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THE PHYSIOLOGICAL ACTION OF BORNEOL. A CONTRIBUTION TO THE PHARMACOLOGY OF THE CAMPHOR GROUP.

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In the following research the pharmacological action of three different substances has been fully investigated, namely, Borneo Camphor, Ngai Camphor, and Borneol prepared artificially from oil of turpentine. In addition, a number of experiments has been made with ordinary or laurel camphor, and with menthol or peppermint camphor.

The first three bodies are known to chemists under the common name of borneol, but although they are identical in chemical composition and reactions, they differ considerably in outward appearance and in certain physical properties. It will be of interest therefore to give a short account of each.

Borneo (Sumatra, Malay, Baros) camphor is obtained in small quantity from the trunk of the Dryobalanops Camphora (Colebrooke), a large forest tree growing in Sumatra and Borneo. After the tree has been felled the camphor is picked out by hand. The finest quality is in large, flat, white crystals, and the inferior qualities in granules. It melts at 198° C. and boils at 212° C., subliming unchanged.

It is slightly heavier than water, therein differing from laurel camphor, and its alcoholic solution rotates the plane of polarized light to the right. It has the formula $C_{10}H_{18}O$, and is to be regarded as a monatomic alcohol of which common camphor ($C_{10}H_{16}O$) is the aldehyde. By appropriate means laurel camphor may be converted into borneol, or vice versa.

According to Flückiger it was known in China before laurel camphor, and was the variety originally introduced into Europe. Since the discovery of the other, however, very little Borneo camphor has been sent to the West owing to the high price which it commands in the Chinese market—about 100 shillings per lb. or more for the best quality.

In Borneo it is used chiefly for embalming the Batta chiefs. In China it is employed as a stimulant, as an aphrodisiac, and in ophthalmia, a single crystal being put under each eyelid[1].

Ngai camphor, obtained from the Blumea balsamifera D. C., is met with crystalline and in granules. It has the same chemical composition as Borneo camphor, and is also slightly heavier than water, but its alcoholic solution rotates the plane of polarised light to the left. In price it is intermediate between Borneo and laurel camphors. It is used in China as a medicine and for perfuming the finer sorts of Chinese ink. The specimen which I used was obtained from the Hanbury collection in Kew Museum[2].

Borneol from oil of turpentine was first obtained by Armstrong and Tilden from "colophene," a product of the distillation of the oil with sulphuric acid. Chemically it is identical with Borneo camphor, but its alcoholic solution has no action on polarised light.

The specimen which I used was in laminar crystals, pure white, and having a mixed odour of camphor and terebene. It sunk in water, and its alcoholic solution was inert as regards polarised light. It melted at 199° and boiled at 211°, which numbers, allowing for slight experimental errors, are the same as those obtained by Pelouze for Borneo camphor[3].

The investigation was originally undertaken with the view of determining whether the exaggerated value set upon Borneo camphor by the Chinese is to be accounted for by any marked difference in action as compared with laurel camphor, or whether its high price is simply due

[1] For an account of the natural history of Borneo camphor see
Martius. *Liebig's Annalen*, xxv. 305, xxvii. 44, 1838.
Pelouze. *Comptes Rend.* xi. 365, 1840.
De Vriese. *Pharm. Journ. and Trans.*, xii. [1] 22, 1852.
Hooker. *Ibid.* p. 300.
Von Kessel. *Sitzungsb. der Wien. Akad.*, viii. 418, 1852.
Flückiger. *Neues Rep. f. Pharm.*, xvii. 28, 1868.
Kachler. *Liebig's Annalen*, 197, 86, 1879.
McEwan. *Pharm. Journ. and Trans.*, March 28, 1885.
Husemann. *Die Pflanzenstoffe*, 2nd Ed. 1882.
Flückiger and Hanbury. *Pharmacographia.*
Wood and Bache. *United States Dispensatory.*

[2] Plowman. *Pharm. Journ. and Trans.*, iv. [3], 710, 1874.
Hanbury. *Ibid. and Science Papers*, p. 393. *Pharmacographia.*
Flückiger. Buchner's *Rep. f. Pharm.*, xxiii. 1874, and *Pharm. Jour.* Ap. 18, 1874.

[3] Armstrong and Tilden. *Journ. Chem. Soc.*, xxxv. 733, 1879.
Lascelles-Scott. *Pharm. Journ. and Trans.*, Oct. 1886.
Hodgkin. *Ibid.* Discussion.

to a superstitious belief in supposed virtues, and to its comparative scarcity. While carrying on the research I obtained specimens of Ngai camphor, and artificial borneol, and found that all three produced similar symptoms when administered to animals.

The physiological action of Borneo and Ngai camphors has not been previously investigated, but Pellacani[1] has published an account of some experiments made with artificial borneol, prepared from laurel camphor by R. Schiff.

The experiments made by him were few in number and give an erroneous idea of its general action, especially on mammalia. Moreover, Pellacani's account of its action on the heart differs greatly from the results which I have obtained with all three substances. These errors are attributable to the small number of experiments, to his having studied its action on rabbits, and to the use of much too large doses.

General Action.

Frogs. In frogs the general symptoms are very similar to those which are produced by laurel camphor. The drug may be given dissolved in almond oil or water, or as a fine vapour from camphor sublimed on the inner surface of a glass bell-jar. If a frog be placed under such a bell-jar there ensues a series of symptoms indicating paralysis of the nervous system. Their onset is much more gradual, however, than is the case with laurel camphor under similar circumstances, owing probably to borneol being much less volatile. In about 10—30 minutes the animal becomes decidedly lethargic and sleepy looking without any stage of previous stimulation. It is disinclined to make spontaneous movements but jumps quite well if irritated. In a short time its jumps become heavier, and its movements lack precision, the animal frequently falling to one side when attempting to leap. The pupils are smaller and the respiration slower and deeper.

After a varying period respiration ceases, it lies quite flaccid and does not return to its normal position when placed on its back.

During this time the spinal reflexes are quite good or may be even slightly exaggerated, but they also become extinguished after a time, and the frog no longer gives any response even to severe stimuli. No muscular twitchings were ever observed.

The motor nerves still remain excitable to feeble electric currents, but after exposure to the camphor vapour has gone on for some time

[1] *Archiv f. expt. Path.* XVII. 369, 1883.

longer their terminations become paralysed, the muscles retaining their excitability to direct stimulation.

As a rule the heart continues beating for a considerable period after this, but it finally stops in diastole, and the animal dies.

When a small dose (0·003—0·01 grm.) is given subcutaneously dissolved in almond oil, the same train of symptoms is observed but not so fully developed.

The frog in a few minutes becomes unsteady in its movements, and then ceases to move spontaneously at all. The reflexes are maintained sometimes very slightly, sometimes considerably, diminished; respiration may be much slowed or may cease entirely; and the animal will probably remain on its back if placed there. The motor nerves are quite unaffected, or apparently so, and recovery takes place in a few hours.

With 0·022—0·032 grm. death generally ensues, but only after an interval of about 24—50 hours. The frog in a very short while after administration ceases to respond to stimuli and lies as if dead, but the heart continues to beat.

The condition of the motor nerves depends entirely on the heart. If it continues beating, they lose their excitability generally towards the end of the first day, whereas if the heart stops earlier, as it sometimes does, they still remain excitable to strong currents after death. Death is due to paralysis of the cardiac muscle.

The following experiments will serve to illustrate the foregoing description.

Frog, 32 grms. Resp. 31 in 15 secs.

11.47. Placed under bell-jar on sides of which Borneo camphor had been sublimed.

11.50. R. 30. Rather restless.

11.54. R. 28. Quiet. Pupils slightly smaller.

11.56. R. 25. Pupils smaller still. Lethargic, but jumps quite well if irritated.

12.0. R. 21. Pupils smaller. Very drowsy looking.

12.5. R. has ceased. When much irritated jumps heavily a short distance. Feels pinching at once.

12.20. Responds very slightly to severe pinching of toes, and not at all to gentler stimuli.

12.45. Sciatic nerve exposed, and found quite excitable to a weak interrupted current.

4.30. Has remained in same condition.

2nd day. Frog quite insensible to pinching. Motor nerves are inexcitable to strongest current.

Muscles are all excitable. Heart still beating feebly.

In this experiment the symptoms developed more quickly than usual. In some of the others the poisoning was much more gradual, the difference being, without doubt, due to difference in the rate of absorption of the camphor.

Frog, 34 grms. Resp. 33 in 15 secs.

11.52. ¼ grain (0·0162 grm.) Ngai camphor subcut. in 6 M almond oil.
12.4. R. 30. Slightly more sluggish.
12.8. R. 30. Does not jump so well. Movements are decidedly sluggish.
12.12. R. 18, very deep, the abdomen and eyeballs moving with each respiration. Pupils are smaller.
12.28. R. 20. Cannot jump well, but still crawls about a little.
12.36. Frog occasionally makes voluntary movements. R. 14. Pupils very small. Head resting on table.
12.44. R. ceases sometimes. Lies on its back if placed there. Reflex is still quite active.
12.54. Lying quite flaccid. Responds to pinching with forceps. Resp. ceased.
2.30. Reflex faint even to severe pinching.
5.10. Only sign of life is faint twitch when pinched with forceps.

2nd day. Remained in same condition. Motor nerves excitable.

3rd day. Has considerably recovered. Resp. 10 in 15 secs. Lying with head slightly raised from the table. Feels pinching at once and attempts to crawl away.

Gradually recovered, and on 6th day was nearly in its normal condition.

In some cases the frog died after getting ¼ grain.

Frog, 42 grms. Resp. 37 in 15 secs.

11.45. ½ grain (0·32 grm.) Borneo camphor in 12 M almond oil subcut.
11.49. Movements unsteady. There has been no excitement.
11.58. R. 28. Very unsteady in its movements, and rather restless.
12.2. R. 23. Pupils smaller.
1.0. Still respiring. Very sluggish and belly resting on table.
1.45. R. ceased.
2.0. Lies in any position in which it is placed. Pinching toe causes marked reflex.
3.45. Reflex only to severe pinching. Motor nerves are still excitable to weak interrupted current.

2nd day. Quite insensible to stimuli. Heart beats 10 per minute. Sciatic nerves are excitable to comparatively weak currents.

3rd day. Heart stopped in diastole and does not contract on stimulation: veins very full of venous blood. Sciatic nerves are paralysed. Muscles are still quite excitable.

Doses of 20—30 M of a saturated solution of borneol in water produce the lighter degrees of poisoning—heaviness, sluggishness, slight loss of coordinating power, &c.

Mammalia. Observations were made on rabbits, guinea-pigs, cats and dogs. It is on cats that the symptoms produced by borneol may be observed in their most typical and aggravated form. As has been shown by Hoffmann[1] and others, laurel camphor causes in cats violent convulsions which resemble in every respect those of epilepsy. With a moderately large dose, the convulsions succeed each other rapidly with short intervals of rest, they are extremely violent, and death generally occurs during one of them, shortly after the administration of the camphor. Wiedemann[2] ascribes the cause of death to paralysis of the over-stimulated nerve centres, but points out that owing to the very great violence of the convulsions, it is difficult to determine how far the respiratory centre is involved. With borneol the symptoms in cats are somewhat similar but the convulsions are never so severe as to directly cause death, having throughout more of a clonic than a tonic character. In addition death never occurs suddenly, but is a slow process, the animal surviving in a state of complete insensibility for two or three days. It is comparatively easy therefore to fix the proximate cause or causes of death.

Thus, after administration of 2—3 grms. by the stomach in emulsion, a cat shows in about a quarter of an hour symptoms closely resembling those of alcoholic intoxication. It wanders restlessly to and fro, its gait becomes unsteady, and in walking it seeks to support itself by leaning against the wall. Its power of coordination becomes much impaired, especially in the hind legs, and even when sitting still it sways gently from side to side. This condition rapidly becomes worse until progression is simply a series of stumbles, the animal finally lying down on its side unable to rise. The cutaneous vessels are dilated, and respiration is slowed, but the heart maintains its previous rate or may be slightly

[1] Beiträge zur Kenntniss der phys. Wirk. der Carbolsäure und des Kampfers. *Inaug. Diss.*, Dorpat, 1866.

[2] *Archiv f. expt. Path.* VI. 216, 1877.

increased. The animal although stupid and intoxicated retains consciousness, while the spinal reflexes are either not appreciably affected or very slightly diminished.

There then begins slight trembling, most marked in the head and neck muscles, which soon developes into violent clonic convulsions involving all the muscles in the body. Every now and again, but by no means frequently, the clonic developes into a tonic spasm with opisthotonos. After it has once begun the trembling is continuous, while sometimes in addition the animal moves its legs backwards and forwards in a rhythmical manner. During this stage the pupils are always widely dilated, and remain so till death. Chloroform completely stops the convulsions.

Consciousness gradually becomes abolished, and the animal lies on its side trembling continuously and having at intervals true epileptic convulsions.

Sensation also becomes impaired, until even stimulation of the exposed sciatic nerve causes no reflex movement. The ability of the spinal cord to conduct motor impulses is, however, quite well maintained, as evidenced by the violent convulsive movements. The animal may remain in this condition for about 48 hours, the heart continuing to beat regularly and with considerable force, although somewhat slowed, or it may die earlier.

The temperature falls very much towards the end, the surface of the body feels cold, and death ensues from paralysis of respiration, largely aided, no doubt, by loss of bodily heat and exhaustion. The post-mortem appearances are those of death by asphyxia, but in addition the tongue was in some cases very much bitten during the convulsions.

With smaller doses (1—1½ grm.) the symptoms are precisely similar to those produced by a moderate dose of alcohol. Frequently twitchings of groups of muscles or of the limbs are present, very similar to what is observed in delirium tremens. With very large doses (4 grms.) death occurs sooner, while paralysis and stupor are more pronounced features of the poisoning than the convulsions.

When menthol (2—3 grms.) is given to cats the symptoms resemble those produced by a full dose of alcohol—restlessness, incoordination and quickening of pulse, passing into stupor. The animal may remain completely unconscious for two or three days, finally recovering, or may die. Absorption from the stomach is evidently irregular, as the animal often remains under the influence of a single dose of menthol for several days, the degree of intoxication sometimes varying a good deal during

this period. In contradistinction to borneol the increase in pulse rate was always considerable (12—22 per min.) during the first few hours, and was followed by a very distinct decrease.

After menthol I never observed well-developed convulsions, the only indication of them being a slight trembling of the limbs, and even this was not always present.

In rabbits the action is not nearly so definite nor are the symptoms ever so pronounced as with cats, this being the case both with laurel camphor, and to a greater degree with borneol. It depends partly no doubt on irregularities in the rate of absorption, and partly on a lesser susceptibility of these animals to the poison. Small doses of borneol are without any apparent effects, while with doses of 2—6 grms. the animal may become simply depressed and inactive, may have epileptic seizures with a train of symptoms resembling those described in cats, or may be rapidly and completely paralysed, as in the two experiments described by Pellacani. The last condition is seen only when very large doses become rapidly absorbed. With laurel camphor convulsions are rarely absent in rabbits, but the attacks are milder and less frequent than in cats. Guinea-pigs (0·75 – 1 grm. borneol) behave exactly as rabbits do.

After the administration of laurel camphor to dogs Hoffmann, Wiedemann, and Pellacani observed epileptiform attacks of a more or less marked character, preceded by psychical disturbance. The last two investigators, however, also gave large doses without producing any marked effects. In man the same thing is observed. Alexander[1], who experimented on himself, experienced, after taking 40 grains, giddiness, great mental confusion and had one epileptic convulsion. He vomited most of the camphor under treatment, but suffered from tremors for some hours afterwards. Harley[2] quotes a number of recorded poisoning cases in which convulsions were a marked feature, but shows that considerable doses (up to 35 grains once, and 30 grs. thrice daily) may be given without producing more serious symptoms than giddiness and lethargy.

Even with very large doses (10 grms.) of borneol, I never observed convulsions in dogs. It was given in a bolus made up with mucilage, as an oily emulsion always caused severe diarrhoea.

Small doses of 1 to 2 grms. cause in medium sized dogs no symptoms.

[1] *Experimental Essays*, p. 127, 1767.

[2] *Practitioner*, II. 210, 1872.

With much larger doses the animal may remain quite unaffected, but it frequently exhibits great restlessness and unsteadiness of gait. The nose and ears become very hyperaemic from dilatation of the cutaneous vessels. There is no psychical excitement, but rather, as the intoxication proceeds, the animal shows a great tendency to lie down and fall asleep. Sensibility to external impressions is diminished, but the spinal reflexes are maintained nearly, if not quite, intact. The symptoms pass off in a few hours. The effects therefore are very similar to those of alcohol.

Menthol in 2—4 grm. doses produced similar symptoms of intoxication, but the effects were much more prolonged. It also can be given in considerable doses (4 grms.) to dogs without any observable effects following.

Action of Laurel Camphor and Borneol on the Nervous System.

From the foregoing description and experiments it is obvious that, in frogs, the part chiefly acted on by camphor is the nervous system. If we carefully analyse the order in which the various symptoms supervene, we can deduce with considerable accuracy the order in which the different parts become affected. Thus, the primary lethargy and dulness show early implication of the cerebrum. The loss of coordinating power, following shortly after, points to rapidly succeeding involvement of the optic lobes and cerebellum; while the next symptoms—inability to get off the back and cessation of respiration—prove that the paralysis has extended down to the medulla oblongata. Much later the spinal reflexes are abolished, and lastly the excitability of the motor nerves. Naturally from the very commencement of the poisoning all parts of the nervous system begin to be affected, but some succumb much later than others, and the order in which they finally surrender to the influence of the camphor is as stated above.

In mammalia the symptoms may be referred almost entirely to the encephalon, the cord being affected much less profoundly, while the motor nerves in every case retained their excitability to the end.

There are certain points to which I wish to draw special attention as regards the nervous system.

(1) In frogs, it is evident that in some cases the reflex power of the spinal cord is not quite abolished before the motor nerves become paralysed. The reflexes are always, however, very much depressed long before the motor nerves show any falling

off in their excitability, and there can be no doubt that the cord tends to be paralysed much sooner than the peripheral nerve terminations. This can be best shown by causing the frog to absorb rapidly a large quantity of camphor. For this purpose it is exposed to dense fumes obtained by heat, when the fine particles of camphor deposit on the skin and are so quickly absorbed that in a few minutes the animal lies quite flaccid. It exhibits no reflex even to the severest stimuli, but on exposing the sciatic nerves they are found to be readily excitable to a weak interrupted current: shortly after, they also become paralysed. Experiments made in this way with different kinds of camphor always gave the same results. The following may serve as an example.

12.17. Frog exposed to sublimed fumes of artificial borneol.

12.23. Quite paralysed; no reflex. Exposure continued till 12.27. There was then no reflex to mechanical, chemical or electrical stimulation of the skin.

One sciatic nerve exposed and stimulated with weak interrupted current, when the muscles of same leg contracted powerfully.

The frog was left under the funnel till 2 o'clock, when the sciatic nerves were found to be no longer excitable. The heart was then beating 9 per 30 secs., and the muscles were all quite excitable.

(2) The continuation of well-marked spinal reflexes in the frog long after voluntary movements have ceased. This has been fully described by Wiedemann. He seems to infer, however, that it is due to a preliminary stimulation of the cord, which only slowly passes into paralysis. Binz[1] and Grisar[2] state explicitly that a stage of stimulation precedes the depression (0·03 laurel camphor).

From my own observations I have formed the opinion that there is no preliminary stimulation of the spinal cord either in frogs or mammalia, but, on the contrary, a gradually deepening paralysis. When a frog begins to come under the influence of camphor the reflexes remain for some time undiminished, or may be even slightly greater than before. It is well known, however, that the latter condition occurs in frogs in which the connection between the brain and spinal cord has been severed, owing to the removal of the inhibitory influence exercised by Setschenow's centres. Camphor paralyses these centres (along with the rest of the brain) and throws them out of action very early in the poisoning, while the spinal cord is still comparatively unaffected, and in

[1] *Archiv f. expt. Path.* VIII., pp. 52 and 63, 1878.

[2] *Cbl. f. med. Wissensch.* 1874, 77.

this, it seems to me, lies the explanation of the increased reflex. That it is so appears to be proved by the following method of investigation. In frogs an incision was made through the atlanto-occipital membrane, and the brain destroyed above this. They were kept till next day, and only such were used as had well-marked spinal reflexes. They were then slowly exposed to camphor under a funnel, or small doses were given subcutaneously, and the reflexes carefully observed. In every case there was a gradual diminution from the beginning. Thus

12.6. Decapitated frog placed under laurel camphor funnel.
12.9. Hardly noticeable diminution of reflexes.
12.12. Slight diminution.
12.18. Very distinct diminution.
12.42. Skin reflexes quite gone: reflex to pinching with forceps marked.
1.15. No reflex to severest pinching.
Sciatic nerve quite excitable when stimulated at 140 mm. (1 Daniell cell and Du Bois induction apparatus).
1.50. No reflex. Sciatic nerve was now inexcitable. Heart exposed beats 18 in 30 sec.

In rabbits, Pellacani has shown that borneol acts to a certain extent as an antidote to strychnine, by diminishing the severity of the spasms and by raising the minimal lethal dose required. Such a method of experimentation, however, while proving that camphor depresses the spinal cord, does not shew the presence or absence of preliminary stimulation. To do this, it is necessary to use an animal in which the spinal cord has been divided, and which has survived until the reflexes have recovered their tone, as described by Goltz. By this means only can the influence of the brain on the cord be satisfactorily excluded.

Accordingly, in a young cat, the spinal cord was divided at the level of the third dorsal vertebra under ether. It made a good recovery and at the end of the third week was ready for experiment. A dose of 0·5 grm. borneol by the stomach had no appreciable effect on the reflexes, but when 1—1·5 grm. was given the reflexes posteriorly were decidedly diminished without any previous increase. The cat anteriorly had the ordinary symptoms of borneol poisoning, while posteriorly there was no trace of tremors.

This result is the contrary of what I had expected, as uninjured cats to which similar doses have been administered give a violent start and draw themselves together when tapped over the spine, simulating great

increase in the reflex excitability. Besides this, cats fully under the influence of borneol and insensible to the severest pain and in which the cord is palpably greatly depressed, start violently if suddenly tapped.

But in both cases the start must be due to some cause other than heightened excitability of the grey matter of the spinal cord, and is probably idio-muscular[1].

(3) The reflex function of the spinal cord is paralysed sooner than its power of conducting motor impulses. This may be most easily demonstrated by rapidly paralysing a frog with dense camphor fumes. When it is quite reflexless, the application of electrodes over the cord high up will still cause violent contraction of the leg muscles. In mammalia also, convulsions are present long after pricking with a pin, or even stimulation of a sensory nerve, have ceased to excite reflex action. The insensibility to pain is probably largely cerebral, as it closely resembles what occurs in alcoholic poisoning.

Flourens showed long ago that in animals under ether there exists a similar condition of the motor and reflex powers along with the general anaesthesia.

(4) Convulsions. The commonly accepted views with regard to the causation of the epileptic convulsions are those of Binz[2] and Wiedemann. The former states that they arise from the parts between the cerebrum and medulla oblongata, while the latter assumes that they are due to stimulation of the medulla oblongata itself. He explains their absence in the frog by the paralysis of the spinal cord and motor nerves which prevents their manifestation. In mammalia, on the other hand, the spinal cord and motor nerves are never fully paralysed, and hence the convulsions are able to manifest themselves to the very end. My own observations however lead to different conclusions, and point to the fact that in mammalia the epileptic condition is due to an action on the cortex. This view is founded on direct experiment, and is besides strongly supported by the non-occurrence of the convulsions in frogs. In these animals it is well known that stimulation of the higher parts of the brain with electricity does not cause convulsions, and that these are only induced when the current is applied so low down as the medulla. Even

[1] The more recent investigations into the cause of the patellar reflex tend to confirm this view, and to show that the jerk is essentially muscular in origin but influenced in various ways by the condition of the spinal cord.

[2] *Archiv f. expt. Path.*, v. 109, 1876.

then the convulsions are not epileptic in character. It is therefore impossible in frogs to produce convulsions by any stimulant which acts only on the higher centres. In mammalia, on the contrary, electric stimulation of the cortex causes irregular convulsion of an epileptiform character, and stimulation by means of a drug will no doubt do the same. These considerations explain the marked difference of symptoms observed in camphor poisoning in cold and warm blooded animals. But further proof is given by direct experiments on rabbits. These were made with the cooperation of Dr Ashdown, and as they opened up a wide field of investigation and are still being proceeded with, it will only be necessary to mention them briefly. We have always used laurel camphor, as it produces convulsions in rabbits with much greater certainty than borneol does. The animal was trephined and the cortex cerebri carefully removed. After some hours a full dose of laurel camphor was given by the stomach, when the rabbit showed great depression, unsteadiness of gait, &c. but never had convulsions. Control experiments were made at the same time with rabbits of similar size and with a similar dose, and in these the epileptic convulsions were always a prominent feature.

Action on the Heart and Circulation.

Frogs. The action of laurel camphor on the frog's heart has been studied by Heubner[1], Harnack and Witkowski[2], Wiedemann, Umpfenbach[3], and Maki[4], all of whom agree in ascribing to its influence a decrease in the rate with marked increase in the energy of the contractions.

With moderate doses of menthol Pellacani obtained similar results, but borneol he regards as occupying an altogether peculiar position with respect to its action on the heart. It is, according to him, a powerful cardiac poison, and even in comparatively small doses brings the frog's heart to a complete standstill within half an hour or even in a few minutes after administration (0·03 – 0·04 grm.). He also gives tracings from the isolated heart (Williams' apparatus), showing that the addition of borneol to the circulating blood causes rapid death

[1] *Archiv f. phys. Heilkunde*, XI. 1870.

[2] *Archiv f. expt. Path.*, V.

[3] *Inaug. Diss.*, Erfurt, 1881.

[4] Ueber den Einfluss des Camphers, Coffeins und Alkohols auf das Herz. *Inaug. Diss.* Strassburg, 1884.

of the organ. These results I am unable to understand, except on the supposition that the borneol used was not pure. I have made a large number of experiments on the frog's heart with Borneo camphor, Ngai camphor, and borneol, and have invariably found their action to be exactly similar to that of laurel camphor. Rana temporaria was used. If the heart be exposed and the borneol given subcutaneously, there occurs in a few minutes slowing of the rate of contraction, along with an easily observed increase in the energy and completeness of the systole and a very full diastole. Nor is the heart rapidly killed, as Pellacani states, but continues beating powerfully for hours even if a large dose be given (0·03 grm.). With lethal doses, however, the systole gradually becomes less pronounced, and in time the heart stops in full diastole and greatly distended with blood. Mechanical or electrical stimulation does not then cause it to contract, the muscle being evidently poisoned.

In comparing the effects of equal quantities of the three kinds of borneol, it became evident that the artificial variety made from oil of turpentine was somewhat more poisonous than the other two, so far as the heart is concerned. Whether this is due to some slight impurity, or to its being really a more powerful muscle (cardiac) poison I am unable to say. This was the only respect in which any difference was observed in the action of the three bodies.

The following experiments show the action on the heart.

Frog. 30 grms.

Time.	Heart in 30 secs.	Remarks.
12.8	22	
12.10	22	$\frac{1}{4}$ gr. (0·016 grm.) Borneo camphor in oil subcut.
12.18	22	
12.22	21	
12.26	21	Energy of contraction greater.
12.34	21	
12.40	19	Very full and regular.
12.58	19	
1.4	18	
1.24	17	
1.45	16	
2.0	15	Very full and regular.
2.30	14	

Time.	Heart in 30 secs.	Remarks.
3.30	13	Diastole occurs in 2 stages; the heart half dilates, makes a distinct pause and then dilates fully.
4.40	11	
5.30	11	Diastole same. Systole quite good. Action full and regular.
	Frog. 34 grms.	
11.26	19	
11.28	19	½ gr. (0·032 grm.) borneol from oil of turp. subcut. in almond oil.
11.32	18	
11.38	16	Contractions more energetic.
11.48	13	Very full and regular.
11.54	12	
12.0	12	
12.8	11	Action full and regular.
12.18	10	
12.28	9	
12.48	8	Regular. Diastole very full, systole is still good.
1.10	7	
2.10	6	Systole rather feeble, but heart's action still moderately good.
3.50	7	
5.45	4	Systole very feeble: heart almost in complete diastole.

With much smaller doses, such as 5—2 mgrms., the stage of increased energy lasts a long time and never passes into paralysis, as it does with large doses.

Previous administration of a small dose of atropine does not in any way affect the action of camphor on the frog's heart, which shows that the slowing is not due to the influence of the drug on the central nervous system, nor to a stimulation of the inhibitory terminations of the vagus in the heart.

Shortly after borneol has been given electric stimulation of the vagus is found to have completely lost its power of inhibiting the heart, stimulation of the sinus being also inoperative. This affords a further proof, if such were necessary after the results of the atropine

experiment, that the decrease in rate cannot be due to an irritation of the peripheral vagus fibres, which are in effect at least paralysed by the borneol.

Accepting Schmiedeberg's views that the heart contains inhibitory and motor ganglia, we are driven to the conclusion that the slowing is due either to an action on these ganglia, or on the heart muscle itself. The inhibitory ganglia are however thrown out of action by atropine, which paralyses the nerve connections between them and the motor ganglia.

Either, therefore, the motor ganglia are stimulated in such a manner that the nervous impulses emanating from them to the muscular fibres cause the beats to become slower and more powerful, or the heart muscle itself is directly stimulated. At present there is no reliable method of distinguishing between the two actions. The subject is one which has been greatly discussed, and still remains unsettled. Harnack and Witkowski deny that the vagus is paralysed, and have endeavoured to show that camphor, physostigmine and a number of other bodies stimulate the cardiac muscle directly to such an extent that vagus stimulation can no longer inhibit its action. They base their opinion chiefly on the fact that in a heart fully under the influence of physostigmine or camphor and on which vagus stimulation has no effect, the administration of a muscle poison such as copper or apomorphine restores the inhibitory power of the vagus by depressing the cardio-muscular energy. In endeavouring to repeat their experiments I found them unsatisfactory in several respects, but I am at present investigating the subject more fully.

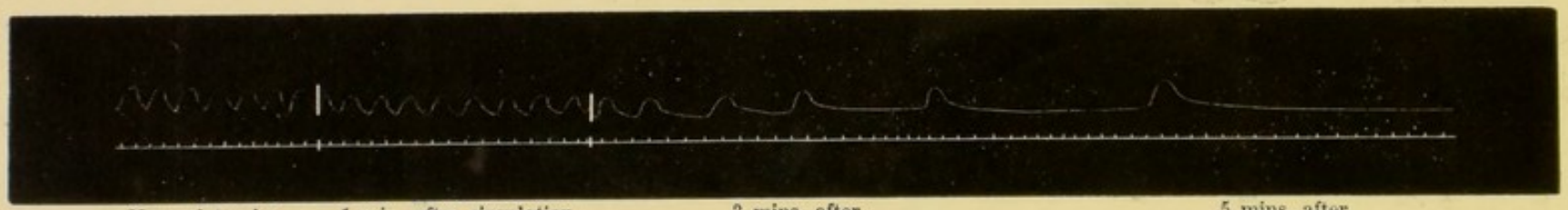
The action of borneol on the isolated frog's heart was also studied by means of Williams' apparatus. This method is so well known[1] as to need no description, but I may mention that by regulating the outflow of the circulating fluid there may be obtained either a simple tracing of the cardiac beats, or a record of the pressure maintained by the heart expressed in millimetres of mercury. The circulating fluid used was defibrinated sheep's blood 1 part, normal saline solution 2 parts. The borneol was added as a saturated solution in normal saline.

Using the first method the observations made on the heart *in situ* were confirmed, viz.—the beats became less frequent while their amplitude was greatly increased, (Fig. 1). If the circulating fluid

[1] Cf. Williams, *Archiv f. expt. Path.* XIII. 1. Harnack und Hafemann, *Ibid.* XVII. 159. Maki, *Inaug. Diss.* Strassburg, 1884.

Fig. 1. Williams' Apparatus. Effects of Borneo Camphor on isolated frog's heart. Circulating fluid = Blood 33 c.c. Saline sol. 33 c.c. Sat. sol. of Borneo. Camphor in Saline 33 c.c.

Fig. 2. Effects of Toxic dose Borneol. Circulating fluid = Blood 33 c.c. Sol. of Artificial Borneol in Saline 66 c.c.



contained too large a proportion of borneol the heart was rapidly killed in diastole (Fig. 2). Here also it was found that the solution of artificial borneol was much more toxic than the Borneo camphor solution.

Using the second method of recording by means of Williams' apparatus, the increase in blood pressure is shown in the two following tables.

Circulating fluid = { Sheep's blood 33 c.c. / Saline sol. 57 c.c. / Sol. artif. borneol in saline 10 c.c.

Time.	Mean press. in mm. Hg.	Heart in 30 secs.	Remarks.
2.30	18	14	
2.50	18	14	
2.52	—	—	Borneol circulated.
2.58	21	12	
3.0	24	12	
3.5	26	13	
3.8	28	12	
3.11	27	12	
3.25	29	12	
3.32	29	13	
3.50	31	12	
3.54	30	12	Heart acting quite well. No symptoms of commencing failure.

Experiment stopped.

Circulating fluid same.

12.50	41	18	
12.55	38	18	
12.59	41	18	Borneol circulated.
1.4	48	16	
1.8	49	14	
1.14	46	14	
1.17	43	14	
1.30	46	14	

The outflow was then relaxed, and a simple tracing taken, when the beats were found to be quite regular and very ample. Experiment then stopped.

Mammalia. Wiedemann found that after the administration of laurel camphor to rabbits and cats, there took place constantly a series of periodic rises of blood pressure, each rise being quickly followed by a return to the normal. After division of the spinal cord these were not observed, and hence he concludes that the rises are due to a series of convulsive discharges from the vasomotor centre in the medulla, whereby contraction of the arterioles is brought about. After section of the vagi the blood pressure invariably fell, but he is unable to explain this in any way. No direct stimulant effect on the heart muscle was made out.

Maki using chloralised animals, so as to exclude any action on the vasomotor centre, found that laurel camphor raised the blood pressure, and hence concludes that it is a stimulant to the muscle substance.

With borneol, Pellacani obtained a marked and rapid fall in the blood pressure and pulse rate of cats. The doses which he used (3 grms.) were undoubtedly very much too large for the purpose, being sufficient to produce great paralysis and collapse within a very short time.

With menthol (2—3 grms.) he obtained the same series of periodic rises as Wiedemann did with laurel camphor.

My experiments were made with borneol and menthol but in much smaller doses than the above and with somewhat different results. The influence of borneol (1 grm.) on the mean blood pressure was found not to be constant. In some experiments there was a gradual slight fall (with larger doses a rapid and large fall), while in others the periodic rises occurred, but in no case frequently. The heart always remained strong and regular, while the pulse rate either rose or fell slightly. The vagus never lost its power of inhibiting the heart.

With menthol I always got a slight fall with 1 gramme doses, preceded in some cases by a rise. Here also the pulse rate sometimes increased and sometimes diminished In the intact animal however (vide supra) menthol invariably caused an increase in pulse rate.

The following tables show the effects on the blood pressure, of doses sufficient only, in the first instance, to cause slight intoxication.

Cat. 2260 grms.

Time.	Blood press. in mm. merc.	Pulse in 10 secs.
11.32	138	40
11.34	140	40
11.35	134	41
11.36 1 grm. borneol in oil by stomach.		
11.37	137	42
11.38	145	40
11.40	136	38
11.44	129	35
11.45	136	36
11.50	130	39
11.54	125	38
11.58	126	40
12.2	124	39
12.5	136	41
12.6	122	40
12.7 1 grm. borneol in oil by stomach.		

Time.	Blood press. in mm. merc.	Pulse in 10 secs.
12.8	130	41
12.10	116	41
12.14	110	41
12.20	108	40
12.27	104	40
12.32	106	40
12.38	96	40
vagi cut.		
12.40	122	39
left vagus stim.	82	28
12.44	127	38
12.46	112	38
left vagus stim.	80	21
12.54	108	38
left vagus stim.	92	33
12.56	108	38
Experiment stopped.		

Cat. 2400 grms.

Time.	Blood press. in mm. merc.	Pulse in 10 secs.
11.55	121	34
11.58	115	35
12.1	119	36
12.3	114	36
1 grm. Borneo camphor in oil by stomach.		
12.5	123	38
12.8	126	39
12.12	122	40
12.15	137	38
12.15½	156	40
12.16	149	40
12.17	143	38
12.18	134	38
12.21	132	39
12.23	118	39
12.27	127	38
12.34	120	40

Time.	Blood press. in mm. merc.	Pulse in 10 secs.
12.40	122	39
12.46	115	39
12.50	120	39
12.54	128	39
1 grm. Borneo camphor in oil by stomach.		
12.56	120	39
12.59	111	39
1.0	102	36
1.3	99	37
1.5	104	36
1.6	122	36
1.8	120	36
1.12	108	35
1.20	106	32
1.24	103	32
Experiment stopped.		

In the first experiment the pressure fell slightly after one gramme, and rapidly after two, while in the second experiment periodic rises are observed, accompanied by a general gradual fall. The effect on the pulse rate was inconstant.

It is unnecessary to give examples of the menthol experiments at length as they resemble the above exactly. One gramme in oil by the stomach caused the pressure to fall from 158 to 128 within an hour, and rapidly to 90 on repeating the dose. A rise was only seen in one case.

Action on the blood-vessels. The action on the peripheral blood-vessels was studied by circulating blood through isolated organs kept at the normal body temperature, when it was found that the presence of borneol caused great vascular dilatation. The following experiment shows the amount of increase in outflow.

Organ used. One horn of sheep's uterus. Inflow cannula in uterine artery, outflow cannula in uterine vein.

0·3 grm. Borneo camphor shaken up with 200 c.c. defibrinated sheep's blood and filtered.

Before camphor outflow averaged		9	drops per minute
3	mins. after circ. of camphor blood =	30	,,
6	,, ,,	33	,,
9	,, ,,	40	,,
12	,, ,,	42	,,
15	,, ,,	47	,,
18	,, ,,	52	,,
21	,, ,,	57	,,
24	,, ,,	60	,,
27	,, ,,	51	,,
30	,, ,,	51	,,
33	,, ,,	45	,,
36	,, ,,	47	,,
42	,, ,,	42	,,
45	,, ,,	44	,,

Kobert has shown that oil of peppermint also greatly dilates the blood-vessels in isolated organs.

From the different experimental results obtained it seems that after the administration of all these substances in moderate dose, the blood pressure may be affected in two ways: (1) it may fall gradually, or (2) may show periodic rises, the heart in both cases maintaining a vigorous and regular beat. When large doses are given the blood pressure falls markedly and rapidly.

In the first case there probably occurs dilatation of blood-vessels and a consequent fall of blood pressure, but these lead to a fuller action of the heart, and a vigorous stimulation of the circulation. From the

results of the experiments on the isolated frog's heart (where the vessels are excluded) I think we may safely assume that in addition the heart muscle is stimulated either directly or through its ganglia, but that the vascular dilatation in mammalia prevents this from raising the blood pressure. In deeply chloralized animals I was unable to get a rise of blood pressure with Borneo camphor. Maki indeed got such a rise with laurel camphor, but Wiedemann, who relaxed the vascular tone by dividing the cervical spinal cord, failed to get it, results which apparently contradict each other. If there does occur in mammalia a direct stimulant action on the heart, such as is seen in frogs, it is very difficult to demonstrate, and unless we assume Maki's results as correct, we can only infer such a stimulation from a study of the amphibian heart.

The dilatation of the blood-vessels is brought about certainly by a peripheral action, but partly also no doubt by a central action on the vasomotor centre, which shares in the general cerebral paralysis. It is most probable also that the rapid fall, seen after large doses, is due chiefly to the latter cause, as we see the same thing after large doses of alcohol.

It is more difficult to account for the periodic increases in blood pressure. As has been seen, at least with borneol and menthol, they are frequently absent, and this is naturally a great bar to the investigation of their causation. In the case of laurel camphor Wiedemann explains their occurrence by assuming that the vasomotor centre shares in the general epileptic condition, and brings about periodic narrowings of the arterioles. This at first sight looks probable enough, but with menthol Pellacani got similar well marked periodic rises, although (with much smaller doses however) I did not, and in this case the theory of spasmodic stimulation of the vasomotor centre is hardly admissible, as the animal has no epileptic seizures and is simply stupidly drunk.

A possible explanation is that camphor and its metabolic products (which form very rapidly) are circulating in the blood in ever varying proportions, and according as one or other is in the ascendant do we get different effects. The whole matter is one which would require a special investigation to elucidate it thoroughly, but the insolubility of camphor in indifferent menstrua throws great difficulties in the way. It has to be given dissolved in oil either subcutaneously or by the mouth, the absorption is always slow and very irregular, and in a given case one can never be certain how much is actually in the circulation.

Respiration. The respiration is always very much slowed from the

first. In cats it falls in about a quarter of an hour from 36 per min. to 26 and after that to 16 or even 10, at which it remains. In rabbits also the rate very rapidly falls until it reaches about a third of its normal frequency.

Action on muscle. With ordinary doses in frogs the muscles are unaffected, but when the frog has been exposed for some time to sublimed fumes the muscular irritability is very noticeably diminished. In mammalia no action on the muscles is observable.

Action on the blood. It has been shown by Binz and his pupils that most essential oils increase the number of white blood corpuscles. Borneo camphor is an exception to this however.

I made a number of experiments on myself and on friends, using doses up to 10 grains by the mouth, but the results were invariably negative. Gower's haemocytometer was used for the enumeration.

Glycosuria. The occurrence of sugar in the urine in camphor poisoning has never been previously noted. This excites the less surprise as it is by no means constant, and in my experience occurs only in cases in which convulsions are a marked feature. Thus I never found it in dogs after borneol or menthol, although possibly 50 or 60 examinations of the urine were made, nor in other animals which got either too small or too large a dose to develope the convulsive stage fully. It was also absent in menthol poisoning, as were convulsions (4 observations, cats).

It is quite possible however that with an extended series of observations glucose might be found in the urine of animals poisoned with menthol, as it seems to occur pretty frequently after the administration of substances which are excreted in combination with glycuronic acid. It has been observed in such cases quite apart from convulsions, as v. Mering and Thierfelder[1] found it in the urine of a dog after administration of 10 c.c. dimethyl-ethyl-carbinol, a body which is excreted in combination with glycuronic acid. The dog showed symptoms similar to those of alcoholic intoxication and had no convulsions. In another case (man 9 c.c. in 24 hrs.) no glucose was present in urine.

In fasting rabbits also, Thierfelder[2] after the same substance found glucose excreted, but by no means in every case.

Its occurrence in such cases must therefore be regarded as inconstant, and dependent on the energy with which oxidation processes are going on in the organism.

[1] *Zeitsch. f. phys. Chemie*, IX. 511, 1885.

[2] *Zeitsch. f. phys. Chemie*, X. 161, 1886.

My attention was first drawn to the glycosuria by observing that the urine of certain animals which had received somewhat large doses of laurel or borneol camphors reduced Fehling's solution very markedly. This I at first attributed to the metabolic products of camphor which are found in the urine, but camphoglycuronic acid does not reduce Fehling's solution[1] although one of its decomposition products—glycuronic acid—does. The latter is only obtained from the former by prolonged digestion with dilute mineral acids, and is not present in the urine when voided, nor does it ferment with yeast. Besides, other urines which contained large quantities of the metabolic bodies had no power of reducing copper salts or of undergoing fermentation.

Those urines which reduced the Fehling's solution were found to ferment violently with yeast over mercury and to give off large quantities of carbonic acid gas. They also gave the other well-known tests for sugar. I cite below several of the cases in which glycosuria was present.

Cat. 2310 grms. Got 1·5 grm. laurel camphor in oil subcutaneously. Had several epileptic convulsions and 7 hrs. later passed urine which reduced Fehling's solution and fermented with yeast. The gas given off was absorbed at once by caustic potash solution. It died in 23 hrs. The urine in the bladder was light straw colour, sp. gr. 1·018, and also on application of same tests was found to contain glucose.

Cat. 3031 grms. Got 2 grms. Borneo camphor in emulsion by stomach. It had the usual symptoms and died in 25 hrs. Urine in bladder contained no albumen, reduced Fehling's solution and fermented over yeast.

Rabbit. 1380 grms. Got 0·8 grm. laurel camphor in oil subcut. Had many slight epileptic convulsions: $5\frac{1}{2}$ hrs. after, the expressed urine contained glucose. Rabbit recovered and was perfectly well next day.

Rabbit. 930 grms. Got 2·5 grms. borneol in oil by stomach. It had clonic but no tonic convulsions. 3 hrs. after, the expressed urine contained sugar; also 5 hrs. after. 10 hrs. after the rabbit had considerably recovered, there being only some depression and unsteadiness of gait. Its urine then contained no sugar.

Temperature. Binz found that comparatively small doses of laurel camphor (0·09—0·2) reduced the temperature considerably both in normal and fevered rabbits.

[1] Schmiedeberg and Meyer. *Zeitsch. f. phys. Chemie*, III. 422, 1879.

In repeating his experiments even with much larger doses I did not obtain such invariable results. In some instances the temperature was lowered, while in others it remained quite unaffected. As has been previously stated this is due partly to differences in absorption, and partly to differences in the rate of metabolism. It was easily observed that a distinct fall occurred only in those animals in which general symptoms of depression or slight convulsions were present. Medium sized rabbits were used, the camphor was given subcutaneously, and the temperature was measured every quarter-hour in the rectum with the usual precautions; 0·5 and 1 grm. were in two cases quite without effect. In other two cases 0·4 and 0·8 grm. reduced the temperature as follows:

I.

Time.	Fahr.	
11.15	103°·1	
11.30	103·6	
11.45	103·4	
12.0	103·4	
1.0	103·2	0·4 grm. laurel camphor.
1.15	102·7	
1.30	101·7	dull and depressed.
1.45	101·0	
2.0	100·2	had slight convulsion.
2.30	100·4	
3.0	100·8	
4.0	101·2	
5.15	101·6	
5.45	102	
6.15	102·4	
8.20	104	
9.15	104	

II.

Time.	Fahr.	
11.15	102°·9	
11.45	102·2	
12.30	102·1	0·8 grm. laurel camphor.
12.45	101·7	quiet and depressed.
1.0	100·8	
1.15	100	
1.30	98·8	
1.45	98·4	convulsion.
2.0	98·2	convulsion.
2.30	97·6	
3.0	97	has had frequent convulsions.
3.30	97·4	
4.0	97·6	
4.30	97·4	convulsions.
5.15	98·6	
5.45	98	
6.15	97·6	convulsions still.
8.20	102·1	much recovered.
9.15	102·2	

When borneol was given the same variableness in the results was seen. Small doses (0·5 grm.) were always without effect, while larger doses (2 grms.) might have no effect, might reduce temperature slightly or might reduce it in a remarkable degree.

Rabbit. 927 grms.

Time.	Fahr.	
12.15	102°	
12.18	——	2·5 grms. borneol by stomach.
12.48	102	
1.18	100·6	
2.0	97	
2.45	95·5	
3.15	94·5	
3.45	94·2	
4.15	94	
4.45	93·2	
6.15	91·4	
7.30	89·8	
10.0	91	
11.0	94·4	
Next day 10.0	101	

The animal had convulsions, passed through the ordinary symptoms, and next day had quite recovered.

In another case where death occurred after 3 grms. the temperature fell from 99° to 80°.

In cats the fall was never considerable unless great collapse were present, while in dogs it was never more than a few tenths of 1° F. As regards the cause of the fall in temperature three factors come into play. The dilatation of cutaneous vessels must increase the radiation of heat from the body, while in cases where the general symptoms are extreme, the state of collapse and consequent interference with the chemical processes going on in the body will be a powerful agent in preventing its production. To the latter cause is probably to be ascribed the great fall observed in some cases.

Besides these, the conjugation of campherol with glycuronic acid will have some effect, especially when large doses are given. Glycuronic acid ($C_{10}H_6O_7$) is a product of the commencing oxidation of glucose, and readily breaks up further into carbonic acid and water, its oxidation being of course a source of heat. When it combines with campherol it is rapidly excreted without further oxidation occurring, and is lost to the body as a heat producer.

Its close chemical relationship to glucose probably explains, in some way yet to be demonstrated, the frequent appearance of the latter body in the urine.

It is evident that laurel camphor ($C_{10}H_{16}O$), borneol ($C_{10}H_{18}O$) and menthol ($C_{10}H_{20}O$) form a group of substances very closely allied to each other in physiological action. To these may be added monobromide of camphor[1] ($C_{10}H_{15}OBr$), a derivative of laurel camphor, the action of which seems to resemble that of borneol more nearly than that of the other two bodies, and there can be no doubt that if other derivatives were investigated they would be found to have somewhat similar actions. They are all closely related to the alcohol group in their physiological effects, menthol approaching the latter most nearly, but as the number of hydrogen atoms diminishes we get an increased tendency to produce convulsions of cerebral origin.

Camphor and the essential oils have long been used therapeutically in conditions of increased spinal excitability, and the results of pharmacological investigation fully confirm their value in such cases.

As cardiac stimulants their modus operandi seems to be closely related to that of alcohol. It is not quite identical, however, as Kobert[2] has shown that ethylic alcohol has practically no effect in dilating peripheral vessels, while we have seen above that borneol and menthol are very powerful in this respect. It must be remembered, however, that we do not use pure alcohol therapeutically, and that the various wines and spirits contain different ethers in sufficient quantity to dilate the blood-vessels and so make up for this deficiency. This being the case, the action of the camphor group and of the ordinary alcoholic stimulants on the circulation is probably identical.

Borneol can be manufactured in large amount from oil of turpentine, but whether it would have any advantages over laurel camphor as a therapeutic agent can only be determined by long clinical experience. It is certainly a less irritating substance locally, and could be given in much larger doses than the latter without causing untoward cerebral symptoms.

In conclusion, my thanks are due to Messrs Clarke, Hill, Holmes Howards and Sons, and Jackson for their kindness in supplying me with material to carry on the investigation.

The blood pressure experiments were made in the laboratory of the Royal College of Physicians, Edinburgh.

[1] Bourneville. *Practitioner*, II. 112, 1874, and Pellacani, *loc. cit.*

[2] *Archiv f. expt. Path.* XXII. 77, 1887.