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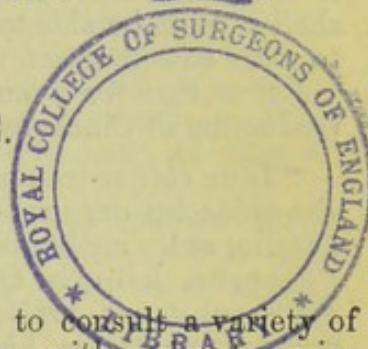


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CINCHONINE.

$C_{20}H_{12}NO$.

By MR. JOSEPH INCE.



Scarcely is there anything more perplexing than to consult a variety of authors on the subject of Cinchona and its preparations, with a view to arriving at any definite conclusion; every man appears not only to entertain a special theory of his own, but to think lightly of the speculations of contemporary or preceding writers, from Guy Patin, who in 1662 decided:—

“Le Quinquina ne guérit pas la fièvre intermittente, et nous l'avons abandonné. Jacet ignotus sine nomine pulvis.”

Cinchona bark does not cure intermittent fever, and we have abandoned it.

to Briquet (1853) who, in his elaborate treatise, ‘*Traité Thérapeutique du Quinquina et de ses Préparations*,’ thus introduces his observations:—

“Il existe déjà quelques travaux sur cette matière; mais comme ils ont tous été entrepris dans des vues particulières, et plutôt dans l'intention de soutenir tel ou tel point de doctrine, que dans le but d'obtenir des notions générales et d'arriver à connaître le *modus agendi* de la médication par le Quinquina à haute dose, ils manquent, ainsi qu'on va le voir, de ce caractère de généralité qui est indispensable même pour l'étude d'un simple médicament.

“Ainsi M. Magendie, voulant lors de la découverte de la quinine, ajouter les résultats de l'experimentation sur les animaux à ceux de l'observation sur les maladies, injecta du sulfate de quinine à des doses assez fortes, mais qu'il n'a pas indiquées, dans la veine jugulaire de plusieurs chiens, et n'ayant rien observé de particulier, il en conclut que cette substance était douée d'une innocuité complète et qu'on pouvait l'administrer sans inconvénient à des doses fort élevées.”

Various researches on this substance have been made already, but as they were all undertaken to confirm particular views, and rather with the intention of supporting such and such a theory, than to arrive at general conclusions, and to gain a knowledge of the *modus agendi* of the medical action of Cinchona in large doses, they are deficient, as will be seen in the sequel, in that character for impartiality which is indispensable even in the study of a simple remedy.

Thus M. Magendie, wishing, after the discovery of quinine, to add the results of experiment on animals to those derived from the observation of disease, injected sulphate of quinine in tolerably strong doses (which he has not indicated) into the jugular vein of many dogs, and not having observed anything remarkable, he concludes therefrom that this substance is completely innocuous, and that it may be administered without inconvenience in very large doses.

The truth is, no one seems able to approach the question without a theory; and yet out of the mass of conflicting evidence one fact stands out in bold relief, namely that from *Cinchona* bark two active principles are obtained, Quinine and Cinchonine; while at the same time it is matter of daily experience that the one alkaloid has almost superseded the other, Quinine enjoying universal reputation, and Cinchonine comparative neglect.

I am desirous of bringing forward some considerable amount of evidence to show that there is no just reason for this exclusive choice, and I think I shall at least be able to demonstrate that the salts of Cinchonine are entitled to more consideration than they receive at present.

Let us turn for a moment to the account given by Briquet of the first introduction of *Cinchona* bark:—

“D'un côté se trouvaient la plupart des médecins des grands hôpitaux de l'Italie, et les meilleurs praticiens de l'Espagne, lesquels, étonnés de voir cette substance arrêter comme par enchantement les fièvres qu'on ne guérissait point auparavant, ou qu'on ne guérissait, en quelque sorte, que par hasard, ne savaient comment proclamer assez haut des vertus si remarquables, et devenaient nécessairement les partisans du nouveau remède. De l'autre côté se voyaient de nombreux contradicteurs, les uns, protestants enthousiastes (et c'était le plus grand nombre des médecins anglais) ne voulaient pas croire qu'une poudre propagée, disaient-ils, par l'art infernal des Jésuites, fut autre chose qu'une préparation diabolique destinée à faire périr les gens du peuple, sous prétexte de les guérir. Il est vrai que Morton prétend tenir de bonne source qu'il entraînait un peu d'intérêt dans ce beau zèle contre la poudre des révérends pères: ces messieurs d'Angleterre trouvaient que les malades guérissaient trop vite.”

On the one hand were the majority of medical men attached to the chief hospitals of Italy, and the best practitioners of Spain, who in their astonishment at seeing this remedy arrest, as by enchantment, fevers which beforehand they were unable to cure, or cured only by accident, were unable to extol too highly such remarkable virtues, and necessarily became the partisans of the new remedy. On the other hand were numerous opponents. Some of them, being Protestant enthusiasts (for the most part English physicians), were unwilling to believe that a powder (as they said) introduced by the infernal art of the Jesuits, could be any other than a preparation of Satan, destined to destroy humanity under the pretext of effecting their cure. Morton, it is true, pretends to have good authority for stating that this fine display of zeal against the powder of the reverend fathers contained a sprinkling of self-interest. These English worthies discovered that their patients were too quickly cured.

When this prejudice had been happily surmounted, and the devil was allowed no more than his share in the transaction, another prejudice had its origin in the time of Pelletier (1820) the effect of which has remained to the present day, to the effect that Cinchonine was at best a possible substitute for Quinine.

Chomel, who was commissioned to report on the two Sulphates of Quinine and Cinchonine, with regard to their therapeutic agency, gives but one (published) trial to the latter; Magendie's note is open to the same objection; whilst by universal consent, Quinine is all-paramount as a remedy both here and on the Continent. Yet if we seek for evidence to prove that there is no sound chemical or therapeutical reason for this singular transmitted preference, the difficulty will consist in the selection of authorities; let us begin by consulting the exhaustive pages of Mérat and De Lens, and read the following extracts ('Dictionnaire de Matière Médicale,' vol. ii. p. 288):—

"Le sulfate de cinchonine, qui est très-soluble dans l'eau et dans l'alcool, et l'acétate, qui ne l'est bien que dans un excès d'acide, ont seuls été expérimentés en médecine. D'après les essais de M. Magendie, ces sels, ainsi que la cinchonine elle-même, n'exercent aucune action sur les chiens, auxquels on les donne, ou dans les veines desquels on les injecte. Quant à leur action médicinale, elle se confond tellement avec celle de la quinine et de ses sels, qu'il nous serait difficile, sous ce rapport, d'en isoler l'histoire.

"On avait cru d'abord, cependant, d'après une observation de M. Chomel, que la cinchonine était beaucoup moins active que la quinine; mais les observations de [list omitted] ont prouvé que leurs sulfates peuvent réellement se suppléer l'un l'autre. MM. Nieuwenhuis, Mariani et Bleyne ont en outre constaté, par des faits multipliés, que ces bases, au moins aussi actives que leurs sels, peuvent être substituées avec avantage, soit comme moins altérables et moins faciles à sophistiquer, soit comme plus agréables à prendre, soit enfin comme moins coûteuses."

Again, vol. v. page 596 :—

"Quoi qu'il en soit, ces alcaloïdes et leurs sels offrent, du moins sous le point de vue thérapeutique, tant d'analogie que nous n'avons pas dû en isoler l'histoire."

Finding then the impossibility of isolating the effects of Quinine and Cinchonine, these painstaking authors treat of them under one head,—in itself one of the strongest arguments in favour of Cinchonine. When Dr. Barrow was once preaching before Charles II., the monarch remarked at the conclusion of the discourse that the doctor was the most unfair divine he knew, for he so thoroughly exhausted his theme that he left nothing for any one else to say. The royal compliment may be extended to Mérat and De Lens. Should we however be more influenced by an English authority, the short statement of Dr. Royle may be adduced ('Materia Medica,' p. 515) :—

Cinchonæ Disulphas.—The salt of cinchonia is much more soluble than that of quina, being dissolved by fifty-four parts of cold water, and six of alcohol. It crystallizes in short, oblique prisms. It is considered by Pereira and others to be equal in medicinal activity to the disulphate of quina.

"It may be given in the same doses to produce the same effects, and will form a valuable substitute in the case of a failure of yellow bark. There is, however, a strong prejudice among medical men in favour of the quina salts."

Still more decisive is the opinion of Dr. Christison :—"Prejudice, together

The sulphate of cinchonine, which is very soluble in water and alcohol, and the acetate, which is only so in an excess of acid, have alone been tried in medicine. According to the experiments of M. Magendie, these salts, as well as cinchonine itself, have no action on dogs, either when administered or when injected into their veins. With regard to their medical action, it is so closely allied to that of quinine and its salts, that it would be difficult for us, on this head, to offer a separate account.

It was first thought however, from an observation of M. Chomel, that cinchonine was much less active than quinine, but the observations of — have proved that their sulphates may be mutually interchanged. MM. Nieuwenhuis, Mariani and Bleyne have moreover shown, by multiplied facts, that these bases, at least as active as their salts, could be substituted with advantage, whether as being less changeable and less easy of sophistication, or as being more agreeable to take, or lastly as less expensive.

Be that as it may, these alkaloids and their salts offer, at least in a therapeutic point of view, so much analogy that we have not thought fit to furnish a separate account.

with the unquestionable energy of quina as a remedy, has led to the other alkaloid, cinchonia, being overlooked in practice. The equally strong prepossessions, however, which were long entertained in favour of crown-bark as a febrifuge and stomachic, though it contains little quina, or perhaps none at all, and the proofs which have been given of the great efficacy of grey or Huanuco bark, would justify the inference that cinchonia too is eminently active. Accordingly trials made with it by Dr. Bardsley in England, as well as by various practitioners of credit in France, Germany, and Italy, seem to leave little doubt that it is scarcely inferior to quina in the treatment of intermittent fever, and some Continentalists maintain, that while equally energetic, it is likewise less apt to disorder the stomach in large doses."

Last, certainly not least, comes the masterly summary by Pereira (vol. ii. p. 1407):—

"*Difference in the Operation of Quina and Cinchonia.*—When we take into consideration the analogy of composition and of chemical properties of these two alkaloids, we are led to suspect analogy of physiological effects. When they were in the first instance submitted to examination, cinchonia and its salts were thought, principally on the evidence of Chomel, to be much inferior in activity to quina and its salts. But the subsequent observations of Dufour, Petroz, Potier, Bally, Nieuwenhuis, Mariani, Bleyne, and others, have proved that the disulphates of these alkalis may be substituted for each other. Nay, Bally gives the preference to the disulphate of cinchonia, on the ground that it is less irritating than the disulphate of quina."

In presence of such statements, we are I think justified in taking the subject of Cinchonine and its salts under our serious consideration as pharmacutists. An admirable description of this alkaloid is given by Pelletier and Caventou in their original memoir:—

"La cinchonine a encore une saveur amère particulière; mais cette saveur est longue à se développer, et a peu d'intensité, en raison de l'insolubilité de cette substance. Elle se développe dans la cinchonine rendue soluble par son union avec les acides; elle est alors très-amère, styptique et persistante, en tout semblable à celle d'une forte décoction de quinquina, à cela près qu'elle est moins astringente; l'astringence de quinquina étant particulièrement due à un autre principe."

Cinchonine has moreover a peculiar bitter taste; but this taste is slowly developed, nor is it remarkably strong, on account of the insolubility of the substance." The bitterness is developed in cinchonine when rendered soluble by its union with an acid. It is then very bitter, styptic, and permanent, exactly resembling the taste of strong decoction of bark, only less astringent; the astringency of bark being specially due to another principle.

Full details of the preparation of its salts may be found in the memoir by Pelletier and Caventou, in the dictionary of Mérat and De Lens, in the last edition of Brande's Chemistry, and elsewhere. I believe it would be undesirable to quote these processes at length, firstly because those interested in the manufacture of the Cinchona alkaloids are perfectly well acquainted with all the available sources of information, especially those of an original character; and secondly those who should be tempted to undertake their preparation without long experience, adequate resources, and something beyond the teaching of a printed formula, might possibly be disappointed in the results obtained. Nor can I for one moment endorse this declaration:—

"La préparation des sels cinchoniques est très-facile, puisqu'elle consiste dans l'union directe des acides avec la cinchonine ou la quinine." (Pelletier.)

The preparation of the salts of Cinchona is very easy, because it consists in the direct union of acids with cinchonine or quinine.

Though the concluding sentence may be most honourably meant:—

“Quant à l'extraction de ces deux bases, fidèle à notre système de n'avoir aucun médicament secret, et de faire toujours part à nos confrères des résultats de nos recherches, nous en avons donné le procédé dans notre mémoire lu à l'Académie des Sciences; on peut y avoir recours.”

With regard to the extraction of these two bases, faithful to our plan of having no secret remedy, and of always communicating the result of our researches to our brethren, we have given the process in our memoir read before the Académie des Sciences, which may be consulted.

I make these remarks the more willingly at the present time, as a most elegant and inexpensive salt of Cinchonine is before the public,—the Muriate of Cinchonine,—which may be obtained through the usual commercial channels; it has the decided advantage of being very soluble in water, as well as being attractive in appearance. I see no reason, though laboratory difficulties seem to oppose, why an equally soluble Sulphate of Cinchonine should not follow in its wake. The best authority (Pelletier) declares, “L'acide sulfurique s'unit à la cinchonine, et forme avec cette base un sel neutre très-soluble: ce sel peut s'obtenir facilement cristallisé.” Again, Mérat calls it “le sulfate de cinchonine, qui est très-soluble dans l'eau.”

Meanwhile we must rest satisfied with the Muriate, and the following preparations naturally suggest themselves to the pharmacist:—

Tinctura Cinchoniae Comp.
R. Cinchoniae Muriat. ʒv ʒj;
Tinct. Aurant. 2 pints.
M.

None would probably be sorry to see the Tinct. Quinae Comp. of the present Pharmacopœia omitted on account of the great difficulty of effecting the solution of the Quinine. Mr. Squire says, “I find by experiment, that in seven days, 39-40ths were dissolved,” but the weather, or rather the temperature, has an unfortunate influence in modifying this result; by substituting the Cinchonina salt, the embarrassment disappears.

Solution of Cinchonine.
R. Cinchoniae Muriat. ʒj;
Aquæ destillat. ʒj;
Tr. Aurant. ad ʒxx.
Ol. Cinnam. ʒj;
Sp. rectific. ʒss.

Dissolve the Muriate of Cinchonine in the water, add the solution to the tincture, to which add the Oil of Cinnamon previously dissolved in the spirit, filter. A strong solution of cinchonine (three grains to a drachm) is thus effected, the oil of cinnamon effectually masking the bitterness of the preparation. It is right to state that Briquet estimates the strength of Cinchonina at one-third less than that of Quina; and Howard estimates the strength of the Muriate of Cinchonine at one-fifth less than that of the Disulphate of Quina. Both statements are open to a doubt.

Syrup of Cinchonine.
R. Cinchoniae Muriat. gr. xxiv;
Aq. destillat. ʒj;
Syrup. Simpl. ad ʒj.
M.

This syrup contains three grains in each drachm. Whilst on this point,

Magendie's syrup may be noticed, although it is rarely used in Continental practice.

Syrup. Cinchoniae Sulph.
(Magendie.)

R. Cinchoniae Sulphat. gr. xlviij ;
Syrup. Simpl. 1 lb.

Dissolve the salt in one ounce of water, then reduce the syrup one ounce by boiling, and add the solution.

One last point deserves attention, namely, that there is a degree of irritation connected with the exhibition of Quinine which is much less marked in the use of Cinchonine, and may therefore be fairly brought forward in favour of the latter. Briquet, no mean physiologist, bases his medical treatment on this fact, summing up his remarks as follows :—

(Page 506.) “ Les correctifs des sels de quinine se réduisent à peu de chose ; il est aisé de voir qu'avec des notions aussi simples que celles qu'on possède maintenant, on n'a plus guère à prévoir que l'action irritante de la quinine sur les voies gastriques et son influence stimulante sur l'encéphale.”

The correctives of the salts of quinine are included in very small compass. It is easy to see that being in possession of our present clear and definite notions, we have only to guard against the irritating action of quinine on the gastric canals, and its stimulating influence on the brain.

I have before mentioned that Dr. Livingstone declared that he had little faith in the disulphate of quinine unless combined with an aperient, and no man can claim to have been more successful in the treatment of febrile diseases than that sensible and intrepid traveller.

Let it not be imagined that in these remarks I wish to throw the shadow of disparagement on an admirable and sterling remedy ; but I am anxious to rescue a kindred alkaloid from unmerited neglect : and I do so on this ground, that some of the first writers and practical physiologists (both here and on the Continent) have pronounced the salts of Cinchonine to be cheap, soluble, and good.

26, St. George's Place, Hyde Park Corner.

Note.—Two muriates are mentioned by Pelletier and Caventou.

Dimuriate of Cinchonina.

Cinchonia	89·5
Acid. Muriat.	10·4

100·0

Muriate of Cinchonina.

Cinchonia	81
Acid. Muriat.	19

100