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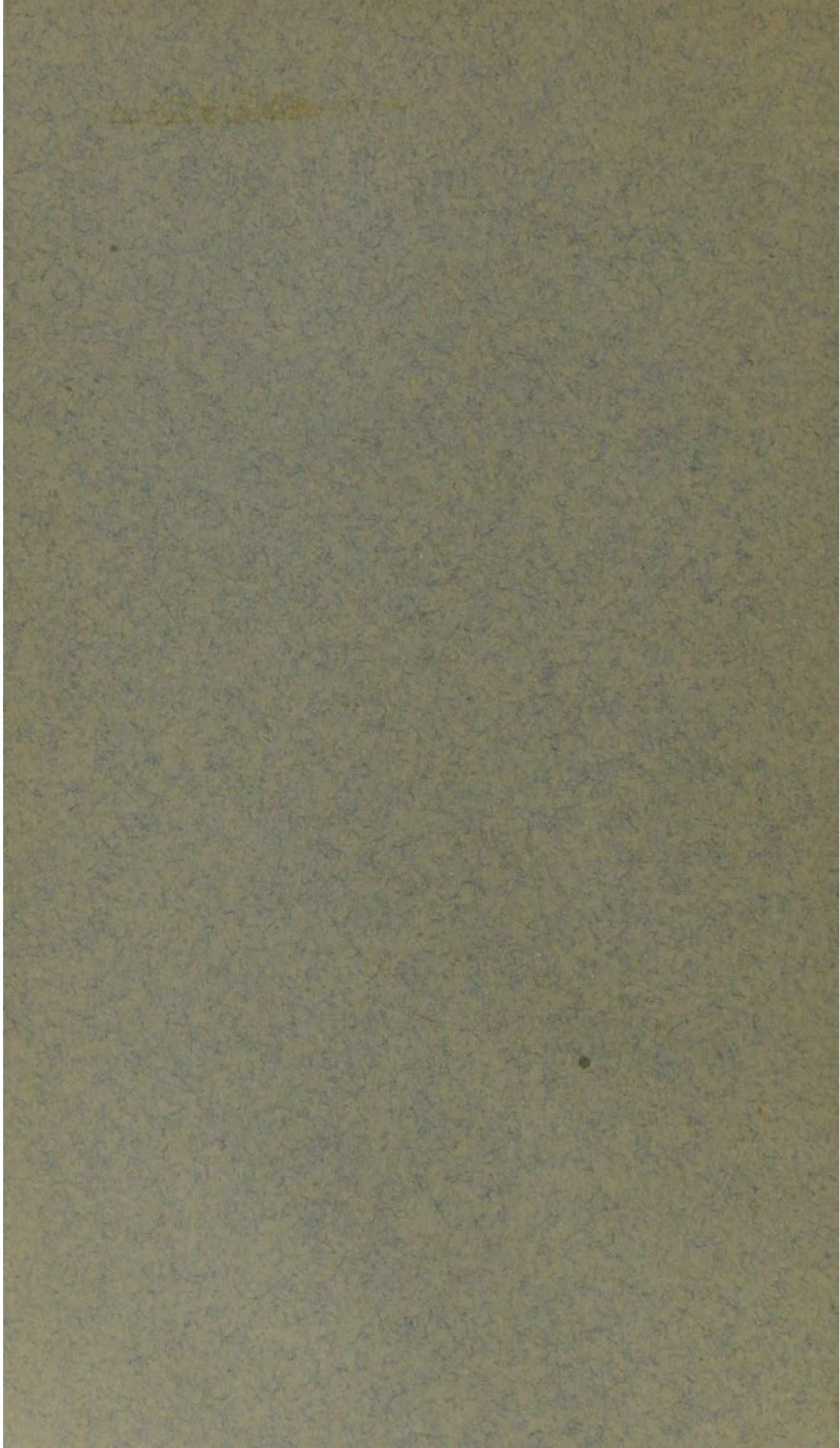
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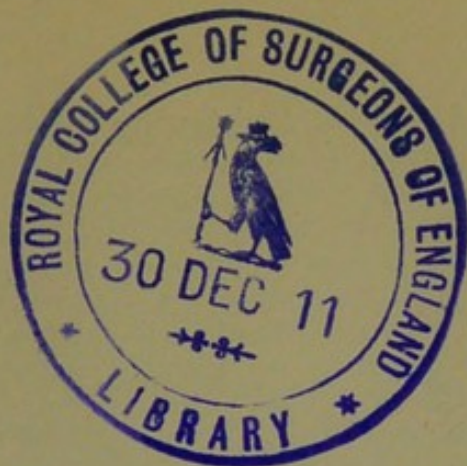
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THE DERMATITIS PRODUCED BY EAST INDIAN
SATINWOOD ("CHLOROXYLON
SWIETENIA.")

Two kinds of satinwood appear in commerce in the United Kingdom, derived respectively from *Chloroxylon Swietenia* and *Fagara flava*—the former an East Indian and the latter a West Indian species. Both varieties of satinwood are highly ornamental when smoothed and polished, and are extensively used for the fittings of cabins and saloons in ships.

In 1898 and again in 1904 there were outbreaks of dermatitis in wood-working departments of shipyards on the Clyde which were traced to the irritant action of satinwood, and on the latter occasion a number of papers on this subject were published by medical men.¹

The attention of the Imperial Institute was directed to this matter by Mr. J. Whitton, Superintendent of Parks and Curator of Botanic Gardens to the Glasgow Corporation, and as both kinds of satinwood are produced in British colonies their examination for irritant substances likely to be the cause of dermatitis was undertaken at the Imperial Institute.

At this time considerable doubt existed as to whether both East and West Indian satinwoods possessed irritant properties and were equally active, but my examination of the substances isolated from both woods submitted to me from the Imperial Institute indicates that the East Indian wood is the more active and is probably the usual cause of the satinwood dermatitis. This conclusion is in harmony with that stated in the *Annual Report* of the Chief Inspector of Factories for 1907, and arrived at as the result of an inquiry by inspectors of factories in workshops using both kinds of satinwood in the United Kingdom.

CHEMICAL EXAMINATION.

The chemical examination of both varieties of satinwood was undertaken at the suggestion of Professor Dunstan, F.R.S., Director of the Imperial Institute, by

Dr. S. J. M. Auld, Senior Assistant in the Scientific and Technical Department of the Imperial Institute, who published the results of his work on the East Indian wood in 1909.² These results show that the chief constituents of East Indian satinwood are a crystalline alkaloid, chloroxylonine ($C_{22}H_{23}O_7N$), two resins, a fixed oil, a peculiar protein compound, and calcium oxalate. It is of interest to note that the quantity of alkaloid present in East Indian satinwood shows great variation, some specimens examined at the Imperial Institute containing only traces, whilst others yielded up to 0.07 per cent. of the alkaloid.

Considerable progress has also been made at the Imperial Institute with the investigation of West Indian satinwood, and the products isolated have been examined pharmacologically. The chemical and pharmacological results obtained will probably be of sufficient interest to form the subject of future papers.

SATINWOOD DERMATITIS.

Reference has been made by Jones,³ and subsequently by Gardiner⁴ to the condition of the skin which arises amongst satinwood workers. The former describes a case in which not only the hands and wrists, but the face and neck of a joiner in a Govan workshop showed an acute inflammatory condition of erysipelatoïd character, but without concomitant sickness or fever. The inflamed surface became moist in places and subsequently desquamated. Improvement followed on suspension of work, but a return to the workshop caused a speedy reappearance of the symptoms. The first attack was slow in developing (six weeks after first handling the wood), but relapses were rapid after recovering from the initial disorder and return to work. Thus, in the case of the mechanic just mentioned, three days sufficed to determine a second dermatitis. Gardiner saw a papulo-vesicular rash on the backs of the hands extending to the forearms and a condition of the face and neck at first strongly suggestive of erysipelas, his description being quite in harmony with that given by Jones.

Wechselmann⁵ refers to a case of satinwood dermatitis demonstrated by Oppenheim to the Vienna Dermatological Society, and contributes the record of one severe and five milder cases which came under his own observation. There is considerable agreement amongst these writers regarding the incidence and general character of the inflammation. Some workers (especially those exposed to the dust of the wood) develop after a varying period of contact great irritation of the skin of exposed areas—forearms, hands, neck, face—succeeded by a papular and to some extent vesicular eruption, which in its full development has distinctly erysipelatoïd characters. Other workers equally exposed may show complete indifference to the irritant. Again, of the first division there are two distinct types: (a) The worker who, after more or less primary dermatitis and ensuing absence from his employment, is

able to resume his occupation amongst satinwood dust without further inconvenience resulting (as if in his case some degree of immunity by acquired resistance had been established); (b) those who, on resuming work, immediately suffer a relapse, and are obliged permanently to abandon the workroom in which satinwood is prepared for manufacture.

EXPERIMENTAL INQUIRIES.

In the spring of 1907 I received from the Imperial Institute, at Professor Dunstan's direction, samples of East and West Indian satinwood. Each was represented by a small billet as well as by the derived sawdust, the latter contained in glass jars with accurately fitting stoppers. Subsequently, in February, 1908, a specimen of the alkaloid chloroxylonine, extracted from East Indian satinwood was received. With these materials many observations were made in 1907-8, which satisfied me that the alkaloid was an irritant and capable of causing dermatitis; but the supply becoming exhausted, further experiment had to be postponed until the autumn of 1910, when two of the alkaloidal salts were sent. In 1909 I received two resins, No. I, an amorphous body, easily soluble in alkalis, and No. II, a crystalline resinous substance, sparingly soluble in alkalis; whilst this year a sample of fixed oil, likewise derived from East Indian satinwood, was forwarded.

I propose to consider here the action of this wood and of the principles enumerated.

EAST INDIAN SATINWOOD (*Chloroxylon Swietenia*).

In order to ascertain whether any toxic principle is extracted by water from this wood, (a) infusions made with cold water, the process being continued for 120 to 180 minutes, and (b) decoctions (90 to 150 minutes) were prepared. The proportion of each finished preparation was the extracted matter from 1 gram of the sawdust to 10 c.cm. of water. The fluid (whether infusion or decoction) was found to be neutral, and contained neither tannic acid nor soluble oxalates.

Action on Frogs.

Ten c.cm. of these filtered fluids were placed in a series of large jars, into each of which a healthy frog (*R. ex.*) was introduced. The fluid, which was from its small bulk in contact with the ventral surface only of the animal, was renewed every third day after thoroughly washing out the jar.

At no time was there any evidence of cutaneous irritation being experienced. No symptoms beyond free evacuation of bile containing dejecta occurred for the first few days, but thereafter, animals placed in the decoction became apathetic; there was usually slight increase of the natural process of epidermic sloughing. Death took place in from five to twelve days. The skin on the ventral surface of the body showed some increase of vascularity—this phenomenon may be due mainly to hypostasis resulting from cardiac failure—but no distinct lesion of the skin was present. The mucous membrane lining the mouth, stomach, and upper portion of the small intestine was in every instance congested, and in one of the five animals

placed in the decoction there was slight extravasation of blood into the stomach. It may also be recorded that reflexes failed at a time when the heart was still beating effectively. The gastrocnemii responded feebly to indirect as well as to direct galvanic stimulation, and showed evidence of early fatigue after repeated contraction.

The corresponding infusion had lower activity than the decoction, the earliest fatal issue being in nineteen days, whilst the latest was in forty-one. There was no distinct increase of biliary evacuation and no augmentation of epidermic sloughing when contrasted with a control animal kept in a like amount of tap water, but otherwise under parallel conditions. No haemorrhage was present in the alimentary canal, but there was a limited congestion of the mucous membrane of mouth, stomach, and intestine.

Whilst the infusion can scarcely be regarded as definitely toxic towards frogs, the decoction is distinctly more active, but the symptoms of an irritant character (apart from other effects which do not concern us here) are at most but slight, and are chiefly displayed by the mucous lining of the alimentary canal rather than by the skin. The possibility of the entrance of fluid by the mouth in these experiments must be held in view.

The distinctly aromatic (coumarin-like) odour of the East Indian satinwood suggested the presence of a body possibly volatile and active. Experiments were therefore made by conducting a current of air through a flask containing 5 grams of the sawdust, and thence by a rubber tube 2 ft. in length through a wide-mouthed bottle, into which a frog had been introduced. The flask was gently warmed over a water bath. At the expiration of two hours the atmosphere of the large laboratory in which the experiment was conducted was redolent of the peculiar coumarin-like odour, but the animal showed no sign of excitement, nor was there subsequently the slightest evidence of desquamation or other positive effect.

Application of Satinwood to the Skin.

(a) *Rabbits*.—Application of the wood of *Chloroxylon Swietenia* to the inner surface of the outer ears of rabbits was practically without effect. In one series of experiments the dust was placed in bags of fine muslin 4 cm. in length by 1.5 cm. in width; in a second series fragments of wood 3.5 cm. in length by 1.5 in width, carefully shaped to fit the ear, were prepared. The ear was folded longitudinally over the bag or fragment, two thin strips of adhesive plaster being used to keep the body in position. Contact was maintained for five consecutive days. The result was negative. Moistening the dust or wood with (a) water, (b) almond oil, or (c) very dilute acetic acid, was also practised; but in no instance was redness, eruption, or the slightest evidence of itching or discomfort observed at the time of application or subsequently.

(b) *Man*.—Application of the unreduced wood to the skin proved an awkward proceeding for the ambulant subject, and as such was abandoned, the sawdust being substituted for experiment; of this, 5 grams was placed in a muslin bag of fine texture. The bag was moistened with

water and secured in position above the internal malleolus. (It must be noted that this observation was made subsequently to a dermatitis of both arms occasioned by the alkaloid chloroxylonine.) The bag was worn for fifteen hours daily, was removed at night, and readjusted in the same position, subsequent to moistening with water, after the morning bath.

On the morning of the fourth day there was considerable irritation, with redness, and some brawny induration at and around the area of contact. (The bag was not reapplied.) Later in the day several elevated papules were noted on the reddened surface; much irritation, with itching and sensation of heat at intervals, becoming worse after retiring to rest; the night was much disturbed. I was aroused several times by the intense itching, and no doubt the part was rubbed, though protected as far as practicable by enveloping in a silk sock. On the sixth day a few moist points (vesicular) were observed. Desquamation ensued, and was very evident for the succeeding ten days. The skin felt harsh, dry, and uneven. Irritation continued at intervals for three weeks after its first development. It was worst after exercise or under the influence of warmth, as when sitting in proximity to a fire or after retiring to bed. Subsequently the observation was modified by preparing two similar bags, each charged with 4 grams of sawdust, and applying these above the right and left internal malleoli respectively. The right bag was moistened daily with water, the left with almond oil. Each application produced a moderate degree of dermatitis, though the oily preparation was somewhat the more effective in this respect.

The dry dust applied in like manner was less rapid than either of the above in producing its action.

These observations are in correspondence with statements made by Jones and others, who have described the origination of dermatitis amongst artisans who are employed in workshops in which satinwood dust is abundantly present. The skin areas exposed to direct contact are the first to be affected, but the local results are not manifested at once in the case of those who have not previously suffered, but ensue after very various intervals of time. After the experimental applications just described it is probable that the interval was reduced by the chloroxylonine dermatitis which had preceded. The skin area selected had not been the seat of any application or eruption, but the dermatitis at a distant part of the body had induced a condition of hypersensitiveness which extended to all parts of the cutaneous system (though especially to the more delicate), rendering them quite abnormally receptive towards irritants. How long this hypersensitiveness lasts is unascertained, but probably for a considerable time. It is more than three years since the induction of dermatitis in my own case, and I still respond promptly to applications of satinwood products which have such a low degree of irritant property that they are inert to the skin of others. During this time, however,

it has been necessary to test so many irritants that my condition is probably different from that of an individual who has suffered only a single dermatitis at some more or less remote period.

PRINCIPLES OF EAST INDIAN SATINWOOD.—

CHLOROXYLONINE.

In 1909 Auld⁶ gave a detailed description of the alkaloid chloroxylonine, which he had separated from East Indian satinwood. After obtaining it in well-defined prismatic crystals from solution in ethylic alcohol, he found it to be soluble in acids and very soluble in chloroform. The addition of ammonia precipitates it from acid solution, but in excess causes resolution. (For further details concerning the chemistry of this body reference can be made to Dr. Auld's paper.)

The earlier part of the observations about to be recorded was made in 1908, with the pure base which had been sent in the spring of that year from the Imperial Institute; but in the latter part, two salts received in the autumn of 1910, were employed, chloroxylonine hydrochloride ($C_{22}H_{23}O_7N, HCl$) and nitrate ($C_{22}H_{23}O_7N, HNO_3$). It may be stated at once that the action of the salts is essentially that of the base in such amounts and proportions as those in which they have been employed for pharmacological purposes.

Information regarding the activity of the alkaloid, chloroxylonine, from East Indian satinwood is of the scantiest description. Wechselmann,⁷ indeed, mentions an auto-experiment which consisted of rubbing alcoholic solution of the crystals upon the skin of the arm, with the result that an itching, burning sensation ensued, but no appearance of dermatitis is recorded. He also applied the alcoholic solution to skin areas previously the seat of satinwood dermatitis in three workmen, two of whom yielded no reaction, whilst the third reported that he developed a distinct, slight inflammation; apparently Wechselmann did not see the result himself.

The observations which are now recorded were made upon frogs, rabbits (applications to the external ear) and upon the human subject. In the last group auto-experiments as well as observations by Dr. Croll and Dr. Dilling and a number of my students who kindly consented to make the applications I wished to test, will be recorded.

Frog (R. esculenta).—Local contact of almond oil solutions of the alkaloid (1 in 50) were inoperative towards both swim web and skin of the axilla. Even unguents of the hydrochloride, (1 in 10) applied thrice on alternate days to the swim web after it had been dried, were not productive of any more definite reaction than slight localized vascular dilatation, certainly no inflammatory condition was established, nor was there any indication of discomfort on the part of the animal.

Hypodermic Injection.—February 9th, 1911. A healthy *R. esculenta* of 37 grams received in the dorsal lymph sac 0.005 gram of chloroxylonine hydrochloride, thoroughly triturated with 5 drops of neutral sterile almond oil. No evidence of irritation; copious bile-coloured dejection on the 10th; a small

blood point appeared over the sternal region on the 18th; active purgation was recorded on the 25th, the animal succumbing on the 30th. There appeared to be some increase of desquamation during the later stage of the observation, but it is difficult to form a reliable judgement upon the extent of this phenomenon.

Post-mortem Examination.—A few blood points observed in the lining of the dorsal sac; from these there had been slight extravasation of blood into the cavity; some petechial spots also in the muscles of the legs and abdomen. Many of the coloured corpuscles are irregular in form (poikilocytosis). Nervous excitability was unimpaired in the nerve-muscle preparation, but the tetanus at first yielded to faradization, soon dwindled to a feeble clonus on repeating the stimulation.

A second frog of 38 grams received 0.005 gram of chloroxylonine nitrate under parallel conditions to the first. Bilious purgation, swelling of the thighs, with no objective evidence of irritation. The animal was decapitated on the nineteenth day.

Post-mortem Examination.—Heart beating regularly, 24 per minute. Some free haemorrhage under skin of thighs and in dorsal sac, none in the muscles or internal organs. Alimentary canal in general hypervascular. Other conditions as in No. 1.

In both cases the action is that of a slowly acting irritant producing localized haemorrhages, intestinal injection with ultimately petechial haemorrhages in remote tissues. Absence of discomfort on the part of the animal was conspicuous throughout.

Rabbits.—Application of the alkaloid in ointment form (1 to 9 of paraffin molle) was made by gently rubbing the weighed amount upon the internal surface of the ear, the edges of which were afterwards approximated with sticking-plaster. The amount of the alkaloid present in each application was 0.5 mg., and there were three reapplications at intervals of two days. The ear was closely examined daily. No sign of inflammation or eruption of any form resulted, nor was there any evidence that the animal experienced any irritation of the part. An ointment of double alkaloidal proportion (1 in 5) was then substituted for the weaker one and applied in like manner to the ear of another animal. But, even though no fewer than five reapplications were made (the treatment in all occupying ten days), there was no inflammatory reaction, nor indeed positive result of any kind excepting a very slight subsequent desquamation. These experiments were not further persisted with, as it had been amply demonstrated that the skin of the rabbit's ear is not a sufficiently sensitive surface for testing such applications.

Local Application to the Human Skin.

In the spring of 1908 the writer rubbed 0.05 gram of a 1 in 10 ointment (therefore containing 5 mg. of the alkaloid) into a marked area, as large as the surface of a florin, of the flexor aspect of the left forearm, 10 cm. above the wrist; the part was protected by gutta-percha tissue secured by strapping. At the expiration of twenty-four hours the dressing was removed and the skin thoroughly washed. No effect, subjective or objective, resulted at the time of the application or during the succeeding ten days, after the lapse of which (March 9th) 0.05 gram of a 1 in 5 ointment (10 mg. of the alkaloid) was applied in like manner to the same skin area, the contact of the ointment being, as before, for twenty-four hours. There was neither

redness, itching, nor other immediate effect, and the experiment having been accepted as negative was no longer in mind when, on March 31st (twenty-two days after application) considerable itching was experienced at the seat of contact, which now showed five small papules upon a flushed base. These papules multiplied and increased in size individually, so that three days after attention had been called to the part they had extended for 5 cm. upwards towards the elbow beyond the upper border of the original inunction. A few oozing points also made their appearance on the inflamed area. The sensation meanwhile was of much heat with stinging or "wire-point" impactions, whilst at intervals itching was so pronounced that it was impossible to refrain altogether from rubbing. This itching intermitted completely from time to time; it was aggravated by warmth, and peculiarly by free muscular movement of the affected arm. At night-time sleep was much disturbed by the recurrence of this symptom, and, even though the forearm was enveloped in a large silk handkerchief, some rubbing took place (the prompting to this was powerful during light sleep), and this undoubtedly served to aggravate and extend the local condition. On April 6th a slight furfuraceous desquamation commenced; the affected area, no longer extending, showed less vascularity, but the skin retained a harsh, infiltrated, knotty feeling, and intermittent itching was still experienced.

The symptoms thereafter gradually abated, but the skin of the affected area remained in an extraordinarily sensitive condition. As it seemed advisable to test the effect of a third application, 0.05 gram of 1 in 10 chloroxytonine ointment was rubbed into the original area on May 5th (thirty-five days after the eruption had first shown itself). The skin, though harsh and still desquamating, showed no rupture of surface. There was no delay in the result; forty minutes after inunction great burning with "wirepoint" sensations were experienced locally, and the part rapidly assumed an erysipelatoid appearance, which soon extended to the elbow and on to the extensor surface of the forearm, though it did not encircle the limb. This local condition was favourable to urticarial manifestations, a blunt point drawn across the affected area immediately provoking an oedematous elevation along the line of contact. Twenty-four hours after the application inflammatory action had extended upwards above the elbow and 2 cm. further on the extensor surface, but it did not pass beyond the flexure of the wrist. Several small weeping points, the serum exuded being clear, were observed at and around the area of contact. The limb was brawny and hot to the touch; it pitted on digital pressure.

The effects of this application extended over a period of five weeks. Slight pigmentation was observed after the subsidence of desquamation.

After dermatitis had been developed on both arms as a result of chloroxytonine contact or that of its salts, it was

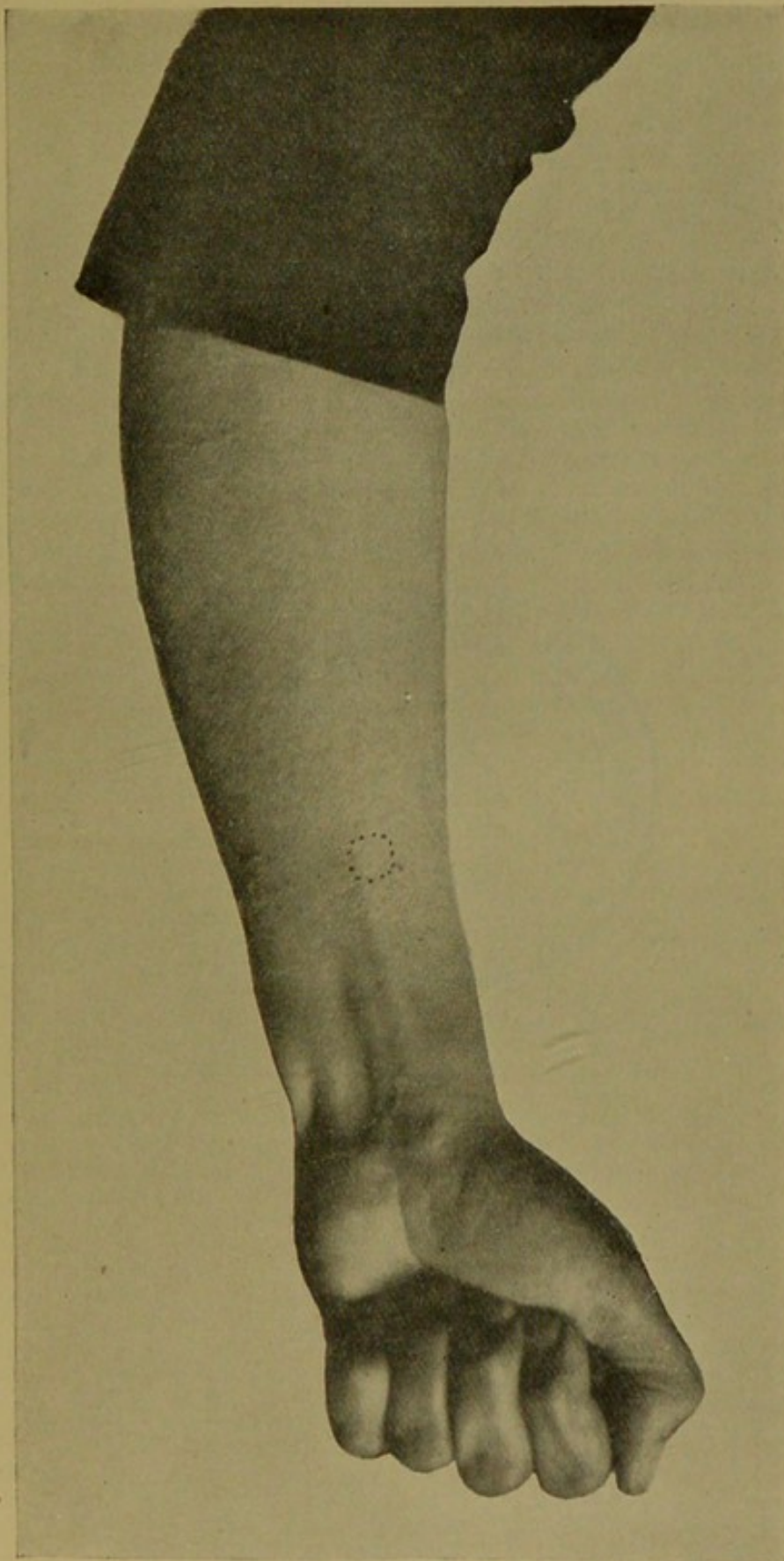
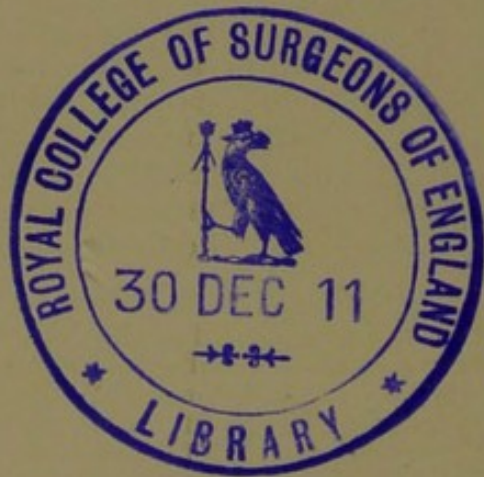


Fig. 1.—Forearm forty-nine hours after inunction of 0.0017 gram of chloroxylonine. (The dotted circle indicates the extent of application.)



found that a prolonged rest having been permitted, re-application of the alkaloid not only developed its local effect, but that the other arm, to which no recent application had been made, became hot and irritable at the site of the previous dermatitis.

Although relatively strong unguents (1 in 5, 1 in 10 of alkaloid) were used in the experiments detailed, those of much lower alkaloidal proportion, as 1 in 30, 1 in 50, sufficed to cause a return of dermatitis when applied to a previously affected area. Fig. 1 is derived from a photograph taken forty-nine hours after the application of 0.05 gram 1 in 30 ointment (=0.0017 gram actual alkaloid) to an area of the forearm which had been unused for nine weeks.

The results hitherto recorded deal with slight and moderate types of chloroxylynone dermatitis in which the condition remains localized to the area of contact and the tissues in close proximity, but it is important to illustrate an observation in which remote effects were undoubtedly produced.

No application had been made to the left arm for thirteen weeks. The skin in the selected area on the flexor surface was unabraded, though somewhat dry and inelastic. Into this area on February 15th, 1911, inunction of 0.05 gram of ointment containing 0.005 gram of chloroxylynone hydrochloride with 0.045 gram paraffinum molle, was made at 4 p.m. Except for a turn of fine linen round the limb, no dressing was applied.

Four hours later itching commenced at the seat of contact; at 10.30 p.m. the irritation was intensified, a burning, stinging sensation extending beyond the original area. At 11.30 a few papules were showing on a flushed and raised general surface (enveloped in a light silk handkerchief, fastened with safety pins to the sleeve of the pyjama). Rest was much disturbed, as on five occasions the would-be sleeper was roused by stinging pain, great heat, and almost unbearable itching.

February 16th, 8 a.m. (16 hours): Swelling, with dark flush, papillae prominent; a few papules, no vesicles; condition extends from 2 cm. below flexure of elbow down to the wrist. The arm was purposely used freely during the ensuing day, the discomfort and sensation of heaviness becoming very marked in the afternoon.

Twenty-six hours: Swelling and redness now 4 cm. above the elbow on the flexor surface, and thence passing over on to the extensor aspect. There are many papules and oozing points, also formed vesicles, the latter being mainly in lower third of forearm. The limb is brawny, pits on pressure; no pulse can be detected at the wrist. Diameter of limb at marked point 3 cm. above wrist fold is 20.8 cm., or +3 cm. of the normal. Feeling of weight with burning and tension, occasionally lancinating pain and itching. The discomfort of the dependent limb was such that a sling had to be employed. In the evening (twenty-eight hours) swelling of the left upper eyelid was observed, a distinct hard nodule being located towards the inner canthus; considerable oedema of the lid developed in the course of the evening. Tumefied swellings also developed before bedtime in the helix of the right ear, which became hot and occasionally painful over the mastoid on the left side, also under the right ramus of the lower jaw, the swelling being in the substance of the skin and not in the submaxillary gland. The ensuing night was a time of great

discomfort. Considerable itching occurred of the right arm in the area corresponding with that to which the application had been made on the other side.

Forty hours: Masses of flat papules on a brawny base, especially above wrist, many oozing vesicles interspersed; relatively few excoriations, as the limb has been well protected by silk stocking. The right eyelid is now very oedematous. Diameter of arm at measuring point 20.4 cm.

Forty-two hours: Fig. 2 is from a photograph taken at this time.

Forty-nine hours: Stiffness of left shoulder and discomfort in axilla, but no glandular swelling could be detected. A knotty swelling is felt on the chin; flat papules are showing on the forehead; a very irritable raised roseolar patch has developed in the epigastrium.

Fifty-one hours: Upper lip and alae feel swollen and are somewhat indurated to the touch. Much heat and itching in nostrils. No elevation of body temperature; urine clear, specific gravity 1016, no albumen.

Seventy-four hours: Still great irritation locally and in the remote swellings. Night following, no sleep till 3.30 a.m., and this owed to 2 grains of opium.

On the fourth day symptoms abated somewhat. Local heat, feeling of weight less, irritation more occasional. Arm diameter 19.5 cm. Swelling of ear, lip, forehead, and abdominal skin patch still marked, but irritation less. Great irritation and thin secretion from nostrils, fissures at angles of mouth, a spasmodic laryngeal cough prompted by suddenly supervening sensation as of a hair in the larynx.

Seventh day: Arm diameter 18.6 cm. Papillae prominent, paler, much excoriation; skin cracked, harsh, and in many places desquamating. Nostrils itching, painful in places, discharge thin, abundant. Cough as before, troublesome, expectoration (exceptional) thin.

Seventeenth day: Arm diameter 18.2 cm., desquamating freely; many small fissures above wrist, which has raw-meat appearance. Itching great at times, aggravated by heavy overcoat sleeve and by exercise. Sitting near fire or warmth of bedclothes provokes. Nostrils exhibit a few small ulcerations as well as fissures, covered with yellow serous flakes, blood-stained, cough extremely troublesome at times, explosive and without warning, the secretion is now slightly muco-purulent.

Forty-two days: Excitement has been declining. Now (April 7th) the diameter of the arm is normal—17.8 cm. Papillae still prominent, and an oedematous condition develops in them if back of nail be drawn over part. Touching still provokes itching.

Affection of the upper air passages after the development of dermatitis by chloroxylonine is conspicuous. There is a long-continued errhine action with thin watery secretion, followed by minute fissures or even small ulcerations of the nostrils, the adherent serum and mucus blood-stained and tenacious. The explosive cough following instantaneously upon a sudden sensation as of a hair in the larynx, the secretion, hardly noticeable at first, becoming abundant but watery, and so remaining for six to eight days, form a characteristic group of symptoms. Whilst I have twice experienced these conditions after the local application of chloroxylonine, they developed in the most intractable form after experimenting freely with East Indian satinwood resin No. II. After the dermatitis had occurred the paroxysms of coughing were so violent and frequent that for eight nights it was impossible to lie

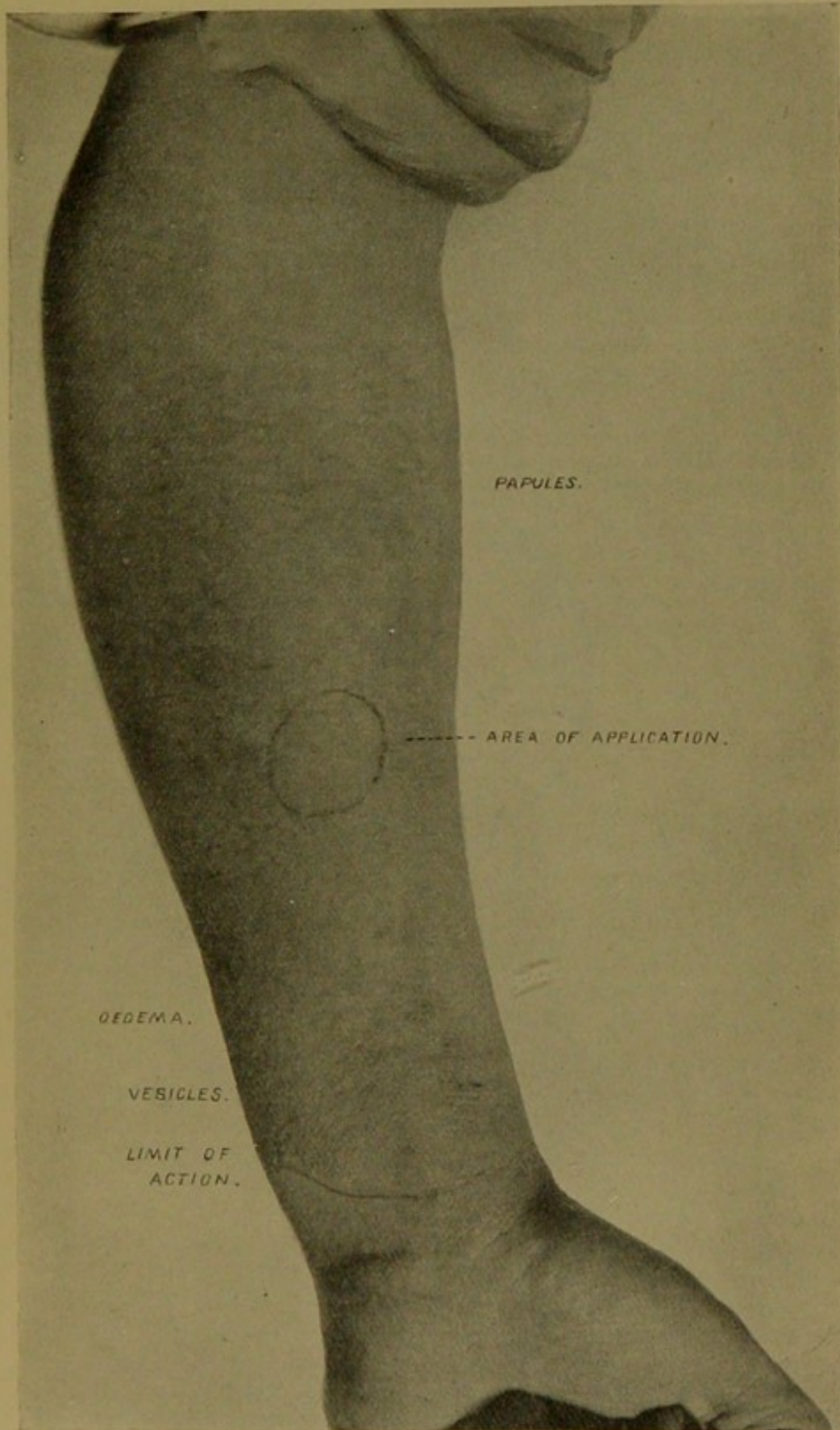
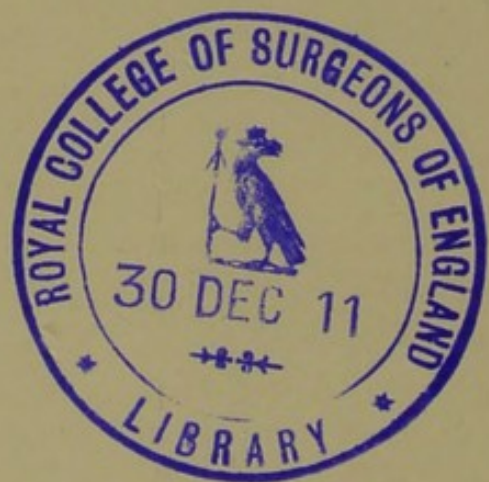


Fig. 2.—Forearm forty-two hours after inunction of 0.005 gram of chloroxylonine hydrochloride. The inked circle indicates extent of application, the curved line above the wrist the limit of inflammation. Formation of vesicles abundant for 5 cm. above this line.



down, and a scanty measure of sleep could be assured only after liberal use of opium.

As a second case of dermatitis induced by chloroxylonine is of importance as corroborating the results experienced by myself, I add a summary of the chief points. The observer, Dr. W. Dilling, had previously applied to his arms No. II resin of East Indian, and certain resinous derivatives of West Indian satinwood (*Fagara flava*).

The result of these applications was uniformly negative, except for the occurrence of a few papules which followed inunction of the West Indian satinwood products indicated as B₂:

On April 20th 0.005 gram chloroxylonine nitrate incorporated into an ointment with 0.02 grams paraffinum molle was applied to a marked area the size of a half-crown on the flexor surface of the right forearm. The result was in every respect negative. On May 1st a similar application to the same area. Up to the 5th there was no effect, but on the morning of that date a papular eruption appeared (there had been no antecedent irritation) which rapidly extended itself to the wrist, on to the extensor aspect, and halfway up the forearm. In the afternoon characteristic irritation commenced. The appearances, which were similar to those already described, need not be detailed further. It was interesting, as the possible occurrence of these symptoms had not been mentioned, that the notes of the observer reported marked tickling in the larynx, as if from the presence of some foreign object, with a distinct but transient coryza. A fortnight after the dermatitis had appeared the papules were still evident, but itching had subsided, and by May 22nd had disappeared.

Application of a West Indian resin derivative (which had been used without effect before by the same observer) now occasioned, in thirty-six hours, active irritation, with a return of vascularity to the papules and some extension of the affected area. In other words, there was a distinct relapse in the local condition, and this lasted for several days. The associated experiments confirm the observation that bodies which are incapable of causing a dermatitis primarily, readily do so after chloroxylonine has produced such a condition.

As in my own case, it was the second application of chloroxylonine that determined the dermatitis, though the lapse of time after the second inunction was only four days in Dr. D.'s case, whilst in my own it was twenty-two.

It has been recorded by all writers who have described the condition of workmen engaged in satinwood manufacture that some show a natural indifference or immunity towards the irritant. I add a few notes from an instance of this kind, in which the alkaloid was freely and repeatedly applied without any distinct result:

Applications were made in the first instance of solutions of chloroxylonine hydrochloride to the arm of the observer, Dr. Croll. The strength of solution was 0.00066 gram of the alkaloidal salt per 1 c.cm. absolute alcohol, and each application being the fortieth part of 1 c.cm. contained of this salt less than one-sixtieth of a milligram. From these applications, of which five were made at intervals of three days, there was no effect whatever. (In the case of the two observers who ha

experienced chloroxylonine dermatitis previously, a single application of the solution containing 0.0000165 alkaloidal salt caused a sharp reaction.)

Three weeks after the final employment of the solution inunction of 0.005 gram of chloroxylonine hydrochloride in 0.045 paraffinum molle was made into a marked area, which was employed throughout the observation. As there was no result a similar inunction was made on the fourth day following, and this was repeated on the eighth day. There was neither objective nor subjective result, excepting that curiously enough a tickling in the laryngeal region, provoking sharp cough, unaccompanied by secretion, made its appearance, but lasted only for a couple of days. Again, after an interval of eight days reapplication of 0.005 alkaloidal salt, incorporated with 0.02 gram paraffinum molle, was made.

It is now six weeks since the last application took place and no dermatitis has ensued; whether the observer is definitely and altogether indifferent to chloroxylonine cannot yet be stated, but it seems justifiable to conclude that he is towards its irritant action much more indifferent than the other two observers whose experiences have been detailed. The cause of such indifference is at present obscure and I do not propose to attempt its solution here.

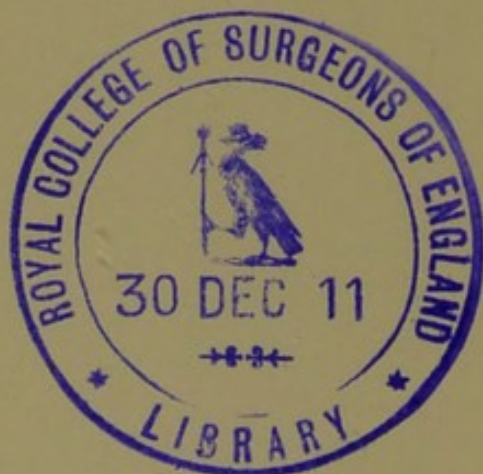
RESINS OF EAST INDIAN SATINWOOD.

The resins are two in number. The first (I) an amorphous body soluble in alkalis, the second (II) a crystalline substance sparingly soluble in alkalis. Experiments with ointments containing 1 in 10 to 1 in 5 of the respective resins were made by repeated application to the inner aspect of the ears of rabbits. The results were completely negative. No effect was produced on contact of these bodies with the frog's swim web. Injected into the dorsal sac after thoroughly triturating with almond oil (neutral) doses of 0.015 gram of No. I were practically inoperative. No. II was not, however, entirely negative in action, as death ensued in animals receiving 0.015 gram in, on an average, thirteen days. There were no evidences of excitement upon injection nor afterwards, but slight haemorrhage was found *post mortem* in the dorsal sac whilst the stomach and upper portion of the small intestine were obviously congested. In one instance (out of four observations) there was a droplet of blood in the stomach which had escaped from a minute lesion in the posterior surface of the mucous lining.

Resin No. I: Application to the Human Skin.—Single applications of ointments, varying in proportion of resin from 1 in 10 to 1 in 2, were made to the arms of five individuals who had not experienced a previous dermatitis, with entirely negative result; 0.1 gram of the 1 in 10 ointment was applied to a defined area of the left forearm of a woman, daily, on five successive days. There was not the slightest effect. In my own case a single inunction caused in seven hours itching with sensation of heat at the area of contact; subsequently papules developed on the injected and slightly elevated patch. The symptoms were quite moderate in degree when, two days later,



Fig. 3.—Forearm six days after East Indian satinwood resin, No. 2. The subject had experienced dermatitis on several occasions previous to this application.



a second identical inunction was made in the same place. A sharp dermatitis followed eruption and swelling, spreading rapidly upwards beyond the elbow and over on to the extensor surface of the forearm, with itching almost intolerable and rest at night much disturbed.

In kind the symptoms produced by the resin were similar to those caused by chloroxylonine.

Resin No. II.—This body was applied in 1 in 10 ointment form to the arms of five observers; of these four had not suffered from induced dermatitis. No result followed in the case of three of the latter, but six hours after inunction of 0.1 of the ointment (the amount used in each instance) the fourth (Ge.) had distinct local itching, and on the following morning the arm showed four distinct papules on a reddened patch which corresponded to the area of application. In forty-eight hours the papules were barely visible, and the general vascularity had disappeared. (Note, this observer informed me that he had always evidenced extreme sensitiveness to every kind of cutaneous irritation.) Applied to my own arm to an area which some months before had been involved in chloroxylonine dermatitis, No. II ointment provoked in five hours' time heat and itching, followed by a very distinct inflammatory condition, this being more severe than that occasioned by No. I resin. The congestion with oedematous swelling extended above the elbow. Fig. 3 is from a photograph taken six days after the application; it shows the papules and excoriations existing at that time.

Auld, in his paper already referred to, speaks of the two resins as non-irritant, and doubtless they are so to the skins of most individuals; but that they provoke a condition similar to that produced by chloroxylonine in those who have experienced the action of the latter is evident from my own case. That No. II may even cause a slight primary inflammation in a sensitive subject who is not otherwise predisposed is demonstrated by the reaction of Ge. Of the two resins, No. II is without doubt the more active.

THE FIXED OIL OF EAST INDIAN SATINWOOD.

Auld⁸ describes the separated oil as viscous, yellowish-brown in colour and having a specific gravity of 0.965. It remains clear on keeping, and in its action, Auld states that it appeared to him to be non-irritant. Wechselmann⁹ refers to an experiment in which he employed (by applying to the skin of the arm) a resinous oil which Loeb had separated from satinwood. His result was negative.

EXPERIMENTAL.

Frog.

Two frogs received $\frac{1}{20}$ and $\frac{1}{30}$ of a c.cm. respectively of the undiluted oil in the dorsal lymph sacs. There were no symptoms. Excited movement was entirely absent. After the lapse of fourteen days the animals were destroyed by chloroform. Examination of the muscles, alimentary canal, and dorsal lymph sac did not reveal any haemorrhages or even an

abnormal degree of vascularity. There was no abnormality about the heart's action, nor yet the response of the gastrocnemii to electrical stimulation.

Rabbit.

The inner surface of a rabbit's ear was rubbed on five separate occasions in the course of ten days with $\frac{1}{50}$ c.cm. of the pure oil. No irritation resulted.

Human Skin.

Applications were made of ointments having strengths of 1 in 10 and 1 in 5 of the oil, as well as of the latter undiluted to the forearms (flexor surface) of seven students who had not participated in any previous experiment with East Indian satinwood or its derivatives. The largest amount of pure oil employed in any of these observations was $\frac{1}{20}$ c.cm. The result was perfectly uniform whether the strongest or weakest preparation had been employed, for in no one of the seven did any subjective or objective symptom ensue.

But a positive result was obtained from both the subjects of an anterior chloroxytonine dermatitis. D. applied $\frac{1}{20}$ c.cm. of the pure oil to the flexor surface of the forearm; no effect had been produced up to bedtime (twelve hours after the inunction), but five hours later he was awakened by violent itching of the part, which next day showed the presence of papules on a reddened base. I applied $\frac{1}{20}$ c.cm. in each of three localities: (1) to the front of the ankle-joint; (2) to the inside of the thigh 10 cm. above the knee; and (3) to the skin of the upper arm over the biceps. Dermatitis had been occasioned in the first locality, but there had been no application to it for thirteen months. Areas 2 and 3 had not been previously employed. In eighteen hours itching commenced in No. 1 area, and in twenty-nine hours in No. 2 a limited redness coextensive with the contact of the oil was developed. There was neither heat nor pain. Area No. 3 remained unaffected.

I found subsequently that inunction of 0.5 gram of the ointment containing 1 in 10 of the fixed oil was active in limited measure when applied to the forearm which had many times been the seat of dermatitis.

Regarded as agents which are capable of arousing dermatitis in those who have been rendered abnormally susceptible by chloroxytonine action, Resin No. II of East Indian satinwood is the most active, the oil is least active (moderate and slow effect, even when undiluted), whilst Resin No. I occupies an intermediate position.

But whichever of these derivatives is applied (allowing for variation in activity and modifications due to the concentration or dilution of the preparations used), the symptoms, subjective as well as objective, are so closely similar to those occasioned by chloroxytonine as to be practically indistinguishable. One would, indeed, be inclined to regard the resin and oil effects as provoking a chloroxytonine relapse were it not that the term might mislead, in so far as they can produce a distinct action on the more sensitive parts of the cutaneous surface which have not been the seat of the alkaloidal dermatitis.

TREATMENT OF DERMATITIS.

Treatment of the local dermatitis was attempted experimentally by many agencies. The indications are to relieve the cutaneous inflammation, and particularly to check the

violent itching which sooner or later leads to friction, a proceeding which greatly aggravates and extends the area of excitement and inflammation. Amongst preparations combining astringent and sedative properties, the ung. gallae cum opio, lead acetate (aqueous solution of various strengths) and the *B.P.* unguentum glyc. plumbi subacetatis, were employed. The most satisfactory of these is the last named, which fulfils the main indications for treatment best of any of the series. A thorough but lightly made application to the affected area and the skin in proximity is necessary every four hours to perpetuate the sedative effect and reduce inflammation. Purely sedative applications are also of much service, especially in the earlier and later stages of dermatitis, but they must be chosen with due regard to the possibility of their absorption. Thus, whilst the ung. veratrinae is of value at the very commencement of the condition it cannot be safely used after damage to the epithelium has supervened.

The internal administration of potassium bromide is not without value, especially given at bedtime in 15-grain doses. During the period of excitement of the laryngeal mucous membrane internal administration of 2 grains of opium was necessary to procure cessation of the violent cough, and this treatment had the further advantage of reducing the thin concomitant secretion for several hours—cocaine as the *B.P.* trochiscus with krameria was only of temporary value.

But beyond medication other measures must be adopted. The contact with rough fabrics which would promote friction is to be carefully avoided, and for this purpose a fine silk handkerchief (or, if for an arm, the footless leg of a silk stocking secured to the vest by two safety pins) should be employed, whilst underwear and cloth clothing must be as light as practicable. Active muscular work greatly enhances the irritant effect of chloroxylonine and of the conditions succeeding application of the resins; whilst, conversely, rest and even the slinging of the arm is often desirable. At night time the sleeping-room should be kept cool by free ventilation; the bed coverings should be light.

Hitherto no prophylactic treatment has shown itself of value. Gardiner¹⁰ suggests that acids might neutralize alkalinity of the wood, and so, on application, frustrate the advent of dermatitis, but I have not found any protection from the proceeding; moreover, both infusions and decoctions of the wood were devoid of alkalinity.

CONCLUSIONS SUMMARIZED AND DISCUSSED.

The absence of reaction of the skin of the rabbit's ear to East Indian satinwood and its principles has been uniform, even when the applications were frequently repeated. Possibly longer continuance of chloroxylonine inunctions (for which my supplies were insufficient) might eventually have yielded a positive result, but even so, the relative insusceptibility of the area as contrasted

with that of the human integument would have rendered such results of small value. Some degree of toxicity towards frogs is attributable to the wood decoction, but this may be due to absorption from the alimentary canal to which the fluid might gain access. No active inflammatory condition of the skin is developed in frogs by local contact with 1 in 10 aqueous preparations, though in some instances slightly increased desquamation was noted.

When injected into the dorsal lymph sac of frogs, even in relatively large doses, chloroxylonine does not cause either pain or excitement, the toxic action is slow of development, whilst the tendency to haemorrhagic extravasation is neither powerful nor general.

Local application of East Indian satinwood dust, whether (1) dry, moistened (2) by water or (3) by almond oil, occasioned dermatitis in an observer who had already experienced that condition after chloroxylonine contact. The preparation No. 3 appeared to be the most active of the series.

Towards the human skin chloroxylonine and its salts (hydrochloride and nitrate) proved themselves to be, towards two out of three individuals, insidious but powerful irritants. The action did not supervene on the first but on the second application, an interval of four and twenty-two days respectively intervening before the occurrence of definite symptoms. Subsequent reapplications acted with much greater rapidity. (Whether any detectable lesion of the skin results from a primary contact with chloroxylonine, which, whilst producing no subjective or naked-eye changes, predisposes to the effective action of a second application, cannot be determined until successful induction of dermatitis in animals makes it possible to examine the skin histologically at all periods after contact has taken place.)

The local effect produced in the human skin indicates increased vascularity, at first limited to the extent of contact, and then extending widely beyond it. In the mildest form papules only may show upon the reddened surface; vesicles, oedema, and an erysipelatoid condition are evidences of more energetic action. Whatever be the degree, urticarial manifestations are readily induced (*urticaria factitia*). There is thus evidence of a strong tendency to serous exudation from the vessels, the tension at which this occurs being in correspondence with the severity of the local condition.

Sensations of heat, weight, and stinging pain arise mainly when inflammation and exudation are considerable, the two former being constant in character, but the itching which is associated with even moderate eruption intermits. At times it borders on the unendurable, and is developed at once by contact of rough objects, the slightest scratching, warmth, etc. Not infrequently a symmetrical area of the corresponding limb is the temporary seat of irritation, which may probably be referred to an overflow from excited nerve cells to those linked with them.

The remote inflammatory tumefactions which arise in

sequence to the local condition of the arm following chloroxylylonine were mainly situated on the face, ears, and neck, to a very limited extent on the trunk. The leg were unaffected, although, unlike the skin of the face,^s they had suffered dermatitis previously. The swellings were distinctly intracutaneous and not glandular in their seat. Involvement of the upper air passages is relatively late in occurring.

It is an open consideration at present whether we are to regard these remote effects, from which the nature of the experiment precluded all possibility of local contact, as vascular conditions produced through the agency of the vasomotor centre by the unusually powerful cutaneous irritation, or whether they are to be referred to absorption permitting the distribution of the alkaloid to distant parts of the body and its elimination subsequently by cutaneous and mucous surfaces, as well as by other channels. As adverse to the latter supposition are: the absence of renal effect, the long continuance of some of the remote symptoms, which do not, however, outlast the local irritation at the seat of contact, absence of pyrexia and malaise, and the non-involvement of the lymphatic glands. The abundant examples which could be adduced of remote vascular changes brought about reflexly through nervous intervention only, when an organ, and especially a highly sensitive structure such as the skin, is in an abnormal condition, make the former hypothesis more probable.

The local irritation following chloroxylylonine causes a long-continued enhanced susceptibility of the nervous organization which predisposes the cutaneous system in general to respond with abnormal activity to bodies which have otherwise little or no claim to be classed as irritants.

Of the non-alkaloidal principles contained in East Indian satinwood: No. I resin is not (as it was employed in this inquiry) irritant to the skin of normal individuals. No. II resin is not devoid of action, for it produced a slight irritant effect in one instance where there had not been any previous dermatitis. No irritation followed the employment of the pure oil as an application to the normal skin.

But to individuals who had already experienced a chloroxylylonine dermatitis all three bodies acted as irritants, No. II resin being in this respect very active, No. I resin moderately, and the fixed oil slightly active. In my own case the acquired hypersensitiveness appears to be discriminative in its tendencies, for whilst the satinwood products just mentioned as indifferent in action towards most individuals never fail to occasion dermatitis on auto-application, mustard causes no more than the simple rubefacient effect which is proper to its action.

Whilst in this inquiry, in correspondence with statements founded upon clinical observation of satinwood workers, one of the subjects of chloroxylylonine applications has proved refractory to the irritant action of the alkaloid it would be premature to assume that such tolerance has no limit; all that can be safely stated is that he has

shown a much greater resistance than the two observers, who each developed dermatitis after application of smaller amounts than have been used by him without definite result. No case has presented itself in the course of these observations which would illustrate the statement made by Jones¹¹ and Wechselmann,¹² to the effect that some satinwood workers, after a first attack of dermatitis, may acquire resistance towards the irritant, and so remain immune, although still exposed to the contact of the dust; on the other hand, towards the two individuals who reacted to the second application of chloroxylonine subsequent contacts were markedly more severe in their result, and the same may be said of the reapplication of both oily and resinous principles of East Indian satinwood.

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