PHYSOSTIGMA

VENENOSUM (CALABAR)

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PHYSOSTIGMA VENENOSUM (CALABAR).*

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The plant that yields Calabar bean is a woody African vine which was described by Balfour in 1860. (See history.) The genus, which was founded on this species, belongs to the great natural order leguminosae, tribe phaseolae, and it is a curious fact that these poisonous seeds are so closely related botanically to the ordinary edible beans (phaseolus) of our gardens that the structural difference mainly resides in the stigma. The genus at present consists of three species.** Physostigma venenosum is one of the numerous woody climbers which inhabit the tropical forests of Africa, sometimes reaching the length of fifty feet, with a stem two inches in diameter. The leaves are pinnately trifoliate and in size and shape very closely approximate the leaves of the common " Lima bean " of our gardens.

The flowers are borne in pendulous racemes similar to the garden bean, but are of a darker color, the keel and wings being of a deep-purple color. The standard is folded and curved back; it is of lighter color than the wings. The wings and keel are almost concealed by the sheathing standard. The keel is spirally twisted at its apex, a character only found in a few genera (three) of the leguminosae. The pistil has a stalked ovary, a slender style, curved with the keel and densely bearded on the inner side, and has a dilated triangular blade prolongation beyond the stigma which forms the generic distinction from the genus phaseolus.*** The fruit is a

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**Viz.: Physostigma venenosum, Balf; physostigma cylindrosperma, Holmes[2], and a recently described species, physostigma mesoponticum, Taubert[3], all from tropical Africa.

***Hence the name physostigma, from physa, a bladder, although the prolongation mentioned is not hollow.

thick brown pod containing each two or three large seeds which are familiar to us as "Calabar beans."

HISTORICAL NOTES.

The plant of the Calabar, or ordeal, bean seems to be confined in its habitat to a limited area only around the gulf of Guinea, and particularly about the mouth of the old Calabar river, hence its common name. The first report we have from that region concerning the use of this seed as an ordeal poison is due to Dr. W. F. Daniell, who stated in 1846[4] that among the natives "persons suspected of a crime are forced to swallow a deadly poison made from the poisonous seeds of an aquatic leguminous plant which rapidly destroys life." The seed is called esere by the natives, which accounts for one of the alkaloids of calabar being named eserine. We are informed that the Calabar bean as an ordeal is administered in various quantities. Less than half a bean is sufficient to destroy life if retained on the stomach, while, on the other hand, numbers of them may (exceptionally) be eaten without fatal effects to the person if they quickly produce vomiting and purging.[5] In the native ordeal test, if the culprit vomit the nut, he is pronounced innocent and liberated; if it has a purging effect without killmg him, he is considered guilty and sold into slavery. If he dies, which as a rule occurs, this is taken as being in consequence of his guilt. On the authority of the Rev. Mr. Waddell, a missionary at old Calabar, Dr. Christison states that the general confidence of the African in the infallibility of the calabar ordeal test is so great that innocent persons accused of a crime often demand to be subjected to it, and thus pay the penalty of their blind superstition.[6] It is intimated[7] that the officials charged with administering the poison know how to select the less potent seeds when they desire to show favoritism. It is also stated that the test is often resorted to as a means of gratifying private revenge and its use, in the opinion of the African missionaries, is a great moral evil on that account alone.

Prior to 1860 attempts to classify the ordeal seed botanically had been fruitless because it was almost impossible for any European to obtain possession of

specimens. According to Mr. Waddell, the plant at that time was everywhere destroyed by order of the native king, who exercised a complete monopoly over the few that were preserved to conserve the demands of justice.[8]

However, in 1855, Mr. Waddell secured a few specimens of the seed, which he sent to Dr. Christison, at whose suggestion they were planted in the Edinburg botanical garden by Professor Balfour; but although they attained a vigorous growth, they failed to produce flowers, and thus it was impossible properly to classify the plant. It was not until 1859 that the Rev. W. C. Thomson, a good botanical observer of old Calabar, finally secured flowering specimens of the plant, which were preserved in alcohol and sent to Professor Balfour for the purpose of identification. The first account of the plant under its proper name was then given by Balfour in the proceedings of the Royal Societyl, Edinburg, January, 1860.

The Calabar bean, however, is not the only native poison that had been used as an ordeal among the blacks in Africa. The custom of subjecting persons accused of witchcraft, murder or other crimes, to the ordeal of swallowing poisonous vegetable infusions, has unquestionably prevailed among African tribes from the west to the east coast. In the eastern regions the cubera tanghin, or tanghin poison-nut, of Madagascar (tanghinia venenata) has been employed[l], while on the western coast there has been in use beside the Calabar bean the bark of a certain tree which has been differently named by different observers. This bark has become conspicuous. It is the "redwater ordeal," in use among the negroes of Sierra Leone. The interesting account given of the ordeal trial by Dr. Winterbottom as early as 1803[9] was extensively quoted by Prof. Wm. Proctor in the American Journal of Pharmacy of 1852[10].

Redwater poison was obtained from the bark of a leguminous tree, erythrophlaeum guineense, Don[11], which is identical with fillaea suaveolens, a tree occurring in Senegambia, and described and named by Guillemin and Perrotet[12]. Finally, the much discussed sassy bark, used under the name of casca, or casca bark, as an ordeal poi-

son among the natives on the banks of the Congo river, has also been shown to be identical with erythrophlaeum guineense Don.[13] It will thus be seen that calabar is but one of several ordeal poisons.

CHEMICAL CONSTITUENTS OF CALABAR BEAN.

In 1855 Christison[6] described his unsuccessful attempt to isolate definite active principles from Calabar bean. He obtained only 2.7 per cent of an alcoholic extract possessing the physiological properties of the bean. In 1863 Jobst and Hesse[14] succeeded in isolating from the bean its active principle, obtaining it as an amorphous alkaloid which they called *physostigmine*. Its formula was ascertained in 1867 by Hesse to be $C_{15}H_{21}N_3O_2$.[15] Vee and Leven in 1865 obtained the same alkaloid in crystallized form and gave it the name *eserine*.[16]

A second alkaloid was discovered in the Calabar bean in 1876 by Harnack and Witkowski,[17] which they called *calabarine*, distinguished from eserine mainly by its insolubility in ether. The discovery of this alkaloid shed considerable light upon a much disputed question among physicians regarding the efficiency of Calabar bean extract in cases of tetanus. (See further on.)

In 1888 another alkaloid, called *eseridine*, first obtained by the firm of Boehringer & Soehne, was investigated by Wm. Eber.[18]

According to its molecular formula, $C_{15}H_{21}N_3O_3$, it seems to be physostigmine plus the elements of water, and is distinguished from that alkaloid by its property of powerfully reducing iodin from iodic acid. Ehrenberg, in 1894, claims the discovery of another alkaloid, which he called *eseramine*, this being physiologically inactive.[19]

Beside the alkaloid the cotyledons contain much inert matter, e. g., 48.5 per cent of amylum and 23.3 per cent of albumen. [26] Alcohol extracts about 2.5 per cent of fatty substance. In 1878 Hesse, by extracting the cotyledons with petroleum, discovered a substance closely related to cholesterin, which he named *phytosterin*.[21]

The chemical tests for physostigmine (eserine), the most valuable alkaloid of the Calabar bean, are very delicate and striking, and are in part indicated in the various pharmacopeias. In this connection it may be stated that

Eber[22] has found the ordinary test reagents for alkaloids to be so sensitive for eserine that one one-millionth of a gram may thus be recognized. The physiological test, however, which we will mention later, is that which affords a sharp identity reaction.

TOXIC PROPERTIES AND MEDICINAL VIRTUES.

The poisonous properties of the plant seem to reside almost exclusively in the seeds, especially the cotyledons, not so much, however, in the hulls. It has been ascertained by Vincent[23] that the leaves and stems are not poisonous, which confirms an observation made by Fraser[24] with regard to the stems.

In Europe two cases of wholesale poisoning by Calabar beans are on record, both having occurred in Liverpool, one in 1864[25], the other in 1871.[26] They resulted from careless dumping of the sweepings from merchant marine vessels that had arrived from west African ports. These sweepings, being thrown in an accessible place on the dock, were culled over by children, some of whom ate freely of the beans. As a result vomiting and purging followed. Owing to prompt medical attention one only out of fifty-seven died.

The Calabar bean and its derivative, eserine, permit of a most important and beneficial application in medicine. In July, 1862, Dr. Fraser was the first to publish the observation that an alcoholic extract of Calabar bean, when applied to the eye, has the property of contracting the pupil, in which respect Calabar bean is directly antagonistic to the action of atropine and hyoscyamine.[24] Dr. Fraser's observation was confirmed in 1863 by Dr. Argyll Robertson,[27] and subsequently sustained by the fact of its general adoption in ophthalmic medicine.

For the purpose of conveniently applying the drug to the eye, Hanbury recommends that definite sizes of bibulous paper be saturated with the solution of the extract of definite strength.[8] These paper saturations were replaced later by the more convenient gelatin tablets, the preparation of which is described, e. g., in Hager[28]. According to Squire (1894),[29] these tablets are now official only in the British and the Italian pharmacopeias.

The physiological reaction has subsequently been considered such a decisive identity test for physostigmine that it is always resorted to in order to confirm the chemical tests.

In Flueckiger-Nagelvoor[30] the following directions are given for carrying out this test: Dissolve 0.010 gram of an eserine salt in 10 cubic centimeters of water, and drop one or two drops of the solution into the eye; within fifteen minutes, the time varying somewhat according to individuality, the pupil becomes contracted to the size of a pinhead. This experiment causes little or no inconvenience and passes off unnoticed.

Fraser employed the bean internally, finding that it acts simultaneously on the eye and the heart. Christison[6] had previously studied on his person the effects of taking one-fourth of a bean internally, coming to the conclusion that the drug causes depression, probably ending in paralysis, of the heart. The absolute absence of pain in his personal experience suggested to him that the drug might be humanely employed in the execution of criminals condemned to death. Fraser especially recommended the employment of the drug in tetanus, but the experience of other physicians has not been favorable to the remedy, and in some cases has been decidedly against it.[31]

However, as before stated, the discovery in 1878 of the alkaloid calabarine, and the fact that it produces tetanus in cold-blooded animals, has led to the theory that the varying proportion of this alkaloid may be the cause of the contradictory reports. It has subsequently been established[32] that an extract of Calabar bean may scarcely contain any eserine at all, but instead mostly the alkaloid calabarine.

ALLIED SPECIES AND SPURIOUS CALABAR BEANS.

In 1879 E. M. Holmes called attention to certain specimens of Calabar beans of commerce[2] bearing a close resemblance to the genuine beans. They were longer, of circular cross section, and the hilum did not extend the full length of the beans. Holmes found these beans identical with the mucuna cylindrosperma Welw., of the Welwitsch collection in the British, museum, and on account of its close relationship to physostigma veneno-

sum he gave it the name physostigma cylindrosperma. He also observed a chemical difference between the true bean and the allied species. On touching the cotyledons of the true beans with solution of potassa, a permanent pale-yellow tint was produced; on treating the cylindrical similarly, a deep, almost orange, color is formed, turning a greenish hue. However, no subsequent experimental evidence is on record, as far as we can ascertain, to demonstrate that the deeper coloration in the second case is due to an increased amount of alkaloid.

The Chem. Zeitung (in 1890) states, on the authority of Helbing, that the cylindrical species occurs in original packages mixed with the genuine bean, from which they are carefully sorted, because, it is stated, they command a higher price. [33] However, the drug as found on the American market appears to be of the official variety only.

Spurious Calabar beans have been called cali beans in European commerce. those occurring most frequently belonging to the following species: Entada scandens, entada gingalobium D. C., mucuna urens D. C., and seeds of oil palms, elaeis guineensis Jacq.

For a more detailed description of these sophistications consult the appended literature.[33]

PHARMACOPEIAL MENTION.

Evidences heretofore named would seem to make it advisable to exclude the extract of Calabar bean entirely from our pharmacopeias, and substitute for it the unexceptionally pure active principle, eserine. In this connection it may be stated that the German pharmacopeia has, since its 1882 edition, discarded the extract, and is using at present physostigmine salicylate and sulfate. The British pharmacopeia adopted the extractum physostigmatis in the edition of 1867. The French codex alone (Squire) carries the free alkaloid, eserine, with directions for preparing the same. The U. S. pharmacopeia introduced the extract of calabar in 1870, the physostigmine salicylate in 1880, and in addition the sulfate in 1890.

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