morbid cutaneous manifestations is probably more complex than appears on the surface. As in the production of all disease, various factors are at work, some of which are at present unknown. Recent study of the blood and of immunity points the way, I think, in the direction of a solution.²⁸ Behrend's view that drug eruptions may be the result of the production of toxins in the body is probably correct in some cases. It receives support from the fact that eruptions may occur some time after the exhibition of the drug. The rashes due to antitoxins may be mentioned in this connexion. The sweat-excretory view was put forward long ago by Trousseau.²⁹ Other hypotheses are that drug eruptions depend on changes in the tissues themselves or in their vessels. Others rely on the peripheral nerves, on the vasomotor centres, on trophic nerve influence. As to the last named physiologists state there is no proof of the existence of such. Howbeit, it can be safely said at the present juncture that the intimate mechanism of drug eruptions is not known. Normally, the tissues are bathed in sodium chloride, but may not the use of bromides and iodides lead to rashes by substituting bromine and iodine for the chlorine?

I will conclude with the practical application of a knowledge of drug eruptions. I have already insisted on the part played by zoster in the Manchester epidemic. Sir William Gowers relates an interesting instance bearing on this point.³⁰ In a case of peripheral neuritis in a young Indian civil servant, arsenical pigmentation gave the clue to his disorder. It was ultimately found that there had been a prolonged attempt to poison the patient in India. A curious fact, too, was that about the commencement of his illness, which had been diagnosed as intermittent fever, he had had an attack of shingles. I need hardly tell you that in India arsenic is largely used as a poison, and the same custom apparently prevails in other Eastern and semi-Eastern countries.³¹

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DATURA POISONING IN THE FEDERATED MALAY STATES.

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It has long been known that *datura fastuosa*, *datura stramonium*, and some other plants of the nightshade family, such as *atropa belladonna* and *hyoscyamus niger*, possess poisonous properties.

Botany of the *Daturas*.

The species *D. fastuosa* and *D. alba* are members of the genus *datura* which are commonly found in the Federated Malay States. They are wild or semi-wild plants, which grow on the refuse land of our native villages or thrive on the borders of cultivated land, in the kitchen gardens, near stables, and elsewhere. These two plants of the Peninsula are identical with the *datura fastuosa* (Linn.) and the *datura*

alba (Nees) of India, where they are also found more or less commonly with other members of the same genus.

Datura fastuosa (Linn.), the black *datura*, is generally taken as a type of the tropical varieties of the *daturas*. It is a quickly growing herbaceous plant belonging to the natural order *Solanaceae*, about 4 to 6 ft. high, with widely-spreading branches and conspicuous trumpet-shaped flowers.

Habitat.—Common almost everywhere, especially when protected. Malay name—"kechubong hitam" or "kechubong ulong"; "trong punga" in Kedah.

Distribution.—South-Eastern Asia and Malay Archipelago. Leaves: broadly ovate, often about 5 to 10 in. long (12.5 to 25 cm.), and 4 in. broad (10 cm.) at the widest part, margin repandly toothed, petiole $\frac{1}{2}$ in. (11 cm.) long, apex acute, base unequal, glabrous or sparsely tomentose upper surface dark greyish-green, under surface paler. The fresh leaves exhale a fetid smell when bruised, and have a slightly bitter taste. Flowers: axillary, on short peduncles about $\frac{1}{2}$ in. (1 cm.) in length, single erect. Calyx tubular, five-angled, five-toothed, teeth reaching about half the length of the corolla tube. Corolla funnel-shaped (infundibuliform), purple or white without, and white within; five-lobed, twisted in bud. Lobes oblong-ovate, cuspidate, length of funnel about 6 in. (15 cm.). Stamens inserted near the base of the tube, included, anthers linear with parallel cells, opening by introrse slits. Ovary two-celled, falsely four-celled by false septa, ovules attached to both the true and the false septa. Style filiform, stigma bilamellate. Fruit an oblong globular capsule, $\frac{1}{2}$ in. (4 cm.) in diameter, spinous, dehiscing by halves, seeds indefinite embryo with characteristic curvature. Fruit stalk recurring with maturity until the ripe fruit becomes pendent.

Datura alba (Nees), the white *datura*, *kechubong puteh*, is a taller plant than the preceding, with trumpet-shaped flowers, either pure white in colour, or yellowish-white tipped with violet. The flower is smaller and more tubular in shape than that of the *datura fastuosa*, the teeth of the calyx being less than half the size, and lanceolate acuminate in shape. The differences between the two plants, however, are so slight that they can scarcely be classed as being specifically distinct from each other.

Datura alba is the common *datura* of the Federated Malay States, but in certain districts *datura fastuosa* is said to be the more common of the two. Both plants are found in the Straits Settlements.

Datura stramonium (Linné), owing to its wide distribution in Europe and America, as well as in Asia, the best of all the ten or twelve species which have been recognized, is probably *D. stramonium*, or the dwarf thorn apple, which, however, so far as I know, does not occur in the Federated Malay States. It is necessary to refer to it, as it has been taken as the type of the temperate or tropical-alpine series, and because of the almost identical toxicological significance which is attached to the *datura fastuosa*, *datura alba*, and *datura stramonium* at the present time.

Popular descriptions of the tropical *daturas* as the black and white kinds has led to a great deal of confusion, it having been often taken for granted, on the authority of natives of India, that the black *datura* possesses more powerfully poisonous properties than the white, but of the same nature. No proof of this, however, has yet been given. By reference to the colour of the flowers alone no botanical distinction can be made, and it may be remarked that soil and circumstances may modify the colour of the flower or even double or treble the corolla.

Description of the Datura Seeds.—The seeds, in which the poisonous property chiefly exists, bear some slight resemblance to those of the common chillies (*capsicum*), and at times have been mistaken for them.

In many instances the light colour and the pungent taste of the latter would be sufficient to make a distinction, but when either is cooked and mixed with food, such as boiled rice, recognition by means of the taste alone cannot be relied upon. The resemblance is most marked in the unripe seeds, but a careful comparison of the two kinds shows many morphological points of difference; the *datura alba* seed is almost reniform in shape, having one end smaller than the other. It has been not altogether fancifully compared to the human ear, but the margin is angular; size about $\frac{1}{4}$ in. (5 millimetres) in length, rather less in width; no marked odour; taste slightly bitter; surface somewhat shrivelled except on the two compressed sides; testa tough and rough, being made up of a convoluted series of thick-walled cells, so arranged as to give a pitted appearance when seen with a lens. *Datura* seeds in powder may be distinguished by means of the cavernous appearance of their exosperm when seen under the microscope.

The embryo is embedded in a white oily albumen, and curved in a manner peculiar to the genus. By cutting parallel to the flattened side the embryo may be seen by the naked eye to be curved, twisted, and recurved, so as to resemble the head of a shepherd's crook.

A watery decoction of the *datura* seeds, when placed in the eye, will cause dilatation of the pupil.

The seed of the *capsicum* is kidney-shaped, a little shorter and wider than that of the *datura*, pale yellow in colour, uniformly rough, and when

seen in section as described above, the embryo is found in a flesh albumen and curved like the figure 6. Capsicum seeds in powder may be recognized by means of the application of heat, the acrid vapours of capsaicin being at once detected by heating even a small portion.

A watery decoction, when placed in the eye, causes irritation without dilatation of the pupil. The seeds of the datura fastuosa resemble those of datura alba. They are about $\frac{1}{4}$ in. (4 millimetres) long, of an oblong kidney shape, flatter, and darker in colour. About eight of them weigh 1 gr. in the dried state.

DATURA POISONING: CLINICAL CASES.

Death from datura poisoning seems to be comparatively rare; but, although the drug has been known medicinally in the East from time immemorial, and is often used by Asiatics for purposes of revenge or for drugging victims with criminal intent; lethal doses are seldom given intentionally. Three instances of drugging by datura have recently occurred in Pahang and one in Selangor. It is to be observed that these four cases merely furnish examples of the datura poisoning which is of every day occurrence in India.

CASE I. *Datura Seeds Mixed with Food by Pahang Malays.*—In the month of April, 1896, a Malay named Salyed, was charged at Kuala Lipis, Pahang, with causing hurt by means of poison. He pleaded not guilty, but, although the motive of his crime was never actually discovered, he was eventually convicted of having mixed datura seeds in a curry, thereby stupefying a Malay constable, his wife, and their niece, and a girl friend, as well as two men, all of whom happened to eat of the same dish. The symptoms in each case were similar, namely, attacks of giddiness, passing into unconsciousness for a few hours, followed by complete recovery. This group of cases is of some interest, owing to the fact that one of my colleagues, who appeared for the prosecution, was able to give evidence of a very practical kind. A sample of seeds and powder which had been found in the prisoner's handkerchief was sent to Dr. D. H. McClosky for identification. I am indebted to him for the following notes of his personal experiment. He says: "I took pinch doses of the sample, which consisted of the bruised seeds, and had the following experience: I felt flushed, dry about the mouth and throat, and became hoarse. When I tried to walk I staggered about like a drunken man and got very excited. I then took an emetic of zinc, vomited, and slept for about five or six hours." Dr. McClosky is further said by an eye-witness to have been in a delirious state, rolling on the floor, and uttering inarticulate cries.

CASE II. *Datura Seeds Mixed in Food by Pathans.*—In February, 1900, a Pathan was found by the roadside in Kuala Lipis, and brought to the hospital about midnight. He was half conscious, very restless, had dilated pupils, and was supposed to be intoxicated with alcohol. Mr. Henry Phillips, the chief dresser, who saw him the next morning, fortunately suspected datura poisoning. He applied the stomach pump, and found datura seeds, together with partially-digested rice and green peas, in the gastric contents. The patient made a complete recovery, and two of his fellow countrymen were subsequently sentenced to rigorous imprisonment for having administered the poison with intent to facilitate robbery.

CASE III. *Datura Seeds Mixed in Tea by Kedah Malays.*—At Kuala Kuantan, in July, 1901, two natives of Kedah were tried at the assizes and found guilty of administering datura seeds to a party of Chinese. Five different preparations of datura were found in their possession, some of which had been successfully used to produce unconsciousness in three Chinese, whose goods had then been stolen from their shop. They had been administered in tea and the stupor produced lasted apparently for several hours. The Chinese recovered without treatment. They stated that they had suffered from dryness of throat, uncertainty of vision, and "drunkenness."

CASE IV. *Datura Seeds Mixed in Tea by Chinese.*—In January, 1902, a family of Japanese in Kuala Lumpur, consisting of a man and his wife and son of about 10 years of age, were poisoned by datura seeds, which had been administered, as far as could be ascertained, in tea by a Chinese cook. I am indebted to Dr. Travers for the following brief and excellent notes: The man and the woman had flushed faces, bright eyes, dilated pupils, and suffered from giddiness. The man felt hot, dry, and parched in the throat, and had uncertainty of vision. The woman was semi-unconscious for a time, and kept picking at imaginary objects. Both recovered by the aid of emetics. The effect of the poison on the boy was more severe. About one hour and a-half after taking it he was seen rolling about the floor; he crawled, but could not walk without falling. He kept uttering inarticulate cries not unlike the mewing of a kitten, and appeared to be in a state of delirium, with flushed face and dilated pupils. He could not be induced to swallow anything, and gradually became very excited. He then fell into violent fits of temper, struck at imaginary objects, and was delirious all day, from 7 a.m., but slept soundly at night, and had completely recovered by the next morning. Dilatation of the pupils was very marked and persistent. It is noteworthy that in this case the drug was given on an empty stomach. The tea in which it was administered was the ordinary weak infusion of Chinese tea which is used every day by natives in the Federated Malay States.

MODES OF ADMINISTRATION.

The favourite mode of administering the drug for criminal purposes is by the mouth, the raw seeds being commonly used. In the Federated Malay States they are generally crushed and put into ordinary tea or into the common food,

which is some form of rice curry. Cases have been known, however, of the seeds being mixed with other poisons, such as *chandu* (opium prepared for the pipe) and *ganja* (Indian hemp), with the addition of a little sugar.

It is also, perhaps, worthy of note that they are sometimes mixed with other substances which are commonly supposed to be poisonous. For example, one of the exhibits in the Kuantan trial (Case III) was a carefully-prepared powder of datura seeds mixed with the fine hair of the young bamboo shoot (*miyang rebong*); *kulat taun*, a kind of toadstool; *gadong utan*, a wild yam (*dioscorea daemona*); and the fruit of the *rengut*, a climbing plant (*epipremnum giganteum*, Schott). These were all in dry powder, and being inodorous were in a form calculated to escape observation when mixed with food. In Pahang the seeds have been burnt with *gaharu* (*agularia malaccensis*), an incense wood well known as *lign-aloes*, also with *dama mata kuching*, a common local resin, for the purpose of producing lethargy by means of the fumes, and in the Temerloh district I have known of two cases in which this state was successfully produced in the victim with the object of profligacy or plunder.

POISONOUS EFFECTS.

The three most characteristic symptoms of poisoning by datura are the same as those of poisoning by atropine, namely:

1. Paralysis of the salivary nerves, leading to dryness of the mouth.
2. Paralysis of the third nerve, causing dilatation of the pupils, with imperfections of vision.
3. Paralysis of the inhibitory fibres of the vagus in the heart, causing sometimes very rapid action of the heart.

Other effects which should be noted are—that when the seeds are given internally (and the professional thief appears to know the exact dose necessary) symptoms of insensibility may commence early—within a quarter of an hour¹. The effect of the drug may last for two days, and is more severe, as a rule, if it is administered during childhood and old age. Many fatal cases of poisoning by the fruit and young seeds of datura are reported by Chevers,² as well as five fatal cases of poisoning by the leaves. They are mostly in children and aged persons.

Excessive dilatation of the pupil may be regarded as a dangerous symptom in datura poisoning. The loss of power of accommodation which is thereby produced, and the hallucinations caused, may explain the disorders of vision which are so common. There is also a certain degree of impairment of memory before complete recovery.

In India this after-effect has been regarded as one of the causes of insanity, and it seems not at all improbable that slow or chronic poisoning by datura would tend to weaken the intellect. In absence of any suspicious circumstances the differential diagnosis of datura poisoning may be difficult. As with atropine, the symptoms of daturin poisoning have occasionally been confounded with those of rabies, delirium tremens, and mania.

NATIVE THERAPEUTICS.

The datura plants are generally recognized as being poisonous. The leaves are almost universally used in the treatment of asthma, but it is significant to note that datura is not often given internally as a remedy by natives. The Ma'ys mix leaves with urine or powdered rice and saffron, and apply them externally for various pains and swellings. They will heat them over a torch until smoked, and then apply them as a poultice over the spleen in intermittent fever. The root is powdered and applied to the gums in order to relieve the pain of toothache. The flowers are dried and roughly powdered with or without the leaves and rolled into cigarettes for the relief of asthma.

An instance of alarming narcotism from the application of *D. stramonium* leaves to an extensive burn is recorded by Christison; but although datura is frequently used as a therapeutic agent for local application, I have never heard of a similar accident in Malaya. It may be of interest to remark that datura is highly prized by Malays, all parts of the plant being used and valued; an infusion is often employed by agriculturists as a dressing to prevent the destruction of the young padi (rice) plant by insects. The datura, or "devil's trumpet," is regarded as a good medicine by Tamils, and is often used by them in the Federated Malay States, but generally as an external remedy. They are fond of applying the leaves with cowdung in the form of a poultice to relieve the pain of boils, carbuncles, and piles, and also use them in

powder, mixed with "ghee" (clarified butter) in their treatment of facial neuralgia and dogbite, or steeped in spirits as a lotion to promote the growth of the hair. They are said to administer the powdered root in cases of epilepsy and insanity.

The dried flowers of *datura alba* (called *Nai yeung fa*) can be bought in most Cantonese drug stores, where they are frequently dispensed for the relief of asthma and chronic dry cough, but the use of the seeds seems to be eschewed by the Chinese druggist.

TOXICOLOGY.

So far as is known at the present time the active principle of the *datura* plants is a mixture of a kind of atropine and hyoscyamine. The term "daturin" has been applied to this mixture, but the true nature of the component alkaloids has yet to be finally determined. Schmidt properly insists on speaking of stramonium atropine as contrasted with belladonna atropine; because, although chemically identical, some difference may be recognized both in their physiological and therapeutical actions.³

The medicinal dose of daturin has been given as $\frac{1}{2}$ mg. to 1 mg., or $\frac{1}{16}$ gr. to $\frac{1}{8}$ gr.,⁴ but it is difficult to say from the reports of fatal cases by *datura* poisoning how much daturin will constitute a fatal dose in any given case.

With regard to clinical experience of poisoning by the closely-related *datura stramonium* seeds, a child has died in twenty-four hours after swallowing a dose of 16 gr. (128 seeds), although 20 seeds had previously been dislodged by vomiting, and 80 by purging.⁵

Luff states that about 100 seeds form a fatal dose, death occurring in seven hours.⁶ Taking the mean of the proportions of the total alkaloid stated to be contained in the seeds by Squire⁷ and by Gunther⁸—namely, 0.5 per cent. and 0.318 per cent. respectively—this is equal to about $\frac{1}{25}$ grain of the alkaloid daturin. The whole plant is said to contain the active principle in the proportion of only $\frac{1}{50}$ per cent.¹⁰

Seventeen or eighteen gr. of the official extract of stramonium seeds (dose, $\frac{1}{4}$ to 1 gr.) have caused death.⁹ Recovery, on the other hand, has occurred after the vomiting of more than 100 seeds.⁹

RECENT CHEMICAL EXPERIMENTS.

Important points to discover are:

(a) The amount of poison which is present in the common *daturas* of the Federated Malay States.

(b) The relative degrees of strength of the poisonous principle in each.

(c) The difference, if any, between the daturin contained in *D. stramonium* and that contained in *D. fastuosa* and *D. alba*. I have attempted to elucidate this by examining both the fresh plants and the dried seeds. The experiments were made at the Institute for Medical Research at Kuala Lumpur. I am greatly indebted to Dr. H. E. Durham for the results that have so far been obtained by them, and have much pleasure in expressing my appreciation of the valuable experience which his kindly instruction has afforded me. It was found that the mixed alkaloids could be easily removed from an ammoniated extract by shaking out with benzol. In the case of a full-grown *datura alba* plant which was treated in this way, the refuse remaining after extraction by benzol was found to have no further mydriatic effect on a cat's eye, and had no poisonous effect when given in large doses to a puppy. It was therefore concluded that the whole of the active principle had been removed by means of the benzol. Want of time and opportunity prevent me from making further experiments in this direction, but I hope to resume my investigations on account of the great importance of this branch of the subject.

DATURA POISONING; TREATMENT.

Cases of poisoning by *datura* are generally treated by more or less time-honoured methods. It has been proved, however, that implicit reliance cannot be placed on emetics, and the early administration of a purgative is often advisable. Daturin is precipitated by tannic acid; and the use of any decoction containing tannin, such as tea or coffee, which is strong enough to destroy the active principle, may be of value. Like atropine, it is excreted from the system by means of the kidneys.

Opium administered by the mouth or through the rectum, the various salts of morphine, pilocarpin, and chloroform inhalations have been given successfully in cases of stramonium poisoning, but no chemical antidote by which daturin has been decomposed in the animal economy ap-

pears to have been either used or suggested up to the present time.

Nevertheless, there is reason to believe that we possess an efficient antidote in potassium permanganate. Potassium permanganate has the important chemical property of oxidizing the vegetable alkaloids, and has been used with success in many cases of opium poisoning. This salt may be introduced into the stomach without danger in solutions not stronger than 1 gr. to the oz. Washing out, therefore, by means of a tube with a dilute solution of this strength appears to be indicated so long as any *datura* remains in the stomach.

Experience alone can settle the question as to whether the potassium permanganate will be of any therapeutic use after daturin has been absorbed into the system, but as the action of the poison is doubtless prolonged, especially when taken with large quantities of food, we should expect that repeated small doses would be of great value in many cases.

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EXPERIMENTAL HAEMOGLOBINURIA IN A CASE OF BLACKWATER FEVER.

UNDER THE CARE OF

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At the Branch Seamen's Hospital, Albert Dock, E.,

REPORTED BY

W. G. ROSS, M.D., M.R.C.S., and GEORGE C. LOW, M.B.,

INABILITY to take quinine is a bar to residence in highly malarious countries. Therefore, idiosyncrasy in the direction of quinine haemoglobinuria is a definite indication against return to West Africa. When the patient (who is the subject of the following notes) declared that quinine always gave him black water, and we were requested to advise his employer as to his future for further service in West Africa, and as he expressed willingness to give a demonstration of the fact, his offer was accepted partly in his own and his employer's interests, and as an object lesson for the students at the London School of Tropical Medicine.

T. R., aged 25, English, last from the Gold Coast Colony, was admitted on March 10th, 1903.

Previous History.—He went to the Gold Coast in June, 1901, and had his first attack of fever in January, 1902; it was not severe, and he was not laid up. He had three similar attacks up to September, 1902, and was always treated with quinine, 10 gr. at a time, and also took this dose irregularly at considerable intervals as a prophylactic. In October, 1902, he had an attack of blackwater fever; the first symptoms led him to believe that he was about to have an attack of malaria. He took 10 gr. of quinine at 5 p.m. one evening (he cannot remember the date), and about midnight he had vomiting, diarrhoea, and frequent micturition. He noticed that his urine was black. He was attended by a doctor, who stated that his temperature at one time was 107°. He was in bed three days and was deeply jaundiced. The black water passed off in twenty-four hours, and he had no further attack in Africa, and arrived home early in March. On March 11th, feeling chilly and feverish, he took 10 gr. of quinine at 7 p.m., and at midnight diarrhoea and vomiting set in, and he began to pass black water. All symptoms had disappeared in the morning. He consulted Dr. Manson, who sent him for observation and experiment to the Branch Seamen's Hospital in connexion with the London School of Tropical Medicine.

State on Admission.—On March 10th, 1903, temperature 99.6°; isanaemic, spleen enlarged, not tender.

Blood Examination.—No malarial parasites; no pigmented leucocytes. Red corpuscles, 3,425,000; leucocytes, 10,000; haemoglobin (von Fleischl), 65 per cent.

Differential Leucocyte Count.—Polymorphonuclear, 59 per cent.; large mononuclear, 18 per cent.; lymphocytes, 21 per cent.; eosinophiles, 1 per cent.; mast cells, 1 per cent.

On the following day the temperature was normal and he felt quite well—he remained so until March 23rd, when Dr. Manson decided to test his statement that quinine gave him haemoglobinuria. His blood was examined during the day and gave red corpuscles, 3,635,000; leucocytes,