THE STORY OF DRUGS, WITH SPECIAL REFERENCE TO SIAMESE MEDICINAL PLANTS.*

By A. Marcan, f. i. c.

You will all have seen in Bangkok shops and stalls selling fresh and dried medicinal plants, but perhaps may not have realised the relation between these and the modern pharmacy; the relation is, however, a very intimate one, and we may say they form one of the early stages in the modern treatment of disease by drugs. It is my object this evening to give some idea of the steps whereby the ancient and empirical lore of the jungle has been translated into the medical practice of to-day.

I do not imply that all the drugs of repute in Siamese medicine are of therapeutic value, but no doubt medical men will say the same of many of the products of modern pharmaceutical industry. It is a fact, however, that some of our most valued remedies now in use throughout the world have a history stretching into the dim past beyond historical records, and modern science is indebted for the knowledge of these materials to jungle lore in some instances over 2000 years old.

The treatment of disease must have been a very early phase of man's activity, and he naturally turned to the vegetable world for his needs in this respect. For plants are easily gathered, fairly easily distinguished, and their varied physiological effects must have been learned by attempts to extend his menu, sometimes with fatal endings. The results of these innumerable experiments on the human body formed in time a mass of knowledge and tradition which was handed down from generation to generation, and forms a vast collection of experience for the application of modern scientific methods.

Superstition also played its part in the selection of herbal remedies; some plants were believed to be under the influence of special planets, indicated by the colour of their flowers, and they were used in the treatment of diseases ascribed to the same planets. Again, according to the doctrine of signatures, peculiar shapes had their special therapeutic effects, so that the renowned Ginseng of

* A paper read at a meeting of the Natural History Section of the Siam Society, December 14th, 1926.

China, which has roots resembling the limbs of a man, is in consequence imputed to have invigorating properties. Medicine has not substantiated this claim, but it is significant to note that the Mahuang *(Ephedra vulgaris)*, a drug which has been used in China for centuries, has just been found to contain an active principle, ephedrin, which is closely related to one of the most recent developments of medical research, an animal gland product, epinephrin.

To observe this drug lore in practice, one has only to travel up-country, when one's guide often sets out under stringent instructions from his friends to bring them the simples they need, and returns home laden with plants, barks, fruits or roots. On these occasions one can only deplore the fact that the investigation of these materials is such a long and costly procedure, and that these crude collections may perhaps contain a drug of great value.

We will now consider shortly the general lines by which science develops this collected knowledge. Assuming that the empirical reputation of a drug has been critically examined, and is considered to be worthy of investigation owing to its potency, its widespread use, and its apparently specific action, the first stage is to discover its source, that is the botanical species of plant or tree from which it comes. As we shall see, this may be a matter of much difficulty, extending over many years. It is essential that the Botanist should furnish it with one of his dreadful Latin names. In these names there is much that meets the eye, but there is more that is not so apparent. For the name of a plant includes its genus and implies its natural order, so that we are at once on intimate terms with its relatives. It also implies an accurate description of the plant, enabling us to recognise it with certainty when met. By reference to the literature we can ascertain whether these relatives are of known pharmacological value, and if so what class of active principles they contain.

The next stage is the chemical examination, and this may occupy a Chemist, or a team of Chemists, many a laborious month. At first, attempts will be made to ascertain what active principles it contains. For early in the 19th. century it was established that the action of many drugs could be traced to the presence therein of definite chemical compounds of great potency, often in minute quanti-

ties, which could be isolated and administered in a pure state, so that nowadays we are not obliged to consume the bark of the Cinchona tree to cure malaria, but are dosed with a definite weight of one of the chief alkaloids contained in it, Quinine.

Experiments with the active principle, or perhaps the crude drug, if none be found, are made on animals, and finally on man, to ascertain its effects. If beneficial, it will be introduced to the medical profession, and arrangements inaugurated for the collection, or perhaps the cultivation, of the drug. When eventually experience has proved its value, it will find a place in a Pharmacopoeia—a list of drugs officially recognised—and it is only when this consummation takes place that its struggles may be considered over.

The Chemist is never content with things as they are, and even seeks to improve on Nature. Some drugs have deleterious as well as beneficial effects—Cocaine for example the active principle of Coca leaves, of such value as a local anaesthetic, is toxic. Once the chemical constitution of cocaine was established, it was the Chemist's aim to determine what particular portion of the molecule exerts this toxic effect, and whether these groups could be removed without detracting from the narcotic effect. This work on the relation of chemical constitution and physiological action was in this instance successful, and we now possess novocain, beta eucain, and several other cocaine substitutes.

Chemistry has gone a step further, and has introduced valuable drugs which are the products of the factory, and have no similarities with the drugs of natural origin. A laboratory boy by mistake gave a bottle of acetanilide to a doctor, and it was found to have remarkable antipyretic properties, and this chance has resulted in the use of many valuable drugs. Many other synthetic products, such as some of the coal tar dyes, are now established remedies. The "hit or miss" method, tempered with common sense, is thus still in use, as it must have been in ages past when early man learned to select his remedies from the wild plants around him.

We will now illustrate these general principles by examining the stories of Quinine and Chaulmoogra. Quinine is of great interest as one of our most highly prized medicines, its scientific development took place, comparatively speaking, a long time ago, in which

the Botanist was the chief actor. It also portrays the deplorable results of reckless exploitation of natural resources. Chaulmoogra, on the other hand, is one of our newest drugs, and it was through the Chemist's work that it has reached its place in medicine. It is also of particular interest to us here in Siam.

Quinine is derived from the bark of a tree whose home is in the Andes. Evidence as to the knowledge of the curative properties of the bark amongst the Indian tribes inhabiting these regions is obscure and conflicting, but we know that the Countess of Cinchon, wife of a Spanish Viceroy of Peru, was cured of fever by the bark, and she brought back a supply to Spain in 1639, and its fame and use spread rapidly in Europe under the name of Jesuit's powder or Peruvian bark. The identity of the tree producing it was unknown for one hundred years after the use of the bark in Europe, but in 1739 herbarium specimens were collected by Le Condamine and Jussieu, and sent to Linnaeus, who established it botanically by describing the genus under the name Cinchona, and one species as *Cinchona calisaya*. The supply of the bark came entirely from the Andes, but reckless collection was seriously endangering the world's future supply of the material. It was imperative to cultivate the tree where its utilisation could be scientifically controlled, and the Government of India decided to attempt to procure supplies of the seeds and plants for cultivation. Spruce, one of the great botanical explorers of central America was commissioned by the Indian Government to carry out this decision, and he spent the whole of the year 1860 in this arduous work.

Under the prosaic heading "List of excursions during the year 1860" (in his "Notes of a botanist on the Amazon and Andes") is the following :—

January to March – "Chiefly at Ambato, making preparations for entering the forest of red bark."

April 10th. "Struck deaf in the left ear on this journey."

April 29th. "Woke up this morning paralysed in my back and legs. From this day forth I was never able to sit straight up, or to walk about without great pain or discomfort, soon passing to mortal exhaustion."

But he did not let such matters interfere with his quest.

June 18th to September 12th. "At El Limon, superintending the work of getting plants and seeds. The seeds were all gathered under my eye, and were dried, sorted, and packed by myself. Partly on horseback, partly dragging myself about on foot by the aid of a long staff, I explored the neighbourhood pretty thoroughly."

November 27th. to December 24th. "Putting together 15 Ward's cases and preparing a raft for them." And finally on December 31st: "Had the cases embarked on board the Pacific steamer."

These bald notes in a diary give no idea of the difficulties that had to be contended with. Spruce was particularly anxious to collect the ripe seeds, which could be used for germinating, but all July the weather was unfavourable, and many of the young capsules on the trees became diseased. Then the Indians got the idea that Spruce would buy the seeds, and commenced stripping the trees of them before they were ripe. He planted cuttings depending for his water supply on a small canal, which being unfenced was dammed by roaming cattle at least once every day. When this happened during an outburst of sunshine, all hands had to rush with buckets to a deep glen, toiling back with the water. When finally the cuttings began to root, they were attacked by caterpillars. However, 2,500 well grown capsules were collected, the cuttings struck root, and the whole collection was embarked on a raft for river transport. The river was in flood, and owing to overhanging trees it was essential to keep in midstream. The dreaded misadventure occured, the raft was swept into a mass of overhanging branches — the cases were lifted bodily up and dashed against each other. It is not difficult to imagine the explorer's feelings; fortunately the precious cargo had not sustained severe damage, and Spruce's labours were crowned with success. The young plants reached India in good condition, the seeds germinated, and served as the starting point of extensive plantations. The result as seen today is that in every Post Office of British India, a dose of quinine can be purchased for the equivalent of one farthing.

The development of the cultivation of the Cinchona tree is a long story, but as is well known, Java has now the practical monop-

oly of the export of the drug.

The chemical examination of the bark was commenced about 50 years after its botanical determination, and the quinine with which we are familiar is the chief of the 31 alkaloids contained in the bark.

The development of this drug has therefore extended over 200 years, from its first introduction into Europe to the making available of supplies of the pure active principle in the quantities required at a price within the reach of all.

Leaving malaria and Cinchona, we turn to Leprosy, a disease which until quite recently has been considered incurable, and as one of the most terrible afflictions of mankind. Ancient history, however, has a different tale to tell, and within the past few years the applications of modern science to ancient jungle lore has entirely altered the situation.

The earliest reference to a cure of leprosy is from the Mahawin, and the story goes that before the time of Buddha, Piya, a much revered Princess of northern India, became a leper. A cruel form of isolation was inflicted on her, she was taken to a jungle cave by her brothers and sisters, and there left to die. At the same time, Rama, King of Benares, was afflicted with leprosy, and after the royal physicians had expended their art in vain, he abdicated in favour of his son, and subsisted alone in the forests, living on wild fruits, including those of a tree named the Kalaw, — and became completely cured. During his wanderings he one day heard a piercing scream, and discovered the cave, the abode of Piya. Piya's terror had been caused by a tiger attempting to enter her cave, fortunately protected by a rock. Rama carried Piya off to the hollow tree which served him for protection, and persuaded her to eat the fruit, roots and leaves of the Kalaw tree which had cured him. Her disease disappeared, he took her as wife, and the legend states that Piya gave birth to twins 16 times, bearing 32 sons, and a new city was founded. So secure of their health did they feel, that it is said they actually felled the Kalaw trees to make room for their new city.

Whatever may be the truth of this story, the fruit of the Kalaw and related species, and the oil expressed from it, generally

known as chaulmoogra oil, has been used in Asia for many centuries, and had acquired a great reputation in the treatment of leprosy, the seeds being a common article of trade in Siam, India, Burma and China. But strange as this may appear, the ident ty of the tree or trees producing these seeds was unknown. Even the actual gatherers of the seeds may have had no exact knowledge, for there are several closely allied species which could easily have been confused with one another, and by the time the seeds reached the oil mill, they would have passed through many hands, and all track of their botanical source would have been lost. The problem was tackled in in India, but for nearly 100 years they were erroneously believed to come from the *Gynocardia odorata.* In 1899 Desprez came to the conclusion that the oil was derived from the *Gynocardia Prainii*, but this was again a mistake—Gynocardia oil is of no medicinal value. The mystery was finally solved through the work of Sir George Watt, who had herbarium specimens collected in India from trees purporting to be the true source of chaulmoogra oil. One of these fruiting specimens was found to possess seeds identical with the chaulmoogra seeds of the bazaars, and it was identified as *Taraktogenos Kurzii.* The genera Taraktogenos and Hydnocarpus have recently been combined, so that the *Taraktogenos Kurzii* is now known as *Hydnocarpus Kurzii.* There are however seeds from several species of the genus Hydnocarpus which from olden times have been used as leprosy cures, the one that interests us most being the Siamese "Lukrabao" the "Ta Feng Tzu" of China, the source of which is the tree named *Hydnocarpus anthelmintica*, the "Krabao nam". The exports of these seeds from Siam to China must have been going on for centuries, for they are mentioned under the name of "Ta Feng Tzu" in a Chinese Herbal, the Pen Tsao, written in 1597. Japan also draws her supplies indirectly from Siam, and the oil of *Hydnocarpus anthelmintica* is official in the Japanese Pharmacopoeia. In the record year of 1916 the export of Krabao seeds from Bangkok was over 500 tons, a very respectable total for a drug.

The first occasion on which scientific information was sought concerning this country's position with regard to the supply of these oils was in 1919, when Mr. Rock, Agricultural explorer to the United

States Department of Agriculture, visited Bangkok; unfortunately but little information could be given him. Happily the situation is now changed, the localities of the occurrence of the Krabao tree have been explored, and an estimate has shewn that we possess enormous natural resources of this oil. The commercial source of the seeds is the Prasak and Supan Rivers, where they are easily collected, and transported. The seeds are not likely to be adulterated with those of other species, and chemical examination rapidly shews whether the oil has been sophisticated, so that its control could be a simple matter. It is to be hoped that Siam will gain and retain a reputation for being the reliable source of this oil, and so perform a service to mankind, a service that would be widely acclaimed.

The oil is extracted from the seeds by pressure, and a modern mill has just been erected in Bangkok, specially for the production of this oil.

The Krabao tree is to be found in Bangkok, off Klong Sarn, or more conveniently at Wat Benchamabopit; it is also planted as a roadside tree near Wat Saket.

The tale, however, is not yet told, for another tree of the genus Hydnocarpus, *Hydnocarpus ilicifolia*, " Krabao krak," is to be found in Siam in its thousands. The oil has been chemically examined, and found to be very similar to the well tried *Hydnocarpus anthelmintica*, and a derivative is now being tested clinically in India. Should the results be satisfactory, it will still be a matter of several years before a trade is established. A successful competitor with the scientist is the bear, who very wrongly regards the flesh of the fruit as a delicacy, and last season scoffed at all the majesty of government by getting in first. And it will only be when the villagers learn that the seeds command a ready sale that the bear will be outwitted.

The modern development of chaulmoogra therapy dates from the chemical investigation of the oils. The work was commenced at the Wellcome Chemical Reseach Laboratory in 1904, and yielded surprising results. For it was found that the fatty acids of these oils had an entirely different constitution from those of any of the hundreds of oils with which we are familiar. The formula of all previous known fatty acids is represented by a straight, open chain,

whilst that of the chaulmoogra oils is a closed ring. This is a fundamental difference of great importance. The two fatty acids isolated are chaulmoogric and hydnocarpic acids. It is interesting to note that the *Hydnocarpus anthelmintica* seeds used in one of these classical investigations in London, came from Siam.

The old time method of treatment was by eating the powdered seeds or taking the oil by mouth, which had the great disadvantage of upsetting the digestion. The oil was also applied externally. The discovery of the peculiar fatty acids of the oils led Sir Leonard Rogers to prepare derivatives which were suitable for injection and he made use of the sodium salts of the acids, with encouraging results. Eight years ago, Dean, in Honolulu, injected another derivative of the fatty acids intra-muscularly, and this ethyl ester treatment is the one generally adopted to-day. Some favour injecting the natural oil, which is more easily obtained than any preparation.

In the history of chaulmoogra we again observe that the starting point was empirical knowledge garnered in the dim past, then came the gradual awakening of interest by modern science, and the labours of the Botanist and the Chemist which pointed the way to successful medical treatment.

We leave accomplished stories and enter the realm of the unknown with all its possibilities—to indicate two interesting materials whose history is still before them, one a fungus, known as Het rang haa, a species of Dictyophora. It is used as a narcotic by burglars. The fungus is dried and powdered, and the fumes blown on to the sleeper. It has a narcotic effect, producing a deep sleep, and the house is robbed in safety.

The other is the leaves of the Kratom, *Mitragyne speciosa.* The leaves of this tree are commonly chewed in the Peninsula, and act as a stimulant. They are now being chemically examined, and have yielded two alkaloids new to science.

I am afraid that those who have come here this evening with the expectation of seeing on exhibition a vast array of miracle-working herbs will be sorely disappointed, but an indication of the courses by which our Pharmacopoeias have become established should in fact be the cause of the reverse of pessimism, when considering the future of Siamese vegetable remedies. One must remember too, that now-

adays the development of a new drug is far more rapid than in the past. It must certainly be measured in years, but no longer in hundreds of years.

There are two lines of development, one the creation of a local industry supplying drugs containing the recognised active principles, and replacing imported products. Though well worth bearing in mind, this is not of compelling scientific or economic interest, and it would probably be a matter of difficulty to obtain supplies of standard quality on which the medical profession could rely. Far more valuable should be research on Siamese drugs unknown to modern science. This work has already been initiated, and is indeed fascinating. In addressing the American students the other day, His Majesty pointed out the happy coöperation of East and West in Siam. Now research on Siamese drugs forms a peculiarly favourable field for this joint enterprise, for our scientific organisations here can be brought into the closest living contact with the accumulated empirical experience and tradition of centuries. This was not the case in Europe, for by the time that science had gained a position enabling it to make use of the knowledge of the peasant, European populations had become herded into large towns, the original flora had been destroyed, and the traditional lore of bygone days forgotten. The Siamese flora is rich in species and in new species, and the peasantry are very prone to make use of the most varied resources of the vegetable world. Though the results of any such discoveries would hardly necessitate the enlarging of the Treasury vaults, a country could hardly wish for a fairer way of earning fame.

The goal is attractive, but the path is long and arduous. We have not that almost essential factor, a Flora of Siam, but in Professor Craib's "Enumeration" now appearing is the basis on which we hope it will soon be erected. Our scientific institutions are still very young, and can only be built up by steady and quiet effort. In the Botanical Section, the Government Laboratory, and the Medical School, we have the necessary organisations for this work, and though not advocating that an ambitious programme be launched, under the present administration no pains will be spared in collecting data, and advancing as opportunity offers.

The Siamese scientist of the future should be in the position of being able to utilise the foundations now being laid. May he be not so much impressed by that air of authoritative finality imparted by the neatly printed text book, as to disdain the jungle lore of his peasants, and should he at times despair of the gulf between the old and the new, let him remember that every physician of to-day heads his Prescription with a symbol representing an invocation to Jupiter.