ON THE TREATMENT OF INTERMITTENT FEVER.

SUMMARY:—The Marsh Poison—Its Nature—Atmospheric Influences—Cinchona Fevers—Cinchona Bark—Alkaloids of Cinchona—Quinine—Cinchonine—Cinchonidine—Quinidine—Quinoidine—Quinoleine—Physiological, Toxic, and Therapeutic Action of these Different Alkaloids—Superiority of Quinine—Absorption and Elimination of the Salts of Quinine—Sulphate Chlorhydrate, Tartrate, Bromhydrate, Salicylate, and Tannate of Quinine—Mode of Administration—Pills—Potions—Gastric Method—Intestinal Method—Lavements—Dermic and Hypodermic Methods—Pomades of Quinine—Pulmonary Method—Intra-tracheal Injection of Quinine—Mode of Introduction—Modes of Administration—English Method—Italian Method—French Method—Doses—Massive Doses—Fractional Doses—Duration of Medication by Quinine—Contra Indications of the Employ of Quinine—Influence of Pregnancy—Succedanea of the Salts of Quinine—Alkaloids by way of Synthesis—Quinolein—Aromatic Series—Salicylic Acid—Resorcine—Kairine—Cedron and Valdivine—Picric Acid and the Picrates—Arsenic—Animal Substances—Spider Web—Hygienic Treatment—Hydrotherapy—Thermal Treatment—Treatment of Pernicious Intermittent Fevers—Treatment of Paludal Cachexia—Conclusions:

GENTLEMEN:—You know that in marshy localities there prevails a fever of an epidemic kind, which is described under the name of intermittent fever, fever and ague, marsh fever and malarial fever. It is to the treatment of this fever that I shall call your attention to-day.

What is the *materies morbi* of this paludal intoxication? This is an etiological consideration of considerable importance, and concerning which we have not yet obtained positive knowledge.

We find two opinions which are prevalent: according to one theory there exists a miasm which is in the cause of the disease; according to the other, atmospheric influences alone may engender it. With regard to the first theory, there exist two hypotheses; that of a telluric miasm, and that of a marsh miasm. The first has had for its principal defender, Leon Colin, who holds that all organic substances contained in the soil, may, when they are brought in contact with the air, by upheavals of the soil, determine intermittent fevers, and thus constitute the telluric miasm. Much more numerous are the partisans of the doctrine of marsh miasm.

Relying on experiments on animals, the supporters of this doctrine have maintained that stagnant waters are the origin of the marsh poison. Some have even localized the toxic principle; Salisbury, for instance, considers certain low vegetable organisms of the palmella genus as competent to occasion by their introduction into the economy, the symptoms of intermittent fever, while Klebs and Tommasi-Crudeli have attributed the same effects to micro-organisms of the genus bacillus. Bouchardat, moreover, arraigns the infusoria which abound in stagnant waters, as being the originators of a virus which may thus poison the economy.[1]

[1] Vitruve and Varon claimed that the insalubrity of certain countries depends on the introduction of minute insects into the economy. Lancisi and Rusoki attributed malaria to

To this theory of the toxic action of ferments, or virus, Eisenmann, Burdel, Durand and Munro have opposed another doctrine which, repudiating the idea of telluric or paludal miasm, affirms that all the disorders of certain febrigenous animalcules, called by the Italians *cerafici*. From this came the usage of filtering the breathing air through certain respiratory apparatuses worn by patients, or modifying this air with garlic from the supposed antiseptic properties of the latter.

J. Lemaire has also studied the influence of the animalcules, and vibriones, which are found in abundance about the marshes. These bodies act, according to Gautier, as a ferment, and are the cause of intermittent fever.

Klebs and Tommasi-Crudeli have studied experimentally the pathogeny of intermittent fevers by injecting under the skin of hares the products of culture of microbes from the water, soil, and air of countries ravaged by malaria. These experiments have shown that the germs of malaria impregnate in great abundance and on a large scale the soil where the malady prevails, and even the air in strata which are in contact with the soil. Stagnant waters do not seem to hold the germs in suspension.

When you introduce under the skin of a hare liquids holding in suspension either particles from the infected soil, or products of culture, you determine in this animal intermittent febrile phenomena; the filtration of the liquids prevents these accidents. In all cases of this kind where artificial malarial fever has been induced, tumefactions of the spleen are found at the autopsy.

The micro-organisms belong to the genus bacillus; they constitute mobile brilliant spores, and when cultivated develop in the form of elongated filaments, which undergo segmentation. They are not aerobic, that is to say, they have no need of oxygen for their development; it is in the spleen and the marrow of bones that their micro-organisms develop most actively.

Salisbury has noted on the surface of the soil of certain marshy regions of Ohio, certain organized cells, resembling an alga, of the genus palmella.

These spores are met with in the atmosphere, but only in the night time, and rise only to a certain altitude above the soil, viz: from 35 to 100 feet. Salisbury has detected these same spores in the expectoration and in the urine of patients affected with intermittent fever.

He has placed earth containing these palmellæ in the night time in the windows of the sleeping rooms of various persons, and has seen these individuals contract malarial fever.

Fever and ague has also been attributed to certain microscopic vegetals found on the surface of the water in the marshes of Dombes and of Pontines; these microphytes are different from palmellæ. Salisbury gave the name of *gemiasma* (miasm of the earth) to the organisms which he discovered, He describes them thus:

"Plants having the appearance of cells, consisting of a thin exterior wall, containing a nucleus full of minute spores, simple or aggregated; the colors of these plants are varied, they are red, green, and yellow."

Bouchardat also believes that the marsh miasm is produced by a vital act of infusoria, which pullulate in the mud of marshes that are in the process of drying; he compares the effects of this miasm to those determined by animal poisons. Therefore, the most probable hypothesis, according to him, as to the nature of the marsh effluvium, is that it is a poison produced by one of the species of microscopic animalcules resulting from fermentation of the marshes. Bouchardat, moreover, does not specify the variety of animalcule which causes the disease in question.

Laveran attributes impaludism to certain organisms which he has found in the blood. Richards has also detected in the blood the same organisms having a pigmented appearance. (*a*)

(*a*) Salisbury, On the cause of intermittent and remittent fevers, with investigations which tend to prove that these affections are caused by certain species of palmellæ (Amer. Journ. of Med Sc., vol. LI, jan. 1866.

intermittent fever are the product of modifications of the atmosphere, and in particular, of atmospheric electricity.[2] To which of these hypotheses shall we give the preference? Undoubtedly the influence which the labors of Pasteur have had on the study of fermentations, makes the balance incline toward the miasmatic doctrine of paludal fevers. Nevertheless I am ready to adopt, with Arnould, a mixed theory, which, while assigning a preponderant role to miasms, attributes also a certain part to meteorological influences.[3]

Although we cannot determine just what the veritable nature of the marsh miasm is, we know, nevertheless, by clinical experimentation, that all the symptoms which result from it are amenable to one and the same treatment, viz: treatment by cinchona and its derivatives; hence the name of cinchona fever, by which intermittent fever is sometimes designated. But in this application of

[2] Eisenmann puts forth the hypothesis that augmentation and change in the kind of atmospheric electricity is the cause of intermittent fevers; he considers the marshes as presenting circumstances favorable to the production of these electric modifications.

Burdel adopts the theory of electric influence, attributing the fever to sudden abstraction of electricity. He has noted by means of a particular apparatus—the hydro-thermo electric condenser—that the production of ozone and of electricity attains its minimum at the middle of the day, and it is at this moment that persons generally contract the fever. Durand, of Lunel, also admits this electrical influence; according to him the presence of the marsh miasm in the circulatory passages has for its effect to neutralize or depress the electric state of the blood.

Munroe believes that there is no especial poison associated with malarial fevers, and that the action of heat upon fermentations suffices to determine the electrical states which induce a more or less intense paralysis of the ganglionic nervous system, and that this paralysis is the occasion of all the febrile accidents. (*a*)

[3] Arnold has divided into three groups the present views respecting the etiology of marsh miasm: 1. Doctrine of miasm which comprehends that of impaludism and that of telluric miasm; 2. Doctrine of meterological elements in which the idea of miasm is rejected, and in which meterological elements alone are regarded as the cause of the malarial poisoning;

3. Mixed doctrine in which are admitted both the influence of miasmatic elements and that of meterological elements. (*b*)

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p. 51–75).—Lemaire, Acad. des sc., 1864, p. 426–317.—Gautier, Etude sur les fermentations (thèse de Paris, 1869).—Klebs et Tommassi-Crudeli, Einige Saëtze über die Ursachen der Malaria. Studien über die Usache des Wechselfieber und die natur der Malaria (Arch. f. Exper. Path. und Pharm., Bd. XI, Heft 1 et 2, p. 122, et Heft 5 et 6, p. 311, 1877).—Bouchardat, Des poisons et des venins (Ann. de thér., 1856, p. 299, et Bull de thér., 15 déc. 1883.—Laveran, des Parasites de l'impaludisme (Soc. méd. des hôp., 28 avril 1882).—Richard, Acad. des sc., 1883. [Some of the older observers believed the malarial poison to be a gaseous emanation from decomposing vegetable organisms(CO_2, H_2C and CS_2). This view is now abandoned, as refuted by the facts. Others have attributed it to the gaseous effluvia from a volcanic soil, others to a modification of the electricity of the earth or air. None of these views have been established on sufficient proof, and even the supposed microscopic vegetable organisms of low grade, the spores and algæ, with regard to the influence of which in producing malaria, so much has been said, lack as yet all practical confirmation.—TRANS.] See Hertz, in Ziemssen's Cyclopædia, Vol. II. page 585.

(*a*) Eisenmann; voir Hirsch, Recherches sur l'étiologie de la fièvre intermittente (Zeitsch. für die Gesamm. Med., 1849, et Gaz. méd., 1850, p. 821).—Burdel, Recherches sur la fièvre paludéenne, Paris, 1858, p. 88.—Durand (de Lunel), Traitement dogmatique et pratique des fièvres intermittentes, Paris, 1852.—Munro, Remarks upon Malarious Fevers and Cholera, etc. (Arm. Med. Rep., Feb. 1882, p. 263, London, 1874).

(*b*) Arnould, on climatal affections and the climatic element in malarial fevers. Arch. gen de Med., April and May, 1874.

cinchona bark to fever and ague, it is empiricism alone which has guided the physician, and which guides him to-day. Since first the Indians of the village of Malacatos gave cinchona in intermittent fever,[1] (centuries ago); since the time when the wife of the Viceroy of Peru, the Countess del Cinchon brought to Spain this precious medicament, or when, at a later date, the Jesuit fathers spread the knowledge of it all over Europe; and since the time, finally, when Louis XIV bought of Talbot the formula of this anti-febrile remedy, the question of the anti-periodic effects of Peruvian bark has made little progress towards solution. Despite the persevering researches of chemistry which have made known the principal alkaloids of cinchona, and despite much careful phy-

[1] It is only since the middle of the 17th century that cinchona bark has been known as a therapeutical agent. It is probable that for a long time the Peruvian Indians were acquainted with the properties of cinchona. But it was not till about 15 years after the conquest, that the Europeans learned the benefit of this medicament, which Geoffry calls "God's gift," and which Held qualifies with the attribute of "Divine;" which Morton styled as the "Herculean" antidote; and Redi, a miraculous medicine; and which Sydenham called admirable.

According to Jussieu, who was sent to America in 1735 to study the natural history of the country, it was the Indians of the village of Malacatos, several leagues to the south of Loxa, who were the first to discover the properties of cinchona. He is the author of the following note in a work published in Latin in 1739, as cited by Le Maout:

"It is certain that those who were the first to know the virtue and efficacy of this tree were the Indians of the village of Malacatos. These poor people were subject to intermittent fevers, caused by the moist heat of their climate, and by the variability of the temperature, and they had necessarily to look for a remedy against this sorry malady. As, moreover, during the time when the Incas reigned the Indians were versed in the knowledge of plants and skilled in discovering their virtues, the experiments which they make with divers vegetal productions led them to find in the bark of *Kina-Kina*, the supreme and almost sole specific of intermittent fever. This tree was designated by them by a name derived from its properties; they called it *yara choucchou, cava-choucchou;* yara signifies tree; cava signifies bark; and choucchou means a chill, cold, the horripilation of the fever; it is as if one had said, 'the tree of fevers,' 'the bark of fevers;' they called it also. *Ayaca cava;* that is to say, 'bitter bark.' By a happy accident there came, on a brief visit to the village of Malacatos, a Jesuit priest afflicted with intermittent fever; the Indian chief, Cacique, having been informed of the sickness of the 'reverend father' said: 'Give me a chance, and I will cure him.' The priest having assented to the proposal, the Indian ran to the mountain and obtained the aforesaid bark, and gave a decoction to the Jesuit; the latter, happily rid of his fever and restored to health, inquired for the remedy which the Indian had given him. He was made acquainted with the bark and obtained a great quantity of it, and returning to his country he proved by further trials that it produced the same effects as in Peru. The fame of it spread abroad, and the name of Jesuit's powder was given to it, and it was by this that it was first known in Europe.

According to a popular tradition, the wife of the Viceroy of Peru, the Countess del Cinchon, had been cured of an obstinate attack of fever and ague by a government officer of Loxa, who administered to her some cinchona. On her return to Spain, in 1640, the Countess and her physician, Jean Lopez de Vega, brought with them a supply of the precious bark and divulged the remedy which took the name of 'Countess' powder.' Later, in 1670, the Jesuit fathers sent home, from Peru, some samples of this bark which was consigned to the Cardinal de Luco, at Rome, and the remedy took the name of 'Jesuit's Powder,' 'Powder of the Cardinal,' 'Peruvian Bark,' and 'Febrifuge Bark.'

Immediately the new remedy was received with favor and enthusiasm, but barks of

siological experimentation to ascertain the *modus operandi* of these preparations of bark, we are still in the dark respecting this subject. Experimental physiology has in fact in the last few years given origin to a great number of works on the action of cinchona, and particularly on that of quinine, and to the primal researches of Magendie, of Giacomini, of Desiderio, of Melier, and Briquet, it has added a considerable number of treatises whose results are unfortunately contradictory.[2] Let us, for example, examine the conclusions which these writers have furnished respecting the action of cinchona and its alkaloids upon the circulatory and nervous system.

Some authorities affirm with Briquet, Giacomini, Chirone, Laborde, that under the influence of quinine there is a diminution of the arterial blood pressure, while on the contrary Desiderio, Germain Sée, and Bochefontaine maintain that arterial pressure is augmented and that consequently quinine is a tonic of the heart.[3] We find the same contradictions with reference to the nervous system;[4] according to some, quinine abolishes the sensibility and motrocity; according to others, it is an excitant of these functions. There is the same want of agreement moreover in explaining the quinine intoxication, and while Hammond sees here the effects of cerebral hyperæmia, Gubler regards it as resulting from ischæmia of the brain.

How explain such contradictions? Are we to believe that experimental physiology applied to the study of therapeutics can give only false and deceptive results? Must we accuse the experimenters of want of skill? Must we impeach the reliability of our instrumental apparatus? By no means, and all

bad quality having been furnished, by merchants little scrupulous as to what they were selling, a good many disappointments resulted, and the medicament fell into disrepute. A violent opposition was raised on the part of certain physicians of the time; Guy Patin, Chifflet, Plempius, Ramazzini, Baglivi, etc., declared it to be useless and worse than useless. But the cure of Louis XIV, in 1679, by Talbot's remedy again called attention to this bark. The king bought this remedy, which was nothing but a concentrated vinous tincture of cinchona, caused it to be made the subject of new trials, which were published by Paul de Blegny in 1682. Then all were loud in its praises. Lafontaine composed a poem in its favor; physicians experimented anew and with more care, and the works of Sydenham, Raclo, Morton, Torti, Lancisi, Werlhoff, etc., all agree in affirming the therapeutic value of the precious bark.

Down to the year 1820, the powder of cinchona, or the decoction of the bark alone was used. But Pelletier and Caventou, at this epoch discovered the alkaloids of cinchona and these were henceforth put into exclusive use.

[2] Experimental researches on cinchona and its alkaloids date from Magendie, who at the time of the discovery of quinine, injected this alkaloid in the jugular veins of several dogs. He pretended that quinine was without toxic action and innocuous in animals.

Giacomini, of Padua, showed on the contrary, in a series of experiments made on hares, that sulphate of quinine has very grave toxic effects when administered in large doses, and he noted among the toxic phenomena a considerable depression in the functions of the circulatory system; he concludes that this alkaloid is a cardio-vascular depressant.

Desiderio, of Venice, repeated the experiments of Giacomini, and maintained, on the contrary, that quinine was a *hypersthenisant* medicament (an augmenter of tone). Landri, Balardini, Leidi and Bergoni, who in their turn made experiments with this salt, advanced the same opinion as Giacomini. Melier, in France, repeated these experiments and proved the toxic action of this medicament. Finally, in 1853, Briquet published a large work on cinchona and its alkaloids, and maintained that these preparations are agents which attack and annihilate the nervous power, wherever it exists; hence he considers quinine as a hyposthenisant medicament of the nervous system. Since then very numerous works have appeared on the subject of the action of the salts of cinchona; it cannot, however be said that the views held are yet altogether harmonious. (*a*)

[3] Experiments made on human beings and on animals to ascertain the action of sulphate of quinine on the circulation, have given opposite results. Some experiments affirm that the beatings of the heart and the arterial pressure are diminished, others that they are augmented.

Giacomini considers this diminution of pressure as a characteristic; hence he places quinine among the *hyposthenisants* (enfeeblers) of the cardio-vascular system, and this opinion is shared by the majority of the Italian physicians.

Vincenzo Chirone has recently repeated these experiments, and this, according to him, is the action of quinine on the heart and on the blood-vessels. The systole of the heart is enfeebled and the ventricles are distended under quinine; it is the same with regard to the blood-vessels—vascular dilatation always resulting. This double action on the heart and blood-vessels pertains directly to the muscular fibre and without the intermediation of the vascular system.

In France, Briquet had also noted the diminution of the arterial pressure. According to him, this diminution is proportional to the quantity of quinine injected, and, moreover, this action is the more intense the larger the doses that are employed.

In a series of experiments he has shown that this depressant action on the blood-pressure is prolonged for twenty-four hours after the introduction of the medicament into the economy. Finally, in other experiments he has demonstrated that the contractile force of the heart gradually goes on diminishing and even is ultimately arrested when sulphate of quinine is injected into the veins. Laborde admits also a special action of sulphate of quinine on the heart. This medicament produces a veritable ataxia of that organ.

In opposition to these views we should cite the experiments of Sée and Bochefontaine, who have accepted the doctrine of Désiderio and of Gubler, who assert that quinine augments the contraction of the heart and is a cardio-vascular hypersthenisant (heart tonic). In experimenting on men and on animals, they have demonstrated that there is augmentation of the blood-pressure and a strengthening of systolic action; quinine is, according to them, a tonic of the heart and blood-vessels.

These differences of estimating the physiological and toxic effects of this drug are owing probably to the doses administered, and Jerusalimski has put this fact in clear light by showing in some recent experiments, that in small and medium sized doses, of from 1 to 22 grains, quinine produces acceleration of the pulse and of the blood-pressure, while in larger doses it produces, on the contrary, a very considerable fall in the blood-pressure, as well as diminution of the pulse.

It is perhaps necessary also, in order to explain these variances, to make some account of the kind of animals which were the subjects of experimentation. In fact Schetschepotjew, in studying the action of quinine on the muscles, shows that this action is different in vertebrates and in the frog; in man and in the dog quinine augments the force of the contractions and accelerates them; in the frog it slows them.

In order to explain this action on the heart, whether tonic or depressant, two opinions have been put forth: Briquet, Leweski, Jolyet, have maintained that quinine acts directly on the muscular fibre of the heart and blood-vessels. Chirone has even affirmed that this effect on the muscular fibre is a direct relaxant action, and he has generalized this influence to all the muscular fibres of organic life, the uterus being included.

Others, on the contrary, have maintained that it is by the intermediation of the nervous

(*a*) Magendie, Journ. de pharm., t. VII, p. 138.—Giacomini, Giorn. Anal. di Med., 1840.—Désidério, Compt. rend. de l'Acad. des sc., octobre 1829.—Melier, Bull. de l'Acad. de méd., p. 727.—Briquet, Traité thérapeutique du quinquina et de ses préparations, Paris, 1853.

these contradictions may be explained by this fact to which I have already called your attention while treating of the tonics of the heart, viz: that the therapeutic action of the medicament is often the opposite of its toxic action.

Have we not seen digitalis, that marvelous tonic of the heart, become a cardiac poison when it is given in large doses? It is the same with quinine, according as it is administered in therapeutic dose or in toxic dose. In moderate doses it tones up the circulation, in large doses it enfeebles it; in moderate

system that this action on the heart and blood is effected, the medicament being either a depressant or excitant of the functions of this system.

Gubler has advanced the opinion that quinine produces its action by galvanizing the great sympathetic.

Schroff, who has always noted a diminution in vascular tension, considers it as resulting from a diminution in the reflex excitability of the vaso-motors. This diminution does not result from a modification in the extra cerebral centres of inhibition, Chaperon thinks, but rather from a diminution of the excitability of the medulla oblongata and spinal cord. (*a*)

[4] According to Laborde, quinine acts especially on the cerebrum, but what chiefly characterizes its action is the absence of convulsions, which readily follow the ingestion of the other alkaloids of cinchona.

Briquet has maintained that quinine causes abolition of the functions of the motor and sensory nervous system.

Dupuis has insisted on the action of quinine on the peripheral sensibility. According to him, quinine almost completely abolishes the general sensibility. This abolition is due to a direct influence on the sensory centres. The nerve does not lose its property of conductibility.(*b*)

According to Chirone and Curci, this effect is not produced except by toxic doses; in therapeutic doses, quinine determines in man only a moderate diminution of tactile sensibility. In animals to which large doses of quinine have been given, sensibility disappears in the following order: first, tactile sensibility, then algesic sensibility, and lastly thermic sensibility; the anterior parts of the body are first affected, then the posterior.

To explain the quinine intoxication, which is a constant symptom in men and in animals under the influence of sulphate of quinine, two contradictory opinions have been advanced. Gubler maintains that this condition is characterized by a veritable cerebral anæmia, demonstrated, according to him, by the antagonism between opium and quinine.

According to Hammond, however, the quinine cerebropathy is due to hyperæmia of the brain.

As for the supposed antagonism between quinine and morphia, it does not exist; there is, however, according to Pantelejeff, an antagonism between quinine and atropine, the one congesting, the other anæmiating the brain.

(*a*) Briquet, Traité thérapeutique du quinquina et de ses préparations, Paris, 1853, p. 58, 61, 63.—Laborde; voir th. Jules Simon, les Succédanés en thérapeutique, Paris, 1883, p. 39.—G. Sée et Bochefontaine, Action physiologique du sulfate de quinine sur l'appareil circulatoire chez l'homme et chez les animaux (Acad. des sc., février 1883].—Jerusalimski, Uber bie Ppysiologische Wirkung des Chinin, Berlin, 1875.—Schtschepotjew. Selbstandige Contraction der Herzspitze, Veranderunged der Muskeln und der weissen Blutkorperchen unter dem Einfluss von Chinin [Arch. f. die Gesammte Phys., t. XIX, p. 53].—Léon Colin, Sur l'action des sels de quinine [Bull. de thér., 1872, t. LXXXIII].—Chirone, Meccanismo di Azione della Chinina sul sistema circolatorio e Azione sulla fibra musculare in generale [lo Sper., fasc. 10 et, octrobre et novembre 1875].—Gubler, Comm. de thér.—Schroff, Beiträge zur Kenntnlss der Chininwirkung [Stricker's Jahrb., p. 175].

(*b*) Dupuis, Etude expérimentale sur l'action physiologique de la quinine [thèse de Paris, 1877].—Chirone et Curici, Azonè della Chinina sensibilita e sul potere lossico [la Scuol. Med. Mapol., ann. II, fasc. 4, 6, 7, avril, juin, et juillet 1880].—Gubler, Comm. de thér.—Hammond, the Influence of the bisulphate of quinine over the intra-cranial circulation [New York Phys. and Med.-Leg. Journ., octobre 1874, p. 230].—Panteleieff, Das Salzaüre und das Schwefelsaure [Centralb. f. a. Med. Wissensch., n° 29, 1880].

doses it excites the nervous system, in large doses it depresses it. Unfortunately experimental physiology can generally study only the toxic action of medicaments, and hence becomes rather experimental toxicology than experimental therapeutics.

Moreover, this experimental therapeutics in operating on different animals may furnish different results, and Schtschepotjew* has well shown that this is the effect of quinine, opposite results being obtained according as one experiments on frogs, hares, dogs or human beings.

Ignorant, then, of the marsh miasm, ignorant of the principal points pertaining to the therapeutic action of cinchona and its derivatives, we are reduced to hypotheses to explain the anti-periodic effects, so evident and so indisputable of these medicaments, and authorities have by turns invoked in explanation (1) a local action on certain organs, (2) an influence on the nervous system, (3) an influence on the blood:

The theory of a local action of the cinchona alkaloids, as advanced to explain their effect on the morbid periodicity, has had few supporters. It is necessary, first of all, to assume that the periodicity characteristic of this fever results from the hypertrophy of the spleen, which influences more or less directly the ganglia of the coeliac plexus, and through that the entire nervous system; quinine, by diminishing the volume of the spleen, removes the cause of the intermittency.

Two opinions, directly opposite, have been advanced in support of the doctrine which attributes to the effects of the salts of quinine on the nervous system their anti-periodic action.[1] The one is defended by Briquet, according to which quinine, a veritable kind of "anæsthetic easily managed," as he says, annihilates the functions of the nervous system and thereby prevents recurrence of the attack; the other supported by Pidoux, asserts that the alkaloids of cinchona act as a tonic of the nervous system, preventing it from becoming enfeebled under the baneful influence of the marsh miasm.

Struck by the antiseptic properties of the salts of quinine, which Pringle was one of the first to point out, and which Binz and his followers, and more recently Baxter have positively demonstrated,[2] the view has been entertained

[1] Briquet considers quinine as a sort of readily manageable anæsthetic, which by its stupefying and hyposthenisant (tone-lowering) action, prevents the nervous fibre from feeling the morbid influence of the marsh miasm, and in this way opposes the paroxysms of intermittent fever.

Barthez and Pidoux, on the other hand, base the anti-periodic effect of cinchona and its derivatives on the force which it gives to the nervous system. The marsh miasm lessens the resistance of the nervous system; quinine acting as a tonic of the nervous system, re-establishes the stability of the nervous functions. (*a*)

[2] In 1750, John Pringle remarked the antiseptic action of the alkaloids of cinchona.

Baxter has repeated the experiments of Pringle, and also those of Binz and his pupils.

Binz had demonstrated that a neutral solution of sulphate of quinine (two-per-cent.)

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* Schtschepotjew, Arch. f. die Gesammete Phys., p. 53.

(*a*) Briquet, Therapeutical Treatise on Cinchona and its Preparations, p. 271, 1853.—Pidoux, Therapeutics and Materia Medica.

that cinchona and its derivatives exercise their remedial power by opposing the development of lower organisms, and the processes of fermentation which are its consequence. They appeal in support of their doctrine, to the prophylactic action of the salts of quinine, which, in fact, prevent individuals from taking fever and ague, as we shall see further on ; they appeal also to the fact of the presence of parasitic elements in the blood of persons affected with intermittent fever ; parasites which Laveran has of late described with great care.[3] This last hypothesis is much the most probable, and it is as an antagonist of fermentation that quinine acts in this periodical febrile disease. We will now study what are the rules which should preside over the administration of this medicament.

Cinchona occupies such an important place in modern therapeutics that it has been found necessary to take measures to prevent the destruction of the trees which furnish this precious bark. The Indians in the valleys of the Andes, whose business it is to gather the bark, the Cascarilleros, as they are called, were in the habit of destroying the trees to obtain the bark ; hence the rapid rise in the price of this medicine, and the danger of a complete exhaustion of the supply. So on all sides we have seen Europeans making efforts to cultivate cinchona trees in their colonies. The Dutch, for instance, have imported them to Java ; the English to the Himalaya mountains, to the isle of Mauritus, and to Australia ; the Portuguese to the Canary Islands ; and the French to Martinique, to Guadeloupe, and especially to the Reunion.

I shall not say much about the botanical characteristics of this member of the Rubiaceæ, referring you to your treatises on botany. Moreover, the number of the true and false cinchonas is so large that their study constitutes a science of itself, which is called quinology. I will then only remind you that from a therapeutic point of view these barks are of three kinds ; the yellow cinchona of which the cinchona calisaya is the type ; the red cinchona, represented by the cinchona succirubra; and the gray cinchona, furnished by the cinchona condaminea.[4] The chemical analysis of Peruvian bark has furnished a great

produced antiputrescent effects comparable to those of phenol; it arrests the process of fermentation, especially those which are caused by the microzymes.

According to Baxter, a solution of $\frac{1}{250}$ arrests the spontaneous movements of the microzymes. According to him, the order of activity of these different alkaloids is as follows: quinine, quinidine, cinchonidia, and, finally, cinchonine. He has also studied the salts of berberine, and picrate of potassa. The latter has an action as powerful as quinine. Baxter has also studied the action of quinine on the movements of the leucocytes; movements which are arrested when the proportion of the alkaloids is as one to 1,500. (*a*)

[3] Laveran's pigmented parasites, described minutely in a monograph of his on the subject of the "Parasitic Nature of Impaludism" (Paris, 1882), are believed by Duclaux and Bouchardat to be simply a result of an alteration of the blood globules by bacilli.(*b*)

[4] At the commencement of the therapeutic employment of cinchona only the bark was known. The first descriptions, which were nearly complete, were made in 1737 and 1739,

(*a*) Baxter, on the Action of the Cinchona Alkaloids on Bacteria and the colorless Corpuscles of the Blood [Practitioner, Nov. 1873].

(*b*) Bouchardat on "Impaludism, its Causes and Remedies." (Bull. de Thér., Dec. 15th, 1883.)

number of alkaloids. Pelletier and Caventou, in analyzing the crystallized product which Gomez has just made known under the name of cinchonino, found, in 1820, the two most important derivatives, quinine and cinchonine.

by La Condaminé and Jussieu, who obtained knowledge of the tree in Peru at Loxa. Then came the works and researches of Desportes, in 1742 ; of Jacquin, in 1763, in Cuba and San Domingo ; of Dombey, in 1776 ; of Ruiz and Pavon, in 1789, who established the botanical character of a great number of cinchonas of Peru. At the same epoch. Mutis studied the cinchonas of New Granada ; Humboldt and Bonpland, in 1801, those of Granada, Equador, and the northern parts of Peru ; Weddel, in 1804, those of Bolivia and southern Peru.

Many other admirable writers were also occupied with the cinchonas, and have left remarkable works, whose names, even, we cannot mention here.

The cinchonas are dicotyledonous plants of the Rubiaceæ family, tribe cinchoneæ. They are sometimes trees of large size, sometimes simple shrubs ; their leaves are opposite, sometimes smooth and shining, sometimes pubescent with large petioles and caducous stipules. The flowers form cymes, in corymbs or panicles; they are white or rose colored, and present a calyx adherent to the ovary, pubescent, with five parted limb ; a hypocrateriform corolla, with lanceolated lobes, smooth interiorily, and furnished along its borders with wooly hairs, five stamens included; the ovary surrounded by a fleshy disk, containing numerous anatropous ovules ; the style is simple, smooth, the stigma bifid. The fruit is an ovoid capsule, oblongate, or linear lanceolate, with septicide dehiscence ; it contains numerous seeds, imbricated from below upward, surrounded at their circumference by a denticulated membraneous wing.

The cinchonas grow at a medium altitude of 1,600 to 2,400 metres, and are met with in the parts of the Andes which extend from Venezuela and New Granada, about 10 north latitude, as far as Bolivia, about 19 south latitude.

Beside these countries where the cinchonas are indigenous, other localities to-day possess this tree, thanks to transplantation and an intelligent culture.

The Dutch have planted it in Java ; the English in certain dependencies of the Himalayas, at Mauritius, in Australia, in St Helena, in Trinidad, and Jamaica ; the Portuguese in the Canary Islands ; the French at Martinique, at Guadeloupe, and with more success at the Reunion. Several attempts have also been made in Algiers.

The cinchonas are very numerous, and present a variety of species. Weddel admits 33 species (1870) and Hooker (1873) describes 36. From a geographical point of view, they are divided into cinchonas ; 1, of Bolivia ; 2, of Peru ; 3, of New Granada. From a commercial point of view in France, the cinchonas are divided into three groups, founded on their outward appearance.

1. The gray cinchonas, the bark of which is sun-dried, shrivelled, and in the form of quills ; gray, rough externally, and covered by its epidermis, and certain lichens which grow on it ; yellow externally. It has a woody odor, an astringent savor, contains much tannin and cinchonine, and but little quinine.

2. The yellow cinchonas. The bark is thick, quilled, but not rolled inwards, deep yellow, without odor, more bitter, less astringent, poor in cinchonia, but very rich in quinine.

3. The red cinchonas. The bark is very thick, flat, or quill-shaped, blood red color ; chemically, is intermediate between the two others.

In fine authorities have admitted a further group, the white cinchonas, which contain but little cinchonia, and are almost inert.

Among the gray cinchonas have been classed : 1, The cinchona of Loxa, which is furnished by the cinchona condaminea (cinchona officinalis) of Linnæus ; 2, the cinchona of Huanco, in Lower Peru, or of Lima, which furnishes three principal varieties, the fine cinchona of Lima, the coarse cinchona of Lima, and the white Lima cinchona ; 3, the cinchona Huamalis of Peru is got from the cinchona purpurea, and is little esteemed ; 4, the red cinchona calisaya of Bolivia.