramps of varying severity and persistence. The bladder, too, or, rather, the sphincter, is kept in a state of spasm when daily doses are administered, so that micturition becomes slow, difficult, or impossible, the catheter becoming necessary in rare instances.

The actions of ergot have been studied by many observers, and their reported observations differ widely, and are often, indeed, diametrically opposed. Faulty methods are frequently responsible for discordant and contradictory views. Thus, attempts have been made to arrive at a knowledge of the influence of ergot on blood-pressure by injecting a quantity of the infusion or fluid extract into the jugular vein. We are told, with a remarkable *naïveté*, that under these circumstances the blood-pressure at first falls and then rises remarkably. Professor Wood admits what Dr. Holmes has asserted with regard to this experiment. Brown-Séquard long ago demonstrated that ergot had the power to contract the vessels, and this fact has since been confirmed by a number of observers at different periods,* and he also asserts that which in itself has a high degree of probability, that the vaso-motor spasm which first comes on is followed by vaso-motor paralysis. The results of the very numerous experiments made are nearly uniform in proving that ergotin causes a rise in the

* Among those who have demonstrated the narrowing of the vessels caused by ergotin are the following: Dr. H. Koehler. Vergleichend-experimentelle Untersuchungen über die physiologischen Wirkungen des Ergotin Bonjean und des Ergotin Wiggers. Virchow's Archiv, Band lx. p. 381. M. Laborde, Gazette des Hôpitaux, March 10, 1877. Dr. A. Wernich, Beitrag zur Kenntniss der Ergotinwirkungen. Virchow's Archiv, Band lvi. p. 505. This research was in part determined by some experiments of Handelin, made under the direction of Schmiedeberg,—these experiments having shown that ergotin causes the blood-pressure to fall.

blood-pressure, a necessary sequence of the contraction of the arterioles.

Ergot exerts an influence on the heart in accordance with that on the arterioles,—it diminishes the number and lessens the power of the heart-beats. A toxic dose arrests the heart in the diastole, not by reason of a poisonous action on the cardiac muscle, but through the agency of the pneumogastric nerves, for when these nerves are divided the heart is not arrested by the same or a larger toxic dose.* Paralysis not due to an action on the motor nerves or on the muscles, and therefore centric in origin, is a result of the poisonous action of ergot on the lower animals. Convulsions are also produced by it. An explanation of these symptoms is afforded in the extreme cerebral anæmia induced in animals by the large quantity of the drug administered.

The following is a summary of the symptoms of *acute ergotism* in man: nausea, vomiting, abdominal pain, dryness of the throat, thirst, anorexia, itching of the extremities, numbness, lassitude, vertigo, dilatation of the pupils, drowsiness, delirium, and stupor, diminution of the force and frequency of the pulse (rarely the opposite state), with tendency to syncope, pallor, and lividity of the face, etc.

Chronic ergotism, witnessed occasionally on a large scale by reason of the consumption of diseased rye as food, exists in two forms,—*convulsive* and *gangrenous*. Generally the convulsive form begins by vertigo, disorders of vision, *tinnitus aurium*, numbness of the fingers and toes, and afterwards of the whole integument. Tetanoid cramps follow, —of the fingers, of the forearms, on the arms, and of the

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* Eberty, Abstract in Schmidt's Jahrbücher, Band clviii. p. 126.

arms against the chest; of the toes, on the palmar surface of the foot; of the leg, on the thigh. The muscles of the thorax, abdomen, and diaphragm are also attacked, making respiration difficult and painful, and inducing attacks like asthma. Cramps of the same character attack the intestine,—the muscular layer,—and pains like colic and diarrhœa ensue, but the appetite continues ravenous. Usually, or at least frequently, the uterus becomes affected, expulsive pains come on, and abortion takes place. The action of the heart is weak and slow, the pulse feeble, the surface cold. At first the spasms are occasional, but they become more frequent, ultimately continuous, resulting in opisthotonos or emprosthotonos. Complete anæsthesia of the whole surface succeeds to the tetanoid attacks, and gangrene in spots of small extent may occur. The organs of sense lose their power to react to their physiological stimuli, and taste, hearing, and smell are abolished. The pupils are dilated, sometimes unequal, and various disturbances of vision ensue. Epileptiform attacks may occur as well as the spasms; delirium sets in, and the poor victim passes into a state of complete insensibility.

The convulsive and gangrenous forms, although clinically separable, are not pathologically very different. The gangrenous form sets in by tingling, numbness, formication, an insupportable sense of fatigue in the members, an earthy hue of the skin, coldness of the surface; nausea, vomiting, and diarrhœa then occur; muscular contractions take place; an eruption of vesicles filled with a dark ichorous fluid appears on one or more extremities; and gangrene, dry or moist, quickly destroys the toes, the legs, the nose, or other parts. Doubtless, not infrequently, owing to the contraction of the arterioles in front, a weak heart behind, and blood containing a great excess of fibrin, sudden co-

agulation of the blood in a large vessel takes place, and gangrene of a member is the result. These are the factors probably concerned in the formation of gangrenous spots of greater or less size.

To enter so largely in the consideration of these topics may seem an unnecessary elaboration, but at the present time so freely is ergotin used, and in such large doses, that any details in regard to the results of its administration should not be omitted.

THERAPY.—The therapeutical uses of ergot are based on the modern conception of its physiological actions.

One of the most effective remedies against *hemorrhage* in any situation not remediable by surgical means is the hypodermatic injection of ergotin. Originally used against *uterine hemorrhages*, it has become generalized in its application to the treatment of hemorrhage in general. Not to enter into tedious details, it will suffice to state that the hypodermatic injection is the most effective way of treating all cases of uterine hemorrhage to which ergot is adapted.

Subinvolution of the uterus, a state of things fruitful of mischief, is most effectively treated by a daily hypodermatic injection of ergotin.* The same treatment used persistently, about twice a week, will cure the so-called *chronic metritis*. Local thickening and *hypertrophy* of the uterine wall just developing into, or well-formed, intramural *fibroids* can be cured in a large proportion, and are being cured since the beneficent discovery of Hildebrandt† was announced. The relative proportion of cures to cases cannot be stated in numbers, notwithstanding the enormous experience now accumulated. Selecting out of a

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* Keating, The American Journal of the Medical Sciences, July, 1873.

† Berliner klinische Wochenschrift, June 17, 1872.

mass of reports, probably no better or more accurate can be found than that of Professor Byford, of Chicago. Of his group of one hundred and one cases, twenty-two were cured, and all the rest, except twenty-one, were more or less ameliorated. Various modes of introducing the agent were employed, and probably not all were treated by the best method, or by ergotin of the best quality. Besides the arrest or diminution in the growth, it is, as Professor Hildebrandt remarks, "of great significance that those distressing symptoms, the profuse hemorrhages, the debilitating serous discharges, and the harassing pains, totally disappear."

Hypodermatic injections of ergotin are also used to effect the expulsion of *polypi* from the uterine cavity. The *hydatid mole* may be most effectively expelled by the same agent.

Hypertrophied prostate, as Professor Langenbeck has shown, may be reduced in size by the subcutaneous injection of ergotin. I have succeeded better, I think, by injecting the lobes of the prostate through the rectum, an expedient which is easily practised. A bivalve rectal speculum must be first introduced; then vessels felt for, and the point for puncture selected, when the needle may be introduced and some five minims inserted. The utmost care must be exercised in regard to each detail, for inflammation and suppuration of the prostate would be a serious addition to the sufferings and hazards of the case. Hemorrhoids that are recent, not previously inflamed, and bleeding in consequence of increase of pressure in the portal system, can be relieved greatly by ergotin injections.

Varicocele, if not too far advanced in respect to the size of the vessels and atrophy of the testis, may be cured by

the injection of ergotin. The needle must be inserted between the vessels, and entrance into a vein avoided,—a fact which must be ascertained with absolute certainty,—and the fluid must be sufficient in amount to diffuse among the vessels. Great pain attends the operation, so great that the patient may faint or suffer considerable shock, and there will be subsequently a good deal of inflammation and swelling, with the usual concomitants of feverishness and pain. An injection of ergotin on the dorsum of the penis in the neighborhood of the dorsal vein is an efficient expedient to promote the vigor of the *erections* when they are not well maintained. Injections in the perineum once a week is an excellent remedy in cases of *spermatorrhœa* with feeble erections and a discharge of mucus from the urethra.

Probably the most efficient means we now possess for the arrest of *hæmoptysis* is the hypodermatic injection of ergotin. It acts promptly, and does not interfere with the simultaneous use of other means of treatment, but the injection is usually sufficient of itself. Numerous cases of hæmoptysis have been reported in the treatment of which ergot was the principal or only agent employed, but the most carefully recorded and instructive series of cases which have come under my observation are those of Dr. Anstie.* His conclusions are as follows:

"We have now established the facts (*a*) of the direct action of ergot in the cases which I have recorded; (*b*) of its superiority in several of these cases to other styptics that had been tried; (*c*) the probability, from physiological analogies, that ergot would act more universally as a checker of hæmoptysis than the routine remedies with

* The Practitioner (London), vol. x. p. 279.

which we are familiar; (*d*) also, that it is perfectly safe for the purpose in view, and in this respect is superior to digitalis, which otherwise resembles it a good deal." These good effects were obtained by the stomachal administration, but Dr. Anstie makes a remark which has been abundantly confirmed since,—"For getting the best results, I can scarcely doubt that the hypodermic injection of ergotin is a decidedly superior method."

Scarcely less important than Hildebrandt's discovery of the value of ergotin in uterine fibroids is the observation of Langenbeck with cases showing the curative power of the ergotin injections in *aneurism*.* Soon after the cases of Langenbeck were reported, Plagge,† of Darmstadt, published a case of traumatic popliteal aneurism, in which the ergotin injections were signally beneficial. In a case of femoral aneurism, Schneider has succeeded by the ergotin injections, and Dutoit in one of the subclavian.‡ I have myself seen remarkable diminution in size and great improvement in condition in a case of aneurism at the transverse arch of the aorta, death being due to other causes entirely. After death the walls of the aneurism were very thick and firm by deposition of successive layers of fibrin, and rupture was not possible. In Langenbeck's and other successful cases the aneurisms treated were on superficial arteries, except that of Dutoit. It has been asserted that these injections are useless in the case of aneurism of the aorta, since this vessel possesses but rudimentary elements of the organic muscular fibre to be acted on by

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* Berliner klinische Wochenschrift, No. 2, 1869.

† Betz's Memorabilien. Quoted in The London Medical Record, vol. ii. p. 87.

‡ Berliner klinische Wochenschrift, 1872, p. 115. Quoted from Langenbeck's Archiv, Band xii.

such an agent as ergot. Such critics overlook the fact that ergot, by slowing the heart and raising the tension of the periphery by contracting the arterioles, brings about the most suitable conditions for securing the coagulation of blood in the aneurismal sac.

In *varicose veins*, Voit* has proposed and has used successfully injections of ergotin in the immediate neighborhood of the diseased vessels.

Enlarged spleen has been cured by the injection practised at any indifferent point,† but preferably under the integument of the abdomen.

The disease *leukæmia*, which is closely connected pathologically with a condition of the spleen, has been cured by Dr. Da Costa, and *exophthalmic goitre* benefited by the same treatment.

Brown-Séquard was undoubtedly the first to use ergot systematically, and from the stand-point of a correct appreciation of the nature of its action, in diseases of the brain and nervous system. It has been used with advantage, hypodermatically, in the treatment of the *acute affections* of the *meninges* of *the brain and spinal cord*, and in *cerebro-spinal meningitis*. It is highly serviceable in these affections if used at the proper time—during the stage of excitation—and before depression comes on, when it is harmful. It ought to be serviceable in those cases of *cerebral hemorrhage* in which the escape of blood occurs slowly and there is a gradually deepening coma.

In the congestive form of *migraine*—flushed face, injected conjunctivæ, quick pulse, severe pain, coincident with each

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* Berliner klinische Wochenschrift, *supra*.

† Dr. Miller, The New York Medical Record, April 15, 1876, and Dr. Da Costa, who was the first, in The American Journal of the Medical Sciences, January, 1875.

arterial pulse—the hypodermatic injection of ergotin is highly useful, and often affords immediate relief. In ordinary *headaches* of the congestive variety, but not in the headaches of anæmia, it is equally efficient and curative. The most ardent and comprehensive advocate for the use of the subcutaneous injection of ergot is Dr. Marino,* who finds it superior to all remedies in *sunstroke*, *tic douloureux*, and *hemicrania*. In *sciatica*, the results of its use are sometimes "brilliant," but it often fails without apparent cause.

Ergot has been prescribed by Da Costa with conspicuous success in the treatment of *diabetes insipidus*. Recently, Laurens† has given the ergotinine with success, hypodermatically, in *diabetes mellitus*. Dehene had injected this alkaloid in some cases of retinal hemorrhage due to diabetes, and with such success that the remedy was immediately applied to the treatment of cases of diabetes. It was found that during the administration of the ergotinine, not only the hemorrhagic extravasations were improved, but the sugar in the urine rapidly lessened, and cures, partial or complete, followed in a comparatively short time. So important a statement, if true, should receive close attention and be made the subject of careful clinical experiment.

M. Christian, in calling attention to the gravity of the epileptiform attacks which occur in the course of general paresis and are the cause of many deaths from this malady, found that in a series of cases the temperature was elevated, reaching 40° C. For the relief of the febrile state and of associated conditions, Christian determined to prescribe the subcutaneous injection of ergotinine. The success of

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* Quoted in The London Medical Record, vol. v. p. 456.

† Bul. Général de Thérapeutique, tome cxix. p. 357.

this measure was surprising, and the result such as to diminish considerably the mortality of *Charanton* (the asylum).

The solution employed was 1 milligramme of ergotinine to 1 cubic centimetre of water, and one or two injections sufficed!

QUININA: QUININE.

The Chief Alkaloid of Various Species of Cinchona.

Salts: **Quininæ Sulphas.** [*Sulphate of Quinine.*]
Quininæ Hydrochloras. [*Hydrochlorate of Quinine.*]
Quininæ Hydrobromas. [*Hydrobromate of Quinine.*]
Quininæ Kinas. [*Kinate of Quinine.*]
Quininæ Hydrobromidum. [*Hydrobromide of Quinine.*]

Quininæ et Ureæ Hydrochloras *vel* **"Quinia Bimuriatica Carbamidata."**

Many have been the suggestions made as to the salt of quinine best adapted to hypodermatic use. Of these but few have survived the immediate trials, proving too bulky or too irritating. As the sulphate is the salt chiefly prescribed in this country, so it became the preparation most frequently given hypodermatically. There are several reasons for its protracted popularity: It has a larger relative proportion of the base; it is more soluble—as was supposed—than any of the other salts of quinine, and is less rather than more irritating to the tissues.

As the sulphate was thus preferred, a solution was proposed that contained more quinine than any other then in use. It was the formula of Dr. Lente, a physician then

practising with great acceptance at Cold Spring, New York:

"℞ Quininæ disulph., gr. l (50);
Acid. sulph., dil., ♏ c (100);
Aquæ font., ℥ i;
Acid. carbolic. liq., ♏ v (5). Solve.

"Place the quinine and water in a porcelain dish over a spirit-lamp; heat to the boiling-point, and add the sulphuric acid, stirring with a wooden spatula. Filter at once into a bottle, and add the carbolic acid. This gives six (6) grains to sixty (60) minims, or one (1) grain to ten (10) minims. Even this solution will deposit some crystals at a temperature of 50° Fahr. and below."

Such were the instructions as given by Dr. Lente.*

The determination of the particular salt to be used subcutaneously is not to be made solely from the degree of solubility; but something is due to the relative proportions of the alkaloidal base, in respect to which the salts vary considerably, as can be seen in the following comparative statement:

Bromhydrate (basic) contains 76.06 in 100 parts.
Bromhydrate (neutral) contains 60.00 in 100 parts.
Chlorhydrate contains 81.71 in 100 parts.
Salicylate contains 68.79 in 100 parts.
Sulphate contains 74 in 100 parts.
(Dujardin-Beaumetz.†)

Of these salts, it is evident that the chlorhydrate stands first because of the greater quantity of quinine contained in it, and next to this comes the bromhydrate, and both of these are comparatively but slightly irritating to the tissues. The chlorhydrate is employed almost exclusively throughout Germany.

Beurmann and Villejean‡ urge the use of the bichlorhy-

* The New York Medical Journal.
† Dictionnaire de Thérapeutique. Op. cit.
‡ Bul. Général de Thérapeutique, tome cxix. p. 68.

drate because it is the most soluble of the salts of quinine, is but little painful, and never gives rise to any local disturbance in the form of inflammatory nodules, abscesses, and other troubles. Their formula contains 5 grammes (77.5 grains) and sufficient distilled water to make up to 10 cubic centimetres. Each cubic centimetre represents 50 centigrammes of bichlorhydrate of quinine.

By the late Professor Gubler, then an authority on these subjects, the hydrobromate was preferred, and this continues to be the favorite with many. The lactate of quinine, the sulphovinate, and other combinations have been urged by their promoters, with varying success. Among these must be named the *kinate*, which comes supported by the high authority of Guy's Hospital, London.

Kinate of quinine is soluble in the proportion of one to four of water. It can readily be obtained by a reaction between solutions of kinate of barium and sulphate of quinine. At Guy's Hospital the strength of the solution used is one to four, prepared according to the following process: "Put into a beaker ʒvi of distilled water and ʒij of kinate of quinia, and heat until the salt dissolves, which it does almost immediately, and then add enough distilled water to make up to ℥i."

The use of so concentrated a solution of kinate of quinine is attended with some difficulty, as the neck and stopper of the bottle become incrusted with a deposit of the kinate, and the syringe used to make the injection must be frequently cleaned.

Recently a new compound salt of quinine has been introduced for hypodermatic injection, and it seems to possess very distinct advantages over all other preparations hitherto proposed. It is "termed *quinia bimuriatica carbamidata*, and is formed by Drygin from a combination of

twenty parts of muriate of quinine, twelve parts of muriatic acid, and three parts of urea. The resulting salt is soluble in equal parts of water.* The trials that have been made of it at Hamburg have proved so successful that it is highly desirable it should be known more widely. A fifty-per-cent. solution has always been employed, and the quantity injected has varied from a half to three syringefuls. The local irritation was in most cases very slight, and at the worst consisted in a circumscribed burning pain, without redness or swelling."

In an editorial which recently appeared in *The Therapeutic Gazette* this compound salt of quinine and urea was asserted to be the best of those in use at the present time for the subcutaneous injection of quinine.

Actions and Uses.—Beside the local irritation, little is to be said respecting the physiological effects of quinine. The solutions of quinine, when injected beneath the skin, excite considerable burning and a zone of more or less intense redness for some distance around the puncture. If care be not used in the preparation of the solution, inflammation will follow at the site of the puncture, matter will form, and possibly a diffuse inflammation of the areolar tissue will ensue. Before I had learned the necessity for caution, a small accident of this kind occurred in my own hands, and several years ago some very bad cases were published as occurring in New Orleans, where, it is said, a *mixture* of quinine sulphate and water was injected under the skin, there being no real solution. Some cases of tetanus have been reported caused by subcutaneous injection of quinine, but there must have existed a peculiar state of

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* Centralblatt für die Med. Wissenschaft, June 14, 1879. Quoted in The Medical Times and Gazette, July 12, 1879.

the nervous system, in which, as is well known, very slight injuries may be followed by this malady, or the most singular carelessness must have been the rule of action during the treatment.

But little systemic effect follows the subcutaneous injection of quinine. The actions are similar in character to those produced by the stomach administration, and, although well known, require some consideration. The physiological facts are stated in the course of the discussion on the therapeutical application of the remedy. Dr. Chasseaud published, in 1862, an account of the great success which he had obtained in the treatment of *malarial fevers*, in the hospital at Smyrna, by the subcutaneous injection of quinine. He ascertained that this agent, administered in this way, had a more decidedly curative power, without occasioning its usual physiological effects, than when given by the stomach. This practice has since been continued with undiminished success at the same hospital by Dr. J. McCraith. Dr. Moore, of the Bombay Medical Service, repeating these experiences, concludes "that 4 or 5 grains of quinine injected beneath the integument are equal to five or six times that amount taken into the stomach."

Not only is the immediate therapeutic effect of the quinine given in this way greater, but more permanent cures thereby result. In one hundred and fifty cases treated in this way, Dr. Chasseaud had but a single relapse. Such has been my own observation.

From 5 to 10 grains, injected under the skin, will suffice to cure an ordinary intermittent. Fevers of the remittent type, and pernicious fevers, will require a larger amount. In those deadly malarial attacks, known as *pernicious*, the efficacy of this treatment is most conspicuous. Much

depends, as everybody knows, upon bringing the patient promptly under the quinine influence; the subcutaneous injection is the quickest and most powerful means of accomplishing this object, except the intra-venous injection. This practice for the permanent cure of malarial infection is exciting renewed interest. Bocelli* has shown by experimental trials that quinine can be injected into the blood-current without doing any mischief to the proper elements of the blood. The white and red corpuscles remain unaltered. It has a toxic action, however, on the *bacillus malariæ*, and when these bodies are present, they yield in from six to twelve hours to the destructive effect of the quinine.

It should be remembered, however, that the action of quinine on the protoplasmic constituents of the blood, and on the amœbiform movements of the white corpuscles, had been demonstrated by Professor Binz, of Bonn, who failed, however, to discover the parasitic form on which, as it now seems to be settled, the morbid complex is dependent, and hence fell short of a complete and final triumph.

If it becomes clear that the intra-venous injection of quinine is an entirely safe procedure, this method of introducing the medicament should be generally employed; for the parasitic form of Laveran being shown to have a causative relation to the disease, nothing could be more exact than the treatment, which consists in so injecting the remedy as to come into immediate contact with the pathogenic parasite.

Recent malarial fevers may be aborted at the beginning

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* Annuaire de Thérapeutique, June 23, 1890. Quoted from Gaz. di Ospitali.

of the cold stage by a full injection, but it is better to anticipate the attack by an hour or two, in order to procure the physiological effects before the onset of the expected paroxysm. It is true that the injection may be administered at any time during the febrile movement, but it is better to anticipate and prevent it. The ultimate cure will depend upon the amount of quinine received by the patient, and not upon the period at which it was administered.

The subcutaneous injection is much more effective also against *chronic malarial poisoning* than the stomach administration, but here we meet with new conditions, requiring other management than the use of quinine. We may confidently expect to prevent the febrile movements by frequent repetition of the injection; but we do not thereby cure the disease, for the changes induced by the long-continued action of malaria, in the liver, spleen, gastro-intestinal mucous membrane, cerebro-spinal axis, must be corrected if we would arrest the morbid complex and destroy the pathogenic power of its parasitic form.

Eulenberg offers the following opinions in regard to the forms of malarial diseases most suitable for hypodermatic injection:

"When gastric disorder is a pronounced feature of the case.

"In the cases of children to whom the bitter taste and large quantity required to accomplish the object are repugnant, the stomach proving rebellious through association of ideas.

"In the cases of poor people and in hospital practice, where, owing to the cost of the drug, economy in its use becomes necessary.

"To these must be added cases of chronic malarial tox-

æmia, and of pernicious intermittents requiring sufficient dosage and the utmost promptness of action."

The antipyretic effects of quinine are constantly made use of in the treatment of continued fevers, as all the world knows, the administration being by the stomach; but Drs. Ravicini,* Bamberger, Eulenberg, Binz, and all of the members of the Berlin and Vienna schools of medical philosophy who maintain the paramount necessity of reducing fever-heat, urge the hypodermatic use of quinine in typhoid. Ravicini combines a minute quantity of morphine with it. He gives three injections daily, making in the aggregate about 70 grains, and this practice he continues for several days. The results are most favorable: the sordes disappear from the mouth and teeth, the headache, meteorism, and gurgling in the right iliac fossa are greatly diminished, the spleen is reduced in size, and the countenance becomes more composed. The disease, although not cut short, is much alleviated, as nearly all convalesce at the end of the third week, or, at most, of the fourth. The morphine, he thinks, affects the nervous phenomena favorably. If the statements are dependable, nothing can be more satisfactory than this mode of treating typhoid. By using the new compound—quinina carbamidata hydrochlorate—there need be no apprehension, which otherwise might be felt as to the effect of an irritant on the tissues of a typhoid-fever patient.

Mr. Hall,† of the British army, serving in India, reports remarkable success in the treatment of *heat-apoplexy* (sunstroke) by the hypodermatic injection of quinine. He reports in all seven cases of a severe type in which this

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* Revista Clinica di Bologna. Quoted in The London Medical Record, vol. ii. p. 324.

† The Practitioner, March, 1876.

treatment proved uniformly and invariably successful. He refers also to the experience of Mr. Waller, of Calcutta, which was equally favorable.

In some cases of *neuralgia* good results have been obtained by quinine, subcutaneously. One notable example of ovarian neuralgia, accompanied by, or caused by, menorrhagia, has been reported, and I can confirm from personal observation the special utility of quinine under these circumstances.

For the general purposes of the antipyretic treatment, quinine stands among those remedies known to be the most effective, consistent with entire safety. It is, however, only in the exceptional cases, such as referred to already, that it is employed, and this subject need not, therefore, be further discussed here.

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3. *Depresso-motors.*

CONINE: CONICINE.

Conhydrine. [*Alkaloid of Conium Maculatum.*]
Cicutine. [*Alkaloid of Cicuta Virosa.*]

Conine, or conicine, represents the activities of the conium, and as conhydrine is merely a derivative, with impaired rather than increased powers, it is better to make use of conine.

Cicutine is identical with conine, or nearly so. The variation, if any such exist, is too insignificant to require separation in any account of their actions and uses.

Conine is an oily, colorless liquid, having an offensive odor, a pungent taste, and is volatile and readily under-

goes decomposition. The alkaloid itself is insoluble, but as combined with acids to form salts it becomes soluble.

The bromhydrate is the form in which it is usually now employed:

℞ Coninæ hydrobromat., gr. i;
Aquæ destillatæ, ℥i. M.
Sig.—Five (5) minims contain about $\frac{1}{90}$ of a grain.

Physiological Effects.—The local effects of the injection are the same as those of other alkaloids. In the largest dose which can be safely administered, it induces sleepiness, vertigo, coldness of the surface, diminished sensibility, and weakness of the inferior extremities. The respiration becomes slower and less full. The pulse diminishes in number and force, falling so much as thirty to forty beats per minute.

In a case of poisoning carefully observed by Dr. Bennett,* weakness of the legs and staggering were first noticed. Loss of all power of voluntary movement next followed. He became unable to swallow, and completely lost his power of vision. "His pulse and breathing were perfectly natural," but at the expiration of a half-hour after this, paralysis of the muscles of respiration had taken place, the action of the heart continuing, but was "very feeble." Meantime his intelligence was preserved, but he was without power of articulation.

In another case of poisoning narrated by Professor Schulz,† there were symptoms of mental disturbance of a mild kind, but involving ideation. In Dr. Bennett's case there was no change in the patient's intelligence, but the power of articulation was lost. Schulz includes "trip-

* Clinical Medicine, p. 413, Am. ed.
† Therap. Monatshefte, 1887, p. 285.

ping speech" among the symptoms, but in the other case the same function was lost. Observations made at different periods may in the course of the toxic action explain the differences noted.

The mode in which conine produces these effects has been elaborately examined by Kölliker and Guttman. The last-named observer has shown that conine does not act on the spinal cord, nor does it destroy the irritability of muscle, but paralyzes the peripheral terminations of the motor nerves. Death is produced by asphyxia—paralysis of the muscles of respiration—and not by cessation of the heart's movements, for these continue after respiration has ceased.

THERAPY.—The remarkable change taking place in the strength of the preparations of conium is the chief cause of that lack of favor which this remedy has had in recent times. Harley* demonstrated the innocuousness of much of the so-called "extract." Some specimens were shown to be inert, and others possessed of little action. Now, however, the salts of conine, the alkaloid, are available, and as this is the chief representative of the power of conium, it may be utilized most successfully by the subcutaneous method.

Conine has been used in the treatment of *asthma* by Pletzer. Although it appears to be a rational remedy, paralyzes the muscles of respiration, and in this way may be supposed to antagonize that condition of things which exists in asthma, experience is not in its favor, and a careful examination of its physiological effects discloses the fact that the influence which it exerts on respiration is a toxic action only. In the treatment of asthma it is not at all equal to morphine and atropine; nevertheless, in cases

* Old Vegetable Neurotics. Article on Conium.

in which these agents disagree, or in which it is undesirable to use them, it may be tried.

Erlenmeyer procured relief, by the hypodermatic injection of conine, to the difficult breathing of *emphysema*. The same authority reports having cured a case of *angina pectoris* by two injections of conine. He therefore recommends it in these affections.

Lorent, influenced by theoretical considerations,—the action of conine on the pulse and respiration,—has employed this agent hypodermatically in *pneumonia* and *pleuritis*, with the effect of reducing decidedly the pulse-rate. It does not appear that this treatment is worthy of serious consideration. In the spasmodic affections of the thoracic viscera, Lorent has had experiences with conine similar to those of Erlenmeyer.

Conine is also one of the numerous remedies proposed for the cure of *tetanus*. Successful cases have been reported, cured by conium administered internally; but we may be permitted to distrust these, since Harley has shown that the extract is entirely devoid of conine, and therefore innocuous.

More recently cases, also entitled *rheumatic tetanus*, have been reported cured. One of these by Professor Demme,* of Berne, who attributes the cure to the hypodermatic injection of conine, was the instance that led Professor Steinhauslin† to employ it in a similar case. It had had the effect of lessening the difficulty of breathing and the general muscular rigidity; it diminished the number and duration of the spasmodic seizures, but dangers of another kind appeared. At the end of forty-eight hours the effects of conine became too strong for the opposing tetanic action

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* Therap. Monatshefte, 1887, Band i. p. 28. † Ibid., p. 278.

on the muscles of respiration, and a sudden attack of suffocation came on, artificial respiration becoming necessary for restoration of the function. The effect in this case should not be attributed wholly to the conine, as an attack of croupous pneumonia was developing.

As conine produces motor paralysis, it has been held to be *antagonistic to strychnine;* but since it has been shown by Guttman that conine paralyzes the peripheral terminations of the motor nerves, and does not act upon the cord, this view must be abandoned. Besides, clinical experience is wanting.

In a careful course of investigation, Burman* has studied the combined effects of conine and morphine on the condition of mania. He finds the combined remedies very useful to allay the excitement of *acute mania.* The indications are intense motor activity and wakefulness as concomitants of mania.

ESERINE: PHYSOSTIGMINE.

Alkaloid of Physostigma Venenosa,—the Ordeal Bean of Calabar.

Eseridine,—a Derived Product of Eserine.

PREPARATIONS.—Formerly the extract was alone available for hypodermatic injection; but now, as *eserine*, the active principle, is known to represent the drug in its entirety, that has been brought into use for this mode of administration. The hydrochlorate is generally employed;

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* The West Riding Lunatic Asylum Reports, vol. ii. p. 1, *et seq.*

but some prefer the salicylate, and this is official in the U. S. Pharmacopœia.

℞ Eserinæ hydrochlor., gr. iv;
Aquæ destillatæ *vel*
Aquæ lauro-cerasi, ℥i. M.
Sig.—Two (2) minims contain about $\frac{1}{60}$ of a grain.

The dose of eserine ranges between $\frac{1}{100}$ to $\frac{1}{150}$ of a grain for adults.

The extract may be utilized for preparing solutions by rubbing it up with distilled water and filtering. The dose of the extract is from $\frac{1}{6}$ to $\frac{1}{2}$ of a grain, but in *tetanus* much larger doses have been given. It is highly important to obtain a genuine preparation of the extract, otherwise disappointment must ensue. Eserine is now almost exclusively used for subcutaneous injection.

Physiological Effects.—The effects of physostigmine and eserine are the same in what mode soever they may be administered, but are more rapid and pronounced by the subcutaneous areolar tissue. When a full dose is administered, giddiness, a sense of weakness and fatigue, and difficulty in maintaining the vertical position and in walking are experienced. The action of the heart and the arterial tension are lowered for a brief period at first, but in a short time the tension rises, and the heart-beats become more vigorous. Toxic doses in man cause death by paralysis of respiration and of the heart, the whole muscular system, including the sphincters, being in a state of complete muscular relaxation, but the consciousness is preserved until carbonic-acid poisoning clouds the mind. It is a paralyzer, but before complete resolution occurs, the voluntary muscular system is agitated by tremors, which consist in alternate muscular contraction and relaxation.

The contractility of the muscles is not destroyed, nor even impaired.* The peripheral nerves (end-organs) and the trunks of the nerves are not concerned in the paralysis, but it is spinal entirely. Physostigmine heightens rather than impairs the sensibility of the sensory nerves. After merely lethal doses have been administered, the action of the heart continues after respiration; but, as already stated, large, toxic doses paralyze the heart in the diastole, and this organ is found after death flaccid, not at all or very feebly responding to galvanic excitation.†

Contraction of the pupil is a constant result of the action of physostigmine, whether instilled into the eye or introduced into the general system. This result is doubtless due to paralysis of the sympathetic fibres and to stimulation of the third nerve.

As respects the intestinal canal, the effects of physostigmine are very distinctive. It increases secretion decidedly, and therefore the number and laxity of the alvine discharges are greater.

THERAPY.—The applications of physostigmine in the treatment of disease are directly deducible from its physiological action. Its principal effect being on the cord, destroying its reflex function, obviously it is adapted to the treatment of conditions in which the reflex function is abnormally excited, as in *tetanus*, *hydrophobia*, *strychnine-poisoning*, etc. A great many cases of tetanus have been treated, chiefly by the extract, and the average proportion of recoveries to deaths is one-half. The result in many more cases would have been as favorable if a better mode of

* Fraser, Transactions of the Royal Society of Edinburgh. W. Laschkewich, Virchow's Archiv, Band xxxv. p. 291.

† Arnstein u. Sustschinsky. (Abstract in Schmidt's Jahrbücher, Band cxlii. p. 286.)

administration had been followed and a purer drug obtained. In tetanus, the ability of the patient to swallow and the absorption powers of the stomach are alike impaired. Hence the hypodermatic method should always be adopted instead of the stomachal. Furthermore, the quality of the extract used in many of the cases was poor, and the quantity prescribed was too seldom governed by the effects produced. Eserine hypodermatically and in quantity sufficient to keep the spasms in check, so that the nourishment of the patient can be efficiently carried on, is the proper mode of treatment in any case of hydrophobia in which this alkaloid is the remedy depended on.

Although theoretically an exact antagonism exists between strychnine and eserine, in actual trial, according to the report of the British Association committee, "although the symptoms produced by either substance were modified considerably by the action of the other, there was no instance of recovery from a fatal dose."

A very perfect antagonism, through almost the whole range of their effects, has been demonstrated by Fraser* to exist between atropine and physostigmine,—only, however, in respect to lethal doses, and not to large toxic doses. The committee above referred to admits that this antagonism exists to a "slight extent," but is "more limited than even Dr. Fraser has indicated." This committee has also shown that "chloral hydrate modifies to a great extent the action of a fatal dose of Calabar bean (physostigmine), and in some instances saves life from a fatal dose."

The use of physostigmine in *epilepsy*, based on theoretical grounds, has not been satisfactory. Of late physostig-

* An Experimental Research on the Antagonism between the Actions of Physostigmine and Atropine. Edinburgh, 1872.

mine by hypodermatic injection has been used successfully in *chorea*. Riess* employed this remedy in forty cases on which he reports. He injected $\frac{1}{64}$ of a grain once a day with entire success. He has also succeeded in *post-hemiplegic chorea*, an obviously difficult kind of case for any mode of management, and in many forms of trembling more or less closely related to chorea it has often proved beneficial, sometimes even curative. In *progressive paralysis of the insane* the results obtained by Browne, although discredited by Williams, justify further trials by the subcutaneous injection of eserine. Agents acting decidedly as paralyzers of the respiratory function, as conium, gelsemium, lobelia, etc., have long been known to act favorably in *bronchitis*, *pulmonary congestion*, and *pneumonia*, and to them must now be added physostigmine, which is reported to have good effects in these diseases.

Next to the use of eserine in tetanus, its most important applications in the treatment of disease are in the field of ophthalmic practice. It is now largely used to counterbalance the effects of atropine on the pupil; in iritis to break away or prevent the formation of adhesions; in ulceration and suppuration of the cornea; after extraction of cataract to prevent suppuration, and in the operation of iridectomy. The curative influence of eserine in these cases is due to its action in lowering the intraocular tension, in diminishing the conjunctival secretions by contracting the blood-vessels, and in checking the migration of the white blood-corpuscles.† To effect these important purposes, eserine is used chiefly by the subcutaneous areolar tissue.

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* Zeitschrift für Therapie, October, 1884.

† Weeker on Eserine, Pilocarpine, and Atropine in Ophthalmic Diseases, Bul. Général de Thérapeutique.

According to Eber,* *eseridine* is a new alkaloid which has existed preformed in the bean. Recent experimental evidence tends to show that this derived alkaloid is inferior to eserine in respect to physiological activity and therapeutical applications.

It acts with some efficiency when given to the horse by the subcutaneous method, and causes abundant watery stools. In man it has in common with eserine similar properties, but it is distinctly less active than its progenitor.

CURARA: WOORARA.

An Extract made from Several Varieties of the Strychnos Family, Strychnos Toxifera and others, it is supposed.

CURARINE.

An Alkaloid obtained from Curara, and, being more Stable in Constitution, is more fit for Subcutaneous Injections.

℞ Curaræ, gr. i;
Aquæ destillatæ, ♏100. M.
Sig.—Each minim contains $\frac{1}{100}$ of a grain.

As this extract is made up of vegetable as well as animal matters, and has distributed through it various impurities, it is necessary to form some estimate of its activity before giving it in disease, lest an accident occur, or it were better to act more judiciously and make use of the alkaloid curarine. It has been asserted, also, that curarine is uncertain in power and activity; but such variations are due to the pharmaceutical processes.

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* The Therapeutic Gazette, 1889, vol. xiii. p. 36.

The active principle—curarine—had better be employed in place of curara. In the form of sulphate it is readily soluble in water. The dose is $\frac{1}{200}$ to $\frac{1}{100}$ of a grain. The solutions should be carefully filtered, especially those of the crude drug.

Physiological Actions.—The actions of curara have been investigated in the most thorough manner by Bernard, Kölliker, Kühne, and others. It is a necessary part of the equipment of a physiological laboratory since Bernard* made his historical observations on its action.

Curara is locally an irritant. If the solutions are carefully prepared, no little pain and smarting are felt at the point where the injection is made,—inflammation follows, an abscess forms, and an ulcer remains. This is not a constant, but a common result, and should be mentioned before the injections are practised.

Applied to the unbroken skin or mucous membrane no effect follows. Introduced into the stomach it rarely produces any toxic symptoms, although it is probable slow absorption may take place, and ultimately characteristic effects appear. Applied to a denuded surface, or subcutaneously, diffusion into the blood is rapid. It is a paralyzer of the nervous system of animal life. An early symptom is disturbance of vision, strabismus, double vision, ptosis,—the upper eyelids falling well over the eyes. Next, weakness of the lower extremities (paresis) comes on, extending ultimately to all the voluntary muscles. Death ensues from paralysis of the respiratory function. The paralyzing action of curara is not in the muscles, for they retain their Hallerian irritability, but in the terminations of the nerves

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* Leçons sur la Physiologie et Pathologie du Système Nerveux, tome i. p. 196.

in the muscles,—the end-organs of the motor nerves. It is this complete paralyzing action, involving the nerves only, and leaving the muscles intact, that renders curara such an important agent in physiological research.

The careful experiments of Hammond and Mitchell * on two varieties of curara—*carroval* and *vao*—throw some important light on the subject of the action of curara. The two varieties were similar in mode and character of action, but differed in power,—vao being much feebler. In their experiments, death was caused by paralysis of the heart, its muscular tissue having lost contractility.

According to the observations of MM. Voisin and Lionville,† when curara is injected subcutaneously, a state of shivering and feverishness, trembling, a rapid and weak pulse, sweating, quickly follow. In a few minutes the paralysis begins, and extends to all the voluntary system. If pressure by a ligature is made above the point where the poison is inserted, its entrance into the general mass of the blood is impeded. If artificial respiration is maintained in animals, death may be averted, even when a lethal dose has been given, so rapidly is it eliminated by the urine, which, indeed, may be actively poisonous. Distinct traces of sugar are also found in the urine, whence the condition is entitled "curara diabetes." ‡

THERAPY.—When the first publications were made, setting forth its peculiar action, very confident hopes were entertained that a specific for *tetanus* had been discovered. It failed in the hands of Follin, Gintrac, Cornoz, and Richard, and was successful in the hands of Gherini, Demme,

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* The American Journal of the Medical Sciences, July, 1859.

† Archives Général de Médecine, October, 1866.

‡ L. Hermann, Lehrbuch der experimentallen Toxicologie. Berlin, 1874, p. 305.

Lochner, and Spencer Wells.* In most of the successful cases it was used endermatically as well as hypodermatically. Of twelve cases treated by the hypodermatic injection, four terminated favorably. According to the statistics of Demme, of twenty-two cases treated by curara, administered in either mode, eight recovered. Professor Busch treated eleven cases of tetanus by curara, and six recovered; but, as the professor thinks this agent is adapted only to the more chronic cases, our estimate of its value must not be too high, for chronic cases often terminate in recovery under the most diverse methods of treatment.

In the successful cases, large doses of curara were administered. Spencer Wells injected $\frac{1}{12}$ of a grain at a dose. The dose ranges from $\frac{1}{60}$ to $\frac{1}{30}$ of a grain. The frequency of administration will be governed by the effects upon the spasms.

Curara has also been used in *strychnine-poisoning*, but without sufficient success to justify its employment in this class of cases. It does not bear the relation of a physiological antagonist to strychnine, and hence should not be used against the toxic symptoms caused by this agent.

Although the reports are contradictory in respect to the utility of curara in *epilepsy*, it yet deserves a more careful trial than has been accorded it hitherto. Kunze† advocates its use, and reports that in many cases marked improvement followed its administration. He practised the injections once a week, using $2\frac{1}{2}$ grains each time, and this quantity he says produces no distinct physiological effects. Of thirteen old epileptics, three were cured by this treatment.

Dr. Watson‡ reports a case, which he diagnosticated

* Eulenberg, op. cit. † Deutsche Zeitsc. für prakt. Med., 1877, No. 1.
‡ The American Journal of the Medical Sciences, July, 1876.

hydrophobia, an opinion in which Professor Flint concurred; but recovery ensued after the hypodermatic injection of curara. The first dose was $\frac{1}{16}$ of a grain, and subsequently $\frac{1}{9}$ of a grain and $\frac{1}{6}$ of a grain were injected. The details of the case are well and accurately told, and the conclusion seems entirely justified.

An Italian case of hydrophobia has been reported cured by curara. Injections of morphine and inhalations of chloroform had been used without success. Then curara was administered until paralytic symptoms occurred, when it was suspended. Then the symptoms of hydrophobia recurring, curara was used again with like success.*

AMYL NITRITE.

Nitro-glycerin. [*Glonoium, Liquor Trinitrin, etc.*]
Sodii Nitritum. [*Nitrite of Sodium.*]

This group of medicinal agents consists of nitrites, which agree in the "character" of the actions produced by them but not in the "degree."

Being an extremely volatile and diffusible substance, it is difficult to preserve and use amyl nitrite. When administered in vapor by inhalation, the usual mode of giving it, the form of *perl*, or of solution in alcohol, is sufficiently convenient. For subcutaneous injection the agent itself is used,—from 2 to 5 drops being given at a time.

Nitro-glycerin is used in the form of a solution in alcohol having the strength of one per cent.,—one minim of nitro-glycerin to one hundred minims of alcohol. It is this solution which is known as "Liquor Trinitrin,"

* La France Médicale, August, 1879, p. 541. From Indipendente.

"Glonoin," etc. The initial dose is 1 minim, increased at each dose, or each day, by a minim until the characteristic effects are felt by the patient,—flushing of the face, headache, dizziness,—all of the most transient character, and all disappearing at the same time or in seconds, merely, after appearing.

The effects of amyl nitrite, when given by the hypodermatic method, are similar to but less rapid than by inhalation. The actions are uniformly the same. Increased movement of the heart; lowering of the arterial tension; flushing of the face; fulness and distention of the head, and headache sometimes very violent; singing in the ears; vertigo, confusion of mind, and even unconsciousness, result from the inhalation of the vapor. Whilst these effects occur as the inhalation is proceeding, when thrown under the skin an interval of appreciable duration is observed before the action begins. The dilatation of the vessels, a result of the paralyzing action exerted by amyl nitrite on the vaso-motor system, is the central fact of its physiological powers, for on this depends all the other phenomena. The applications of the remedy are based on this property. Although inhalation is a convenient mode of administration, it is not proper when the respiration is failing, or when irrespirable gases have filled the pulmonary vesicles. Consequently, the subcutaneous injection of amyl nitrite may be of immense utility in failure of the heart and of the respiration, in cases of *angina pectoris, chloroform narcosis, surgical shock, cholera asphyxia*, and allied states. The indication is to take off the vascular tension, and the result is the heart is freed from restraint. Dr. F. A. Burrall, of New York,* states that he has "a record

* The New York Medical Record, March 25, 1882, p. 335.

of nine cases, in all of which impending death from chloroform seems to have been averted by nitrite of amyl" administered hypodermatically.

LOBELINE.

An Active Principle derived from Lobelia Inflata, of this Country, and Lobeliæ Nicotianæfolia, of Madras.

These lobelia plants contain two alkaloids,—one a liquid which is lobeline, and the other a solid alkaloid which has a decided emetic quality, but agrees with the liquid alkaloid in properties.

PROPERTIES OF LOBELINE.—The alkaloid lobeline is an oily substance of a yellowish passing into a reddish-brown color, which becomes darker on exposure to air. In physical qualities lobeline resembles *nicotine*, the active principle of tobacco. As the alkaloid is unsuitable for hypodermatic injection by reason of its insolubility, the sulphate, which is freely soluble, is employed for this purpose.

Much difference of opinion exists as to the dosage which shall be both efficient and safe. Murrell holds that $\frac{1}{100}$ to $\frac{1}{60}$ of a grain are the proper gradations of strength to be used by hypodermatic injection; when given by the stomach a larger quantity—about one-third more—can be administered. It is conceded on all sides that lobeline is more suitably, as it is more effectively, given by subcutaneous injection.

Lobeline is a depresso-motor and to a slight extent a sensory depressant. It lessens and ultimately suspends

the reflex functions, causes numbness and tingling followed by paresis of the lower extremities, and, like curara and nicotine, paralyzes the end-organs of the motor nerves first, the paralysis thence extending to the cord. It affects the muscles of respiration in a similar manner,—first weakens and ultimately paralyzes them, so that death occurs by failure of respiration, the lungs ceasing to act before the heart (Dreser*). With the approach of death, tetanic spasms seize the voluntary muscles, and fibrillary trembling occurs in the intervals of the muscular attacks.

At first, lobeline raises the arterial tension, but it soon falls again, passing, indeed, below normal. The heart's action increases, and the rate of pulsation goes considerably above the normal, this result being due to paralysis of the pneumogastric and the consequent removal of the inhibition; finally, the heart's action is arrested in the diastole and the cavities are found fully distended.

During the period of maximum activity the skin grows warm and a more or less profuse sweat breaks out over the whole surface. How much of this is a mere relaxation of the skin, due to the nauseating effect of the lobeline, has not been stated, nor has it been estimated.

Excretion of lobeline takes place through the kidneys. In its passage through these organs, lobeline or some of its products stimulate the secretory activity of the organ, and the flow of urine is increased. By some lobelia is regarded as a diuretic, so constant a phenomenon is the larger quantity of urine discharged after its exhibition.†

In its *therapeutical applications* lobeline is restricted to the

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* Archiv für experimentelle Pathologie und Pharmakologie, 1889, p. 237.

† Merck's Bulletin, March, 1890.

treatment of spasmodic diseases. Especially in *asthma* has lobelia long been considered a valuable remedy, although known to lose its effects by repetition. The alkaloid, or rather its salts, are given, of which the sulphate is preferred. Administered hypodermatically, the effects can be obtained with $\frac{1}{100}$ to $\frac{1}{60}$ of a grain, according to Murrell, but larger doses are necessary if decided effects are to be produced. According to Nunez,* it is safe to give in pill form from $\frac{3}{4}$ of a grain to 6 grains in twenty-four hours. Nevertheless, it may seriously be doubted whether a daily dose of 6 grains be safe, since Dreser, in a criticism of Nunez's statement, says respecting his own experience, "Von gutem Merck'schen Lobelin aus Samen möchte ich 40 cg. (6 grs.) am Menschen sicher nicht riskiren." As the subcutaneous injection of lobeline is much more effective than the stomachal and much more decided in therapeutical property, it is necessary to have a clear notion of the dosage required. As in the case of children the dose given has ranged between $\frac{1}{10}$ and $\frac{7}{10}$ of a grain, and so much is clear, that 1 grain will not prove too much for adults, provided smaller doses—$\frac{1}{12}$ to $\frac{1}{6}$ of a grain—are given until the physiological susceptibilities of the patient are ascertained; for idiosyncrasy plays so large a part in the action of medicaments that its influence should always be measured, if possible.

Besides asthma, cases of bronchitis after the acute symptoms have subsided, of emphysema with spasmodic seizures, and the neuroses of the respiratory organs in general are benefited by lobeline suitably administered by subcutaneous injection.

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* The British Medical Journal, 1889, p. 1051. Quoted by Therap. Monatshefte, 1890, p. 190.

NICOTINE.

An Alkaloid obtained from Nicotiana Tabacum.

It is an oily liquid, colorless when fresh and pure, with little odor, but a pungent taste, leaving in the throat an after-sense of acridity with constriction.

It is feasible to prepare a solution from the alkaloid itself, and Dujardin-Beaumetz suggests the following formula:

℞ Nicotine, 1 gramme;
Aquæ destillatæ, 1000 grammes. M.

Sig.—Each gramme of this solution contains one (1) milligramme of nicotine.

So powerful is nicotine that the initial dose should not exceed 1 milligramme, or $\frac{1}{100}$ of a grain.

Physiological Effects.—Nicotine is one of the most deadly poisons, ranking in this respect with prussic acid. In its local action it is somewhat irritant. In its remote or systemic action it strongly depresses the nervous and vascular systems. At first respiration is slightly accelerated, and is accompanied by a bruit, produced, according to Bernard, by a very abrupt contraction of the diaphragm. Slowness and feebleness of respiration soon succeed to this acceleration. The pupils dilate, and convulsive phenomena make their appearance in the eyes and extremities, partly of a clonic, and partly of a tonic or tetanic character. Complete adynamia supervenes, accompanied by muscular trembling; the action of the heart becomes exceedingly feeble, and death takes place by failure of the circulation (paralysis of the heart).*

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* Vulpian, Med. Tox. Article on Nicotine.

THERAPY.—Nicotine has been employed with success in the treatment of *tetanus*. About one-half of the traumatic cases treated with it get well,—a proportion of recoveries greater than with any other remedy except physostigmine.

Professor Houghton, of Dublin, who was probably the first to employ this agent in tetanus, ascertained experimentally that it is a physiological antagonist to strychnine. More recent investigations have shown that this antagonism is partial only, and cannot be depended on in the treatment of poisoning.

Nicotine is indicated in *spasmodic asthma*, certain cases of *angina pectoris*, *colic*, *strangulated hernia*, etc., but I know of no instance in which it has been used for the relief of these conditions.

Cases of obstinate *convulsive tic*, "*histrionic spasm*," and local *muscular spasm* are of a nature, theoretically speaking, to be benefited by the subcutaneous injection of nicotine.

HYDROCYANIC ACID.

THE SOLUTION AND DOSE.—The *Acidum Hydrocyanicum Dilutum* of the U. S. Pharmacopœia is the preparation which I have employed for hypodermatic use. The maximum quantity which I have used is 4 minims, but this amount may not be safe in many cases. It should not be forgotten that the action of hydrocyanic acid is so rapid that a toxic dose introduced under the skin would infallibly destroy life before any measures could be employed for relief. For ordinary purposes, 2 minims of the official solution will be sufficient for hypodermatic injection.

As its effects are quickly expended, it may be repeated frequently,—as often as every two hours.

Physiological Effects.—Locally, the effects are somewhat irritant, but are not more so than a solution of morphine. A metallic taste, slight salivation, faint nausea, giddiness, and sighing respiration are the only systemic effects which I have observed from the doses I ventured to administer.

Therapy.—The good effects sometimes produced in *mental disorders* by prussic acid, when administered by the stomach, are more conspicuously exhibited when the remedy is injected under the skin.* It is adapted to acute cases, in which power is in excess. Cases of mania or melancholia, in which the subcutaneous injection of morphine proves hurtful, are benefited by prussic acid, and *vice versa.*

I have used hydrocyanic acid hypodermatically in spasmodic asthma, but without moderating the paroxysms. It is indicated in *angina pectoris* and other cardiac neuroses, but I am not aware of any instances in which it has been tried.

As a remedy for *gastralgia* when a simple neurosis of the stomach, it is undoubtedly useful. In *nausea* and *vomiting* due to functional disturbance, and especially those cases in which morphine and atropine disagree, it may be used with a confident expectation of affording relief. But, as a general practice, the subcutaneous injection of prussic acid in those stomach disorders is, in respect to promptness and efficiency, greatly inferior to other remedies now available for this mode of treatment.

The injection may be practised over the epigastrium in cases of vomiting.

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* McLeod, The Medical Times and Gazette, March, 1863.

W. Preyer,* who has carefully investigated the physiological action of prussic acid, affirms that atropine is a physiological antidote. His researches have conducted him to the conclusions that prussic acid acts by depriving the blood of its oxygen, and that in very large doses it paralyzes the heart. He considers atropine the antagonist to this action by maintaining the action of the heart. I have carefully repeated the experiments of Preyer, and am unable to confirm them.† I find that animals (cats) fully under the influence of atropine are speedily destroyed by poisonous doses of prussic acid,—just as speedily, indeed, as if atropine had not been administered. If administered simultaneously, or atropine soon after prussic acid, the result is the same.

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* The Practitioner, vol. i. p. 106.

† Prize Essay of American Medical Association, for 1869, on Atropine.

C. AGENTS ACTING ON THE GASTRO-INTESTINAL CANAL.

Emetics.

APOMORPHINE: APOCODEINE.

Apomorphine. [*An Alkaloid derived from Morphine.*]
Apocodeine. [*An Alkaloid derived from Codeine.*]

Apomorphine is obtained from morphine by heating it in closed tubes with hydrochloric acid. An atom of water removed from morphine leaves *apomorphine*, and hydrochlorate of apomorphine is formed by the combination of the alkaloid with the hydrochloric acid.

Apocodeine is procured from the principle in opium called *codeine*, by acting on it, in closed tubes, with zinc chloride. The result here is the same as in the former case,—*i.e.*, an atom of water is removed and *apocodeine* remains, and this may be combined with an acid forming any desired salt: as, for example, with sulphuric acid, forms sulphate of apocodeine.

The following recipes are suitable for hypodermatic injection:

℞ Apomorphinæ hydrochlorat., gr. ij;
Aquæ destillatæ *vel* aquæ chloroformi, ℥ i. M.
Sig.—Fifteen (15) minims contain $\frac{1}{15}$ of a grain, nearly.

℞ Apocodeinæ hydrochlorat., gr. ij;
Aquæ destillatæ *vel* aquæ chloroformi, ℥ i. M.
Sig.—Dose, fifteen (15) to twenty (20) minims.

Dr. Gee * made the first proper study of the physiological actions of apomorphine. He ascertained that it has emetic property, and that its action is characterized by suddenness in coming on, and efficiency. In a few minutes after the injection is practised some nausea, giddiness, and headache are experienced and vomiting occurs abruptly and thoroughly in from five to twenty minutes. At the first effort the stomach is well emptied; but the vomiting recurs a few times at intervals of a quarter- to a half-hour. Such is the ordinary course of action of a sufficient but still small dose. If a full dose is given by the subcutaneous areolar tissue, there occur headache, vertigo, nausea, a cold sweat, a quick, small, feeble pulse, depression and drowsiness, and profuse vomiting, followed by prolonged sleep.

A very alarming condition of depression—a state of collapse, indeed—has been caused in children and inebriates by the hypodermatic injection of a full dose. Toxic doses in animals cause at first great excitement, vomiting, followed by muscular trembling, paralysis, and convulsions.† It does not seem to affect the blood-pressure,‡ nor the motor and sensory nerves; the respirations at first greatly increase in number, but ultimately become more shallow and infrequent, death occurring from paralysis of the respiratory function. §

The dose to procure emesis, in giving apomorphine by the stomach, must approach the toxic to bring about the result with certainty; whilst administering it subcutane-

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* St. Bartholomew's Hospital Reports, 1869, vol. v.

† E. Harnack, Archiv für experimentelle Pathologie und Pharmakologie, Band ii. p. 291.

‡ Siebert, Schmidt's Jahrbücher, Band cxv. p. 14.

§ Transactions of the Royal Society, vol. xvii. p. 460.

ously, the ordinary dosage suffices. From $\frac{1}{20}$ to $\frac{1}{8}$ of a grain, according to the age of the patient, by the hypodermatic method, apomorphine is a safe and efficient emetic, acting in a relatively short time,—from fifteen to thirty minutes,—and then coming on with marked suddenness.

We owe to Dr. Murrell the demonstration of the important fact that by the stomachal administration apomorphine is an efficient expectorant rather than emetic. The expectorant property is the more powerful the more decided the dose, if the stomach be the avenue of admission to the blood; but it is also exhibited very decidedly when thrown under the skin. The facts may be formulated thus:

To obtain certain, prompt, and powerful emesis, prescribe apomorphine subcutaneously.

To obtain the most efficient and certain expectorant action, prescribe apomorphine or apocodeine (see *post*) by the stomach or by the subcutaneous injection.

As an *expectorant*, apomorphine acts with unusual success, for these agents—the expectorants—are notoriously uncertain and inefficient, except, if we may do so, this new contribution to the group. The mode of its action is rather uncommon; indeed, it may be said that none other can properly be individualized in this way. It acts within ten to thirty minutes, and causes the separation and extrusion of a large amount of bronchial mucus. The larger the dose, provided it does not cause emesis, the more certain and satisfactory its expectorant effects. Besides contributing to the formation of mucus, apomorphine has a sedative effect, and allays cough and various kinds of spasm which occur in the broncho-pulmonary area.

Apocodeine has properties similar to apomorphine. It is rather more powerful as an expectorant, *per se*, without

considering the dosage. In respect to this particular quality, Dr. Murrell * says,—

"The hydrochlorate apocodeine acts as a powerful expectorant when given in the form of a pill. From 3 to 4 grains may be administered daily with perfect safety."

THERAPY.—As respects the emetic action, the best results, it should be remembered, are had from the hypodermatic injection, and the dose to be given varies from $\frac{1}{20}$ to $\frac{1}{8}$ of a grain, according to age and other circumstances.

The administration of apomorphine is a valuable means of getting rid of *narcotic and irritant poisons*. When thrown into the subcutaneous tissue, it acts with energy and empties the stomach thoroughly. It should not be forgotten that apomorphine acts suddenly, and with a simple effort removes all the contents of the organ. Every preparation should be made in advance, for often no warning is given, but the act of vomiting and the presence of the nausea are usually coincident. The administration of apomorphine in cases of narcotic poisoning may be questioned, because in some instances a pronounced narcotic effect has followed its introduction into the system. Murrell † gives some cases illustrating this occasional tendency, although he maintains that no such accident is to be dreaded; but if the remedy be safe under all circumstances, it becomes of still greater value as an emetic and as an expectorant.

Apomorphine has been used successfully in the treatment of *chorea* and such spasmodic diseases as *laryngismus stridulus*, *whooping-cough*, *asthma*, to remove tenacious *mucus* obstructing the finer *bronchi*, and for dislodging *foreign*

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* Proceedings of the Royal Society, vol. xvii. p. 455. † Op. cit.

bodies in the *œsophagus*, in the *nares*, and elsewhere, and for that troublesome affection, *winter cough*. Attacks of *epilepsy* have been prevented by injecting apomorphine just before the seizure, or in the interval between the aura and the onset of the convulsion, if the time permit.

In *poisoning*, when the irritant and toxic matters are yet in the stomach (and especially in narcotic poisoning) and the ordinary emetics make no impression, the subcutaneous injection of apomorphine is a precious resource.

Instead of apomorphine, apocodeine may be utilized as the remedy. Although possessed of the same or corresponding powers, it is less active and can be used in full doses with less danger. The dose of apocodeine ranges between $\frac{1}{10}$ of a grain and 1 grain, without inconvenience, provided the smallest dose mentioned is first administered, and a gradual increase in the amount made subsequently until the maximum is reached. If the dose is rightly proportioned to the conditions present, there is no doubt of the utility and success with which apocodeine may be prescribed, and in the cases to which apomorphine is adapted. Especially does it seem to be best suited to the treatment of such diseases as the catarrhal affections of the broncho-pulmonary mucous membrane, when the state of the part is such as to require an efficient expectorant or emetic.

Dr. Kormann* states that he has found apomorphine of exceeding utility in the catarrhal affections of the bronchi and lungs succeeding to measles, scarlatina, and other maladies. Without causing nausea, vomiting, or disorders of the digestive organs, it lowers the temperature, makes expectoration easy, and lessens the cough. Dr.

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* The New York Medical Record, 1881, p. 290.

Fliesburg,* of Hudson, Wisconsin, has expressed a decided opinion in favor of apomorphine, in the class of cases above mentioned, as the proper sphere of its action,—namely, catarrhal inflammation of the lungs and bronchi. Fliesburg has had the same success in the class of cases referred to by Kormann, in respect to the manner in which the remedy acts and the nature of its curative powers. Dr. Samuels also finds apomorphine a most valuable medicine in croup.

Besides others, some of whom have been mentioned, Beck has used apomorphine as an expectorant with much success. His paper originally appeared in the *Deutsches Med. Wochenschrift* for February, 1881. His conclusion is that apomorphine is superior to any of the older expectorants that have hitherto been employed in the treatment of pulmonary affections. Beck also asserts that the earlier in the case the apomorphine is used the better the results, —that is, during the first and dry stage, before the onset of the expectoration, its effects are most favorable because it starts some flow of mucus and moderates the distressing symptoms.

In the treatment of catarrhal affections of the broncho-pulmonary mucous membrane, apocodeine may be given instead of apomorphine, for the reason that the former is quite as effective as the latter, and is far less dangerous and less apt to produce those anomalous symptoms in which so much danger lurks.

NOTE.—It is said that the injection of five (5) to fifteen (15) drops of chlorodyne cures an acute diarrhœa immediately. The best point for inserting the medicament is in the walls of the abdomen.

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* The Therapeutic Gazette, 1887, vol. ii. p. 656.

Cathartics.

The attempts that have been made to utilize the subcutaneous tissue of the abdomen and back as the point of entrance into the system of various purgatives have not resulted very happily. It is true that in this way various remedies may be administered, but the after-consequences are apt to prohibit their further use.

The resins of podophyllin, jalap, scammony, and others have been injected. They are best dissolved in oil of vaseline for this purpose. The dose should be regulated by the age and susceptibility of the subject.

In a research on podophyllinotoxin, Neuberger * shows that this agent acts on the central nervous system, and that local effects only are produced in the intestine.

A striking illustration of this fact is afforded by the report of a case of poisoning by resin of podophyllin, made by Professor W. L. Dudley,† of Cincinnati. There was an apparent recovery in twenty-four hours from the gastro-intestinal disturbance. Then came on symptoms referrible to the central nervous system, and the patient passed into a deep coma, from which she could not be roused, and died with the symptoms of respiratory paralysis. The quantity of the resin of podophyllin taken in this case was 5 grains.

Aloin can be used subcutaneously. In an elaborate research on this subject by Professor Meyer, he demonstrated that the aloin of Barbadoes and Curaçoa acted efficiently as a cathartic whether given by the stomach or subcutaneously. Barbadoes aloin can be given by solu-

* Archiv für experimentelle Pathologie u. Pharmakologie, Band xxviii. p. 32.

† The Medical Record, April 12, 1890.

tion in water, but Meyer prefers to make use of formamide as the vehicle for all the aloins employed by hypodermatic injection. The dose of aloin is the same whether given subcutaneously or taken into the stomach. He found that Natal aloin was always active, but the aloins do not act more speedily by injection than when taken into the stomach. Aloin can always be detected in the fæces and urine. It causes burning pain when thrown under the skin, but only for a few minutes.

From the foregoing observations it seems clear that only when there is complete insensibility or excessive and uncontrollable irritation of the gastro-intestinal mucous membrane is the subcutaneous injection of cathartics advisable.

D. TOPICAL AND IRRITANT INJECTIONS.

AQUAPUNCTURE.

The method now designated *aquapuncture* consists merely in the subcutaneous injection of water at ordinary temperature. A special instrument has been invented by M. Guérard for the simultaneous introduction of a number of fine streams of water (*douches filiformes*), but an ordinary hypodermatic syringe will answer the purpose very well by making a number of punctures within a certain area.

The immediate effect of the sudden introduction of a fine jet of water is a sense of burning, which lasts a few minutes, a feeling of distention and warmth lasting longer, for about the point of puncture considerable swelling takes place, presenting the appearance of a wheal of urticaria. The immediate effect of the introduction of cold water is to cool the nerve-filaments; of hot water to raise their temperature, and the distention of the parts stretches the nerve-filaments. Undoubtedly, therapeutical effects are produced by such impression. What difference of physiological or therapeutical effects will follow the introduction of very warm or very cold water, or greater or less stretching of nerve-fibres, remains to be determined by further investigations.

The method of aquapuncture has been used in fourteen cases of various forms of *neuralgia* by Servajan,* with the

* De l'Aquapuncture, par J. Servajan, Paris, 1872, p. 41.

result of a cure in all but one. Among these were examples of facial, sciatic (5), lumbar (3), and other forms.

The injection of water has been gravely proposed* as a substitute for morphine in the treatment of painful affections, and a medical eccentric has propounded the extraordinary theory that the systemic effects of a solution of morphine are due not to the morphine, but to the water! If this was not intended as a practical joke,—if the author is really sincere in his proposition, it is a curious example of that morbid desire for notoriety which is indifferent to the means employed to secure it.

Water injections have been used with success to deceive the patient in cases of morphine habit of a few days' or weeks' duration; but ancient and experienced morphine-takers cannot be so deceived, for they quickly realize the difference in the amount of effect produced. In making an effort to cure them, it is never useful to practise any deceit; their co-operation must be sought and their confidence gained. If water merely is to be injected, let them be informed, but do not commit the professional error (not to speak of moral wrong) of being concerned and caught in an attempt to deceive.

I have had excellent results from the injection of water into the paralyzed and wasting muscles: it promotes their nutrition, and contributes indirectly to the regeneration of voluntary power.

In the various cases to which the aquapuncture is applicable, the quantity injected will range from 30 minims to 1 drachm. When the first injection does not relieve in two minutes, another should be inserted. As far as practicable the "painful points," or the tissue in which the pain is felt, should be the site of the injection.

* Lafitte, Union Médicale, No. 113, 1875.

OSMIC ACID.

This preparation occurs in the form of reddish crystals, freely soluble, styptic in taste, and but little irritating to the tissues, yet somewhat painful.

The solution employed in hypodermatic practice is one per cent.,—that is, 1 grain of the acid to 100 grains of water.

ACTIONS AND USES.—For the purposes here indicated osmic acid is a topical application, and its therapeutical effects do not extend beyond the point injected. Its first use by a Russian physician was a mere matter of accident: it was injected by mistake for cocaine, and the doctor was grievously troubled, expecting his patient to suffer the most serious results in inflammation and sloughing, but to his amazement quite the opposite effect followed, for his patient had a degree of relief not experienced for a long time from the use of any remedy.

Since the publication of this report the use of osmic acid has been taken up in all countries. Thus, Professor Seeligmüller,* of Halle, had "brilliant results" from the injection in cases of *intercostal neuralgia.* Dr. S. Solis-Cohen,† of Philadelphia, reports excellent results from the use of osmic acid in the neuralgic affections. Mr. James Merces‡ gives an account of eighteen cases of sciatica, many of them of extreme obstinacy, twelve of which were relieved completely and the other six obtained alleviation only. Grinevitski,§ a Russian physician, whose paper,

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* Therap. Monatshefte, December, 1887, p. 507.

† The Medical News, April 6, 1889.

‡ The Lancet, January 7, 1885, p. 58.

§ The Practitioner, September, 1888, p. 198.

which first appeared in *Wratsch*, was subsequently translated into English by Dr. Granville, reports many cases of neuralgic rheumatism cured promptly by osmic-acid injection having the strength of one per cent., the dose of this solution ranging from 2 or 3 drops to a syringeful. But Dr. Grinevitski asserts that the larger doses are better than small ones: they are more prompt in affording relief; they are permanent in the results achieved. In the majority of cases two injections sufficed to effect a cure. Dr. Turner,* of St. Petersburg, was equally successful in an inveterate case of neuralgia of the ulnar nerve.

To the cases of neuralgia in its various forms, neuralgic rheumatism, etc., must be added the effects of osmic acid in a case of goitre, which was cured by the parenchymatous injection. The solution employed for this purpose had the strength of 2 grains to 1 drachm, and of this a syringeful was injected daily into the substance of the gland. Iodide of potassium was given internally, but the amount is not stated.

With these uniform successes, some untoward results must be compared. In a few instances local inflammation and abscesses have occurred, together with some sloughing. In a case of pain in the little finger reported by Mr. W. A. Ellis, great swelling of an apparently permanent character took place, but the pain disappeared.

The unpleasant accidents just mentioned are, however, not equal to the good accomplished, and with suitable care may be avoided.

Irritant Injections.—Dr. Luton,† of Rheims, under the singular designation "parenchymatous substitution," de-

* The London Medical Record, 1885, p. 77.

† Archives Générales de Médecine, Octobre et Novembre, 1863.

scribed a method of treating neuralgias, new formations, hypertrophies, etc. This method consists in the injection into the substance of the affected part of such irritants as tincture of iodine, nitrate of silver, chloride of sodium, etc. The term applied to this process was intended to express the theoretical views of its author in regard to the nature of the therapeutical action which takes place. The pain and irritation set up in the part were assumed to be *substituted* for the morbid process.

Dr. Ruppaner imitated this method of Luton in the treatment of sciatica and other neuralgias. Dr. Bertin (de Gray) also, attracted by the results obtained by Luton, practised the method for several years and then published the results.* I have had myself a limited experience with this method.

The substances employed in this way are chiefly the following:

A solution of iodine.

A saturated solution of common salt.

A solution of the nitrate of silver.

The tincture of cantharides.

The following is the solution of iodine employed by Bertin:

℞ Potassii iodidi, gr. xv;
Tinct. iodinii, ʒ ijss;
Aquæ destillatæ, ʒ x. M.

The quantity of tincture of iodine may be increased to 5 drachms.

The tincture of iodine is sometimes employed alone and undiluted.

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* Archives Générales de Médecine, Avril, 1868, p. 444.

The following is a suitable formula for the nitrate-of-silver solution:

℞ Argenti nitrat., ʒ ij;
Aquæ destillatæ, ℥ i. M.

To illustrate at the same time the class of cases to which this method is applicable, and its therapeutical power, I subjoin the statistics of Bertin:

1. Tumors formed by development of the thyroid gland	8
Cured	5
Ameliorated	1
Failed	2
2. Lymphatic ganglions	3
Cured	3
3. Bursæ	1
Cured	1
4. Neuralgias	7
Old sciaticas treated by injection of nitrate of silver	2
Cured	2
Old sciaticas treated by solution of common salt	2
Cured	0
Recent sciaticas treated by solution of common salt	2
Ameliorated	2
Recent sciaticas treated by injection of nitrate of silver	1
Cured	1

Ruppaner employed the nitrate-of-silver injection in one case of cervico-brachial neuralgia, and in four cases of sciatica; two cases were ameliorated, and three cases of sciatica were cured.

As respects *neuralgia*, this method of treatment seems specially adapted to cases of sciatica,—obstinate cases in which structural alterations have probably taken place (neuritis). To be effectual, the injection—5 drops of the nitrate-of-silver solution—should be thrown into the vicinity of the nerve. It produces great pain and burning, and is followed by considerable inflammation, not diffused,

but localized to the site of the injection. Abscesses, of course, frequently happen from this practice, and, indeed, sufficient irritation to result in this way seems necessary to produce the best effects. It is probably true that the irritation, and not the agent, is the principal factor in the curative process. This subject has, however, been fully treated elsewhere in this work.

Solid tumors may be destroyed by injecting such irritants into them as will give rise to violent inflammatory action and sloughing. Into the substance of cancerous new formations various corrosives may be injected; but this practice, although rational, has not hitherto proved satisfactory,—a remark equally true of Dr. Broadbent's method of injecting dilute acetic acid,—of the success of which such confident expectations were at first entertained. Solutions of chloride of zinc of varying strength have lately been proposed for "interstitial injection" as a means of curing certain cystic tumors. It is asserted that when the air is excluded eschars are not produced. The strength of the weaker solution is about 5 grains of the chloride of zinc to the drachm of water, and of the stronger solution about ½ drachm to 1 drachm. The method consists in introducing an aspirator and withdrawing some part of the contents of the cyst, and then injecting from 5 to 20 drops of the zinc solution.

The treatment of morbid growths by the injection of gastric juice, especially soft and fast-growing and malignant, formerly in vogue, was subsequently discredited, but is now brought forward again as a curative measure for which considerable success is claimed. The injection (parenchymatous) into the substance of tumors has been discussed in another part of this work.

The method here proposed consists in the injection of

gastric juice fresh and active, and from the stomach of the pig, into and among the cellular elements of a morbid growth. It is assumed that the cells are attacked and disintegrated, and thus the active part of a malignant tumor is destroyed by a process akin to stomachal digestion.

Far more effective, according to recent reports, is the juice of the *Carica papaya*. It has been shown by Darwin that certain insectivorous plants possess the power of holding and gradually digesting, with a fluid having this ferment quality, such insects as fall within their petals. It is assumed that if a plant—such as the *Carica papaya*—can digest animal substances, it may also digest the softer parts of a morbid growth. Such reports as have been published lately have been altogether favorable; but it is not unusual to find the author of a new proposal or the reviver of an old one pass quite beyond all reasonable bounds in the first flush of his enthusiasm.

Making due allowance for such claims, there seems to be, nevertheless, something in the method of Dr. Mortimer Granville which must arrest attention. He recently reported the cure of a malignant growth about which there could be no doubt. It was a specially unfavorable case, and many more of a similar character now under his charge are proceeding to a favorable issue. His method consists in the injection into the morbid growth of the juice of the *Carica papaya*,—of as much as the interstices will contain. This is the main feature of the treatment, but he also administers the same digestive juice internally, and employs other measures which he considers suitable.

The juice of the *Carica papaya* is also employed as a solvent for false membrane, and is used with a considerable measure of success in diphtheria.

Professor Lannelongue has lately come forward with a

new expedient for the treatment of tuberculosis, especially of surgical tuberculosis. This method consists in the injection of a chloride-of-zinc solution into the diseased parts,—for example, into a tuberculous joint. This agent sets up a sclerosis of the parts, the vessels are much narrowed in calibre and the capillaries are obliterated. This sclerosis constitutes a real fibroid change. Other changes occur, including the outpouring of new cells and the gradual destruction and elimination of the bacilli. Twenty-two cases have been reported on, but future experience can alone determine whether this plan of treatment is a really curative one.

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