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ON THE

ANTAGONISM

BETWEEN MEDICINES

AND

BETWEEN REMEDIES AND DISEASES.

BEING

THE CARTWRIGHT LECTURES FOR THE YEAR 1880.

BY

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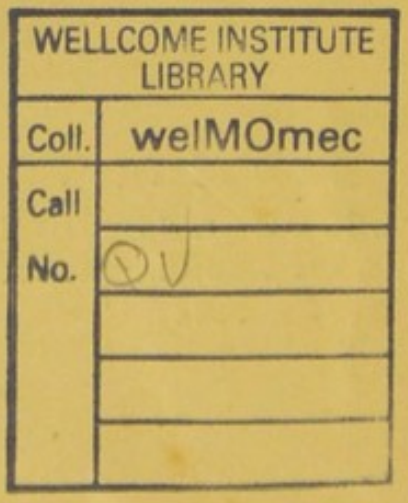

TO

DRS. W. H. DRAPER AND ROBERT F. WEIR,

LATE AND PRESENT PRESIDENTS OF THE ALUMNI ASSOCIATION OF THE COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK,

I Dedicate this Volume,

IN APPRECIATION OF THAT HONEST WORK WHICH HAS ADVANCED THEM TO THE FRONT RANK OF PRACTITIONERS,

IN TESTIMONY OF MY ESTEEM FOR THEM PERSONALLY,

AND IN GRATEFUL RECOGNITION OF

PERSONAL KINDNESSES.

PREFACE.

THE Lectures which now appear in this form owe their existence to the well-directed liberality of the late Mr. Cartwright, of Newark, New Jersey. On the opening night of the course, Dr. Weir, President of the Alumni Association of the College of Physicians and Surgeons, in an introductory address, gave an interesting account of the circumstances under which the Cartwright Lectures originated. The bequest of Mr. Cartwright, made to the Alumni Association, provides for an annual course of lectures and a prize essay. A committee of the Association, appointed to select a lecturer to inaugurate the course, kindly nominated me; and they designated five or six as the number of lectures to be delivered, leaving to the lecturer the selection of the topic. Not to establish a precedent which might be construed to favor the minimum number, I delivered six lectures. The topic selected is one to which I have given much consideration and considerable experimental work, and is, I think, of importance to the profession. Although the literature of the subject is extensive, the papers referring to it are widely distributed through the medical periodicals of various countries. To this statement I must except the prize essay of Dr. Fothergill,* which contains an interesting discussion of the topics embraced in these lectures. I should also

* "The Antagonism of Therapeutical Agents; and What it Teaches," the essay to which was awarded the Fothergillian Gold Medal of the Medical Society of London for 1878. By J. Milner Fothergill, M. D., Edin., etc. Philadelphia: H. C. Lea, 1878. Pp. 160.

except some of the monographs, referred to in the course of the lectures, but most of these are not accessible to the great body of practitioners. I have attempted to collect here all of the contributions to the subject, and at the same time have brought forward my own work in this field. From these materials I have sought to develop a therapeutical system, which, while the oldest, is at the same time the newest phase in the treatment of disease.

An abstract of these lectures appeared, as they were delivered, in the "Medical Record," and they were published in full in the "New York Medical Journal" for January and February, 1881. Their appearance in this volume is in deference to the judgment of those who supposed their preservation in a permanent form desirable.

R. B.

PHILADELPHIA, *February* 1, 1881.

TABLE OF CONTENTS.

LECTURE I.

PAGE

Introductory 9
History of the Subject 10
Physical Basis of the Principle 20
Opium and Belladonna 22

LECTURE II.

Opium and Belladonna, continued 31

LECTURE III.

Atropia and Physostigma 49
Atropia and Pilocarpin 57
Atropia and Muscaria 61
Atropia and Quinia 64
Atropia and Bromal Hydrate 64
Atropia and Aconite 65

LECTURE IV.

Chloral and Strychnia 67
Chloral and Picrotoxine 71
Chloral and Atropia 72
Antagonists to the Cardiac and Respiratory Depressants . . 74
Opium and Veratrum Viride 74
Opium and Gelsemium 77
Morphia and Theine, Caffeine, etc. 79
Morphia and Chloroform 79
Strychnia as a Respiratory Stimulant 81
Strychnia and Nitrite of Amyl 82
Aconite and Digitalis 82
Digitalin and Saponin 83
Digitalin and Muscaria 83
Atropia and Phytolacca 84
Anæsthetics and Convulsants 85

LECTURE V.

PAGE

The Antagonism between Remedies and Diseases 86
Strychnia and Paralytic States 86
Spasm and the Paralyzers 88
Pain and the Anodynes 92
Mental States and their Antagonists 94
Cardiac Remedies and Diseases 95
Respiration Remedies and Diseases 98
Intestinal Remedies and Diseases 99
Remedies acting on the Skin 99
Remedies acting on the Kidneys and Bladder 100

LECTURE VI.

Antagonism between Remedies and Diseases 102
Antagonists to Inflammation 102
Antagonists to Fever 106
Antagonists to Specific Diseases 111

APPENDIX 115
INDEX 120

THE

ANTAGONISM BETWEEN MEDICINES,

AND BETWEEN

REMEDIES AND DISEASES.

LECTURE I.

HISTORY OF THE SUBJECT; PHYSICAL BASIS OF THE PRINCIPLE; OPIUM AND BELLADONNA.

In this country, private beneficence, although vast in the extent of its exercise, is rarely directed to merely medical objects. Therefore, in opening this course of lectures, provided for under the bequest of the late Mr. Cartwright, it behooves us to honor the memory of the founder. In this gift, precious indeed on account of its rarity, the medical profession is offered a new opportunity, when such opportunities are few, for honorable distinction. The possibilities of this benefaction are great. The opportunity stimulates to the acquisition of new truths, and encourages the growth of a medical literature. Benefits inure to the memory of the giver. His name is perpetuated among the alumni of this great school, and they have it in charge to honor through all time. His benefaction is especially celebrated annually, and he is enrolled among the philanthropists who, by a wise dispensation of their wealth, have sought to promote the good of their fellow-men.

I esteem it a high honor to be called upon to inaugurate the

Cartwright Lectures, and I am deeply indebted to the Committee for the kind partiality which led them to nominate me. I do not conceal from myself the difficulties of this position. The Cartwright Lectures will be expected to take and maintain an honorable position alongside of the Gulstonian, Lumleian, and other lecture courses, which have done so much for English medical science and literature. It will doubtless be expected of the lecturers to bring forward new facts, to develop new principles, and to throw new light on obscure but familiar topics. Brought into comparison with such standards, and confronted with the just expectations of the profession, it is but natural to apprehend that my effort will fall far short of a true ideal, and unhappily become a precedent for inferior performances in the future. After careful consideration, I have selected a topic for this course which has strong claims on the attention of physicians, and to which I have contributed some facts by recent researches. Accordingly, I have decided to ask your attention to the subject of the Antagonism between Medicines, and between Remedies and Diseases.

By physiological antagonism is meant a balance of opposed actions on particular organs or tissues. As disease is a pathological physiology, so far, at least, as relates to function, the derangements produced by disease may be opposed by other derangements set up by medicinal substances. The antagonism, or opposition of actions, may extend throughout the whole range of effects, or it may be limited to a few points. Indeed, some of the most valuable instances of antagonism are thus limited, and there are few, if any, examples of antagonism, in which the opposition of actions is universal. In popular medical opinion, by the term physiological antagonism is meant an opposition of action of poisonous medicinal agents, in that the effects of the one may be exactly counterbalanced by the effects of the other. According to this conception of the subject, when a lethal dose of one agent is administered, the effects may be removed by an opposing agent so given as to produce exactly opposite effects. Therefore, the poisonous action ceases, because in the whole range of the effects of the two agents they are exactly antagonized. This conception of physiological antagonism is exaggerated—for such completeness of opposing action is as rare as exact similitude in remedies acting in the same way.

In an interesting discussion* of the problem of therapeutical

* "Bull. Gén. de Thérap.," vol. lxxxiv, p. 570.

antagonism, MM. Gubler and Labbée proposed to retain the word *antidotism* in accordance with its ancient signification. As, however, usage has restricted the employment of the word *antidote* to express chemical rather than physiological antagonism, it is better to adhere to the present nomenclature. Moreover, the word *antidotism* expresses the conception of a chemical combination of the opposing agents, and the formation of a new compound different in character from those entering into its composition, and without toxic power. Physiological antagonism means simply a balance of opposed actions on the same tissue. It does not include a change of structure. The opposing agents counterbalancing each other, the functional disturbance subsides and the normal equilibrium is restored.

Some such conception as our modern doctrine of physiological antagonism has existed from the earliest period. Various aphorisms of Hippocrates express it in most precise terms. Thus: "Diseases which arise by repletion are cured by depletion; and those which come from depletion are cured by repletion, and in general diseases are cured by their contraries." In another aphorism it is stated: "Some diseases are cured by contraries, some by similars"—an aphorism on which Carus based his famous saying, in his controversy with Hahnemann: "Whatever is new in homœopathy is not true, and what is true is not new." Although the practice of Hippocrates and his immediate followers was empirical, that is, based on observation and experience, they used, whenever the circumstances admitted, their favorite dogma of contraries. Some of the most famous teachers of the Alexandrian school—for example, Herophilus and Eristratus—opposed the doctrine of contraries. Galen was essentially a trimmer, for, while he practiced on the system of contraries, he spoke respectfully of the empiricists. There has been no period in medical annals when theories, and systems, and specialisms of all kinds were more numerous and distracting than in Galen's time. The only rational expedient applicable to medical practice at that time was the principle of contraries, which continued up to the revival of learning as the chief guide in therapeutics, how much soever other theories may have dominated in the schools.

About the middle of the sixteenth century, there was published by Jean Fernel, physician to Henry II, teacher of Vesalius, and the most celebrated physician of his time, an elaborate treatise on the fundamental maxim, "Every disease must be combated by contrary remedies." It is a curious circumstance that Fernel should attempt

to prove that the law or doctrine of similars was only an application of its opposite or law of contraries. "Many men," he states, "conceive that this sovereign principle is annulled when it is affirmed that there are diseases which are cured by similars; but these persons do not reflect that such remedies, although apparently similar in their effects to the symptoms of the disease, are opposed to the causes which produced it, so that they destroy the disease by removing its cause; thus rhubarb, though heating, extinguishes fever by purging the matter which feeds the fire. A purgative arrests a dysentery by evacuating the peccant matter which causes and sustains it." The ingenious attempt of Fernel could not prevent the decline of the ancient doctrines, which had maintained universal sway for so many centuries. When that boasting pretender and iconoclast, Paracelsus, burned the works of Galen and Avicenna, the doctrine of contraries disappeared in the smoke. On the labors of the alchemists rose modern chemistry. With the new light afforded by the discovery of the circulation of the blood, and the progress of the knowledge of anatomy, new theories prevailed in therapeutics. The iatrochemical doctrine of the great Boerhaave, the animus of Stahl, the irritability of Cullen, and the sthenic and asthenic theories of Brown, for a time held sway within the range of influence of their respective authors.

The doctrine of contraries, then, quite disappeared amid the contentions of rival schools and professors. Next arose that eccentric and mystical reformer, Hahnemann, near the close of the last century, whose notions, tinctured with the spiriticism of Mesmer, were rendered still more visionary by the radical theories engendered by the French Revolution. Before that period, in his senility, when he developed his idea of the spiritual essence in medicine, Hahnemann's doctrine of similars was merely an application of the Hippocratic maxim. The law of similars was associated with the law of contraries in the Hippocratic system, and Fernel, in the sixteenth century, in expounding and defending the latter, showed its relation to the former. A little consideration must, I think, tend to the conclusion that, when a remedy acts in a similar manner to a disease, there must be an antagonism between the force of the remedy and the momentum acquired by the disease. The disturbance in the functions caused by a drug must interfere with the disturbance caused by a morbid process. If the actions were the same, the result of the combined impression would be an increase of the disturbance. As they are similar only, and proceed from different

sources, there are, then, two forces acting on the same tissue or organs, and necessarily opposed in action. Any truth in the homœopathic law or doctrine of similars is not, therefore, new, as Carus well said, for, if there be similarity of action, it must of necessity be opposition.

The initial movement in the great development which has taken place in our knowledge of the physiological action of drugs was begun by Bichât. I can not too strongly insist on the importance of this epoch for a right understanding of the influences contributing to this development. When Bichât came on the scene, therapeutics was in an utterly chaotic state. To the previously existing wild theories of the iatro-chemists, the animists, and the contra-stimulant school, were added the vagaries of Hahnemann and of Mesmer. It is not surprising that he expresses a severe judgment: "Materia medica," says Bichât, "a collection of incoherent opinions, is perhaps, of all the physiological sciences, that which most exhibits the contradictions of the human mind. In fact, it is not a science for a trained intellect; it is a shapeless mass of inexact ideas, of observations often puerile, of imaginary remedies, strangely conceived and fantastically arranged. It is said that the practice of medicine is repulsive. I go further than this: it is, in respect to its principles taken from our materia medicas, impracticable for a sensible man." From Bichât dates modern physiology, for, although great acquisitions had been achieved before, it was not until he rendered general anatomy * possible that this science could proceed in the remarkable course of development which has since taken place. Here is the initial period in the rise of experimental physiology. Bichât died in 1802. Magendie was then passing through his course of study, and, brought under the influence of Bichât, was thoroughly indoctrinated with the ideas of that brilliant genius. Demonstrator of anatomy in 1805, a few years later (1808–'9) his important researches on physiological subjects began to appear. The first investigation by physiological methods into the action of a medicine was made by Magendie, the subject being the upas poison. This research became possible only after the functions of the spinal nerves had been correctly interpreted—a feat accomplished a short time before by Magendie. He next investigated the then new alkaloid, strychnia, and so successfully did he work out all the details

* "Anatomie Générale, précédée des Recherches Physiologiques sur la Vie et la Mort," par Xavier Bichât, Paris, 1818. Two volumes, with a portrait.

that subsequent experimentalists have been able to add but little to his results. The first example of the physiological antagonism between a remedy and a diseased state was that between strychnia and paralysis, and this principle, based on Magendie's studies, was applied, not empirically, but with a conscious purpose, by a physician, after the publication of the great physiologist's results. I am the more explicit in stating this fact, because it is generally supposed that the employment of strychnia in these maladies was merely empirical or accidental. The physiological study of the actions of medicines has gone on actively since Magendie's time, but the question of physiological antagonism has not excited inquiry until within a few years past. The doctrine of contraries, without being distinctly formulated in men's minds, influenced therapeutics to a greater or less extent. The scientific application of the principle of antagonism to medical practice, I purpose to consider in detail in future lectures.

Taking up now for examination the special instances of antagonism between medicines, we find, so long ago as 1570, Pena and De Lobel relating that the overaction of belladonna, when given to allay thirst, was relieved by theriaca. Prosper, according to Giacomini, held that theriaca was an antidote to all poisons. Horatius, in 1661, states that a man poisoned by a teaspoonful of belladonna juice recovered after taking theriaca. In 1677 Faber narrated several cases of poisoning by belladonna berries, in which theriaca was partly successful. It is probable that theriaca was reputed to be an antidote to the poisons in general at this period, and was used in belladonna poisoning as in other forms of poisoning, but further observation demonstrated that it was especially adapted to belladonna poisoning. 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

* Braithwaite's "Retrospect," 1855, part xxx, p. 301.

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 atropia were removed by considerable doses of morphia. Influenced by these results of Mr. Bell's, 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 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

* "Cincinnati Med. Observer," vol. i, 1856, p. 70. There were but two volumes issued of this periodical, when it was united with the "Lancet."

† "Edinburgh Med. Jour.," vol. iv, 1859, p. 1.

‡ "Med. Times and Gaz.," Dec. 3, 1859, p. 551.

§ "Am. Jour. of the Med. Sci.," vol. xlii. ‖ *Ibid.*, vol. xliv.

¶ "Am. Jour. of the Med. Sci.," July, 1865, vol. l, p. 67. "On the Antagonism of Atropia and Morphia. 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.

thus far published number one hundred and twenty 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 cats. He regards the following experiments as conclusive against the view that an antagonism exists. To a cat he gave a dose of morphia 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 atropia 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 atropia and morphia, 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. While it is true that clinical experience strongly supports the belief in the existence of such antagonism, there have been published unsuccessful cases.

Although opium and belladonna were the first, they are not the only examples of antagonistic action. In fact, we find that more perfect illustrations of antagonism have been discovered between

* "Jour. de la Physiol.," etc., tome iii, 1860, p. 726.

† "Gaz. des Hôp.," 71, 1865.

‡ "Gaz. Hebdom.," 2 sér., xii, 32, 1865.

§ "Schmidt's Jahrbücher," Band 128, p. 288, abstract.

‖ "The Old Vegetable Neurotics," p. 280, and p. 291.

other agents. A capital example of a remedy being applied in antagonism to a diseased state is that of strychnia. Magendie undertook the examination of the properties of this poison, demonstrated its mode of action on animals, and suggested its therapeutical application in opposition to certain diseased states. When Magendie's results were announced, M. Fouquier applied it in accordance with the deductions of experiment. Magendie, also, when the opportunity offered, used the agent as he had suggested its use, in the following comprehensive statement: "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." Producing tetanic rigidity, the opposite condition to paralysis, it was suggested that it might prove useful in paralysis. I need not say that this suggestion was abundantly confirmed by clinical experience, and since that time many cases have demonstrated the correctness of the antagonism. Could any fact more strikingly prove the benefits derived from the physiological study of the action of remedies, and the applicability of the law or principle of antagonism to therapeutics? In the remarkable study of woorara made by Bernard, the pupil of Magendie, we have another illustration of the same fact. Woorara is a paralyzer; it destroys the irritability of the end organs of the nerves in the muscles, and as a paralyzer is used against the opposite condition, or spasm, in tetanus and in hydrophobia. In respect to the latter disease, woorara is the single remedy which has appeared to have a curative influence. These researches of Magendie and Bernard stand out prominently in medical history as the initiation of that course of physiological study of remedies which has yielded such important results, and ought to be sufficient in themselves to silence for ever the absurd cavils of the antivivisectionists.

Taking the examples of physiological antagonism in their chronological order, the next one is that between atropia and physostigma. The first attempt to determine the existence of an antagonism, which had been suspected previously, was by Kleinwächter,* in 1864, who, in a case of atropia poisoning, used with distinct advantage a preparation of physostigma. The next observation consisted of a single experiment by Bourneville,† in which the effects of a supposed lethal dose of Calabar bean, intro-

* "Berlin. klin. Woch.," 1864, p. 3, 369.

† "De l'Emploi de la Fève de Calabar dans le Traitement du Tétanos," Paris, 1867.

duced into the stomach of an animal, were counterbalanced by the subcutaneous injection of atropia. The account of this experiment did not appear until 1867, and was then interpolated in a memoir on the use of Calabar bean in tetanus. During the same year, I was engaged in some experimental investigations on the actions of atropia, and on its antagonists, with a view to the preparation of an essay to be offered in competition for the annual prize of the American Medical Association. This essay appeared in the volume of "Transactions" for 1869, and in it I distinctly asserted the existence of the antagonism, and submitted experimental evidence in its support. The following year, the remarkable paper of Professor Thomas R. Fraser * appeared, on the antagonism of atropia and physostigma. In this paper, not only is the antagonism established, and its limits defined, but the method pursued is so admirable as to remain the model for all similar investigations.

The next study of the physiological antagonism of remedies is that of Professor Preyer, of Jena, the first part of whose elaborate treatise on prussic acid appeared in 1868.† In this, and in the second part which appeared two years later, Professor Preyer maintained that the actions of hydrocyanic acid and of atropia were opposed, especially as respects the effect of each on the respiratory function. This opinion has been much controverted by Drs. Lecorché and Meuriot, ‡ of Paris; Drs. Hare and Keen, § of Philadelphia; Professor Schroff, of Vienna; Professor Boehm, ‖ of Dorpat; and myself.¶ In a subsequent paper,** Professor Preyer pays his respects to all of us in turn, and maintains his own position with fresh arguments and illustrations.

In 1869 MM. Schmiedeberg and Koppe isolated, defined the properties, and studied the antagonisms of muscarine, the alkaloid of agaricus muscarius. They conclude that the effects of muscarine

* "An Experimental Research on the Antagonism between the Actions of Physostigma and Atropia." From the "Trans. of the Royal Soc. of Edinburgh," vol. xxvi, 1872.

† "Die Blausäure physiologisch untersucht." In zwei Theilen. Bonn, 1868.

‡ "Arch. Gén. de Méd.," May, 1868, p. 529.

§ "Am. Jour. of the Med. Sci.," vol. lviii, p. 436. [Proc. of the Path. Soc. of Phila.]

‖ "Ueber die physiologischen Wirkungen der Blausäure und den angeblichen Antagonismus von Blausäure und Atropin." "Arch. f. experiment. Pathol. u. Pharmacol.," Band ii, p. 129.

¶ Prize Essay.

** "Die Blausäure physiologisch untersucht," Band iii, p. 381.

are similar to those of physostigma, and that it is like the latter, also, in being an antagonist to atropia. In 1869 the remarkable memoir of Dr. Oscar Liebreich,* in which he announced the discovery of chloral, appeared, and soon after the same author demonstrated the antagonism of chloral and strychnia.

A notable event, in connection with the history of this subject, was the appointment of a committee by the British Medical Association "to investigate the antagonism of medicines."† The committee was composed of Dr. J. H. Bennett, the great Edinburgh clinician, Dr. McKendrick, physiologist, and Dr. Alexander Bennett. Their researches included the supposed antagonism of strychnia and chloral; atropia and Calabar bean; chloral and Calabar bean; muriate and meconate of morphia and Calabar bean; sulphate of atropia and meconate of morphia; theine, caffeine, and guaranine and meconate of morphia; Calabar bean and strychnia; and bromal hydrate and atropia. The next year, Dr. Milner Fothergill‡ made a report to the British Medical Association on the antagonism of aconite and digitalis. Soon after the introduction of pilocarpus (jaborandi) and the isolation of its alkaloid—pilocarpin—the antagonism of this agent with atropia was shown by Vulpian.§ An extensive research into the general subject of physiological antagonisms, and including special investigations into the antagonisms of chloral, was lately undertaken by Professor Husemann, the results being published in 1877. Besides these, several memoirs of a polemical character have appeared within a few years past. Of these I may mention the papers of Knapstein,‖ Heubach,¶ and Kay,** in addition to those already referred to. To such importance, indeed, has this subject attained, that no research into the physiological action of a remedy is complete until its range of antagonisms has been determined.

From this brief history of the rise and development of the subject, we may now turn to the examination of the facts which support the doctrine of the antagonistic action of remedies. As

* "Das Chloral Hydrat, ein neues Hypnoticum und Anaestheticum," etc., Berlin, 1869.

† "Brit. Med. Jour.," Jan. 25, 1875. [Report of the Committee.]

‡ *Ibid.*, 1876.

§ "Gaz. Hebdom.," 6, 1875, p. 81.

‖ Knapstein, Adam, "Berlin. klin. Woch.," 47, 1878, p. 691.

¶ "Arch. f. experiment. Pathol. u. Pharmacol.," Band viii, p. 31.

** C. Chr. Kay, "Ueber den Antagonismus zwischen Opium und Belladonna." Inaug. Diss., Jena, 1866.

we have seen, the therapeutical conception which has obtained the widest and most enduring influence is that of the doctrine of contraries. The clinical experience, which under the crude and imperfect methods and the slender knowledge of past times led to such conclusion, must have been occupied with decisive examples of the applicability of such a principle. We certainly encounter many such examples in the medical practice of to-day. We might indeed be content with the confirmatory evidence which is afforded by carefully conducted clinical observations. There is, however, independent testimony of another kind. The doctrine of physiological antagonism—of an opposition of actions—finds its strongest support in the mechanism of many functions. Let me ask your undivided attention to these important facts. In the brain are centers for the inhibition of reflex movements. The maximum amount of stimulation both increases and generalizes reflex action, if communicated to the same part of the spinal cord; but, if a sensory nerve at some distant point is irritated at the same time, the reflex action which would have been produced by the first stimulation is completely and entirely restrained or *inhibited.* Here an opposition of actions suspends activity, or, to express the fact in technical language, reflex actions are inhibited or suspended when coincident impressions from different sources are made on the nerve centers. An illustration of this fact is afforded in the arrest of singultus by a faradaic current applied to the integument of the chest or abdomen. If, at the moment the spasm of the diaphragm is to take place, a strong faradaic current be passed, no attack occurs. This arrest of the impending spasm is due to the simultaneous impressions made on the spinal center concerned—one from the strongly irritated nerves of the skin; the other from the diaphragm, the seat of spasm.

In the medulla oblongata is situated a center of extreme reflex sensibility—the spasm center of Nothnagel, and above it is an inhibitory center of reflex movements—Setschenow's inhibitory center. If there were not some antagonist to the spasm center, every trifling peripheral irritation would produce most extravagant reflex effects. An intimation of the wild irregularities which would ensue, if there were no inhibiting control of reflexes, is afforded in the abnormal readiness to react to impressions when the influence of the cerebrum is withdrawn from the medulla oblongata and spinal cord, these organs acting independently. In the cardiac and respiratory mechanism we have admirable illustra-

tions of opposing forces producing order and rhythm. The movements of the vessels are regulated by a vaso-motor center in the medulla. The vascular tonus is affected by the condition of this center and its associated nerves. By the opposed action of the dilator and constrictor forces, the vascular tonus is maintained at the normal. A similar mechanism controls the cardiac movements; there is a motor apparatus for carrying on the action of the heart, and a regulator apparatus for restraining the movements within proper limits. The manner in which the action of the heart may be affected by opposing forces is admirably shown in the simple experiment with cold and heat. Lay a turtle's or frog's heart on a metallic plate—it will continue to act rhythmically for some hours. Cooling the plate with ice slows the heart, and will presently arrest its movements; then, on applying the heat of the spirit lamp, it begins to pulsate again, and presently, under increased warmth, acts more and more rapidly. Expose the heart of a frog in the usual way, remove it entire, then drop upon it a minute quantity of serum containing a trace of muscarine—the heart will be arrested in diastole. On adding to the heart a few drops of serum containing 0·2 per cent. of atropia, the pulsations begin again and go on energetically.

The reciprocity of action provided for in the nervous apparatus of the heart and blood-vessels serves to restrain variations in the blood pressure, and to keep them within safe limits. If the arterioles of the body suddenly dilate, the blood pressure as quickly falls, but danger to the circulation is prevented by an increased action of the heart. Conversely, when the blood pressure is high, the inconvenience which would result is compensated for by the slowing of the heart. Here opposing forces maintain an equilibrium, or the normal. Similar regulating mechanism coördinates the respiratory, cardiac, and vaso-motor movements. Variations in the blood pressure and in the pulse occur with respiration, the pulse quickening during inspiration, and slowing during expiration. In the movements of inspiration and expiration; in the tidal flow of secretion and excretion; in the tonic contraction of the sphincters; in the action of antagonistic muscles, etc., we have exhibited the beneficent purpose in opposition of action.

The same principle obtains in physics. The undulations by which light and sound become cognizable by our senses are, probably, similar to those by which impressions and impulses are transmitted along nerves. I need not inform this audience that when

rays of light interfere there is darkness, and that when rays of sound interfere there is silence. Interference means meeting in opposition of phase: when the crest of one wave coincides with the depression of another, the surface becomes even. When two bodies of equal weight and momentum come together from opposite directions, both are arrested at the point of impact. The physical force, electricity, exists in a neutral or unexcited state, when the equilibrium of positive or negative remains undisturbed. When the equilibrium has been ruptured, and the two modes of electrical force are separated, they combine, when afforded the opportunity to do so, and restore the equilibrium. In chemistry, also, do we find that opposition of action, combination of opposing forces, and the formation of new substances are constantly going on. But why multiply examples? Nothing can be more evident than that the principle of antagonism prevails widely. In the facts supporting this doctrine which I have brought before you, there would seem to be a justification for the doctrine of antagonisms. We can now proceed with confidence to the study of individual examples. As the question was first concerned with opium and belladonna, it is most fitting to commence with the consideration of their supposed antagonism.

OPIUM AND BELLADONNA.

In the observations to follow, morphia and opium, atropia and belladonna, will be used synonymously.

The investigation of the opposing actions of medicines resolves itself into two inquiries: Does the antagonism exist? What is its nature? The facts which have been accumulated supporting the doctrine of an antagonism between opium and belladonna are clinical. The experimental facts are negative, or are not conclusive for or against the antagonism. The paper of Dr. Norris was the first attempt to collect and tabulate the results of clinical experience to that date. I have collected all the recorded cases which have occurred since, and have added some unpublished cases, and two which were unknown to Dr. Norris, or escaped his search. The table of Dr. Norris began with the cases of Dr. Thomas Anderson, which occurred in 1854. During the same year (1854) Dr. W. Lauder Lindsay * reported two cases of opium poisoning, treated successfully by belladonna, and in 1857 Dr. Sibson † published a

* "Assoc. Med. Journal," 1854. † *Ibid.*, Oct. 24, 1857.

case in which opium and belladonna were taken together, the effects of the one being neutralized by the antagonistic action of the other. The total number of cases of opium and belladonna poisoning, treated with the antagonist, is 120, of which 15 proved fatal, being 12·5 per cent. of failures. These statistics, considered apart from any other question, certainly indicate that the remedy exerted a favorable influence of a curative kind—something more than a *post hoc*. As, in almost all cases, doses of the poison unquestionably lethal were administered, the agents used must have averted death. In very few cases was the antagonist only administered. The part played by emetics, the stomach-pump, coffee, ambulation, faradism, etc., when these were used as well as atropia or morphia, must be estimated. The history of fatal cases is peculiarly instructive. It is necessary to know why the antagonist failed to exert its power. If, in a case in all respects appropriate, the antagonist, without an adequate explanation, proved useless, the antagonism does not exist. The success of a remedy used with a number of other remedies may be apparent and not real. It is, therefore, highly important to study the cases which proved fatal. Not to weary your forbearance too greatly, I condense the histories into the smallest possible space.

Unsuccessful Cases.

Case I (Reported by Dr. Ludwig Pollak. "Wiener med. Presse," xi, 28, 1870).—A physician, aged sixty, who had experienced four years before an apoplectic seizure, but of robust constitution, took, with suicidal intent, 0·36 gramme (about five grains) of atropia. At the end of six hours he was in a condition of profound insensibility, with labored respiration, expiration blowing; the conjunctivæ injected, corneæ glazed, pupils dilated to their utmost; and urine and fæces passed involuntarily. A syringeful of morphia solution, strength not stated, was then injected. As this had no influence on the pulse, respiration, or pupils, another injection, half the first amount, was given. Death occurred in fifteen hours after the poison was taken.

Commentary: The condition of the brain, the large dose of the poison taken, the length of time which elapsed before the antagonist was administered, but especially the inefficient method followed, serve to explain the untoward result. If we assume that the morphia solution had the usual strength, and that the syringe was of the usual size, the amount administered could not have exceeded two grains. The proper mode of introducing the morphia in such a case was to inject one fourth to one half a grain every twenty minutes, until some movement in the pupil, or change in the respira-

tion, indicated that the antagonistic action was being exerted. Then the result of the antagonism could have been awaited for a time. Having had a cerebral hæmorrhage, it is probable that additional mischief was done by atropia.

Case II (Reported by Mr. James Seaton. "Med. Times and Gaz.," Dec. 3, 1859).—This was one of ten cases of poisoning by belladonna berries. Opium was used in all of the cases requiring treatment, with success, except the fatal case. S. W., aged fourteen, ate an unknown quantity of the berries, which produced dryness of the mouth, dilatation of the pupil, and delirium. At the expiration of twelve hours the child vomited, and was then ordered eight minims of the tincture of opium every two hours. After taking 16 minims, the dose was increased to 12 minims every hour until she had taken 60 minims. The opium was then suspended, and the whole amount taken was given after the first twelve hours, and before the expiration of twenty-four hours. During this period, the delirium was diversified by attacks of unconsciousness. At the end of twenty-four hours, she passed into a condition of insensibility, and died at the expiration of twenty-nine hours from the time of eating the berries.

Commentary: The whole amount of tincture of opium taken (72 minims) was about equivalent to three grains of crude opium—an amount entirely inadequate to counterbalance a lethal dose of belladonna. Furthermore, the administration of the antagonist was suspended when most demanded by the violent symptoms of belladonna poisoning. The lesions discovered at the autopsy, however, quite explained why death should occur despite the administration of an antidote. The heart was found pale and flabby, and the pleural surfaces adherent throughout.

Case III (Reported by Dr. Samuel W. Gross. "Am. Jour. of the Med. Sci.," Oct., 1869, p. 401).—Mrs. H., a stout woman, aged forty-three, took at 8.20 A. M. four pills containing three grains of atropia, by mistake of the druggist. In a half hour she had lost control of her limbs, was deeply flushed and delirious, the hallucinations consisting in her thinking she was shopping, sewing, nursing a child, etc. This pleasant delirium lasted about ten minutes, when she sighed, yawned, and then fell into a deep sleep, and at 10 A. M. could not be roused. An enema and a number of emetics were administered. At 11.15 one of the several physicians reported that Mrs. H. was unconscious—eyes closed, pupils dilated, muscular system relaxed, except of the jaw, which was in a state of trismus, so that it was very difficult to get anything into the stomach; respiration labored, pulse good. Half a grain of acetate of morphia was then given. At 11.40, Dr. Gross states, the muscular system was relaxed, the trismus having passed off; the skin was cool and moist; pulse 106; respiration 26 and heavy without stertor; the countenance somewhat livid; the conjunctivæ injected; pupils dilated three fourths and insensible to light; the eyes fixed, with a brilliant stare; the roof of the mouth, the tongue, and the soft palate were parched and glazed; deglutition was impossible, and the attempts to introduce remedies

by the mouth brought on suffocative attacks. Half a grain of sulphate of morphia was then given subcutaneously. The effect of this was a scarcely perceptible contraction of the pupil, reduction of the respiration to 20, slight stertor, no change in the pulse. The stomach-pump was then used, the faradaic current was applied, and artificial respiration was carried on. After the stomach was washed out, whisky and ammonia were injected. At 12 M., a third injection of a half grain of morphia was inserted under the skin. In fifteen minutes the respiration was at 14, but very decidedly stertorous; the pulse 102, full, but rather weak. On account of the stertor, no more morphia was given, and the treatment subsequently consisted of flagellation, artificial respiration, and faradization. Whenever artificial respiration was suspended, the breathing became labored, and threatened to cease entirely. At 6.30 P. M., however, the breathing became more natural, and at 7.45 all the measures were suspended, as the patient appeared to be in a quiet sleep, respiration 18, pulse 108, weak, but of pretty good volume. At 8.45 P. M. the respiration increased, râles became audible in the chest, the face turned livid, and respiration was about to cease, when the measures before used were resorted to, and veratria ointment was in addition vigorously rubbed in over the spine and chest. At 9 P. M. the pulse was at 128, respiration 28, and she executed various voluntary movements when hurt by the flagellation. At 10 P. M. she cried out, "Oh, my!" and turned on her side. At 11 P. M., in response to the question, she replied that she was "better." Artificial respiration had been kept up at intervals. Some urine was drawn off, and a small quantity was injected into the family cat, producing decided dilatation of the pupil. At 11.10 P. M. symptoms of suffocation suddenly set in, and, notwithstanding the vigorous application of the methods before used, she soon expired. At the autopsy, the superficial veins of the body were found gorged, and there were extensive suggillations posteriorly. The veins of the brain were very full, there was much serum in the sub-arachnoid space, and the cerebral tissue was generally softened [by imbibition, probably]. The lungs were deeply congested, and the tissue of the heart was soft and easily torn.

Commentary: Although I have placed this among the unsuccessful examples of atropia poisoning treated by morphia, it can only be so regarded with some distinct limitations. The quantity of morphia required to antagonize such a dose of atropia is hardly less than six grains. The first injection was given in three hours after the atropia was taken, the last one in four hours, and nearly twelve hours before death. After the first injection the pulse was reduced to 108, the trismus had ceased, the skin was cool and moist, and the respirations were 20, without stertor. These were very favorable indications, and were produced by one half a grain of morphia only. Under these circumstances, it seems to me it would have been better to await the further antagonistic action of morphia, for, although the amount given was insufficient to antagonize the quantity of atropia taken, it will be shown hereafter that the condition of the respiration and circulation was such as to justify the

belief that the antagonism was sufficient. Furthermore, by this time, no inconsiderable part of the atropia had been eliminated, as proved by the effect of the subcutaneous injection of the urine in the cat. It is not a little important, as I shall hereafter demonstrate, to note the rate of elimination of the poison as a factor, before deciding on the quantity of the antagonist to be used. Another element in this case, that goes far to impair its value as a negative fact, is the condition of the heart. The patient was a rather obese subject, and hence it is probable the heart muscle was in a state of more or less advanced fatty degeneration. The fatal result, at last, appears to have been caused by failure of the heart.

Case IV (Reported by F. A. Southam, M. D. "Brit. Med. Jour.," June 8, 1878, p. 824).—A man, aged thirty-eight, had taken two ounces of laudanum eighteen hours before treatment was instituted. He was then in a state of profound coma, the pupils were contracted to the size of pins' points, the conjunctivæ were insensible, the respirations were four a minute, the pulse was very quick and irregular. The treatment consisted in the application of heat, artificial respiration, faradization, and the hypodermic injection of atropia. The patient received in all five injections, of $\frac{1}{36}$ grain each—the first at 7.30 P. M., the second at 7.45, the third at 8.30, the fourth at 9.30, and the fifth at 9.45 P. M., the man dying at 10 P. M. The immediate effect of each injection was to raise the respiration to near normal, and to improve the tone of the pulse, but the effect was brief and lessened with each injection. Extensive congestion of the lungs was found after death.

Commentary: This case is complete in all the terms of the problem. The poison was entirely absorbed, and there were no complications or accidents to affect the result. An obvious deficiency existed in the treatment, however. The good accomplished by each injection was most conspicuous, but the impression made was so transient that no effect remained over to the next dose. As the whole of the poison taken probably remained in the blood, the function of excretion being suspended by the narcotism, the whole amount of atropia administered should have been given at one dose, and repeated according to necessity. In a case almost exactly similar, except that the quantity of laudanum taken was somewhat less, Dr. Milner Fothergill gave at once one grain of atropia sulphate, with entire success. It is evident that the quantity of atropia administered was not sufficient to antagonize the opium, although the return of the reflex sensibility, the improvement in the respiration, and the dilatation of the pupil indicated that a counterbalancing action was exerted, if only for a brief period. The long duration of the toxic symptoms before the administration of the

antagonist was not without influence, for the carbonic-acid narcosis and the congestion of the lungs were developed when the respirations were only four a minute. Nevertheless, an efficient administration of the antagonistic would have secured a favorable result.

Case V (Reported by Dr. G. E. Paget. "Brit. Med. Jour.," Sept. 15, 1877, p. 374).—A child, three and a half years old, received an unknown quantity of laudanum, but only sufficient to cause, in two and a half hours, a drowsy look. The pupils were very small. The drowsiness increasing, notwithstanding vomiting, strong coffee, and ambulation, $\frac{1}{100}$ grain of sulphate of atropia was injected in four hours after the poison had been taken. No effect being produced by this, another injection of $\frac{1}{200}$ of a grain of atropia was inserted. After this the pupil slowly dilated, and, in an hour and a half, had attained extraordinary size, but notwithstanding this the stupor deepened into coma. In five and a half hours, the appearance of the child was almost death-like. Artificial respiration was diligently applied for many hours; and at the expiration of twenty-four hours, decided improvement was manifest, but unfortunately proved temporary. Four hours after the pupils became affected by the atropia, they had regained their natural size. Death ensued in twenty-eight hours after the poison was taken.

Commentary: The important fact in this case is, the predominant effect of atropia on the pupil, and the apparently slight effect on the pulse, respiration, and cerebrum. The quantity of laudanum swallowed being unknown, no guide, except the state of the functions, existed for the administration of atropia. It is probable indeed that the first injection of atropia was sufficient, as after the expiration of four hours, the child was merely "drowsy." The lividity, death-like pallor, and coldness of the extremities came on after the second injection. The report further states that, "while he was in the heavy stupor, his arms were several times extended in tonic spasms, and his eyes now and then squinted divergently." At this time "his pupils were so dilated that scarcely a part of the iris could be seen." As atropia produces more or less tetanizing action, it is probable that the tonic spasms were produced by it. From this point of view, the action of the opium being slight, it would have been better to await the influence of the first injection. Death occurring, probably from exhaustion, in twenty-eight hours, would seem to be a not unnatural result of the poison, the artificial respiration, the emetic, the ambulation, the flagellation, the atropia, etc., acting on the system of a child three and a half years old.

Cases VI and VII (Reported by Dr. F. L. Haynes. "Phila. Med. Times," Sept. 14, 1878).—Two cases of opium poisoning—the first by a half-ounce of laudanum; the second by an ounce of crude opium. In the first case, there

were two injections of atropia—one of $\frac{1}{15}$, the other of $\frac{1}{35}$ grain, without effect on the respiratory function. The amount of the antagonist was much too small. In the second case, there were four or five doses of $\frac{1}{20}$ of a grain of atropia, equivalent to one fourth of a grain in the aggregate, to antagonize an ounce of crude opium. It is merely necessary to state the facts to demonstrate the source of failure, if there were no other unfavorable conditions present.

Case VIII (Reported by Dr. James Johnston. "Med. Times and Gaz.," Sept. 7, 1872).—A man, aged thirty-two, took three drachms of the extract of opium at 8 P. M. At 11 P. M. he was profoundly comatose; pulse 121, weak and irregular; reflexes abolished. At 1 A. M. a quarter of a grain of atropia was injected. At 3.30 A. M. the face was slightly flushed and the pupils were dilated; pulse 130, weak and intermittent. At 9 A. M. another injection of the same quantity was inserted. Respiration was then softer, pulse still very weak, but he could be roused slightly, and he swallowed a little ammonia and coffee; but he gradually failed, and died at 5 P. M.

Case IX (same source. *Loco citat.*).—A girl of sixteen received ten drachms of extract of opium. Six hours afterward the stomach-pump was used, and a half grain of atropia was injected. In an hour the pulse was almost imperceptible, and death ensued in two hours after the atropine was inserted.

Case X (same source. *Loco citat.*).—A man, aged thirty-eight, took three drachms of the extract of opium at 10 A. M. At 3 P. M. he was comatose, with stertorous breathing, and the pulse was weak and irregular. One fourth of a grain of atropia was given, after the stomach had been thoroughly emptied by the pump. At 4.30 P. M. the pupils suddenly dilated to a great extent, the respiration became hurried and irregular, and the pulse ceased at the wrist, death occurring at 5.30 P. M.

Case XI (same source. *Loco citat.*).—A woman, aged seventeen, took an unknown quantity of opium, and was found in a state of profound coma, pulse 150, respiration slow and stertorous. Half a grain of sulphate of atropia was then injected, and artificial respiration was carried on, but without effect.

Case XII (same source. *Loco citat.*).—A woman, aged thirty-six, took two drachms of extract of opium at 8 A. M. At 1.20 P. M. she was drowsy, but could be roused up to walk about, and was vomited by sulphate of zinc. At 2.20 P. M., severe coma setting in, the cold douche was used, and at 3 a half grain of sulphate of atropia was injected. At 4, the face was slightly flushed, and the pupils were dilated a little, but, at 5, convulsions of the extremities and face began, and she died at 5.30 P. M.

Case XIII (same source. *Loco citat.*).—A woman, aged twenty-seven, took a half ounce of extract of opium at 9.30 A. M. At noon the stomach-pump was used, and a half grain of sulphate of atropia was injected. She was then in a profound coma, with stertorous breathing, her pulse was small and quick, her lips livid. At 3 P. M. convulsions set in, and death ensued in a few minutes.

Commentary: The six fatal cases, from the eighth to the thirteenth, inclusive, were reported by Dr. James Johnston, of the Chinese Hospital, at Shanghai, who has had unequaled opportunities of clinical experience in opium poisoning. He thus comments on the fatal cases: "Of the fatal cases in which atropine was used, the

first one reported lived for eighteen hours, and the action of the atropine was very manifest, as the patient partially recovered consciousness, and did not perish from the comatose effect of opium, but from exhaustion following that condition. In the second fatal case, the patient was only two hours and a half under treatment, and died from cerebral apoplexy. The third was under treatment a little over two hours, and died from cerebral effusion. The fourth was two hours under treatment, and died from exhaustion. The fifth was under treatment for five hours, and died in convulsions. The sixth also died in convulsions, and was under treatment for three hours and a half." To these criticisms we may add that there was no proper adjustment of the dose of the antagonist to the effect of the poison, and that in two of the cases the atropia was without effect, owing to the depth of the narcotism and the suspension of absorption. As the experience of Dr. Johnston is quite unprecedented in respect to opium poisoning, I quote his opinion of the value of atropia as an antidote: "The class of cases in which the wonderful powers of atropine as an antidote to opium poisoning are most marked is where profound coma exists; and, for such a condition, I know of no other remedy. You may try to drag the patient about, use the cold douche, carry on artificial respiration assiduously, give stimulants of every description; all in vain—the patient remains comatose and lifeless. Administer atropine, and the effects are marvelous: the pupils dilate; the face becomes flushed; the respiration loses its stertorous character, and becomes slow and tranquil; the pulse is diminished in frequency, and becomes stronger; the patient slumbers peacefully for several hours, and at last wakes up conscious."

Case XIV (Reported by Dr. H. C. Wood. "Phila. Med. Times," Aug. 9, 1873.)—A man, aged sixty-three, received for an attack of cholera morbus 1½ grain of morphia and 1¼ grain of opium. For the opium narcosis which ensued, there were administered fourteen injections of atropia, aggregating ½ grain. The last injection was administered twenty-four hours before death, which ensued in twenty-eight hours after the ingestion of the poison.

Commentary: The probable existence of an underlying morbid state and the exhaustion caused by the cholera morbus must be taken into account in estimating the precise share of atropia in the result. Such a case is, indeed, of small value for determining the existence of an antagonism between, or the opposed action of, atropia and morphia, owing to the uncertainty which must attend the relative influence of the several factors concerned.

Case XV (Reported by Dr. Beddoe. "Lancet," July 16, 1870).—A woman, aged sixty-eight, swallowed a teaspoonful of belladonna liniment at 11 A. M. Emetics and the stomach-pump were used without effect. At 2.45 P. M. she received twenty minims of laudanum, and soon after an injection of one third of a grain of morphia acetate. Previous to this, she could still swallow fluids, and, although delirious, could understand what was said to her. At 3.30 P. M. the morphia injection was repeated, one fourth of a grain being given. She was then reported to be less active in her movements, and seemed more drowsy. After the last injection she became comatose, and breathed stertorously if undisturbed for a few moments. Her pulse was then 100, and of good strength, and the pupils were widely dilated. At 4.30, a third injection of morphia—one third of a grain—was given. At 6.15 P. M. she was decidedly comatose, and ceased to breathe unless artificial respirations were kept up. At 3 A. M., sixteen hours after taking the poison, she died. The autopsy disclosed venous hyperæmia of the brain and lungs.

Commentary: The strength of the belladonna liniment of the British Pharmacopœia is four times that of the extract of the leaves. The patient being able to swallow without difficulty three hours after the ingestion of the poison, and, although delirious, returning correct replies to the interrogatories addressed her, indicate that the toxic effect was not great. Under these circumstances, small doses, only, of the antagonist were proper. When decided stupor followed the second injection, the third should have been withheld, notwithstanding the persistent dilatation of the pupil, for, as I shall show, this sign is not without qualification. In fact, we find that the reporter of the case remarks, "excepting the dilatation of the pupil, the patient's condition exactly resembled that of opium poisoning, after the delirium had subsided into coma."

LECTURE II.

OPIUM AND BELLADONNA, CONTINUED.

A REVIEW of the fatal cases of opium or belladonna poisoning, in which the antagonist was the principal means of treatment, lessens their importance as negative testimony. The maximum and minimum toxic doses proving fatal are equaled by the doses recovered from. Hence it may be assumed that, if the results are not fortunate in any case, we have a right to conclude that one of three propositions is true: that the toxic dose was excessive; that it had been acting so long that the tissues could no more react to the antagonist; or, that the antagonism was defeated by the failure of some vital organ. In the fifteen fatal cases, there were eleven inefficiently treated; in six of these but a single injection was practiced, and in all the actual amount required to antagonize the toxic agent was not given. In two of the fifteen cases the antagonist was used in excess, and the fatal result in both may fairly be attributable to this preponderating action. In six, the persons poisoned were already in a pathological state: one had experienced an apoplectic stroke; one died from cerebral hæmorrhage, and another from cerebral effusion; one was suffering from the effects of a cholera morbus; one had a fatty heart; and one had general adhesions of both pleural surfaces. If, indeed, all the sources of fallacy were excluded, the fatal cases would scarcely aspire to the dignity of negative facts. So preponderating are the examples of success, and of so little value the negative cases, that a high degree of certainty must be admitted to inhere in the application of the antagonism of opium and belladonna.

With respect to the successful cases, if it be claimed that one agent may prevent death from the other, it must be shown that the quantity of poison taken was really lethal. As readily determined

as this may appear to be, it is nevertheless difficult, even impossible, in respect to any single instance. We find in Taylor "On Poisons" that four grains of crude opium, two drachms of laudanum, and one grain of muriate of morphia have each proved fatal to adults. On the other hand, as much as eight ounces of laudanum have been taken without injury. In one instance a drachm of the extract of belladonna did not, and, in another, two grains of atropia did, cause death. The remarkable variations in the toxic effects of poisons, due to idiosyncrasy, to the state of the stomach, to the fullness of the vascular system, to habit, etc., must be taken into account in estimating the influence of the antagonist in the curative result. Harley has collected a number of cases, in which an unquestionably lethal quantity of the poison failed to cause death, when not interfered with by the action of an antagonist, or by any specific treatment. It is necessary therefore to ascertain, definitely, whether in each one of the 106* successful cases the patient had received a dose probably lethal, or presented symptoms indicating that such quantity had been taken. On the other hand, the antagonism may be admitted to exist, if decided symptoms occasioned by one may be removed by the administration of the other. Under the latter, may be classified the cases of Graefe and Fronmüller, in which symptoms of poisoning were produced by a half grain of sulphate of atropia. The antagonizing action may be just as clearly exhibited in such as in undoubtedly lethal cases. Among the patients receiving the largest amount of poison and recovering, were one having had thirty grains of crude opium; one, an ounce and a half of laudanum; one, twelve to fifteen grains of morphia; one, five grains of morphia; one, six grains of morphia; one, a teaspoonful of belladonna liniment, which is of four times the strength of the extract; one, two grains of morphia and one grain of atropia together, etc. In all but two, the quantity of poison received was sufficient, *cæteris paribus*, to cause lethal effects, and this collection of cases, therefore, fulfills the conditions necessary to the determination of the question of antagonistic action in its entirety.

While the necessary conditions are not wanting in the examples of antagonistic action collected here, there is a source of fallacy in the fact that various approved expedients were resorted to, in addition to the exhibition of the antagonist. An emetic or the stomach-pump, faradism, ambulation, various kinds of irritation of the

* Another case obtained from "N. Y. Med. Jour." just before this lecture.

surface (chiefly flagellation), and artificial respiration were employed to a greater or less extent. Sometimes good effects were obtained by these measures, but the antagonism could not be questioned when the respiration, the cardiac movements, and the state of the pupil indicated the action of the antagonist. Very often the protracted efforts at resuscitation, in the way of flagellation, ambulation, artificial respiration, and faradization, exhaust the patient. In several of the cases it is evident that these ill-advised measures contributed to a fatal result, especially the protracted ambulation and flagellation. I quote on this point the fifth and last conclusion of Dr. Johnston, of Shanghai, China: "When the system is fairly under the influence of atropine, with respiration tranquil, however slow it may be, it is undesirable to interfere by artificial respiration, as it only embarrasses the breathing and interferes with the tranquil sleep which usually follows the exhibition of atropine."

All sources of fallacy eliminated, the antagonizing action of opium and belladonna is supported by a great array of cases. The clinical evidence seems conclusive. We have now to examine the evidence in opposition based on experiments on animals. This is deserving of attentive consideration. Unfortunately, the first observations made on animals by Brown-Séquard,* Bois,† Camus,‡ Onsum,§ and Harley,‖ were vitiated by their neglect to ascertain the exact lethal dose of opium or of belladonna. In 1866, Erlemeyer¶ published an experimental research, in which, for the first time on animals, the nature of the opposed action of morphia and atropia was ascertained. He demonstrated that these agents were opposed, or antagonistic, in respect to their influence over the pulse, respiration, pupil, and brain, and that they were much better borne when given in combination than when given separately. Conclusions in some respects the same were reached by Harley. He thus formulates the results of his experiments on dogs:

"1. Belladonna, when administered simultaneously with opium, more or less completely prevents nausea and vomiting, and, when given previously, entirely prevents these effects. 2. Whether given previously, simultaneously, or subsequently, atropia completely counteracts the respiratory restraint on the free action of the heart, which is so prominent an effect of the operation of opium. We can

* "Jour. de Physiol.," etc., *loc. cit.*
† "Gaz. des Hôp.," 71, 1865.
‡ "Gaz. Hebdom.," 2 sér., xii, 32, 1865.
§ "Schmidt's Jahrbücher," vol. cxxviii, p. 288.
‖ "The Old Vegetable Neurotics," *loc. cit.*
¶ "Berlin. klin. Woch.," 2, 1866.

wish," he further says, "for no more perfect an illustration of the beneficial influence of a medicine under suitable conditions than that afforded by the simple and direct action of atropia in relieving the impending syncope which often persists for many hours after a dose of opium. . . . 3. While the spinal effects of opium on the muscles of organic life are thus counteracted by the stimulant action of atropia on the sympathetic, the cerebral and anæsthetic effects are intensified and prolonged by belladonna, and hypnosis is converted into narcosis," etc.

In 1870, Dr. Koning* published a dissertation on the supposed antagonism of morphia and atropia, his research being conducted on animals. As had his predecessors in this inquiry, Koning 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 morphia and atropia—the reporter says: "Extraordinary pains were taken to determine the question whether or not morphia and atropia 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 atropia is physiologically antagonistic to the meconate of morphia within a limited area. 2. Meconate of morphia does not act beneficially after a large dose of sulphate of atropia, 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 morphia is not specifically antagonistic to the action of sulphate of atropia on the vaso-inhibitory nerves of the heart; and, 4, the beneficial effect of sulphate of atropia after the administration of large doses of meconate of morphia is probably due to the action sulphate

* "Schmidt's Jahrbücher," vol. cxlix, p. 18.

† "Pharmakologische Untersuchungen," 1873, pp. 224 and 231.

‡ "Brit. Med. Jour.," 1874, vol. ii, various Nos.

of atropia 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 morphia."

In 1876 the same line of research was taken up by Corona, on dogs and cats. He arrived at the conclusion that a partial physiological antagonism existed between morphia and atropia; but not a therapeutical antagonism—for, while morphia is useful in atropia poisoning, in poisoning by morphia the effects are not removed by atropia. 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.

The various experiments on animals have been singularly uniform in results, how much soever the interpretations put on the facts may differ. In the first place, it is perfectly evident that, when lethal doses of the two poisons are administered, fatal results almost invariably ensue—not invariably, since the Bennett committee succeeded in a very few out of a great many trials. If the experiment of Bois, already described, should always succeed, the lethal power of the two agents combined is greater than that of either alone. If the lethal effects be omitted from consideration, we find that the experiments on animals are of great value in interpreting the antagonism of these agents on man; for they serve to show, not only the nature of the antagonism, but the method of its production. These experiments demonstrate that morphia and atropia are antagonistic on the pupil, on the action of the heart, and on the movements of respiration.

We are now prepared to undertake to investigate the nature of the antagonism as it occurs in man. To proceed from the known to the supposed, we must first form a definite conception of the physiological action of each. What effect has morphia, what effect has atropia, on the organism of man? In what respects do they agree, in what respect do they differ in their action? The action of each must be studied in respect to full and lethal doses. When a full dose of opium is administered, drowsiness—in some subjects an obstinate wakefulness—comes on; the pupil contracts; the mouth,

tongue, and throat become dry; the appetite is lost; constipation occurs in consequence of diminished secretion and lessened power in the muscular layer of the bowel; the action of the heart slows and declines in force; the respirations diminish in number and depth; the urine is passed slowly and with some difficulty, and is scanty; and the skin is covered with a copious perspiration. When a lethal or toxic dose is swallowed, all of these effects are intensified; the individual passes into a condition of stupor, which more or less quickly deepens into coma, from which no form of irritation can rouse him; the pupils contract to the size of a pin's point, and the conjunctivæ are insensible to irritation; no reflex movements are excited by touching the cornea or by titillating the fauces; the respiration is slow, descending to six, to four, even to two in a minute, and is stertorous and shallow; the pulse is slow, weak, and irregular, or very rapid, irregular, and weak; the skin is covered with an abundant cold sweat; the countenance is pale and sunken, sometimes blue with cyanosis or livid; the ears are purplish, and the neck, posteriorly, bluish-black from ecchymosis; and the extremities, as well as the skin generally, are cold and clammy. Death ensues by failure of respiration.

When a full dose of belladonna is taken, the mouth and lips quickly become dry, and swallowing is difficult; the head feels full, and there are vertigo, tinnitus aurium, and flying pains, frequently severe headache; the mind is excited, speech rapid and voluble, and there occur hallucinations—a busy delirium, in which the individual is engaged in his usual occupation—the tailor crosses his legs and goes through the motion of sewing; a carpenter appears to be driving the plane or handling the saw; others are boisterous and quarrelsome, and fall to fighting and struggling, etc.; the pupils are widely dilated; the action of the heart is rapid—the pulse, at first firm, afterward is weaker, and the arterial tension, at first raised, declines subsequently below normal; the respirations are quickened; the bowels are apt to be relaxed; the urine is voided slowly and with difficulty; the gait is unsteady from muscular incoördination, and the muscular system is weakened; the skin is dry and warm, the face is flushed, and often covered with a scarlet efflorescence, etc. When a lethal or toxic dose is taken, the symptoms just mentioned are increased in all directions; a sudden vertigo overpowers the voluntary movements, vision quickly grows dim and uncertain, with the extreme dilatation of the pupil; delirium follows quickly and is occupied with ordinary employments, with talk-

ing, visiting, sewing, or with angry controversy and struggling; but this stage of hallucinations, which, when non-lethal but large doses are taken, is protracted, is comparatively short, and is succeeded by coma, or there come on, in the midst of excited delirium, snatches of stupor, but presently the unconsciousness becomes profound; the pupils dilate until no rim of the iris is visible; the mouth is utterly devoid of moisture, and the tongue, shrunken and dry as a bone, lies in the bottom of the mouth motionless; the flush of the face is succeeded by a deathly pallor; the pulse becomes very rapid, and the respiration is hurried; the temperature of the body rises, but the increased tension of the arterial system is succeeded by paresis of the vessels, the pulse becoming weak and fluttering; and death results from the failure of the heart and lungs.

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 five years, drank by mistake a mixture of equal parts of liniment of opium and liniment of belladonna. The 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 eight years, the son of a physician of Cincinnati, was given internally by mistake an anodyne application for earache, containing two grains of morphia and one grain and a half of atropia. 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

* "Med. Times and Gaz.," Nov. 3, 1866, p. 474.

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 of opium and belladonna, the amount taken being equivalent to twenty-five grains of the extract of belladonna and twelve 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 atropia are certainly thus controlled [i. e., by morphia], as well as the partial deafness and visual defects which in high doses it occasions. On the other hand, when morphia has been fully used, the drowsiness and stupor which are the best tests of its power disappear before the influence of atropia. . . . Perhaps the most peculiar cerebral symptom of atropia 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 morphia. Drowsiness caused by morphia was as surely lessened or destroyed by the counter agency of atropia; and, in fact, atropia 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 morphia over the cerebral effects of atropia. "The influence of opium in

* "Am. Jour. of the Med. Sci.," vol. l, p. 67, *et seq.*

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 morphia and atropia, 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, Erlenmayer* shows that the exciting effect of atropia on the brain is lessened by the narcosis of morphia. Harley's experiments on dogs were similar in results: "The cerebral effects of atropia 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. 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 centers and the centers of respiration and circulation, while in man its effects are exerted not only upon these centers, but upon the higher centers 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 morphia and atropia when administered simultaneously?

* "Berlin. klin. Woch.," *loc. cit.*

† "Arch. f. experiment. Pathol. u. Pharmakol.," 1878, Band viii, p. 31. "Antagonismus zwischen Morphin u. Atropin."

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."

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 atropia 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 morphia and atropia 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 fibers 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 the list of unsuccessful cases, we find that a very large quantity of morphia was given to counteract the effects of some belladonna liniment taken by accident, and that, notwithstanding the apparent preponderance in the action of the

* "Introduction à l'Étude de la Médecine Expérimentelle." Paris, 1865, p. 219.

morphia, 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. There are exceptional manifestations, it is true, but, as there are two examples in 120 cases, the value of the indication afforded by the state of the pupil is correspondingly weakened. The antagonism between morphia and atropia 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. Atropia acts both more promptly and for a much longer time. Atropia 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 can not 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 "morphia has no power to prevent atropia thus influencing the pulse, so that as regards the circulation they do not counteract one another." Harley maintains that morphia, here as elsewhere, increases the effect of atropia. "If, however," he says, "the dose of atropia is small, and the morphia produce considerable derangement of the vagus, the rapidity of pulse is not greater than when the atropia is administered alone. In my own observations I have invariably seen that the acceleration of pulse produced by atropia is lessened by morphia, and *vice versa*, and this is the conclusion derived from a study of the reported cases of poisoning. The effect of the atropia, however, preponderates. The result of the combined effect is not the mean of the two, but is nearer the standard of atropia than of morphia. 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 atropia on the heart is remarkably lessened by combination with morphia. In the careful experiments of Heubach, the same result is shown; the increased pulsations caused by atropia are diminished by morphia, but the general level of effect is above the mean considerably. We must, therefore, conclude that the effects of morphia are antagonistic to those of atropia on the heart to a limited extent, but that the effects of atropia 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 morphia and atropia 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 atropia a respiratory stimulant. The cause of death in opium narcosis is failure of respiration, the action of the heart ceasing after respiration. Atropia 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. Atropia 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.

Atropia proves fatal by exhausting the irritability of the motor ganglia of the heart and of the general vaso-motor system, and also of the respiratory centers. Morphia, by lessening the work of the heart and of the lungs, opposes these effects of atropia. The facts presented in the 120 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 atropia is simply marvelous in stimulating the respiratory function and removing the carbonic-acid narcosis. In the fatal case of atropia poisoning narrated by Dr. Gross, the injection of morphia induced stertor. I have already suggested that the more gradual introduction of the morphia 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 atropia 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 atropia used was rather in excess, as an emetic had caused the discharge of some opium, and the subsequent account shows a preponderating action of atropia. An equally instructive case, as showing the power of atropia to overcome the respiratory depression caused by morphia, is narrated by Dr. McGee.† A stout, muscular man of 40 years swallowed 30 grains of opium in 10 or 12 ounces of whisky. He became profoundly comatose. In two hours an eighth of a grain of atropia was injected, and, this having no effect, in a half an hour the same quantity was repeated. The respirations were then nearly suspended, the face being livid, but under the influence of the atropia 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

* "The Antagonism of Therapeutic Agents." Philadelphia: H. C. Lea, 1878, p. 132.

† "Am. Jour. of the Med. Sci.," July, 1869, p. 282.

on the respiratory function. There is no difference in the lesson taught us in the cases of opium narcosis. The cases of atropia poisoning treated by morphia 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 morphia 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 atropia on the pulse and respiration is in no way altered by the use of full doses of morphia, so that in this particular their supposed antagonism does not exist." In some experiments of my own, made on a medical student, I found that morphia modified to a considerable extent the effects of atropia 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 $\frac{1}{96}$ grain of sulphate of atropia, at intervals of two hours, must be practiced." The facts of Dr. Harley admit of very different interpretations from those which he has advanced; they prove that atropia exerts a distinct stimulant action on the respiratory organs, and are in conformity with clinical experience. We may now regard it as settled that atropia antagonizes the depression caused by morphia on the respiratory function, notwithstanding the adverse opinions just quoted.

* "Schmidt's Jahrbücher," vol. cxxv, p. 350. † *Ibid.*, vol. cxxiv, p. 167.
‡ *Ibid.*, vol. cxxvi, p. 282. § "Berlin. klin. Woch.," 11, 16, 1865.
‖ "Manual of Hypodermic Medication," 3d ed., Philadelphia, 1879.

The antagonistic action of atropia and morphia 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, and clinical experience justifies the remark of Harley, that morphia should not be administered alone, unless its action on the subject is known, but always with atropia. The explanation of the utility of atropia in preventing the nausea and depression caused by morphia 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 atropia, also, excites nausea in some subjects. The coldness of the surface and the clammy sweat caused by morphia are removed by atropia. The importance of this fact is considerable. The first effect of morphia 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 atropia 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.

Atropia stimulates the action of the kidneys somewhat, and morphia 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. Morphia dulls the sensibility of the mucous membrane, and diminishes the contractile energy of the muscular coat of the bladder; atropia 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 morphia 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 morphia poisoning as the type, the quantity of atropia 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 atropia 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 $\frac{1}{20}$ grain of atropia was about equal in toxic power to a grain of morphia. In deciding on the dose of the antagonist, the amount of the poison probably eliminated must be taken into consideration.

Having completed the survey of opium and belladonna, I submit the following conclusions:

Morphia and atropia are antagonistic in their effects on the cerebrum, and the result of the antagonism is to induce sopor, but this deepens into coma if the quantity used is large, and hence the opposition does not extend to lethal quantities.

They are antagonistic in their action on the pupil, but this effect is not constant, owing to idiosyncrasy, and the action of atropia preponderates and is more lasting.

They are antagonistic in their action on the heart, morphia slowing and atropia increasing the rate of movement, but the effect of atropia is both more powerful and more prolonged.

They are antagonistic in their action on respiration, morphia slowing and atropia increasing the respiratory movements. Accordingly, morphia diminishes the excretion of carbonic acid, and causes carbonic-acid narcosis; atropia promotes the excretion of carbonic acid, and thus helps the function of hæmatosis.

They are antagonistic in their action on the arterial tension. Morphia, after first raising, greatly depresses the arterial tension, and suspends hæmatosis by slowing the heart and paralyzing the arterioles. Atropia antagonizes all of these actions.

Atropia prevents to a large extent, in many cases entirely, the depression, coldness of the surface, cold sweating, and cerebral nau sea caused by morphia.

Morphia and atropia are antagonistic in their action on the kid-

neys, the former diminishing, the latter augmenting, the urinary discharge. They differ in their action on the bladder, morphia lowering the sensibility of the mucous membrane and weakening the muscular layer, while atropia stimulates the sphincter. They are not therefore antagonistic in their effect on the bladder.

In therapeutics, these antagonisms are made use of to procure effects not attainable by either drug singly; to avoid unpleasant results produced by each, and to enhance the safety of their administration in full doses. The whole subject affords a beautiful example of the success of the methods employed by modern pharmacological research to improve our knowledge of the action of the oldest remedies, and to increase the safety, certainty, and range of their applications to the treatment of disease.

LECTURE III.

ANTAGONISM OF ATROPIA AND PHYSOSTIGMA; ATROPIA AND PILOCARPIN; ATROPIA AND MUSCARIA; ATROPIA AND QUINIA; ATROPIA AND BROMAL HYDRATE; AND ATROPIA AND ACONITINE.

THE next investigation of the antagonism between medicinal agents is concerned with the opposition of actions between atropia and physostigma, or Calabar bean. The extract and the active principle—eserine, or, as it is sometimes called, physostigmine, or calabarine—are the preparations used to procure the physiological effects of physostigma.

For the first time, in 1864, Kleinwächter treated a case of poisoning by atropia by the internal administration of physostigma, the symptoms being relieved to a great extent. In 1867 Bourneville, in a thesis on the treatment of tetanus by physostigma, 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 atropia. 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 was followed by the report of the Committee of the British Medical Association, Dr. J. Hughes Bennett, Chairman.†

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 atropia and physostigma differ? I have already described the deliriant effect of atropia, its power to

* "On the Antagonism between the Actions of Physostigma and Atropia." From the "Trans. of the Roy. Soc. of Edinburgh," vol. xxvi.

† "Brit. Med. Jour." for 1874.

dilate the pupil, to stimulate the heart and the respiration, to arrest secretion, to flush and at the same time dry the skin. Physostigma does not affect the cerebral functions; it contracts the pupil, paralyzes the voluntary muscles, but does not impair sensibility, increases secretion, energizes the heartbeats 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, atropia causing delirious excitement, with hallucinations and illusions—physostigma not affecting this organ at all; on the pupil, atropia causing dilatation by stimulating the radiating fibers innervated by the sympathetic—physostigma causing contraction by paralyzing the radiating fibers, thus leaving the third nerve unopposed; on the respiration, atropia stimulating the respiratory center—physostigma paralyzing the muscles of respiration; on the heart, atropia increasing the rate of movement without adding to the power—physostigma increasing the power without hastening the movements of the heart; on secretion, atropia drying the mouth and the secretions of the intestinal tube—physostigma increasing the salivary flow and the secretions of the whole intestinal canal; on the voluntary muscular system, atropia causing paralysis of the motor nerves—physostigma producing spinal paralysis. As regards the lethal effects, the tendency to death by paralysis of the respiratory muscles, produced by physostigma, is overcome by atropia. Or, as it is expressed by Professor Fraser, "atropia prevents the fatal effect of a lethal dose of physostigma by so influencing the functions of certain structures as to prevent such modifications from being produced in them by physostigma 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 physostigma, may be prevented by atropia."

The first reported example of atropia poisoning treated by physostigma 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

* "Trans. of the Am. Med. Assoc." for 1869.

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: 'Atropia is not a physiological antagonist to physostigma, except in regard to their action on the organic nervous system. It would be improper, then, to use atropia 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 detail of some typical cases, out of a large number of similar experiments, I came to the following conclusions:

"Atropia and physostigma are antagonistic as to their influence over the respiratory movements—atropia increasing and physostigma retarding them.

"They are antagonistic in their action on the heart—atropia producing excitation of the cardiac ganglia, and physostigma paralyzing them.

"They are opposed in respect to their action on the sympathetic—atropia causing increased action, and physostigma paralyzing this system.

"They have opposite effects on the pupil in virtue of opposite effects on the sympathetic—atropia dilating the pupil by its action on the radiating fibers of the iris, and physostigma contracting the pupil by paralyzing the radiating fibers."

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 conclu-

* "Therapeutics, Materia Medica, and Toxicology," 3d ed., p. 320.

sion 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 views longer probably than they deserve, but historical accuracy is of some moment, and no man wishes his proper opinions mangled and distorted by others.

The quotation I have made from Fraser's paper indicates his belief in the existence of an antagonism in the lethal effects of atropia and physostigma 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 atropia antagonizes to a certain extent the fatal action of Calabar bean," yet they maintain that, "for all practical purposes, atropia 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 atropia as an antagonist to the toxic effects of physostigma.

The special points of antagonism have been elaborately studied by various observers. As respects the heart, atropia 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. Physostigma 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 physostigma, and lessened by atropia. The experiments of Rossbach and Fröhlich, in all respects remarkable and novel,† seem not to confirm these observations. Köhler‡ and Harnack and Wilkowski § found that physostigma lessened the pulse rate, after the peripheral filaments of the vagi were completely paralyzed by atropia. Harnack,‖ in a polemical paper strongly characterized by the *fortiter in re*, controverts the views put forth

* "Centralbl. f. d. med. Wiss.," No. 40, 1867.

† "Pharmacol. Untersuchungen," Würzburg, 1873, p. 77.

‡ "Archiv. f. exper. Pathol. u. Pharmacol.," i, p. 277.

§ *Ibid.*, v, p. 402.

‖ *Ibid.*, iv, 1875, p. 146.

by Rossbach and Fröhlich, and by Rossbach alone, in respect to the action of atropia on the heart and on the pupil. Köhler holds that physostigma slows the heart by paralyzing the accelerator nerve. It had already been shown that atropia stimulated the accelerator nerves (Bezold and Bloebaum). Tachau * and Roeber † maintain that the retardation of the heart is due to a paralyzing action of physostigma 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 physostigma is probably due to contraction of the constrictor fibers 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 atropia and physostigma act in an opposed manner on the heart. As respects the respiration, there are fewer differences of opinion. That physostigma causes death by paralysis of respiration, the heart continuing in action after respiration has ceased, seems abundantly established. ‖ On the other hand, it is generally conceded that atropia stimulates the respiratory function. Physostigma 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 center is stimulated by atropia, and 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 atropia, 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 fibers (Fraser, Hirschmann ¶), and by others to a spasm of the sphincter fibers (Grünhagen and Rogow,** Bezold, and Goetz). That the latter view is

* "Archiv. d. Heilkunde," vi, 69.

† Hermann's "Lehrbuch der experiment. Toxicologie," p. 339.

‡ "Beobachtungen über die physiol. Wirkungen der Calabarbohne," Virchow's "Archiv," xxxv, p. 291.

§ Hermann, *op. cit.*

‖ Hermann, *op. cit.*, p. 341.

¶ "Archiv. f. Anat. u. Physiol.," 1863, p. 309.

** "Centralbl. f. d. med. Wissensch.," 1863, p. 577.

correct seems supported by the fact that the effect of physostigma 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 atropia, but the atropinized pupil resists the action of eserine.

The delirium, hallucinations, and illusions caused by atropia are in no respect affected by physostigma. In all of the instances of poisoning by Calabar bean reported, 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 atropia poisoning. These agents do not, therefore, have an antagonistic action on the cerebrum.

In the spinal effects of atropia and physostigma there are obvious differences. They are both paralyzers, but atropia causes, in cold-blooded animals, a subsequent tetanic condition. When atropia and physostigma 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 atropia poisoning, trismus was a marked symptom. Atropia affects the spinal cord, 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 atropia. Physostigma, 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 physostigma and atropia. An increased flow of saliva, of the intestinal juices, of the tears, and of the sweat, is a constant result of the action of physostigma, and is due, according to Heidenhain,† to a central excitation of the secretory nerves. This conclusion seems established by the fact that the increased

* "Jour. of Anat. and Physiol.," xi, part 11.

† "Arch. f. d. ges. Physiol.," v, p. 40: quoted by Hermann.

secretion of saliva failed to occur when the chorda tympani was divided near the submaxillary gland. The action of atropia 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 physostigma stimulates the secretory centers.

On the motor functions, and on the muscles, atropia and physostigma act differently. I have already emphasized the tetanizing action of atropia on cold-blooded animals, and the trismus which occurs in so many cases of poisoning. Botkin * was the first to show that atropia 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 physostigma, or eserine, and atropia are antagonistic in their effects on the pupil. 2. That they act differently, but probably not antagonistically, on the heart, unless we accept the views of Köhler and Bezold and Bloebaum—the former maintaining that physostigma paralyzes the accelerator nerves of the heart, and the latter that atropia stimulates these nerves. 3. That they are opposed in their action on respiration, physostigma paralyzing, and atropia stimulating, the respiratory function. 4. That they are not opposed in their action on the cerebrum, atropia producing delirium, and physostigma 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 atropia does, and physostigma does not, impair the irritability of motor nerves. As regards the sensory nerves, physostigma augments their irritability, while atropia seems rather to lessen it, if any effect is produced. 6. That they act oppositely on secretion, physostigma stimulating and atropia arresting the secretions in general.

It follows from these conclusions that the lethal effects of physostigma, due to paralysis of respiration, are overcome by atropia

* Virchow's "Archiv," xxiv, p. 85. † *Ibid., loc. cit.*

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 physostigma against the lethal effects of atropia is of doubtful propriety. The paralyzing effect of physostigma on respiration may, doubtless, be successfully overcome by the suitable application of atropia.

ATROPIA AND PILOCARPIN.

The antagonism of action between belladonna and pilocarpus, or atropia and pilocarpin, 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 atropia has been sufficiently elaborated in the preceding sections. Our task is now chiefly concerned with the peculiar powers and attributes of pilocarpin. 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 pilocarpin does.

In a few minutes after the alkaloid pilocarpin 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 in under the skin, more or less nausea, even vomiting, is produced, and not unfrequently a watery diarrhœa.

The opposition of actions, between an agent causing such functional disturbances as I have just described and atropia, 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 pilocarpin is of very short duration, and is followed by feebleness of the heart and diminished arterial tension; atropia induces and maintains a quickened heartbeat and a high arterial tension, during at least the whole duration of the action of pilocarpin. A subjective sensation of heat and flushing of the face is caused by both, but is very transient in the case of pilocarpin. Contraction of the pupil is produced by pilocarpin, dilatation by atropine. Dryness of the mouth and of the skin results from atropia, profuse secretion from pilocarpin. Both of these agents tend to cause nausea and vomiting, and a watery diarrhœa. Both render the bladder more or less irritable, and atropia increases the urinary secretion a little, while pilocarpin diminishes it. As regards the nervous system of animal life, no antagonism exists. Pilocarpin does not affect the cerebral functions directly, while atropia causes delirium. Pilocarpin induces weakness of the muscular system, but atropia 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.* Pilocarpin was injected subcutaneously in both, without any obvious influence over either. The experience in the more important of the two cases demonstrated that one grain and a third of pilocarpin failed to excite perspiration, when one third of a grain of the same sample caused in healthy persons most profuse 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 atropia and pilocarpin 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 pilocarpin, the flow of secretion is almost instantly arrested by the administration of atropia. The mechanism of this antagonism has been thoroughly investigated by Vulpian,‡ Langley,§ Marmé,‖ Petrina,¶ and numerous other investigators. Pilocarpin stimulates the nerve ends in the glands, and, as Heidenhain long ago proved, atropia paralyzes the end organs of these nerves. The chorda tympani and the sympathetic filaments distributed to the submaxillary gland being divided, pilocarpin 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 atropia 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 pilocarpin 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 atropia is not less prompt and de-

* "Lancet," Mar. 4, 1876. † "Gaz. Hebdom.," 1875, 6, p. 81.

‡ *Loc. cit.* § "Jour. of Anat. and Physiol.," xi, part 1, pp. 173, *et seq.*

‖ Virchow u. Hirsch, "Jahresbericht," 1878, p. 173.

¶ "Deutsch. Arch. f. klin. Med.," xxi, p. 258.

** "Centralbl. f. d. med. Wissensch.," vi, p. 97. †† Pflüger's "Archiv," xv, p. 483.

cided. The increased secretion caused by the subcutaneous injection of one fourth of a grain of pilocarpin muriate, or sulphate, is arrested by $\frac{1}{100}$ grain of atropia. In a personal trial of this quantity of pilocarpin, 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 sense of extreme bodily depression came on. A marvelous change was wrought by the subcutaneous injection of $\frac{1}{100}$ grain of atropia. 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 pilocarpin 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 pilocarpin is brief, and is followed by slowing and feebleness of movement. The resemblance in action is only apparent. The increased movement produced by atropia may be explained, as we have seen, in either of two modes—by paralysis of inhibition, or by stimulation of the accelerator fibers. The increased action due to pilocarpin 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,‡ alike demonstrate that pilocarpin 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 pilocarpin on the motor apparatus, and which succeed to the preliminary increased movement, are antagonized by atropia (Service).§

The temperature variations observed by all who have carefully

* "Kymographische Versuche über Jaborandi," "Arch. f. exper. Pathol. u. Pharmacol.," vii, p. 435.

† "Berlin. klin. Woch.," No. 10, 1877.

‡ "Étude Physiologique et Thérapeutique sur la Jaborandi," "Jour. de Thérap.," various numbers for 1875.

§ "Jour. of Anat. and Physiol.," April, 1879.

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° F., 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 pilocarpin is antagonized and prevented by atropia. By raising the vascular tonus, and arresting or preventing the profuse discharge of saliva and sweat, atropia 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 pilocarpin and atropine on this organ. Myosis, spasm of accommodation, and recession of the near point are produced by pilocarpin; 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 pilocarpin 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 pilocarpin are not antagonistic to the delirium, hallucinations, and illusions of atropia. In the cases narrated by Dr. Ringer the delirious excitement of belladonna poisoning was not modified by the action of pilocarpin—so that, viewed from either the theoretical or the practical standpoint, the existence of an antagonism on the brain must be denied.

The nausea and vomiting caused by pilocarpin are probably not affected, or are increased, by atropia. When the action of the drug ceases, the stomachal distress occasioned by it ceases also—hence, in this indirect mode, atropia may prevent or arrest it.

I have already indicated some points of similarity of action between pilocarpin and atropia—the quickened heart and flushed face—but these, as has been shown, are apparent, and not real. They

* "Berlin. klin. Woch.," June 18, 1877.

† "Centralbl. f. d. med. Wissensch.," No. 44, 1877.

‡ "Lancet," Jan. 30, 1875.

§ *Ibid.* ‖ "Med. Times and Gaz.," 1877, ii, p. 358.

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 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 atropia, are not affected by any of the actions of pilocarpin. 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 atropia, we have next to consider the mutual interactions of

ATROPIA AND MUSCARIA.

As muscaria, or muscarin, 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.* Muscarin 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—$\frac{1}{30}$ grain producing in the human subject very decided symptoms. The

* "Das Muscarin, das giftige Alkaloid des Fliegenpilzes," etc., Leipzig, 1869; also, "Arch. f. exper. Pathol. u. Pharmacol.," iv and vi. Hermann, *op. cit.*

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 muscaria 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, muscarin 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 muscarin, 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 muscarin, 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 muscarin acts on the motor ganglia in

* "Gaz. Méd. de Paris," 1870, iii, p. 243.

† F. A. Falck, "Der Antagonismus d. Gifte." Volkmann's "Samml. klin. Vortr.," No. 159, 1879.

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 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 muscarin on the respiratory centers.

When we come to compare these disturbances of function caused by muscaria with those produced by atropia, we must admit, with Schmiedeberg, that no example of physiological antagonism could be more exact. On the brain, the intoxication, with cerebral anæmia, of muscarin is opposed by the active delirium and cerebral hyperæmia of atropia. On the eye, the contracted pupil of muscaria, due to stimulation of the circular fibers innervated by the third nerve, is opposed by the dilated pupil of atropia, produced by stimulation of the radiating fibers, innervated by the sympathetic. The effect of atropia on the eye is relatively more powerful, for, when the pupil is contracted by muscarin, it can be dilated by atropine, but, when dilated by atropia, it can not then be contracted by muscarin. On the function of secretion, the antagonism is not less striking. Muscarin promotes the salivary secretion by stimulating the end organs of the nerves in the gland, and atropia arrests this secretion by paralyzing these nerves.† But atropia is relatively more powerful here, also, for, when the salivary secretion is arrested by atropia, muscaria can not reëstablish 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 muscarin is removed by atropine. On the heart, nothing can be more perfect than the opposing actions of these agents. I brought this fact forward in my opening lecture as a striking exemplification of the doctrine of antagonism. If the heart is arrested in the diastole by muscarin, it is started again by atropia. If an animal is first brought under the influence of atropia, the heart is not stopped by muscarin, notwithstanding it is so readily poisoned by

* "Centralbl. f. d. med. Wissensch.," 97, 1870.

† Luchsinger, "Die Wirkungen von Muscarin u. Atropin auf d. Schweissdrüsen d. Katze," etc., "Archiv. f. d. ges. Phys.," 18, 1878, p. 501.

this agent. The antagonism is equally exerted on the respiratory function—muscarin lessens the respiratory movements and finally arrests them, while atropia 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 atropia and muscaria.

Notwithstanding the rather formidable list of antagonisms in which atropia appears on one side, we have by no means exhausted its capabilities. Let me invite your attention, briefly, to the supposed opposition of actions between

ATROPIA AND QUINIA.

The only systematic experimental investigation of the antagonism between atropia and quinia 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 quinia arrests the heart in diastole, and that the subsequent administration of atropia 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, after the subcutaneous injection of quinia, the caliber of the arterioles was lessened by contraction of their walls, while the opposite effect, or dilatation, followed the administration of atropia. Quinia causes a rise in the blood pressure, after a brief preliminary fall, and atropia retards it.

BROMAL HYDRATE AND ATROPIA.

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 atropia. This research was especially in charge of Professor McKendrick, and the scope of it was limited to the lethal effects.

* "Lancet," July 31, 1880, p. 176.

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 atropia. 2. After a fatal dose of bromal hydrate, the introduction of atropia 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. Atropia 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 atropia 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 atropia by the subsequent injection of bromal hydrate."

ATROPIA AND ACONITE.

The last application of the physiological antagonism of atropia is that with aconite, 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. Aconite, a respiratory and cardiac depressant, ought to be neutralized by atropia, a respiratory and cardiac stimulant. The facts, in the main, support this supposition. "Thus, to a rabbit weighing 2 lbs. 6 oz., I gave," says Dr. Fothergill, "three grains of atropia, and six minutes afterward $\frac{1}{300}$ grain of aconitine; the animal survived. A week afterward, the same rabbit had the aconitine alone, and died in two hours and a half." Small doses of atropia, 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 atropia. "It was found, however, that, if the administration of the atropia was delayed beyond sixteen minutes, it was powerless to arrest the lethal action of aconitine."

In the discussion of physiological antagonisms thus far, atropia has been one of the agents concerned in every instance. But atropia also represents a group. One of the triumphs of modern organic chemistry is the reconstruction of organic alkaloids by synthesis, the physiological demonstration confirming, in the most unmistaka-

* "The Antagonism of Therapeutic Agents." Philadelphia, 1878, p. 41.

ble manner, the accuracy of chemical methods. Atropia has been thus reconstructed synthetically from two secondary products. Not less interesting is the demonstration that apparently different alkaloidal principles, obtained from separate and independent sources, are the same. Atropia, daturia, and hyoscyamia are thus shown to be identical in chemical composition. These, however, are so closely related in origin that identity of composition is not surprising. A new mydriatic has been recently discovered, whose relationship to atropia, on the physiological side, is most intimate—*duboisia*, the alkaloid of duboisia myoporoides. This new principle has the same power to dilate the pupil, to paralyze the accommodation, to produce a busy delirium, with hallucinations and illusions. It has, also, the same power to increase the rate of cardiac movement, to raise the arterial pressure, and to flush the surface, to produce the same stimulating effect on the respiratory function, the same rise of temperature. It has, also, the same effect on secretion, and dries the mouth and fauces in the same degree. Besides its more ready influence on the pupil, the more rapid decline of its effect, and its less irritating action on the conjunctiva, besides its less deliriant and greater hypnotic power, duboisia seems to have the same physiological effects as atropia. The late researches of Ladenburg seem to prove that duboisia is identical with hyoscyamia. In the whole range of the wide antagonisms of atropia, duboisia may take its place, and the facts true of atropia are applicable to duboisia and also to hyoscyamia. Duboisia may, therefore, be substituted for atropia in the antagonism with morphia, with physostigma, with pilocarpin, with muscarin, with quinia, with bromal hydrate, and with aconite. Special researches have been conducted with duboisia in respect to the antagonism with muscarin, and with pilocarpin. It exhibited in these trials precisely the same powers as atropia, although, on the whole, it acted somewhat more energetically in corresponding doses. Thus, in a short time after its introduction to professional notice, duboisia is as fully understood, in respect to its powers and uses, as belladonna after centuries, but the one is studied by the modern physiological method, and the other, coming down with vague traditions and baseless theories, is only properly understood at last when the progress of physiological research enables new investigations to conduct to right conclusions.

LECTURE IV.

CHLORAL AND STRYCHNIA; CHLORAL AND PICROTOXINE; CHLORAL AND ATROPIA; OPIUM AND VERATRUM VIRIDE; OPIUM AND GELSEMIUM; OPIUM AND ACONITE; MORPHIA SUBCUTANEOUSLY AND CHLOROFORM BY INHALATION, ETC.

The discovery of chloral hydrate and the subsequent announcement of strychnia as its physiological antagonist, made by Liebreich,* have been followed by numerous researches, monographs, and clinical reports, so that the literature of chloral is already enormous. As we are now concerned in studying the antagonisms of chloral, I purpose reviewing the work done in this direction only. Liebreich demonstrated that animals in a deep stupor from chloral intoxication, the dose administered being lethal, were aroused, and death was averted, by strychnia. If, for example, two rabbits of equal weight—say three pounds—receive $\frac{1}{96}$ grain of strychnia sulphate, a fatal dose, and to one of them fifteen 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 strychnia, 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 strychnia; and then the result of the administration, at varying intervals, of one subsequently

* *Op. cit.*

† "Brit. Med. Jour.," Oct. 3, 1874, p. 437, *et seq.*

to the lethal dose of the other agent. Their general conclusions are as follows: "1. That, after a fatal dose of strychnia, 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 strychnia than strychnia is to save life after a fatal dose of chloral hydrate; 3. That, after a dose of strychnia producing severe tetanic convulsions, these convulsions may be much reduced, both in force and frequency, by the use of chloral hydrate, and consequently 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 strychnia 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 strychnia that there is danger of death from the effects of the chloral hydrate; 5. Chloral hydrate mitigates the effects of a fatal dose of strychnia by depressing the excess of reflex activity excited by that substance, while strychnia 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 strychnia has been undertaken by Husemann.* He holds that chloral is an antidote to strychnia, prevents the spasms, and averts death, and that it has a corresponding effect in the case of the strychnia bases sold under the name of brucin. 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 strychnia, and also to a certain extent the cardiac depression, but that strychnia 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 strychnia, the converse does not hold good, and strychnia is not useful in chloral poisoning. The 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 morphia is an antagonist to atropia in poisoning by the latter, atropia is not an antagonist in

* "Antagonistische und antidotarische Studien." "Arch. f. exp. Pathol. und Pharmacol.," vi, p. 345.

† "Centralbl. f. d. med. Wissensch.," 17, 1870, p. 261.

‡ "Prakt. Arzt," xiv, p. 11. Quoted in "The Practitioner."

poisoning by morphia. 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 strychnia rather promotes than prevents the poisonous action of chloral.

What is the teaching of clinical experience? I have found recorded seven cases of strychnia 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 practiced 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 strychnia 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 strychnia was properly and adequately used, as it is in animals.

If we now sum up the evidence, we can not fail to be convinced of the antagonistic action of chloral and strychnia; but chloral is an antagonist to strychnia poisoning, rather than strychnia is an antagonist to chloral poisoning. The experience on rabbits shows that $\frac{1}{96}$ grain of strychnia is equivalent to fifteen grains of chloral. In the cases of poisoning in man, thirty grains of chloral subcutaneously was sufficient to allay the spasms and avert death from four grains of strychnia. 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 strychnia was merely estimated, no positive conclusions can be drawn from them. Artificial respiration materially retards the action of strychnia, 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

* "Presse Méd. Belge," 1870, No. 9, p. 69. Quoted by Husemann.

† "Bull. Gén. de Thérap.," lxxxiii, p. 403, *et seq.*

‡ "Jour. of Anat. and Physiol.," May, 1874, No. 14.

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 strychnia by chloral, the amount of the latter administered should be determined by the symptoms. Sufficient chloral should be given to suspend the strychnia 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 strychnia was not known, but the return of the spasms from time to time required repeated doses of chloral, one hundred and five grains in all being given within five hours. When strychnia is used against chloral poisoning, the objects to be accomplished are different. By stimulating the cardiac and respiratory centers with strychnia, 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 $\frac{1}{60}$ grain, and each succeeding dose $\frac{1}{120}$ grain, which may be repeated every half hour, or more frequently, until an approximation to the maximum is reached.

We have next to study the physiological mechanism, or to ascertain how the opposition of actions occurs. A preliminary statement of the main facts in the physiological actions of each will indicate the antagonistic points. Chloral, with or without a brief stage of excitement, induces a sopor closely related to normal sleep, and, in lethal doses, coma and insensibility. It therefore in toxic doses suspends the cerebral functions. It acts in the same way on the spinal cord; it suspends the reflex functions and motility, but sensibility is not destroyed until the cerebral functions are suspended. It does not impair the contractility of muscle or the irritability of the motor nerves. The action of the heart is enfeebled, the arterial tension is lowered, and a very considerable reduction of temperature is caused. The respiration is slowed, then made irregular and shallow, and finally arrested. Death is caused by paralysis of the heart or of the respiration, or by the simultaneous arrest of both functions. Strychnia does not affect the cerebrum, consciousness being retained until carbonic-acid narcosis

* "Med. and Surg. Reporter," June 15, 1872.

comes on. It exalts the reflex faculty of the spinal cord, and is a motor excitant. It stimulates the respiratory center and the cardiac motor ganglia, and raises the arterial tension.

Chloral and strychnia can hardly be regarded as antagonistic in their actions on the functions of the brain, since chloral suspends them, and strychnia does not affect them in any way. In one respect they have opposed effects—chloral producing cerebral anæmia and strychnia 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 strychnia exalting both. Strychnia stimulates the respiratory and vaso-motor centers in the cord, and thus opposes and counteracts the most dangerous tendency of chloral narcosis. The chief danger from strychnia —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 strychnia; whence it follows that chloral is a more useful antagonist in strychnia poisoning than is strychnia in chloral poisoning.

CHLORAL AND PICROTOXINE.

Professor Husemann, in the course of his important researches on the antagonisms of chloral, finds that picrotoxine must be included among those agents (like strychnia, the strychnia bases known as brucin or brucia, and thebaia, the tetanizing alkaloid contained in opium) which are antagonized more or less completely by chloral. The only published researches on picrotoxine and chloral of any value are those of Dr. J. Crichton Browne, of the West Riding Lunatic Asylum. It may be necessary to state that picrotoxine is the active principle of cocculus indicus, is not properly an alkaloid, and does not combine with acids to form salts. As regards its physiological actions, it has distinct deliriant and stupefying effects on the cerebrum, and causes epileptiform or tonic and clonic convulsions, followed by coma and insensibility. The reflex functions are suspended by it; finally, the motor nerves lose their irritability, and the sensory nerves are early affected, their power to transmit peripheral impressions disappearing in the beginning of its action. Respiration and the pulse-rate, at first, for a brief period, are increased, and the temperature also slightly rises, but this preliminary excitement is soon followed by depression—by lowered temperature. After the convulsions especially, the pulse becomes

feeble and irregular, and the respirations shallow and arhythmical. A comparison of the physiological effects indicates antagonistic action on the cerebrum and spinal cord, but not on the heart and circulation. A study of the experimental evidence leads to the same conclusion. Dr. Browne, after an elaborate investigation, summarizes his views as follows:* "Chloral hydrate is physiologically antagonistic to picrotoxine in rabbits and guinea-pigs, and may save life when administered fifteen to twenty minutes after a fatal dose of the latter. There is no antagonism exerted between these two agents on cats, death being caused by paralysis of the heart, a result in which both participate."

No corresponding observations exist in cases of accidental poisoning in man. Picrotoxine is not used with criminal intent, and its scarcity renders accidental poisoning unlikely. It is highly probable, however, that the convulsions and cerebral excitement produced by picrotoxine would be prevented or relieved by chloral. It is doubtful, however, whether the stupor and insensibility induced by chloral would be relieved in the same degree as by strychnia. The experiments of Dr. Browne show that picrotoxine is to a "very limited extent antagonistic to chloral." An examination into the mechanism of the antagonism shows that it must be confined to a few points—to the cerebrum and to the reflex, motor, and sensory functions of the spinal cord, and does not extend to the heart and to the respiratory organs.

CHLORAL AND ATROPIA.

The antagonism of chloral and atropia was, I believe, first studied by myself, and the results were presented in a paper read before the Neurological Society of New York, in 1875. It has also been the subject of a special study by Husemann,† to a limited extent by Fothergill, and has been discussed in a clinical lecture of Volkmann's series by Falck.‡ Both of these agents have been sufficiently set forth in the whole range of their physiological powers, and need not therefore be presented anew. On the brain and spinal cord they are antagonistic to a limited extent. Atropia lessens the sleep-producing power of chloral, and therefore opposes the depression of the respiratory and vaso-motor centers produced by chloral.

* "Brit. Med. Jour.," 1875, i, p. 542. † *Loc. cit.*, p. 443.

‡ Dr. Ferd. A. Falck. "Der Antagonismus d. Gifte." "Samml. klin. Vortr.," von R. Volkmann, No. 159, 1879.

On the spinal cord they act in a different, and in some respects, in an opposed manner. The effect of atropia on the spinal cord and nerves is complex. On the cord it has a tetanizing action, and exalts the reflex irritability; on the motor nerves, a paralyzing effect; and it lessens the irritability of the sensory nerves. Chloral suspends the reflex function of the spinal cord, and causes a paralysis which is purely spinal, since the irritability of the motor nerves and the contractility of the muscles are left intact. While chloral and atropia are antagonistic in their action on the cord, they both produce motor paralysis. A most obvious and important antagonism exists between the actions of these agents on the circulation and respiration. This is confirmed by experimental trials on animals and by clinical observation on man. I have always found it to be the case in my experiments on animals, and Husemann's experiments demonstrate the same truth. Owing to the fact that, in animals, the more powerful and preponderating action of these agents on the brain prevents the antagonism on the heart and lungs exerting the salutary effect it has in man, only rarely do the experiments succeed in averting death from lethal doses. Husemann narrates a striking case of the accidental use of atropia in poisoning by chloral. A man took from 20 to 24 grammes (300 to 360 grains) of chloral hydrate, was profoundly chloralized, and, as his pupils were minutely contracted, it was supposed that the narcosis was due to morphia. Acting on this supposition, an injection of $1\frac{1}{2}$ milligramme (about $\frac{1}{40}$ grain) of atropia was practiced. Neither the pupil nor the respiration was affected. Faradization with the electric brush, mustard plasters, cold douche to the head and breast, and other measures were resorted to besides; but the beneficial influence of the atropia is regarded by Husemann as hardly doubtful.

While the good effects of atropia in preventing death from chloral by failure of the heart's action, or of the respiratory function, are probably very great, the converse is not necessarily true. Although there are no experimental or clinical facts, it must be evident that chloral can act only as morphia does under the same conditions, i. e., moderate the strain on the cardiac and respiratory centers produced by the excitant action of atropia. This is a less important service than that rendered by atropia in chloral narcosis, but is, nevertheless, highly useful. The dose of atropia in chloral narcosis and the frequency with which it is to be repeated depend on the effects produced. A small dose, repeated at short intervals, until the characteristic effects on the pupil, mouth, heart beat, and

respiration are produced, and then awaiting the antagonistic action, is better practice than the administration of a large dose at once. The return of reflex sensibility, the improvement in the pulse and respiration, and the dilatation of the pupil are the evidences that the antagonist is producing good effects. When these results are obtained, all that the antagonist can effect is done, and hence to persist in the further use of it, unless the maintenance of the effect is necessary, is to add atropia poisoning to chloral narcosis.

In his research on a supposed antagonism between thebaia and chloral, Husemann found that this antagonism existed to a limited extent. Chloral, however, only intensifies the effects of morphia and codeia. In a number of experiments on this point, I have found that morphia and chloral are synergists, or promote each other's activity, and that they can be more safely administered by combination with atropia, which counteracts the cardiac and respiratory depression caused by them, and which constitutes the great danger in their use in man, as in the inferior animals.

THE ANTAGONISTS TO THE CARDIAC AND RESPIRATORY DEPRESSANTS.

We have now reached a very interesting and important department of our subject. From the physiological and clinical point of view alike, it is most useful to know the mutual interactions and reciprocal relations of those remedies which act on the lungs and heart. It is by the extension of our knowledge in this direction that we may hope by various combinations to improve the curative powers and enhance the safety of administration of these important remedies.

Let us first consider *opium and veratrum viride.* It has long been known to practical physicians in this country that the tincture of opium counteracts the depression of the circulation caused by veratrum viride. I can not trace this fact to its original source. The first example of opium poisoning treated by veratrum viride I have been able to find, is that of Dr. J. S. Todd,* of Georgia. A man took with suicidal intent an amount of laudanum equivalent to forty grains of crude opium. The treatment of the opium narcosis consisted in the administration of emetics, which did not act, however, until long after complete absorption; the subcutaneous injection of atropia until the pupils were fully dilated; and the subcutaneous injection of whisky and tincture of veratrum viride. Six

* "Am. Jour. of the Med. Sci.," Jan., 1873, p. 131.

drops of tincture of veratrum viride were administered, in all, hypodermically. So many agents being jointly used, it is difficult to assign to each its exact share in the result. Dr. Todd holds that the atropia did no good, and to the veratrum viride he mainly attributes the recovery. Dr. Haldeman,* of Zanesville, Ohio, reports successful cases of the treatment of opium narcosis by veratrum viride. There has been no published experimental evidence submitted in support or disapproval of the popular professional opinion in regard to this antagonism. During the past summer and fall I made a number of observations, on rabbits chiefly, at my laboratory in Jefferson College. I ascertained first that the minimum lethal dose of fluid extract of veratrum viride (U. S. P.) was three minims to the pound weight. This produces nausea, some diarrhœa, weak pulse, labored respiration, and convulsions, death occurring from suspension of breathing. To this quantity of veratrum viride three to five minims (according to the weight of the animal) of Magendie's solution of morphia (gr. xvi–℥j) seems to be antagonistic. When used in the proper proportion, the nausea and vomiting, the muscular paresis, the paralysis of the respiratory muscles and the labored breathing, the feeble action of the heart, were all prevented, and the life of the animal was preserved. When the effects of the morphia preponderate, the pupil becomes minutely contracted, drowsiness deepening into stupor, and morphia convulsions come on, but the effects produced by veratrum viride disappear. Corresponding observations were made on frogs. The antagonism between opium and veratrum viride is clearly established, but the distance apart at which their effects are exerted has not been definitely ascertained—most of the experiments being performed by the simultaneous administration of the two agents. I found, however, that the antagonism was exerted after ten and twenty minutes, but further experiments must be made, to learn if it is sufficient at a longer interval. It is further ascertained that, whether opium be used against veratrum viride, or veratrum viride against opium, the antagonistic action is equally displayed. The cases narrated by Dr. Todd, of Georgia, and Dr. Haldeman, of Ohio, are apparently conclusive as to the existence of the antagonism in man.

We are next concerned to ascertain its nature or mechanism. Is there an explanation afforded us in the physiological actions of the two agents? Veratrum viride does not affect the mental func-

* "Cincinnati Lancet and Clinic," 1879, and 1880, p. 465.

tions, but causes cerebral anæmia; opium produces excitement of the mental functions, quickly followed by stupor, coma, and insensibility. Veratrum viride depresses the vaso-motor functions, lessens the arterial tension, and lowers the temperature of the body; opium in doses less than lethal, especially in the form of morphia used subcutaneously, stimulates the vaso-motor functions, raises the tension of the arterial system, and does not reduce, but maintains, the temperature. On the heart muscle veratrum viride acts as a direct depressant, and on the respiratory muscles as a paralyzer; opium in doses less than lethal has a great power to maintain the heart and respiration. Veratrum viride increases secretion generally, the saliva and sweat especially; opium diminishes secretion usually, but under some circumstances increases perspiration. Veratrum viride is a paralyzer by depressing the motor spinal functions, the motor-nerve trunks and the muscles remaining intact; opium in less than lethal doses opposes rather than promotes the paralyzing effects of veratrum.

I can not too strongly insist on the difference in the action of medicinal and lethal doses of opium. In employing opium against the toxic effects of veratrum viride, no good can result from the administration of such doses as will rather approximate the effects of opium to those of veratrum viride. It should be kept in mind that it is the stimulating effect of opium which renders it an antagonist to veratrum viride. No absolute rule as to quantity can be prescribed with certainty. Referring to the clinical experience now available, we obtain practical data to serve for a decision of the question. In the case of an infant three weeks old, poisoned by four or five drops of laudanum, two and three fourths drops of tincture of veratrum viride dispelled the narcosis. An adult female, aged thirty, took a quantity of laudanum, supposed to be about two ounces, and was in a condition of profound narcosis, respirations only 3½ a minute, when six drops of veratrum viride tincture were injected subcutaneously. In a half hour she could be roused, but lapsed back immediately into a comatose state, and, as she could then be induced to swallow, three drops of the tincture were given every two or three hours by the stomach until she recovered entirely, which occurred in a few hours. The whole amount of the veratrum viride administered did not exceed fifteen drops of the tincture. In a case reported by Dr. Sholl, of Alabama, a negro boy took an overdose of morphia, prescribed for the hiccough of typhoid fever, the quantity not stated. The usual narcosis followed,

and eighteen drops of Norwood's tincture of veratrum viride were administered, with the remarkable effect that in one hour the symptoms of poisoning had disappeared. Dr. A. Sheller also reports a case in which profound narcosis, produced by the administration of 1⅔ grain of morphia within eight hours, was relieved entirely within a few hours by the use of thirty drops of Tilden's fluid extract of veratrum viride.* Unfortunately the details in these cases are not exact, but one patient certainly received a lethal quantity, and the others may or may not have recovered without assistance. Notwithstanding these defects in the details of the reported cases, the proof of the utility of the veratrum viride seems conclusive. Clinical experience is thus in accord with the results of experiment. If further investigations confirm them, the antagonism of opium and veratrum viride will take high rank for the efficiency and extent of its range.

Opium and Gelsemium.—The actions of gelsemium are similar to those of veratrum viride, but they differ also in important particulars. Gelsemium is more distinctly a paralyzer. It causes dropping of the upper eyelid, dilatation of the pupil, and diplopia, by paralyzing the third nerve. The cerebral effects are vertigo, drowsiness, and stupor; but no disturbance of intellect results from it, although a comatose state is brought on by carbonic-acid narcosis. Gelsemium paralyzes respiration, this function ceasing before the heart's. It is not an arterial sedative, as usually supposed, the depressed circulation being secondary to the respiratory depression. The paralyzing action of gelsemium is spinal, since neither the motor nerves nor the muscles are affected. It is obvious that opium, in ordinary medicinal doses, antagonizes the actions of gelsemium, prevents the respiratory and cardiac depression, and averts death, unless the nervous centers are entirely overwhelmed by the amount of the poison. In a case of poisoning by gelsemium narrated by Dr. George S. Courtwright,† we have a striking example of the curative effect of the antagonist. A physician took by mistake, in the dark, what he supposed was a teaspoonful or two of the tincture of cinchona, but proved to be the tincture of gelsemium. In half an hour he began to experience the paralyzing effects, had the drooping eyelids, the dilated pupil, the hanging jaw, the labored respiration, and the weak pulse produced by gelsemium. The physician called in, Dr. Courtwright, recognizing the similarity of this

* Haldeman, "Cincinnati Lancet and Clinic," Aug., 1879.

† "Cincinnati Lancet and Observer," xxxvii, 1876, p. 961.

to belladonna poisoning, at once injected morphia subcutaneously. The quantity used was estimated at one half to three fourths of a grain, and this was repeated in three minutes, at the end of seven minutes, and again at the end of eleven minutes, making four injections, or two grains of morphia, hypodermically. Besides this, he was given half a grain of morphia when able to swallow. After the third injection, "he partially raised his arm, and with an effort, and by an assistant holding up the lower jaw, he said, 'Be spry.'" In two hours the paralysis ended, and the Doctor was able to give an account of the accident. It is hardly doubtful that a tablespoonful of the tincture of gelsemium had been taken, for a less quantity could not produce such severe symptoms. The amount of morphia used in antagonism seems rather excessive, but, as it was estimated, it is probable the amount actually administered was less than supposed. The very remarkable improvement which followed the injection of morphia is a striking evidence of the completeness and fidelity of the antagonism on man.

I have pursued the same line of research with morphia and gelsemium as with morphia and veratrum viride. On rabbits, the lethal dose of the fluid extract of gelsemium (U. S. P.) is about five minims to the pound weight. The antagonism is admirably shown on the pupil, on the respiration, and on the action of the heart, but I have not been able to avert death from the cerebral effects of both. The entire disappearance of the symptoms due to gelsemium is first seen, but then come on the cerebral effects of morphia, and convulsions usually terminate life. In man, as we have seen, owing to the extent and complexity of the cerebral structures, the effects of morphia are diffused into the higher centers, and therefore not expended on the lower centers alone.

Morphia in the same way antagonizes the depressing effect of *aconite* on the respiration and on the heart. Although in the inferior animals, as is the case with the other members of the same group, the lethal effects of both agents are exerted, the antagonism is conspicuously exhibited in the support of the heart and the maintenance of respiration. Clinically, the same facts have been repeatedly observed, and, in cases of accidental use of aconite in poisonous quantity, death has been averted by the timely administration of opium or morphia. As the facts already set forth in regard to the opposed actions of opium and veratrum viride are equally applicable to opium and aconite, further discussion of the latter may, therefore, be unnecessary.

Morphia and Cocaine, Theine, Caffeine, and Guaranine.—One of the most interesting, if not one of the most important, of the researches undertaken by the Committee of the British Medical Association is that series to determine a supposed antagonism between morphia, on the one hand, and the alkaloids of tea, coffee, coca, and guarana, on the other. It was found that the physiological action of these alkaloids was practically identical. They produce "cerebral excitement, succeeded by coma, when the quantity is large; loss of sensibility, which is partial when the dose is small, complete when the dose is large; tetanic spasms and convulsions; paralysis of the posterior columns of the spinal cord and the peripheral sensory nerves, leaving the anterior columns and the peripheral motor nerves unaffected; at first increase and finally diminish the force and frequency of the cardiac contractions, and first irritate and then paralyze the vaso-motor nerves." It is obvious that morphia antagonizes some of these actions, and promotes others. Empirically, strong decoctions of tea and coffee are employed in opium poisoning, because it is a matter of common experience that these infusions cause wakefulness. Cases of opium narcosis, produced by a quantity barely sufficient to induce lethal effects, have been relieved by these means alone, but usually other measures of greater activity are employed. The researches of the committee demonstrate that there is some foundation for this popular opinion. They find that theine is antagonistic to meconate of morphia, and that the action of one so far modifies that of the other as to save life after a fatal dose of either.

Morphia and Chloroform.—As paralysis of the heart or of the respiration, or, it may be, the simultaneous depression of both functions, is the mode of dying by chloroform and by other anæsthetics used for the same purpose, it is extremely desirable to possess an agent which will antagonize and prevent this fatal tendency. I do not, I believe, exaggerate the fact, when I state that we possess such an agent in the subcutaneous injection of morphia. It is an extraordinary circumstance that surgeons have been so indifferent to the remarkable results obtained by the employment of mixed anæsthesia. Claude Bernard, and, about the same time, Nussbaum, the one in his laboratory, the other in the clinical theatre, demonstrated the great utility of the anæsthesia procured by the injection of morphia and the inhalation of chloroform—"mixed anæsthesia." Although the methods of Bernard * and of Nussbaum are usually

* "Bull. Gén. de Therap.," lxxvii, p. 241.

supposed to be the same, they differ—Bernard administering the morphia a few minutes before beginning the inhalation, and Nussbaum giving it after the inhalation is well under way. In this country, the method of "mixed anæsthesia" was advocated some years ago by Professor William Warren Greene. Last year the subject was again brought forward in an admirable memoir, by Dr. J. C. Reeve,* of Dayton, Ohio. In France, interest in the subject has lately greatly revived, and several theses have appeared—the most important being that of Dr. S. Bossis.† In my "Manual of Hypodermic Medication," the first edition of which appeared in 1867, I called attention to this important subject, citing the observations of Bernard and Nussbaum.

Morphia and chloroform act on the same cellular elements of the brain, and agree in the production of anæsthesia, but they are opposed in their action on other structures and organs—an opposition which renders their combined use safer. When morphia is injected subcutaneously before the inhalation of the anæsthetic has begun, the irritability of the bronchial mucous membrane is so far diminished as to permit the inhalation to proceed quietly; the stage of excitement is prevented, and consequently the danger of the asphyxia which occurs under these circumstances; the nausea and vomiting, which interfere with the progress of the inhalation and which may indirectly produce serious consequences, are also obviated; and the stage of narcosis is prolonged without the need of further inhalation. The after-pain, the nausea and vomiting, and the systemic depression which result from the inhalation of the anæsthetic, and the sometimes dangerous syncope, are also in a large measure prevented. By a careful adaptation of the relative proportions of chloroform and morphia, a state of insensibility to pain without loss of consciousness is induced. In the words of Bossis—"There may be obtained in man, with a little attention, by the combined action of chloroform and morphia, a state of complete insensibility to pain, with preservation to a partial extent of the intelligence, of the tactile, auditory, and visual sensibility, and of the voluntary movements. From the practical point of view, the analgesia obtained by the combined action differs completely from the demi-anæsthesia caused by the employment of chloroform or ether singly, in that it is not preceded or accompanied by a period of

* "Trans. of the Ohio State Med. Soc.," for 1879.

† "Essai sur l'Analgésie Chirurgicale," etc., Paris, 1879.

hyperæsthesia with violent excitement, and the tendency to exaggerated reflex arrests of the heart and after syncope."

Clinical experience with the "mixed method" seems to support the deductions of experiment in regard to the antagonistic action of morphia to the cardiac and respiratory failure induced by the anæsthetics. A large experience is necessary to settle the question, however, and the failures which may result from pathological conditions of the organs concerned must be eliminated. There can be no doubt, however, from the experience thus far accumulated, that morphia, by the method of Bernard, greatly facilitates the induction of anæsthesia and lessens its dangers. I have maintained that for this purpose the combination of morphia and atropia should be preferred to morphia alone, because of the power of atropia to stimulate both heart and lungs. It might be supposed, on superficial reflection, that atropia would be better than morphia, but it should be remembered that stimulation has its inevitable reaction. Morphia has a power of support not possessed by atropia. When administered together under the circumstances, the evil effects of both are antagonized, and the power of both to support the heart and respiration is utilized. The quantity of morphia should rarely exceed one fourth of a grain, and that of atropia, one one-hundredth of a grain. The method of Bernard should be preferred to that of Nussbaum, because it facilitates the inhalation, and not less secures the advantages of the "mixed method."

Strychnia as a Stimulant of the Respiratory Function.—The importance of atropia as a special stimulant of the respiratory function has been frequently alluded to. The resemblance in the spinal actions of atropia and of strychnia has been manifest in the study of these agents. Atropia, in therapeutical works, is sometimes suggested as an opponent and antagonist of strychnia; 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 atropia intensified the effects of strychnia, and hastened death by contributing to the tetanic fixation of the muscles of respiration. We find that strychnia stands next to atropia as a stimulant to the respiratory function. Through the heightened reflex activity of the spinal cord and of the respiratory centers in the medulla, strychnia 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 experi-

ment. 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 strychnia twice as great as the lethal. The animals given the aconitine alone died; the same animals receiving the aconitine with the strychnia, in previous experiments, recovered. The existence of the antagonism is therefore undoubted.

An opposition of actions has been determined to exist between *strychnia 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 strychnia. From the physiological standpoint, then, an antagonism must be presumed to exist between them. An experimental research by Dr. Gray,* of Glasgow, strongly supports this view. Thus, he found that one fourth of a grain of strychnia proved fatal usually to the rabbits which he used for experiment. He was able to administer half a grain of strychnia and ten 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 strychnia poisoning.

An antagonism to a limited extent has been discovered by Dr. Fothergill between *aconite and digitalis.* The rate at which these agents are diffused throughout the organism differs so widely that it is necessary, in order to display the antagonism, to administer the digitalis from five to nine hours before the aconite. Besides the interesting fact of the antagonism, this subject is important because of the additional light—if additional light were needed—thrown on the actions of digitalis. In some of Dr. Fothergill's experiments, "aconite was given to frogs with their hearts contracted by digitalis; in others, digitalis, where the heart was paralyzed by aconite. The aconite did not exercise a very marked effect upon the hearts con-

* "Glasgow Med. Jour.," 1871, p. 188.

tracted by digitalis, but the other experiment was more successful. . . . Slowly and gradually the distended ventricle recovered itself under the action of digitalis, the contractions being more rhythmical and perfect, and the distention less and less pronounced, until a return to normal was brought about." A lethal dose of aconitin was antagonized in rabbits by digitalin given a sufficient time before. This slowness in the action is a well-recognized quality of the remedy, and its elimination from the organism seems equally tardy.

Between *digitalin and saponin* an antagonism of considerable extent has been traced by Köhler.* Saponin being comparatively little known, some account of its origin and actions may be a necessary preliminary. Saponin is a glucoside, obtained from saponaria officinalis. It has close relationship to our indigenous polygala senega, and the active principle, senegin, which is probably the same as Quevenne and Procter's polygalic acid, is the same in composition as the glucoside principle, saponin.† The important actions of saponin are its irritating effects on the mucous membrane, producing violent sneezing when applied to the nose; its power as a cardiac poison, arresting the heart in diastole; and its activity as a muscular poison in general. Locally, it has the effect of arresting the heart. Owing to the difference in the rate of movement, the antagonism is exerted after the time requisite to develop the activity of digitalin. A heart arrested by saponin will be started by digitalin, and *vice versa*. Further investigation of saponin, as against atropia and strychnia, will doubtless develop very interesting facts.

To round off and complete the study of digitalis, I should not fail to mention the investigations of Boehm in regard to the antagonism between this agent, on the one hand, and muscaria and aconite on the other. Boehm found that when the heart was arrested by digitalis it was restored to action again by the administration of muscaria and aconite. Digitalis acts chiefly, as has been pointed out, by stimulating the apparatus of inhibition; muscaria and aconite affect this apparatus in the opposite way, relaxing the grip, as it were, of the inhibition, and permitting freedom of movement. I think you must agree with me that these studies are of great importance, if they had no other purpose, in illustrating the action of digitalis, and, indeed, the mechanism of the cardiac movements.

* "Arch. f. exp. Pathol. u. Pharmacol.," i, p. 138.

† "Die Pflanzenstoffe," p. 750.

A very interesting cardiac poison, in regard to which but little is known, is *phytolacca decandra*. This agent arrests the heart in diastole, and long before the motor and reflex functions and the respiration have ceased. The sensibility of the sensory nerves is lessened by poke, but the irritability of the motor nerves and the contractility of the muscles are not impaired by it. It is a spinal paralyzer. The power to arrest the heart is due to a paralyzing action on the motor ganglia, but it also affects the *cardiac* muscle. When the heart is arrested by the fluid extract, and some portion of it is allowed to come in contact with the heart itself, the paralysis is so complete that no form of irritation, including a strong faradaic current, can arouse it to action again. The heart thus remains insensible, when the muscles everywhere respond energetically to the faradaic stimulation. More slowly, but finally as completely, is the heart paralyzed by the injection of the fluid extract into any part of the body. Respiration ceases, with paralysis of the muscles, long after the heart has stopped its beat.

I find that atropia antagonizes these effects of phytolacca completely. It maintains the cardiac action, so that lethal doses of poke do not prove fatal when administered with atropia. The mechanism is obvious. Atropia stimulates the accelerator nerves of the heart and the motor ganglia in the muscular substance; phytolacca exerts a paralyzing action on the same apparatus. The antagonism is exerted not only when they are simultaneously administered, but when the second is given after an interval of fifteen minutes. The number of experiments made was twenty, and included both cold- and warm-blooded animals.

I have recently conducted, and am still engaged on, an elaborate series of experiments with *viscum album*, the mistletoe, for the study of its physiological actions and its antagonists. It is a cardiac tonic, and exalts the vascular tension. The sensibility of the sensory nerves is much diminished by it, but the irritability of the motor nerves is not impaired. The cardiac and respiratory depressants are its antagonists, especially such as aconite and veratrum viride. Further researches promise interesting disclosures.

In discussing the question of the antagonism of chloral and strychnia, I incidentally alluded to the cases of strychnia poisoning treated by chloroform or ether inhalations. I ought not to conclude this part of my subject without some references to this topic. The anæsthetics suspend the reflex functions of the spinal cord, and cause death by the final arrest of respiration and circulation. They

are therefore antagonistic to those remedies which exalt the reflex functions—as strychnia, brucin, thebaia, picrotoxine, etc. Ten cases of strychnia convulsions treated successfully by the inhalation of ether or chloroform are reported. The anæsthetic suspends the heightened sensibility, and thus maintains the functions which would otherwise be over-stimulated until the elimination of the poison is accomplished. What is true of the treatment of strychnia poisoning is also true of poisoning by the other agents acting similarly. The antagonism of the anæsthetic group with the tetanizing group of remedial agents is therefore supported by experimental and clinical evidence.

With the antagonisms discussed in this lecture, rather hastily, as the limits of the course will permit no fuller treatment, I close this part of the subject—or the antagonism between medicines. I have yet to discuss, in the remaining lectures, that large and important practical subject—the antagonism between remedies and diseases. In my next lecture, I shall therefore begin the consideration of this topic, which will not only enforce the lessons derived from the study of the physiological antagonisms between medicines, but will, I hope, demonstrate a path which we may surely follow in the treatment of many diseases.

LECTURE V.

THE ANTAGONISM BETWEEN REMEDIES AND DISEASES.

Some diseases are cured by contraries, was the aphorism of Hippocrates, but, he was also wise enough to add, some are cured by similars. It was obvious enough, even at that remote time, that no single law or dogma could include all the varied conditions of disease. The doctrine or law of antagonisms is necessarily applicable only to the state of physiological pathology—if I may be permitted such a phrase—and not to structural pathology, unless remediable by physiological processes. For example, the pathological state induced by fluxionary hyperæmia may be removed by agencies acting on the vessels in the opposite way. A cachexia or diathesis, as the cancerous or tubercular, sclerosis of organs, etc., can not be affected by opposed or similar remedies, yet some important symptom, occasioned thereby, may be acted on, as, for instance, fever, which may be subdued and its ill effects prevented by the proper use of some antagonist to the fever process.

The limits being thus set to our inquiry, we may proceed to investigate the nature and extent of the antagonism which may exist between a remedy and a disease, or between the actions of a remedy and the symptoms of a disease. As the antagonism between remedies has been treated mainly in the historical order, it will be best to begin with the first historical example of the treatment of a symptom of a diseased state by its physiological antagonist—the treatment of paralysis by strychnia.

STRYCHNIA AND PARALYTIC STATES.

As I have already shown, we owe our present knowledge of strychnia to the labors of Magendie, whose research was so thor-

ough that subsequent investigators have been able to add but little to his results. This pioneer investigation—the parent of all the important work which has since been done in this field—is a striking illustration of the permanence of the results thus obtained, and is in strong contrast with the variable and fleeting opinions, the product of empirical methods. Fouquier and Magendie, recognizing the opposition of actions between the new poison and paralysis, proposed to prescribe it when suitable cases occurred, but Fouquier had the good fortune to meet with suitable cases before the discoverer. Since that trial of strychnia has occurred all the known experience with this important agent. Strychnia exalts the reflex functions of the spinal cord, and is, therefore, properly the antagonist of those conditions of disease in which this function is weakened. Strychnia also energizes the heart and raises the arterial tension, by stimulating the vaso-motor system, and therefore opposes all actions from disease of a contrary kind. Strychnia, further, is a powerful stimulant of the respiratory function, and causes death by asphyxia—by so stimulating the muscles of respiration that they become tetanically contracted, and is, therefore, the antagonist of those symptoms indicating respiratory depression. Let us see, now, how nearly clinical experience with this remedy corresponds to the deductions of theory. Diphtheritic paralysis is an excellent illustration and type of the paralysis to which the action of strychnia is opposed. It is largely a functional paralysis. Although some structural changes have been made out in the spinal-nerve roots, they are remediable under the changed conditions wrought by an antagonistic medicine. No one will dispute, I think, that strychnia is the most important remedy for this disease, and that improvement promptly follows on its administration. Furthermore, it is obvious that strychnia will produce the better results, the more it is concerned with sound tissues. Hence, measures to improve the nutrition of the body will increase the utility of strychnia.

The so-called reflex paralyses are clearly antagonized by strychnia, and they are especially benefited by its administration. It is probable that reflex paralyses are often due to anæmia of the motor center, which ceases to act because, reflex impressions causing strong contraction of the arterioles, the amount of blood normal to the part is no longer received by it. That strychnia produces rather a hyperæmic state of the cord and motor centers generally, while it also stimulates them to greater activity, can hardly be denied.

The power of strychnia to give energy to the cardiac movements

and to raise the arterial tension is not made use of in medical practice as it should be. Degenerative changes in the cardiac muscle and coincident low tension of the vascular system are conditions antagonized by strychnia in the weak heart. Exhausting hæmorrhage, the action of the heart being weak and the vascular tension low, also is a combination to which the action of strychnia is opposed. I find that Fordyce Barker* gives nux vomica tincture in considerable doses, in conjunction with ergot, for the arrest of post-partum hæmorrhage. The effect of nux vomica is most appropriate, because so exactly antagonistic to the conditions present; it stimulates the cardiac and respiratory centers, and, by raising the tension in the vessels, checks the flow of blood.

Modern experience has in a similar way made use of strychnia in the treatment of depressed states of the respiratory organs, by a merely empirical method. The wide-spread popularity of Aitken's phosphate of iron, quinine, and strychnia, not only as a general tonic, but as a remedy for incipient phthisis, is due largely to the constituent strychnia. It has come to be recognized that strychnia is a respiratory stimulant, and of special utility in chronic bronchitis, in asthma from paresis of the diaphragm, and in emphysema with dilated right cavities of the heart.

SPASM AND THE PARALYZERS.

The relation in which strychnia stands to paralysis is comparable to that of the paralyzing agents to spasm and cramp. The first physiological research to determine the existence of muscular irritability was the memorable study of woorara by Bernard. This is the only remedy which has apparently exerted a curative influence on hydrophobia. Woorara—or one form of the poison possessing these properties—destroys the irritability of the end organs of the nerves in the muscles, leaving the muscles themselves intact. But it also depresses and suspends the reflex functions of the spinal cord, and paralyzes respiration. Hydrophobia produces symptoms in opposition to these, and hence they should cease on the exhibition of woorara. Unfortunately for any certainty in results, this agent varies much in composition, and in hydrophobia a peculiar virus is present, which does not, apparently, diffuse out of the blood, but continues in action, death occurring from exhaustion, if not from the spinal effects of the poison. That two well-defined cases of

* "The Puerperal Diseases." New York, 1874.

hydrophobia should get well during the administration of woorara affords us reason to hope that better results may be obtained hereafter from a more uniform and stable preparation, or from a new agent acting similarly. Tetanus is a better type of a spasmodic disease than hydrophobia. No similitude in the action of a remedy and the symptoms of a disease can be greater than between strychnia and tetanus, and this resemblance extends to their behavior under the influence of opposing remedies. As the tetanic symptoms produced by tetanus proceed from a peripheric irritation—a wound—and those due to strychnia are the result of an impression made through the blood on the center—the cord, receiving simultaneously two impressions from different sources, should be strongly inhibited and the impressions neutralize each other. Such would be an adequate explanation of the result, if tetanus were cured by strychnia. As it is not, we have a striking illustration of the fallacies in the ancient doctrine of similars. There are six remedies which have been used with success in the treatment of tetanus: chloroform by inhalation, chloral, tobacco or its alkaloid (nicotin), bromide of potassium, physostigma, and gelsemium. How much soever these agents may differ in other points of action, they agree in the power to diminish or suspend the reflex functions of the spinal cord. They therefore act in opposition to this distinctive symptom—an aggravated reflex sensibility. The success which attends the administration of these agents is not the same, since they differ in the exactitude with which they oppose the morbid complexus. In poisoning by strychnia, the same group of remedies comes into use. Chloral, as we have seen, is a very efficient antagonist, and the inhalation of chloroform seems equally so.

When the convulsions are of the epileptiform type, some antagonists that have a similarity of action, and also some acting in the opposite way, are employed. Picrotoxine represents the former, and potassium bromide the latter. In epileptiform seizures, an abnormal excitability of Nothnagel's spasm center may be presumed to exist, and hence those agents acting against clonic convulsions must have the power to diminish this abnormal excitability. Agents having a similarity of action stimulate the spasm center, but, as inhibition results when two impressions coming from different points are made on the spinal cord simultaneously, so here quiescence, or the normal equilibrium, is the result, when the disease impression and the medicine impression act on the spasm center at the same time. As picrotoxine rather increases cerebral hyperæmia, if it exist, and

promotes the intra-cranial circulation when weak or deficient, it is obviously adapted to those states characterized by anæmia and depression. On the other hand, bromide of potassium produces its best effects when the subject rather tends to plethora, and when the intra-cranial circulation is too active. No fact with regard to the action of bromide of potassium is more distinctive than its power to arrest symptomatic or epileptiform convulsions due to the presence of a neoplasm. When a tumor develops in the brain, there is always present a very considerable degree of cerebral hyperæmia. The abnormal excitability of the spasm center may, indeed, be chiefly due to this increased blood supply, inducing an excessive functional activity. Although under such circumstances the convulsions are prevented, no modification of the disease is effected—an illustration of a fact that the antagonism is exerted, if at all, between a symptom produced by the disease and a symptom produced by the remedy, although the cause of the disease symptom may continue unaffected by the remedy. During the administration of the bromides in epilepsy, the condition of the faucial reflex affords an indication of the state of the spasm center. Thus, Voisin has shown that, when no movement is caused by touching the base of the tongue, the pillars of the fauces, and the walls of the pharynx, the effect of the bromides is sufficient. A capital application of the principle of antagonism, as exhibited in the opposition of the action of a medicament to an important symptom of a disease, is the use of the nitrite of amyl to abort the epileptic paroxysm. It is known to all here present, of course, that the epileptic paroxysm is inaugurated by a sudden deathly pallor, in which the arterioles of the brain are strongly contracted, and an extreme degree of anæmia is induced. Then follows the tetanic stage, with suspension of respiration and cyanosis. By the timely inhalation of amyl nitrite, these phenomena may be prevented and the fit aborted. No sooner is a whiff of the vapor inhaled than the arterioles are dilated, and a bright flush takes the place of the pallor, the stage of rigidity does not come on—in fact, the epileptic paroxysm, which was imminent, fails to develop.

The principle of antagonism applies equally to the treatment of chorea. The most successful treatment is that having for its objects the maintenance of a quiescent state of the motor centers and the prevention of those irregular discharges of nervous force which constitute the physiognomy of the malady. Those who maintain that quiet, repose, the absence of all possible sources of excitement,

are sufficient for the cure, are seeking to accomplish, by merely hygienic means, the same end which those are pursuing who administer calmative medicines. By chloral, by the large doses of morphia prescribed by Trousseau, by cimicifuga, by conium, etc., the excitability of the motor centers is lessened; in other words, the mobile state of the nerve matter is opposed by agents which lessen and finally suspend all motor activity.

In certain neuroses of the respiratory and circulatory organs, the phenomena of antagonism are exhibited in perfection. Here, indeed, is an embarrassment of riches. We are concerned at present with those disturbances of functions characterized by the occurrence of spasm or cramp. In this category are included paroxysmal cough, cough by habit, hiccough, whooping-cough, spasmodic asthma, angina pectoris, etc. Cough, as everybody knows, is a reflex act, in which many parts participate besides the breathing organs. Experimental evidence coincides with the clinical in fixing on the bronchi as the seat of the maximum excitability to this reflex act, and especially at the bifurcation of the trachea, according to experiments. Let us take *laryngismus stridulus* for illustration. Irritation of the sensory filaments of the pneumogastric in the mucous membrane, transmitted to the nucleus, is reflected over the motor branches, and the muscles are thrown into cramp. Hence the resounding cough. To prevent this reflex act is the object of treatment, and those agents having this power—chloral, bromide of potassium, nauseants, etc.—promptly relieve the spasm. Cough maintained by habit, whooping-cough, and paroxysmal coughs are effectually treated only by those remedies which oppose the exaggerated reflex excitability, such as hydrocyanic acid, gelsemium, conium, morphia, chloral, etc. Spasmodic asthma affords a superior opportunity for the trial of the various motor and reflex depressants—the antagonists of the disease symptoms. The inhalation of ether, the subcutaneous injection of morphia, belladonna, tobacco, grindelia, faradism or galvanism, are used as antagonists with more or less success, but the selection of an antagonist is necessarily involved in obscurity, owing to the uncertainty which still surrounds the mechanism of the asthmatic paroxysm.

Singultus, or hiccough, affords us an apt illustration of both modes of antagonism—by similarity and by opposition. In singultus, a recurring spasm of the diaphragm is supposed to be the condition. I have already shown that this disease may be arrested by a spasm-inducing agent—a rapidly interrupted faradaic current. If

a strong current be passed at the moment the spasm is to take place, it is entirely aborted. The mechanism has been explained before, but it is so striking an exemplification of one mode of inhibition that it will bear repetition. The reflex spasm does not take place, because of the strong irritation of the peripheral fibers, inducing inhibition. The remedies acting by opposition are those which lessen and suspend reflex action, as the anæsthetics, morphia, bromides, amyl nitrite, chloral, etc. Another admirable illustration of antagonism of a spasmodic state, and at the same time an example of scientific therapeutics, is the treatment of angina pectoris by the inhalation of amyl nitrite. We owe this ingenious suggestion to Dr. Lauder Brunton, who, ascertaining that in angina pectoris there ensued sudden strong contraction of the arterioles, manifested in pallor of the surface, small strong pulse, labored action of the heart, etc., proposed the inhalation of amyl nitrite to overcome this contracted state of the vaso-motor fibers; and the suggestion has been most successful, giving prompt relief in a condition of imminent danger. Sudden contraction of the arterioles of a member, of the fingers, or other part of the body, the tissues so affected appearing dead-white, and losing their sensibility, occurs in young girls and in women at the climacteric period. Bromide of potassium promptly removes this state by relaxing the vaso-motor fibers.

PAIN AND THE ANODYNES.

The same principle of antagonism obtains in the treatment of pain. The sensation which we call pain is composed of several elements: of the peripheral irritation, the transmission of the impression to the center, and its realization by consciousness. It follows that pain may be relieved by interrupting its transmission to the centers of conscious impressions, or by suspending the functions of those centers. For example, aconite and gelsemium relieve pain in the former, and the anæsthetics in the latter mode. When aconite is applied to the peripheral filaments of a sensory nerve, the power to transmit the sensation of pain is gradually extinguished, and in poisoning by aconite there is ultimately reached a condition in which no pain is experienced from any form of irritation. Aconite is therefore antagonistic to peripheral neuralgia. The anæsthetics, locally applied, have similar effects, and are therefore antagonistic to both centric and peripheral neuralgia. When a few minims of chloroform are thrown into the neighborhood of a nerve trunk, the peripheral expansion of the nerve is put into an anæsthetic and analge-

sic state. The deep injection of chloroform for sciatica, cervico-brachial neuralgia, coccyodynia, and neuralgia of nerves in accessible situations, is an expedient of the highest value. Since I brought this method forward a few years ago, I have had a large experience of its use in sciatica, neuralgia of the infraorbital and supraorbital branches of the fifth, and intercostal and cervico-brachial neuralgia, and can reaffirm with emphasis my original statements. Some foreign experience has been equally favorable. This method is adapted more especially to the cases of some weeks' or months' duration, and to those—it can not be too often repeated—situated in nerves accessible to the treatment. To inject chloroform under the integument, as morphia and other anodynes are injected, is simply useless, unless the affected nerve be in the neighborhood. This expedient is the more valuable, since no danger attends its use, and inflammatory indurations and abscesses rarely result. The most powerful means for the relief of pain which we now possess—the hypodermic injection of morphia and atropia combined—is an illustration of the utility and advantage derived from the study of physiological antagonism. The mutual interactions of morphia and atropia are such that, while the pain-relieving power is not impaired but enhanced by combination, other signal disadvantages of each are compensated for in the action of both. Physiological research has further shown that the advantages of anæsthesia are promoted by the preliminary injection of morphia, and that "mixed anæsthesia" is both more effective and safer. Chloroform certainly should not be administered, under ordinary circumstances at least, without the preliminary injection of morphia and atropia. A sudden death from paralysis of the heart, in a case of ether narcosis which happened in London last month, ought to warn us in regard to the fancied security against cardiac paralysis from ether inhalation, which Schiff especially has inculcated. We ought to recognize the fact that the condition of anæsthetic sleep is a condition of danger, which is merely relative in respect to the agent used, and employ antagonists to the fatal tendency—paralysis of heart or lungs. The antagonist on which, it appears, much dependence may fairly be placed is the subcutaneous injection of morphia and atropia. The danger which attends the administration of chloral may be to a large extent averted by the simultaneous prescription of atropia, as some recent cases of accident unequivocally show.* I several years

* "Allg. med. Centr.-Zeitung," July 21, 1880.

ago demonstrated, in a paper read before the Neurological Society, of New York, that, while morphia and bromide of potassium intensified the effects of chloral in every way, atropia antagonized the effects on the heart, and would thus apparently save life after lethal doses. I then also called attention to the danger of the combination of chloral and potassium bromide as a poison to the heart, which the subsequent experiments of Husemann * and abundant clinical experience have since confirmed.

MENTAL STATES AND THEIR ANTAGONISTS.

The antagonism of a mental state by the action of a remedy implies the fact that the mental is a mere symptom of a physical condition. Those who believe otherwise are indeed few in number, and constantly diminish as the progress of our means of minute research develop more and more fully the dependence of symptoms on lesions. The antagonism of insomnia to sleep-producing medicinal agents is conspicuously demonstrated in the action of chloral. Acute delirious mania, and acute mania, when due to physiologico-pathological states, and not dependent on unchangeable structural lesions, are antagonized by the same agent, and often speedily cured by its timely exhibition. High excitement, with illusions and hallucinations, and great motor activity, are antagonized by gelsemium, duboisia, hyoscyamia, conium, and other remedies acting similarly. Melancholia, with torpid movements and suicidal notions, is antagonized by morphia. Acute cerebral congestion, of the active form, is opposed by such arterial sedatives as aconite, veratrum viride, and potassium bromide; and acute congestion, of the passive form, by digitalis, ergot, etc. Anæmia of the brain is removed by strychnia, brucia, atropia, quinia, and other excitants. It follows that mental changes dependent on these vascular states must be largely controlled by the timely use of the appropriate antagonist. Closely allied to those conditions is that state of the vessels disposing to the formation of miliary aneurisms. It may appear a fanciful speculation to suggest that these changes preparatory to cerebral hæmorrhage, or affecting the nutrition of the brain unfavorably, may be retarded, possibly prevented, by the early use of such agents as ergot, digitalis, quinia, chloride of barium, etc. Although the nutritional alterations in the vessel walls precede the formation of miliary aneurisms, the progress of the changes is pro-

* *Loc. cit.*, p. 335; also the same author, in "Dtsch. med. Woch.," No. 36–39, 1880.

moted by the relaxation of the muscular layer. Agents which improve the vascular tonus have, therefore, the important action of retarding the nutritive changes.

CARDIAC REMEDIES AND DISEASES.

In the whole pathological field there are no more perfect illustrations of the applicability of physiological antagonism to the therapeutics of disease than in the case of the various heart maladies. The most exact antagonism has been shown between remedies acting on the heart. We shall now see similar exactitude in the antagonism between remedies and diseases of the heart. Is the action of the heart excessive from a diminution in the energy of the inhibition? We have remedies to oppose this state. Is the heart acting too slowly from excess in the inhibition? We have remedies to counteract this defect. Is the heart acting too rapidly from excess of energy descending through the accelerator nerves? We have remedies to diminish the production of this energy. Is the heart acting feebly from a paresis or weakness of the accelerator apparatus? We have remedies to give tone and increased power to this apparatus. Is the heart acting feebly from weakness in its motor ganglia? We have remedies to impart strength. Is the heart acting too violently and irregularly, because of too great and frequent discharges of force? We have remedies to moderate this violence and restore the rhythm. Let me briefly illustrate these points in turn.

In that singular malady, exophthalmic goître, the action of the heart is constantly much too rapid, and is often exceedingly so, from the diminution in the inhibitive control of its movements. The carotid and the vessels of the thyroid gland are relaxed and dilated, and hence this gland may pulsate almost like an aneurism. This condition of things is the essential change. It is true, in all advanced cases the heart is the seat of various structural alterations, but these are not necessary to constitute the disease. If exophthalmic goître is treated by the antagonists to that condition of the heart and vessels before the structural alterations above mentioned occur, it is usually curable. These remedies are galvanism (to the pneumogastric and cervical sympathetic), digitalis, and ergot, which increase the inhibition and the vascular tension, substituting a slow and orderly movement for the wild disorder of the disease. In some maladies, such a strong inhibitive influence descends along the pneumogastric that the heart is restrained, tied up, and its

movements are greatly retarded; again, the heart may be slowed by agencies paralyzing the accelerator apparatus or the motor ganglia. If the physician, influenced by the fact of the slow movement, prescribed without reference to the mechanism, he might do serious mischief. The excess of inhibition is overcome by such an agent as aconite, which depresses the function of the inhibiting nerve; the paralysis of the accelerator apparatus or of the motor ganglia is overcome by the stimulants of these organs, of which atropia is the best representative. Palpitation of the heart may be caused by irregular and explosive discharges of nervous force coming from the accelerator nerves, or from paroxysmal loss or depression of the inhibition. In the former case, such an agent as bromide of potassium, and in the latter as digitalis, is required. When the action of the heart is weak from depression of the accelerator apparatus, atropia stimulates this apparatus and antagonizes the conditions which result from it. The most important antagonist to states of depression is digitalis, provided certain conditions are observed. I am the more urgent in presenting this point because I believe the use of digitalis is carried much too far in the treatment of cardiac weakness. Digitalis increases the inhibition, slows the heart by lengthening the diastolic interval, energizes the heart muscle, and, by increasing the force of the recoil, favors the passage of blood into the coronary artery. Digitalis also raises the arterial tension. Long-continued medicinal doses, and, in a very short time, lethal doses, exhaust the irritability of the apparatus on which their effects are expended. In a case of poisoning, reported by Mazel,* a woman of twenty-five died of paralysis of the heart on the fifth day after poisoning by digitalis, her pulse meanwhile having risen from 40 to 65. Traube has shown that large doses of digitalis paralyze the pneumogastric, and hence the pulse thus becomes exceedingly rapid. When a patient, lying recumbent, is taking a course of digitalis, the pulse may be reduced to 40 a minute; but, on assuming the erect posture, it becomes very rapid and weak. The practical deductions from these observations are, that digitalis must be given in moderate doses, and not too rapidly, owing to the prolongation of its effects. In the condition of fatty heart, its use is more than doubtful, owing to the fact that it decidedly increases the arterial tension and thus imposes additional work on the heart. Digitalis opposes the conditions present when

* "Gaz. des Hôp.," 1864, No. 74.

mitral lesions disturb the normal work of the heart. The organ is weak and acts quickly from relaxation of the inhibition; the arterial system has relatively much less and the venous system much greater than the normal quantity of blood; the arterial tension is low, and the venous tension is too high, relatively and absolutely. Digitalis opposes these conditions when used in the proper quantity. It increases the energy of the cardiac contractions, readjusts the distribution of blood by raising the tension in the arterial system and by increasing the power of the heart beats, and so lengthening the diastolic interval as to permit more blood to enter the left cavity. Moderate doses, too frequently repeated, or large medicinal doses, will exhaust the irritability of the apparatus on which digitalis acts, and it will then cease to antagonize the symptoms against which it was prescribed.

The antagonism between remedies and disease is well exhibited in the treatment of aneurism by medicinal means. By slowing the blood current, and diminishing the caliber of the peripheral vessels, blood coagulates in the sac, the clot organizes, and a cure is effected. After learning the success of Hildebrandt in curing uterine fibroids by the subcutaneous injection of ergotine, Langenbeck bethought himself of the treatment of aneurism by the same means. His notion appears to have been that ergot, causing contraction of the muscular fiber of the aneurismal walls, gradually compressed the sac and thus effected a cure. It has been urged, accordingly, that ergot injections could be of no use in cases of aneurism of the aorta, since this vessel contains no muscular coat. Those making this objection are apparently unacquainted with the fact that the solidification of the sac is caused by coagulation of the blood in it, and that the conditions most favorable to such coagulation are a slow action of the heart and increased tension at the periphery—produced by the injections of ergot. In the arrest of hæmorrhage the same principles obtain. Who now trusts to opium and acetate of lead, to tannin, to sulphuric acid, and the medley of ancient astringents? Modern pharmacological research has placed in our hands the most efficient remedies—antagonists to the conditions producing hæmorrhage. Increased action of the heart and relaxation of the vessel walls are the conditions to be antagonized in hæmorrhage, and the most effective remedies are ergot, digitalis, potassium bromide, veratrum viride, etc. The subcutaneous injection of ergotine is the most speedy and certain means of arresting pulmonary hæmorrhage. Menorrhagia is usually more promptly arrested by bro-

mide of potassium. These remedies may usually be given in combination: bromide of potassium and digitalis by the mouth; ergot subcutaneously. The application of cold and heat in the arrest of hæmorrhage is based on the same principle. Cold causes immediate contraction of the arterioles, but relaxation follows; heat, on the other hand, first relaxes, but contraction soon follows, and is more energetic than that at first produced by the contact of cold.

RESPIRATION REMEDIES AND DISEASES.

The function of respiration is affected by remedies that depress and by remedies that excite. The action of those remedies employed against the neuroses of the respiratory organs has been sufficiently elucidated. As regards the remedies depressing the respiratory function, it is sufficient to remark that the only purpose to which they can be properly applied is to impose rest on the breathing organs, by diminishing the number and lessening the excursions of the respiratory efforts. Important results have been claimed from the use of conium and gelsemium in pneumonia, but grave doubts must exist as to the accuracy of the observations. In respect to the stimulants of the respiratory function, much good results from their timely use. Strychnia, as has been pointed out, is a respiratory stimulant of great activity and of much value in suitable cases. In some cases of emphysema and chronic bronchitis, and in the carbonic-acid narcosis due to respiratory failure in acute pulmonary affections, it is antagonistic and of special utility. Probably no remedy so generally prevents the reflex nausea and vomiting of consumption. There is none but a theoretical warrant for the statement, yet it seems probable that much good might result from the hypodermic injection of strychnia in capillary bronchitis, when hæmatosis is suspended and carbonic-acid narcosis comes on, and in pneumonia, when abortive attempts at crisis are made. The utility of strychnia in chronic bronchitis and bronchorrhœa is attested by an immense experience.

Atropia is a more generally useful respiratory stimulant than strychnia. It is much employed in certain neuroses of the lungs, but its chief utility consists in its power to increase respiration when depressed from a variety of causes. Atropia not only stimulates the respiratory center, but it diminishes the irritability of the sensory nerves of the lungs, and increases the circulation through these organs. These properties, more than its power to arrest night-sweats, must be the secret of the influence possessed by it over the

nutrition of the lung. In many cases of caseous pneumonia, before the process of softening and extension of the caseous matter has begun, atropia distinctly benefits the local lesions and improves the general state.

INTESTINAL REMEDIES AND DISEASES.

The action of antagonistic medicines is well exhibited in the diseases of the intestinal tube. A serous diarrhœa is promptly arrested by belladonna. Opium suspends intestinal movements and stops secretion; it therefore relieves conditions of an opposed kind, namely, diarrhœa and dysentery. Constipation due to torpor or paresis of the muscular layer of the bowel is often promptly cured by the faradaic current. When the muscular layer is paretic, and secretion is deficient, the relief afforded by opposing agents is very remarkable. The agents antagonistic to this condition of things are nux vomica, belladonna, and physostigma; and, if given in combination, they will oppose and remove it.

REMEDIES ACTING ON THE SKIN.

In the night-sweats of consumption, atropia, duboisia, hyoscyamia, and other members of the group oppose the conditions present and dry the skin. The value of this treatment is great because of the immense loss of material taking place through the skin. Sometimes the remedies acting by similarity, as Dover's powder, pilocarpine, picrotoxine, etc., are useful, but at present the only indication for their employment is the failure of the other agents. The remedies acting by opposition succeed much more frequently and permanently. A deficiency in the amount of cutaneous secretion may require the use of sudoriparous medicines. Pilocarpine stands at the head of the agents of this class. Picrotoxine has considerable power as a sudorific, but it is far inferior to pilocarpine. Local sweating, as of one extremity, of one side of the head, or elsewhere, is usually arrested by the local application of atropia or belladonna. The milk gland, being a sweat gland modified and enlarged for this special office, is acted on by antagonists in a manner similar to the skin. Pilocarpine increases the flow of milk; atropia diminishes and arrests it.

REMEDIES ACTING ON THE KIDNEYS AND BLADDER.

The functions of the skin and kidneys being to a certain extent vicarious, the activity of one necessitates a diminution in the ac-

tivity of the other. Those remedies acting on the skin antagonize the stimulants of the renal secretion. A state of lessened activity of the kidneys is opposed by those agents having a special action as diuretics. Substances excreted by the kidneys and acting as irritants promote the urinary discharge—as copaiba, cubebs, turpentine, etc.—but these are not proper antagonists. Remedies such as digitalis and squill, which increase the pressure in the renal vessels, and also directly stimulate the secretion, are the proper antagonists to the state of diminished activity. Recent investigations tend to show that diuretics of this kind do not, as was supposed at one time, affect the kidney tissues unfavorably, but rather retard than hasten chronic changes. Excessive urinary discharge, as in diabetes insipidus, may be due to passive cerebral congestion, of a limited area —the floor of the fourth ventricle, for example—and then is checked by such an agent as ergot, which acts by contracting the vessels.

Very admirable results are obtained in vesical irritability by the appropriate and timely use of antagonists. There is a form of vesical irritability in women, especially, which is often admirably relieved by the use of tincture of cantharides. In this form, there occurs an excessive intolerance of the presence of urine in the bladder, but the mucous membrane is unaffected and the urine is unaltered. Tincture of cantharides induces a similar irritability. The mechanism by which relief is effected is the inhibitive result of two impressions on the genito-spinal center. Two bodies can not occupy the same place at the same time, and two impressions coming from different points, and of equal volume, neutralize each other. If the same irritability of the bladder coincides with a catarrh, or the presence of a stone, it need hardly be stated that cantharides will not afford relief. Furthermore, the dose of cantharides tincture necessary to afford relief is the quantity required to cause some irritability of the organ.

The treatment of nocturnal incontinence of urine is most effective when based on antagonism of action. This malady serves to illustrate an important principle, although of slight importance itself. To give a presumed antagonist without reference to the associated conditions, is to invite failure. The incontinence may depend on weakness and relaxation of the sphincter. When a certain amount of urine accumulates, the sphincter is unable to withstand the pressure. In other cases the mucous membrane is intolerant, and a sense of fullness is communicated to the center, and an impulse originates for the expulsion of the urine, the act

occurring in a dream. This state is often connected with abnormal acidity of the urine. In still other cases, the muscular layer of the bladder is in an irritable state, and energetic contraction ensues whenever the urine accumulates sufficiently. For the first condition, the most usual probably, belladonna and ergot are the proper antagonists; for the second condition, bromide of potassium and alkalies; and for the third, such remedies as gelsemium, conium, chloral, etc., are most appropriate. This malady, then, demonstrates how, in the search for antagonists, we must carefully study the physiological pathology of the disease. The conditions of the disease being known, the character of the remedy should follow.

With this general survey of the organs and systems of the body, I conclude the first part of the second division of my subject. In the next and final lecture of the course, I have to discuss the most important of the practical relations of this subject to the treatment of diseases, namely, the application of the principle of physiological antagonism to the therapeutical management of general or constitutional states.

LECTURE VI.

ANTAGONISM BETWEEN REMEDIES AND DISEASES.

It must seem evident to those who followed my last lecture, or who have given any independent thought and investigation to the subject, that the treatment of local maladies is governed largely by the principle of antagonism. Is this principle equally applicable to the treatment of constitutional states? Are there any proper antagonists to inflammation, to fever, and to the diatheses and the cachexiæ. I think it can be shown that such antagonists do exist, and that our most successful therapeutical measures are applied in these maladies in accordance with the principle of antagonism.

First, as to the treatment of inflammation. In what does this process consist? Assuming no points that are in doubt, inflammation may be defined to consist in a dilatation (paresis) of the vessel walls, followed by stasis of the blood; in an increase of the number and a modification of the character of the white blood-corpuscles, and their migration from the vessels into the surrounding tissues; in a simultaneous diapedesis of the red corpuscles; in an increase and change of character of the fibrine and albumen of the blood, and their exudation within the area of inflammation; in the diffusion of the salts of the serum, especially the chlorides, into the inflamed parts; in an increased multiplication of the cellular elements of the tissues, in consequence of the increased pabulum furnished them; and in a breaking up, dissociation, and granular degeneration of the anatomical elements of the inflamed tissues. With these changes in the local condition is associated a febrile state, characterized by increased action of the heart, diminished tension in the vessels, and elevated temperature. No single remedy can antagonize the complexus of symptoms belonging to inflammation, but the

successive steps in its development may be counteracted by agents having effects opposed to those of the existing phase of the process. The initial change—the preliminary congestion—is often compared to the phenomena which ensue when the cervical sympathetic is divided. Such a comparison is of limited applicability, since in inflammation not only do the vessels dilate, but coincident changes occur in the blood and in the tissues. It follows, therefore, that the remedies which prove effective at the onset of an inflammation must act not only on the contractility of the vessels, but also on the corpuscular elements of the blood, for immediately on the occurrence of stasis the migration of the white corpuscles and the diapedesis of the red begin. There are two remedies of special value at this juncture, and three others of secondary utility. Quinia and morphia, administered together in sufficient quantity at the right moment, will often suppress a beginning inflammation. Such a statement can not be supported by any positive facts, for it is impossible to decide whether the morbid process would have proceeded beyond the point it had attained. The negative facts have a high degree of importance, for, if these remedies fail to accomplish the arrest of the inflammation when applied at the right moment, they are not true antagonists, or the antagonism, if exerted, is without influence over the development of this process. There is need of facts on this point, and the profession should on every suitable opportunity try the truth of this supposed antagonism. My own conviction is that it exists, and that failure is due to the inopportune application of the remedies.

A statement of the physiological actions of these agents will indicate the nature of the opposition. Quinia and morphia, if administered together in quantity sufficient to produce their full physiological effects, will raise the tonus of the arterioles, check the migration of the white corpuscles and the outward diffusion of the albumen, fibrine, and salts, and arrest the amœbiform movements and the subsequent multiplication of the white corpuscles outside the vessels. I have already pointed out that morphia possesses the power to raise the vascular tension and to check all vital processes, and in these actions we have an explanation of its powers in inflammations. Quinia has a greater range of action. Modern researches have cleared up all that was uncertain in regard to its physiological effects, and have explained the therapeutical uses formerly known only through empirical observation. It would occupy all the time at my disposal to discuss the physiological powers of quinia from

the historical and critical standpoint; hence I must content myself with the barest statement of the main facts. We owe chiefly to Professor Binz, of Bonn, the demonstration of the activity of quinia as a poison to protoplasm and to the minute forms of life. It is to this property that its power to arrest the movements and other vital acts of the white corpuscle is due. The possession of this property may also serve to explain the curative power of quinia in malarial fevers, if the recent discovery of the bacillus malariæ, by Klebs and Tomassi-Crudeli, is confirmed by further investigations. For, if the malarial diseases be produced by the reception and multiplication of these minute organisms in the blood—as is now known to be the result of the action of Obermeier's parasite in relapsing fever—the agency of quinia in their destruction is readily explained. To act efficiently as a protoplasmic poison, as might be expected, quinia must be given in large doses. Besides this property, quinia, as Binz and others have shown, lessens the oxidizing function of the blood. Ranke, and afterward Kerner and Strassburg,* has shown that it also reduces to a remarkable extent—one half—the excretion of urea and uric acid. As urea represents the oxidation of the nitrogenous tissues, it is obvious that quinia checks this oxidation. It follows from these considerations that quinia antagonizes the increased heat production, the migration and subsequent multiplication of the white cells, and the proliferation of the protoplasm of the tissues, while morphia, by raising the vascular tonus and lowering the work of the heart, tends to remove the congestion.

The other agents, having less important relations to the antagonism of the inflammatory process, are digitalis, aconite, and veratrum viride. While these agree in the power to lower the circulation, they differ in the mode of accomplishing this object. Digitalis slows the heart, but energizes its movements and raises the arterial tension. It also depresses the temperature, but any effect it has over the movements and changes of the protoplasm is secondary to its effect on the tension of the vessels. The amœbiform movements of the white corpuscles are, of course, favored by a relaxed state of the vessel walls, and hindered by a higher tension. The influence of digitalis on temperature is very evident, but it ranks far below quinia as an antipyretic. Hence it is rather as an aid to quinia that digitalis is used than as the chief antipyretic. Among those

* "Arch. f. exp. Pathol. u. Pharmacol.," ii, p. 343.

so prescribing digitalis I may mention Liebermeister. A manifest objection to the administration of digitalis against the initial movements of the inflammatory process is the slowness of its action. After the primary disturbance in the digestive organs, from five to ten hours elapse before the characteristic physiological effects follow. The slow diffusion of the active constituents into the blood is only equaled by their tardy excretion, for in one reported case a patient poisoned by digitalis died on the fifth day from paralysis of the heart. It follows that this agent can not be used effectively against the first stage of inflammation. Aconite behaves differently from digitalis. It reduces the power of the heart, and, although it also lowers arterial tension, the amount of blood reaching the inflamed area is reduced by it. Furthermore, it lessens oxidation by diminishing the work of the lungs, and reduces temperature, partly because less blood is distributed when the heart is working under its influence, and partly because the supply of oxygen reaching the tissues is less. Aconite is especially indicated when the arterial tension in general is high and hæmatosis is active. Veratrum viride possesses powers and properties very similar to those of aconite; but it more distinctly affects the heart, and less, proportionally, the lungs. Its agency in checking inflammation, like that of aconite, consists in lessening the amount of blood going to the inflamed part, and in the diminution of oxidation. The good effects of digitalis, aconite, and veratrum viride cease with the occurrence of exudation, for then new conditions arise which they can in no way oppose or remove.

The antagonists to the second stage of inflammation must, necessarily, have the power to prevent or remove the products of inflammation. The remedies antagonizing these new conditions are quinia, chloral, and the alkalies. The utility of quinia, however, ceases when the exudate has actually formed. Chloral is especially adapted to this stage of the inflammation: it diminishes the fever heat, dissolves exudations, quiets restlessness and delirium. The possession of these properties, except the solvent action on exudations, is nowhere disputed. The experimental evidence of this power to dissolve exudates is conclusive, and the clinical experience, although limited and difficult to define, seems to favor the belief in its existence. It is obvious, however, that the points of contact between chloral in the blood and the exudation in an inflamed area are small. It must, therefore, be more effective when it is administered before the final stasis occurs. The influence of an agent which substitutes quiet for delirium is, in general, favorable to im-

provement in the local state. The reduction of abnormal heat is not less useful. Chloral, therefore, unquestionably exerts a favorable influence if it does not dissolve an exudation. An important contraindication should not be overlooked—that is, the paralyzing effect of chloral on a weak heart. When exhibited for the proposed treatment the dose should be small, and not administered more frequently than every two hours. The tendency to cardiac depression can be overcome by the joint administration of atropia, which does not lessen the utility of the remedy for the purpose for which it is used.

That the alkalies, especially the potash, ammonia, and lithia salts, by increasing the alkalinity of the blood, check exudations, and cause their solution, more or less effectively, after they have formed, seems a perfectly well-established fact in clinical experience. This mode of treating inflammations was made use of on a large scale by the late J. Hughes Bennett, whose exceptional experience on this point entitles his declarations to special consideration. Alkalies may be advantageously given in alternation with chloral. It must be remembered, of course, that the more alkaline the blood, the more active is chloral. As ammonia is more diffusible than the other alkalies, it has always seemed to me to be more effective. It is best given in the form of the carbonate dissolved in the officinal liquor ammonii acetatis. When the exudation is undergoing solution preparatory to absorption and extrusion, digitalis and quinia again come into use. The particular objects of their use at this time are to give tone to vessels long in a paretic state, and to favor the transformation and elimination of the inflammatory products. Digitalis is probably a more serviceable remedy to secure these purposes than is quinia. Besides, as a result of the more or less long-continued strain on the heart, its action is irritable, quick, and wanting in energy—and these conditions are removed by digitalis.

The treatment of fever, or of that complexus of morbid symptoms known as fever, is a very wide subject. We are now concerned with the antagonists of fever, but, taking this restricted view, there is still much to be considered—so much that I must needs confine myself, during the short time at my disposal, to the barest mention of the chief points. The discussion of the nature of fever has been very fruitful in the past few years, but it has not settled the question, and we are still in the dark as to its essence. The existence of a heat-regulating center is both maintained and

denied. Is there in fever increased production or retention of heat? The greater formation and excretion of urea and of carbonic acid indicate that the oxidation processes are accelerated, and therefore there must be increased production of heat; but, as the derangement involves also the radiation of heat from the body, there must in fever be also a less quantity of heat radiated. No single source of heat can therefore be alone concerned in the production of fever, but the truth probably lies to a greater or less extent in all the theories.

The means for reducing fever heat, which we now possess, operate by both modes—on the source of heat production, and by facilitating its dispersion. In the first group are the medicines which stop or hinder those processes on which the formation of heat depends: they are known as *antipyretics*. Besides the antipyretic medicines proper, there are numerous remedies, the paralyzers especially, which diminish heat production among other toxic phenomena.

The first of the agents affecting heat production is repose—the cessation of all activity. I was the first, or among the first, to show that, if rabbits, pigeons, and other small animals are so fettered as to be kept immovable for some time, the temperature of their bodies declines. The period of greatest depression in the temperature of man is in the early morning, after the repose of the night. Medicaments that suspend muscular activity cause a reduction of temperature, which is quite independent of any influence which they may exert on heat production. It is obvious that conclusions drawn from observations in which this cause of lowered temperature is not accounted for must be defective and misleading.

There are numerous agents which affect heat production, the most important being quinia, salicylic acid, resorcin, chloral, digitalis, aconite, and veratrum viride. Besides these, all the remedies which depress the functions of respiration and circulation more or less diminish heat production. Unquestionably, quinia holds the first position as an antipyretic. After an exhaustive examination of the relative merits of these agents, including cold baths and all the methods of hydrotherapy, Liebermeister holds that quinia is entitled to the first place as an antipyretic, and that, if he were restricted to one agent, he would choose quinia. Although this is the testimony of but one clinician, a representative of the German school, his opinion is but an echo of the general sentiment among the more enlightened medical thinkers. The utility of quinia consists in its remarkable power to reduce temperature, con-

joined with a minimum of evil effects. I have already, in discussing its applications to the treatment of inflammation, entered somewhat into the nature of its antipyretic action. I need now merely state that the reduction of temperature effected by quinia is the result of its influence over the vital activity of protoplasm and over the so-called ozonizing action of the blood. The diminution in the oxidizing processes is shown in the great reduction of urea formation. The quantity of quinia necessary to effect any considerable reduction of temperature has been pretty closely ascertained: not less than twenty grains can have any distinct antipyretic effect. It is true, in malarial diseases much smaller doses may diminish fever, but here another element enters the problem. Our German *confrères* give twenty, thirty, forty, even sixty grains for the antipyretic effect, and repeat it as may be necessary, to keep the temperature down at the proper level, and withhold it, when the result is attained, until required again. The popular, and to some small extent the professional, opinion, that large doses of quinia affect the ears unfavorably, has no support in my experience. I have used large doses with excellent results in inflammation of the middle ear. That it has any other injurious effect on the human constitution, in proper medicinal doses, seems to me not at all probable. That quinia exercises the same curative influence over fevers—typhoid, for example—that it does over malarial diseases, can not be entertained for one moment. The effect it has on the course of fever is due to its antipyretic property; on malarial diseases, the action is specific and particular. It is effective, then, in the treatment of fever, according to the degree in which it reduces the temperature, and the value of this is determined by the importance of the febrile element in the morbid complexus.

Salicylic acid has many analogies with quinia. Like quinia, it does not affect the normal temperature to any considerable extent, but has a powerful effect on the temperature of fever. The first demonstration of this fact, by Butt,* has been since confirmed by numerous observers. The quantity required to produce a decided antipyretic effect is not less than sixty grains, but eighty, even one hundred and twenty grains, are sometimes necessary. Profuse diaphoresis usually occurs, and then the decline of temperature begins, about a half hour after the proper quantity has been taken. The duration of the decline is about six hours, and this furnishes

* "Centralbl. f. d. med. Wissensch.," lxxxii, 1875.

the measure for its repetition. Although the first reports of the curative power of salicylic acid in malarial diseases, in which it was ranked next to quinia, have not been confirmed, it still maintains its original position as an antipyretic. For the reduction of the temperature in fevers it does not have the position of quinia, but in acute rheumatism its antipyretic action, which appears to be the secret of its curative power in that disease, renders it highly useful.

A new remedy, resorcin, is likely to become useful as an antipyretic and as an antiseptic. Originally obtained from a resin, and because it has some similarity to orcin, its name was compounded of the two. According to its chemical composition, resorcin is meta-dihydroxyl-benzol, and is a phenol. It has no irritant properties, and may be injected subcutaneously without danger of inflammation and abscess. The dose as an antipyretic is about sixty grains. It produces at first quickened action of the heart, flushing of the face, and a sense of warmth and precordial oppression. Then perspiration begins, and is very profuse. With the appearance of perspiration, the temperature declines. The antipyretic effect on febrile temperature is very decided, and hence resorcin may come into general use as an antipyretic, the more especially as it does not produce irritation of the parts to which it is applied.

The effect of digitalis on febrile temperature, although decided, is not equal to that exerted by quinia. It is also much slower in action. The systemic effects of digitalis require several hours for their development, and, unfortunately for its use in the treatment of fevers, it causes, in any considerable quantity, very great gastro-intestinal disturbance. Furthermore, its administration must be regarded as ill advised in cases with weakness of the heart from granular degeneration of its muscular fiber. The quantity required to effect any considerable reduction of temperature is so great as to excite much gastric irritability, besides being hazardous. When employed as an antipyretic, it should be used to aid the action of quinia, rather than alone. Nevertheless, there are symptoms of the febrile state against which digitalis may be used with signal advantage. In the exanthematous fevers, scarlet fever especially, digitalis antagonizes the symptoms most active in bringing about a fatal result, viz., a weak heart, low arterial tension, quick circulation, high temperature, and deficient urinary secretion. Digitalis slows while it strengthens the heart, raises the tension of the arterial system, and stimulates the kidneys to renewed action. If there

be difficulty in retaining it by the stomach, the effects of digitalis may be procured by external application of the moistened leaves.

The antipyretic effects of aconite are less certain and decided than those of digitalis, and it differs from the latter in the character of its action. Aconite lessens the activity of the motor apparatus of the heart, and lowers the arterial tension, and hence it opposes the febrile state associated with rapid, strong, and turbulent action of the heart and elevated arterial tension. It is against certain symptoms of the febrile condition that aconite is useful, and not as an antipyretic. Whenever high fever is due to sthenic inflammation, it may lower the fever by acting against its source. The same observations are true of veratrum viride. By slowing the heart and diminishing the amount of blood passing into the inflamed area, by limiting the work done by the lungs, and thus lessening oxidation in general, veratrum viride has an unquestionable influence on the inflammatory process and on the accompanying fever, but it has not much value as an antipyretic purely.

The most efficient remedy against fevers of the essential group is cold, which acts on heat after its production. Nothing could be more exact than the antagonism of cold and heat. By the application of cold to the body, the heat is removed. The influence of cold and heat, respectively, on the circulation is admirably shown in the experiment on the frog's heart, to which I have several times alluded. When the blood is heated above the normal by the fever process the action of the heart increases correspondingly; when the surface blood is cooled, presently the whole amount of blood in the body has its temperature lowered, and the heart soon slows its beat. Thus, whether fever means increased production of heat or retention, the action of cold is equally efficient in reducing it. The result is the same, whether cold is applied by the cold bath, by the cold pack, by the rectal injection of ice water, or by ice bags. That part of the blood in contact with the cold surface loses a portion of its heat, and thus gradually the whole mass of blood has its temperature reduced. With the decline of the body heat cease all those changes due to the elevated temperature. How quickly high heat may kill is seen in heat fever, or sunstroke, and in the hyperpyrexia of some cases of acute rheumatism. How life may be saved under circumstances of imminent danger is witnessed when, in the condition of hyperpyrexia, the abnormal heat is removed by the application of cold. In the two conditions, often confounded under the term sunstroke, of heat fever and heat exhaustion, we have an

excellent illustration of the principles of antagonism. In heat fever the abnormal temperature is removed by the cold douche, the cold bath, the cold wet pack, etc., agents which would prove fatal if applied in the case of heat exhaustion, in which the temperature is rather below than above normal, the heart feeble, and the respiration slow and shallow. The remedies suited to heat exhaustion—brandy and tincture of opium—would soon overcome the subject of heat fever. The principle of antagonism, therefore, is the sure guide which we must follow in these dangerous circumstances. Having explained the mechanism of the antagonism, it would serve no useful purpose to enter into details regarding the application of cold. That the treatment of the fevers—of typhoid especially—has been greatly advanced by the method of hydrotherapy, seems hardly to admit of question. The treatment by cold baths is particularly adapted to those fevers in which the temperature is the dominant fact, but hydrotherapy becomes less and less important, the more the morbid complexus is determined by some special poison acting on particular organs. Typhoid represents one group; small-pox the other group of febrile affections.

The third and last division of maladies against which we may direct antagonists is that of the animal poisons, hydrophobia, syphilis, the diatheses, and the cachexias. This is a most difficult subject. Woorara, as I have already mentioned, has in two instances seemed to antagonize the convulsive phenomena of hydrophobia. To this statement may be added the singular case recently treated by pilocarpine, in which the tragic death in a wild delirium may be explained by the accidental moral causes, the spasms having subsided under the action of the remedy. It is not difficult to conceive that the poison may be eliminated by the profuse salivary flow. Very striking are the results obtained by Dr. Guttmann* in the treatment of diphtheria with pilocarpine. Of eighty-one patients with this disease so treated, not one died. He assumes that the free salivary discharge causes softening and detachment of the false membrane, but there must be some other antagonistic influence at work to produce such uniformly good results. It is very desirable to have further experience with the effects of pilocarpine; but it should not be forgotten that this remedy has a depressing effect on the heart, and may therefore coincide with the poison of diphtheria, which also paralyzes the heart.

* "Berlin. klin. Woch.," 1880, No. 40.

Probably no fact is better established in therapeutics than the curative effect of mercury in constitutional syphilis. Some resemblance may be admitted to exist in the constitutional effects of both agents. They manifest a tendency to attack the same tissues, and to produce lesions of a parallel, although not of the same, kind. They must therefore exert an antagonism at the points of contact, for no one can pretend, I think, that the poison of syphilis and the poison mercury are the same or similar. They are antagonists, and of such decided antipathy that they can not exist together in the same organ or tissue—one must displace the other. The action of iodide of potassium is different. This is a most diffusible substance, and in a few minutes after being taken has appeared in all parts of the organism. Its chemical affinities are such that mineral matters deposited in the tissues are sought out and eliminated in combination. It is therefore a chemical antidote, rather than a physiological antagonist.

Reviewing, then, the great subjects of the inflammations, fevers, and specific and diathetic maladies, it is perfectly obvious that the only certain method of management is the use of the antagonist remedies. Although I did not apply the principles to individual examples of inflammation, they are equally applicable to all forms.

Taking finally a comprehensive view of the subject, what are the lessons to be learned? It is obvious, I think, that the only rule which we apply in therapeutics, so far as any rule is applicable, is the rule or principle of antagonism. As respects the treatment of the state induced by poisons, the antagonism is direct. The effects of the two opposing agents counterbalance each other, until the natural powers secure the elimination of the poison. When a toxic substance enters the blood, a series of disturbances follows, due to its presence, to its action on the tissues for which it has a special affinity, and to the efforts made for its elimination. The antagonist pursues a similar course, but affects the particular tissue for which it has an affinity in an opposite manner, and thus prevents the impairment of function, which would otherwise result in death, until elimination occurs. The effort of the organism is always against the retention of organic poisons, and their elimination is always effected if there be sufficient time, and if the organs concerned are in a healthy state.

As respects diseases of particular organs, we find that antagonism is exerted in two modes: by similarity, and by direct antagonism, and that the opposition takes place in respect to the latter

mode, at least, in the symptoms. The antagonism by similarity is the action of the remedy on the same tissue, and with similar objective signs, but the effect on the tissue is opposed, for the disturbance produced by the remedy must necessarily be different in kind from that produced by the disease. Two actions of an opposed kind on a diseased tissue must necessarily result in one of two ways: either the disease is arrested, and an equilibrium is restored, or one or the other action predominates. If a proper balance of actions is obtained, and the disease is a functional one, a cure must be the result. This is, in fact, an exemplification of the old doctrine of substitution, and a scientific expression of its truth. In the process by direct antagonism, the symptoms produced by the disease are opposed by the functional disturbance caused by the remedy. If rightly timed, and if the disease be functional in character, the opposition of actions results in an equilibrium, which is health. If the alterations of structure are of a kind to be removed by the operation of physiological processes, then also may restoration be effected by the exertion of an antagonism. In the treatment of inflammation we have an illustration of how the successive steps in the development of the process are in turn subjected to the action of opposing agents. As this process enters largely into the structural alterations produced by disease, we are thus encouraged in our efforts to obtain results by the application of the law of antagonistic action.

It is obvious that treatment must be symptomatic, but not in the ordinary sense. To apply physiological antagonists with accuracy, a careful analysis of symptoms must be made, and we must proceed from the merely objective to the underlying state. Let us take, for example, the symptom fever. How shall we oppose it? Fever is made up of several symptoms: of increased action of the heart, usually low tension of the vessels, of higher temperature, and increased waste. To counterbalance the symptom fever, then, we must employ agents to lower the action of the heart, to raise the tension of the arterial system, to depress the temperature, and to stop waste. One or two or more agents may be required to accomplish this work in its entirety.

The right use of remedies in accordance with the principle or law of antagonism requires an accurate knowledge of physiological therapeutics. To this study, as a distinguished French therapeutist, Béhier, has lately said, the medical profession should give its unremitting attention. Is it the case? Is there that interest in the

study of modern therapeutics which we find exhibited in other departments of medical science and art? I fear not. There is still present the notion that observation and experience should be the sole foundations for the construction of a therapeutical science. The old principle, that a remedy which has cured a disease must cure all analogous cases, is still the guiding principle with many of the practitioners of our day. Besides the numberless fallacies, the product of individual experience, the observation of analogies is in every way misleading. The advocates of this empirical method are fond of asserting that the observations on animals can not be applied with any certainty to man; that rabbits eat belladonna leaves with impunity, and that pigeons can hardly be poisoned by opium; but physiological research demonstrates that by another mode of administration these animals are affected in the same way as man. While decrying the results obtained by experimental study, by the physiological method, they are hourly indebted to it for the accurate application of remedial agents. I might offer, for the consideration of those who pursue the empirical method, the declaration of Bernard, who affirms that observations on animals by the physiological method are perfectly conclusive as to the effect of these agents on man, but I prefer to remind them that many of the remedies in constant use are those for which they are indebted to the physiological method of research. Until Magendie studied strychnia, it was merely the mysterious upas poison; until Bernard examined woorara, muscular irritability was the dream of Haller. Chloral continued a mere chemical curiosity, until the genius of Liebreich demonstrated by one effort its wonderful hypnotic qualities. The results achieved in that way have a remarkable permanence. While the notions of the actions and uses of drugs engendered by experience and observation are constantly changing, the deductions of experiment have the same value as the same methods in the other experimental sciences. To this end we should direct our best efforts, and rest satisfied with no less certainty than that which belongs to the exact sciences, until we have attained to such a degree of perfection that, the disease being given, the remedy follows.

APPENDIX.

CASES OF OPIUM POISONING.

The fatal cases are not given in this list, since they have been narrated in the first lecture.

No attempt has been made to arrange the cases in any given order, chronological or otherwise. Such facts and the references are given as will enable any one desiring to investigate on his own account to identify the cases.

1. Adamson. "The British Medical Journal," January 6, 1866. 1 oz. of laudanum; 10 drachms of tincture of belladonna. Recovery.

2. Legg, Wickham. "Med. Times and Gazette," November 3, 1866, p. 474. Chas. S., æt. 5. Egg-cupful of equal parts of liniment of opium and liniment of belladonna (B. P.), equivalent to 5½ grs. of belladonna and 36 minims of tinct. of opium. Recovery.

3. Prentiss, Dr. J. L. "Chicago Med. Journal," December, 1866. Adult. 5 grs. of morphia. Received drachm doses of tinct. of belladonna hourly until five doses were taken. Recovery.

4. Droin. "Le Mouvement Méd.," lii, p. 615, 1867. Ptisan of fresh belladonna leaves. Cured by tinct. of opium.

5. Paul, Constantin. "Bull. Gen. de Thérap.," vol. lxxiii, p. 319. Adult. Received 20 grms. of laudanum, and was treated successfully by 16 grms. of tinct. of belladonna.

6. Horton, Dr. "Med. and Surgical Reporter," Phila., June 10, 1876, p. 404. Child, 2½ yrs. Received 45 grs. of extract of belladonna. Four teaspoonfuls of laudanum were used with success.

7. Murrell, Dr. T. E. "Med. and Surg. Reporter," September 30, 1876, p. 269. One fourth of a grain of atropia taken; relieved by 2 grs. of morphia.

8. Wharton, Dr. R. G. "Phil. Med. Times," January 22, 1876, p. 403. Poisoning by 3 grains of opium and cure by $\frac{1}{25}$ gr. of atropia.

9. Swayze, Dr. G. H. B. "Phil. Med. and Surg. Reporter," August 12, 1876. One oz. of laudanum taken. Recovery under coffee and extract of belladonna.

10. Morfit, Dr. Chas. M. "Med. and Surg. Reporter," December 15, 1877. Poisoning by 1 oz. of laudanum. Recovery under atropia.

11. Wilson, Dr. W. J. "Phil. Med. Times," June 8, 1878. Poisoning by opium and cure by atropia.

12. *Ibid.* Poisoning by opium and recovery under atropia.

13. Schmid, Dr. "Schmid's Jahrbücher," vol. cxxiv, p. 167. Atropia poisoning cured by morphia hypodermatically.

14. Graefe, Dr. Von. *Ibid.*, vol. clxxv, p. 356. Atropia poisoning cured by morphia.

15. Fronmuller, Dr. *Ibid.*, vol. cxxvi, p. 282. Atropia poisoning cured by morphia.

16. Cohn, Dr. Hermann. "Berliner klin. Wochen.," xi, 16, 1865. Poisoning by atropia and cure by morphia.

17. Oxley. "Brit. Med. Journal," May 20, 1871. Child poisoned by the liniment of belladonna, equivalent to 1 drachm of belladonna root. Cured by 44 drops of tinct. of opium.

18. Johnston, Dr. Christopher. "Boston Med. Journal," July 27, 1871. Poisoning by atropia. Relief by tinct. of opium.

19. Van Peteghem. "Bull. Med. du Nord, etc.," August, 1870. Poisoning by atropia and cure by morphia.

20. Alden, Dr. C. H. "Phil. Med. Times," May 15, 1871. Poisoning by morphia and cure by atropia.

21. Murdoch, Dr. J. B. "N. Y. Med. Record," October 2, 1871. Poisoning by tinct. of opium and cure by atropia.

22. Carter, Dr. J. J. "Phil. Med. Times," May 1, 1871. Man poisoned by laudanum. Electricity and the stomach-pump, and eleven injections of atropia, ten being of $\frac{1}{30}$ of a grain and one of $\frac{1}{60}$. Recovery.

23. Finney, Dr. Magee. "The Dublin Journal," July, 1872, p. 38. Poisoning by morphia and relief by atropia.

24 to **36** inclusive. Johnson, Dr. James. "The Med. Times and Gazette," vol. ii, 1872, p. 268, and vol. i, 1873, p. 175. All cases of opium or of morphia poisoning treated by atropia.

37. Dobrachotowz, Dr. "Schmidt's Jahrbücher," vol. clxxix, p. 156. Poisoning by morphia; relief by atropia and belladonna.

38. Cotter, Dr. S. K. "Medical Times and Gazette," May 21, 1870. Poisoning by a liniment composed of opium and belladonna. Recovery.

39. Agnew, Dr. D. Hayes. "Penn. Hospt. Reports," vol. i, p. 356. Poisoning by atropia; cure by opium.

40 and **41.** Radcliffe, Dr. "Lancet," vol. ii, 1868, p. 312. Two cases of opium poisoning treated by belladonna successfully.

42. Kühte, Dr. F. H. "Schmidt's Jahrbücher," vol. clix, p. 124. Apothecary poisoned by atropia; cured by morphia.

43. Lamodrid, Julius J. "Phila. Med. Times," March 16, 1878, p. 271. Woman poisoned by laudanum; cured by atropia.

44. Sieveking, Dr. "Med. Press and Circular," July 10, 1878, p. 22. Case of morphia poisoning; cure by atropia.

45. Hanesen, Dr. "Wurtlb. Correspbl.," xxxi, 244, 1879. Child poisoned by atropia; relieved by morphia.

46. Eddison, Dr. "Lancet," June 14, 1879, p. 843. Man had 6 drachms of laudanum; stomach-pump and atropia. Recovery.

47 to **55** inclusive. Seaton, Mr. James. "Med. Times and Gazette," vol. ii, 1859. Ten cases of poisoning by belladonna berries—one fatal.

56. Lopez, Dr. "North Amer. Medico-Chirurg. Review," January, 1860. Poisoning by opium; recovery by belladonna.

57 and **58.** Lee, Dr. C. C. "Amer. Jour. of Med. Sciences," January, 1862, p. 57. One case of opium and one case of belladonna poisoning; cured by opposite.

59. Burritt, Dr. H. L. W. "Med. and Surg. Reporter," April 19, 1873, p. 316. Poisoning by an ounce of tinct. of opium; recovery by an ounce of ext. of belladonna.

60. Schell, Dr. H. S. "Phil. Med. Times," November 29, 1873, p. 134. Opium poisoning; cure by atropia.

61 to **66** inclusive. Wood, Dr. H. C. "The Amer. Jour. of Med. Sci.," April, 1873.

67. Crolas, Dr. "Lyon Médicale," xix, 1874, p. 30. Poisoning by atropia; cure by opium.

68. Lente, Dr. F. D. "N. Y. Med. Record," January 1, 1874, p. 8. A case illustrating the antagonism of morphia and atropia.

69. Lautier, Dr. "Gazette des Hôpitaux," lxv, 1874, p. 575. Poisoning by belladonna; cure by opium.

70. Poole, Dr. S. W. "The Practitioner," October, 1874, p. 251. Poisoning by morphia; relief by atropia.

71. Davidson, Dr. Frank. "Med. Press and Circular," March 31, 1875, p. 267. Poisoning by liniment of belladonna; cure by opium.

72. Hedler, Dr. "Ber. klin. Wochen.," xxxiv, 1875, p. 471. Poisoning by atropia; cure by morphia.

73. Heaton, Dr. J. D. "Med. Times and Gazette," April 17, 1875, p. 413. Opium poisoning; cure by atropia.

74. Abeille, Dr. "Bull. de l'Acad.," quoted by the "Med. Times and Gaz.," vol. ii, 1872, p. 342. Poisoning by morphia; cure by atropia.

75. Wilson, Dr. Benj. "The Med. and Surg. Reporter," November 17, 1868. A case of poisoning by opium; cured by atropia.

76. McGee, Dr. J. P. "Amer. Jour. of Med. Sciences," January, 1869, p. 282. Poisoning by 30 grs. of crude opium; cure by atropia.

77 and **78.** Kavanagh, Bern. "Med. Press and Circular," August 11, 1869. Two children poisoned by extract of belladonna; cured by laudanum.

79. Mason, Dr. E. "Med. and Surg. Reporter," October 2, 1869, p. 284. Poisoning by laudanum; cure by extract of belladonna.

80. Lyons, Dr. J. J. "New Orleans Jour. of Med.," April, 1869, p. 292. Girl of five received 5 grs. morphia for quinia; cure by alum emetic, ambulation, and tinct. of belladonna.

81. Young, Dr. P. B. "Med. and Surgical Reporter" (ref. lost). Poisoning by opium; artificial respiration, ambulation, and belladonna.

82. Sinio, Dr. Baldomero. "Bull. Gen. de Thér.," vol. lxxvi, p. 126. Poisoning by infusion of belladonna; cure by laudanum.

83 to **102.** Cases tabulated by Dr. Norris in "The American Journal of the Medical Sciences" for October, 1862, and not included in the above list.

103. Naismyth, J. Goodal, M. B. "The Journal of Anatomy and Physiol-

ogy," July, 1880, p. 449. A case of the simultaneous taking of 5 or 6 drachms of laudanum and 2 grains of atropia. Recovery by the antagonism.

104. Janeway, Dr. E. G. "The N. Y. Med. Journal," November, 1880. Poisoning by 4 grains of morphia, and cure by atropia, faradism, and an emetic of mustard.

105. Mussey, Dr. W. H., and Bartholow, Roberts. Unpublished. Boy of eight received a mixture containing 2 grains of morphia and 1½ grains of atropia. The antagonism was permitted to be exerted without interference, and recovery promptly ensued.

During the publication of the abstract of my lectures in the "New York Medical Record" I received some valuable communications, several of them containing notes of cases bearing on the subjects under consideration.

A case of opium poisoning in an inebriate is furnished me by Professor Dabney, of Virginia, as showing the antagonistic power of atropia under unfavorable circumstances.

I am also indebted to Dr. McCullough, of Steubenville, Ohio, for the particulars of a case of opium poisoning in an infant, in which belladonna proved antagonistic.

A very interesting case of opium poisoning in an infant is reported in the "New York Medical Record" for January 8, 1881, by Professor Samuel C. Chew, M. D., of Baltimore. In this case the principles sought to be established in these lectures received admirable illustration and support, and its publication is, therefore, most opportune.

CASES ILLUSTRATING THE ANTAGONISM OF STRYCHNIA AND CHLORAL.

1. Mr. Lyon Vasey. "The London Lancet," May 17, 1873. A girl of sixteen took Gibson's vermin-killer, equivalent to a ½ grain of strychnia. A cure was effected by 20 grains of chloral subcutaneously.

2. Dr. Ogilvie Will. "The Edinburgh Medical Journal," April, 1875, p. 307. Attempted suicide with 4 to 6 grains of strychnia; cure by the hypodermatic injection of 30 grains of chloral.

3. Dr. Charteris. "The Lancet," April 10, 1875. Poisoning by Gibson's vermin-killer, equivalent to 4 grains of strychnia. An emetic of zinc sulphate and the administration of chloral effected a cure.

4. Dr. C. Bivine. "The Phil. Medical Times," August 14, 1875, p. 721. A case of strychnia poisoning in a little girl treated by chloral and bromide of potassium with success.

Note. Husemann has recently made a special research on the method of Bivine, as he entitles it, and has pronounced against it.

5. Dr. Angus Macdonald. "The Edinburgh Medical Journal," April, 1872, p. 882. Poisoning by the officinal solution of strychnia. The inhalation of chloroform was also practiced, but the cure was effected by the administration of 50 grains of chloral.

6. Dr. S. A. Turner. "The Phil. Med. and Surg. Reporter," June 15, 1872. A Sioux Indian, poisoned by an unknown quantity of strychnia; cure was effected by large doses of chloral as described in the lecture.

7. Dr. H. G. Landis. "The Phil. Med. Times," October 13, 1877. A case of strychnia poisoning treated by ether inhalations, bromide of potassium, and chloral.

I am favored by Dr. J. C. Dunn, of Pittsburgh, with the details of a case of chloral poisoning in which strychnia was the principal antagonist, strong coffee and ammonia being also administered. As the patient had taken a large but unknown quantity of alcoholic stimulants, it is difficult to estimate the precise share in the result of the injections of strychnia. As remarked in the lecture on this topic, the published examples of chloral poisoning do not supply the conditions necessary for determining the value of the antagonist.

STRYCHNIA AND NICOTIA.

The fact that Professor Haughton, M. D., of Dublin, first brought forward nicotia as an antagonist to strychnia ("Dublin Quarterly," August, 1862) should have been stated more definitely in the lecture on this topic.

ATROPIA AND PHYSOSTIGMA.

I am reminded by Dr. R. S. Wallace, of East Brady, that my statement in regard to the preponderating action of atropia needs some qualification. Although the effects of atropia are both more decided and more persistent than those of eserine on the pupil, yet when the pupil is dilated by atropia it may be contracted by eserine. In order to maintain the contraction, however, eserine must be repeatedly instilled into the eye.

NITRITE OF AMYL AND ERGOTIN.

In a paper devoted to the consideration of certain agents acting on the intracranial circulation, Max Schueller has demonstrated the existence of an antagonism between nitrite of amyl and ergotin. "When the vessels of the ear and the brain are dilated to their utmost extent by nitrite of amyl, a subcutaneous injection of about one fourth of a grain of ergotin will still produce, in ten to fifteen minutes, a very distinct, permanent contraction of the previously relaxed vessels, lasting several days, in those of the ear. On the side of the severed sympathetic this contraction also takes place, although it is of less intensity. If, after a well-marked contraction by ergotin, nitrite of amyl is caused to be inhaled, for even one fourth to one half hour, no dilatation follows; nevertheless, the poisonous effect of the nitrite of amyl is not prevented, although of later occurrence." "Berliner klinische Wochenschrift," Nos. 25 and 26, 1873.

INDEX.

A

Aconite, 65, 78, 83, 104.
Amyl nitrite, 82.
Anæsthetics, 84.
Antagonism of atropia and aconite, 65.
of atropia and bromal hydrate, 64.
of atropia and muscaria, 61.
of atropia and pilocarpin, 56.
of atropia and physostigma, 49.
of atropia and phytolacca, 84.
of atropia and quinia, 64.
of chloral and atropia, 72.
of chloral and picrotoxin, 71.
of chloral and strychnia, 67.
of digitalin and muscaria, 83.
of digitalin and saponin, 83.
of digitalis and aconite, 82.
of morphia and aconitia, 78.
of morphia and atropia, 22.
of morphia and caffeine, 79.
of morphia and cocaine, 79.
of morphia and chloroform, 80.
of morphia and gelsemium, 77.
of morphia and theine, 79.
of morphia and veratrum viride, 74.
of opium and aconite, 78.
of opium and belladonna, 22.
of opium and gelsemium, 77.
of opium and veratrum viride, 74.
of strychnia and aconitin, 81.
of strychnia and amyl nitrite, 82.
of strychnia and chloroform, 82.
Antagonists to fever, 106.
to inflammation, 102.
to specific diseases, 103.

B

Belladonna, 14, 22.
Bromal hydrate, 64.

C

Caffeine, 79.
Cardiac remedies and diseases, 95.
Chloral, 67, 71, 72.
Chloroform, 80, 86.

D

Digitalin and aconitia, 82.
and muscaria, 82.
and saponin, 83.

E

Eserine and atropia, 49.

F

Fever antagonists, 106.

G

Gelsemium, 77.
and opium, 77.

I

Intestinal diseases and remedies, 99.

M

Mental states and their antagonists, 94.
Morphia and aconite, 78.
and atropia, 22.
and caffeine, 79.
and cocaine, 79.
and chloroform, 80.
and gelsemium, 77.
and theine, 79.
and veratrum viride, 79.

O

Opium, 14, 22, 71, 74, 77.
Opium and aconite, 78.
  and belladonna, 22.
  and gelsemium, 77.
  and veratrum viride, 74.

P

Pain and the anodynes, 92.
Pilocarpin and atropia, 56.
Picrotoxin, 71, 89.
Physostigma and atropia, 49.

Q

Quinia, 64.
Quinia in inflammation, 102.
  in fevers, 104.

R

Respiration diseases and antagonists, 98.

S

Saponin, 83.
Spasm and the paralyzers, 88.
Strychnia, 17, 67, 81, 82, 86.
Strychnia and aconite, 81.
  and amyl nitrite, 82.
  and chloral, 67.
  and chloroform, 82.

T

Tetanus and its antagonists, 89.
Theine, 79.

V

Veratrum viride and opium, 74.

W

Woorara, 17, 88.

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