ALLYL ISOTHIOCYANATE: SOME ASPECTS OF ITS PHYSIOLOGICAL ACTION

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There are but two allyl compounds in general use—the sulphide and the isothiocyanate, and with the latter this communication chiefly deals, the former having already furnished the theme of a previous research.[1]

Allyl isothiocyanate, or oil of mustard, is a well-known rubefacient and counter-irritant when applied to the skin, and in addition is in small doses in constant use internally as a condiment; it appeared, therefore, desirable to ascertain in what directions its action resembled or differed from that of its ally, and with this intent a number of experiments were undertaken upon deeply etherised rabbits, the methods followed being precisely the same as those indicated in the previous paper.

In the first instance one minim (0·66 c.c.) of the pure synthesised drug was injected into the jugular vein of a large animal, with the result that it died in convulsions a few minutes later, thereby demonstrating how much more deadly the isothiocyanate is than the sulphide, and the necessity of finding some bland menstruum which would mix with it in all proportions and form a solution of constant and uniform strength throughout. Olive oil proved to be the most suitable vehicle for the purpose, because when injected in small quantity into a vein it exhibits no physiological action either on the heart, blood pressure or respiration, which were the main effects to be attended to in the present research.

Ten per cent. and 20 per cent. solutions of oil of mustard in olive oil were accordingly prepared. For the purposes of this report it will be sufficient to give in detail the stages in one typical case and to comment upon others as occasion arises.

In a rabbit weighing 2,200 grammes, and deeply anaesthetised, 1½ minims (0·09 c.c.) of a 20 per cent. solution of allyl isothiocyanate in olive oil were injected into the jugular vein in six seconds, the initial pressure in whose carotid artery was 72 mm. Hg, with the result that the pressure began to rise slightly at first, reaching 73 mm. in seven seconds;

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this is immediately followed by a rapid fall, reaching its lowest point at 28 mm., twenty-seven seconds after the commencement of the injection; a slow rise in pressure follows to 45 mm., which was reached at the sixty-seventh second, to be followed by a gradual fall to 39 mm. at the 127th second, when it again began to rise very slowly, only reaching 70 mm. at the 387th second, after which it again sank almost imperceptibly to 53 mm. at the 950th second, at which moment the record ceases. (Fig. 1.)

Allyl isothiocyanate, therefore, exerts its maximum depressor effect almost immediately after administration, followed by rapid partial recovery; this is succeeded in turn by another fall of blood pressure of less intensity but of longer duration, and, like its predecessor, followed by a slower rise, but only to fall again, and so on. If sufficient time is given for the drug to be eliminated, chiefly by the lungs, these pressure waves die out and the normal blood pressure is restored.

This drug, like its congener, has a powerful effect upon the respiratory system, which lasts for a considerable time, but the disturbance caused by it is more rapidly recovered from than that produced in the blood pressure.

At first the respiratory movements are diminished in number and in amplitude, but is soon followed by increased frequence, with further diminution, the animal's chest becoming inflated owing to the inspiratory efforts greatly exceeding the expiratory, all the extraordinary inspiratory muscles being brought into play; the tracing, therefore, sinks rapidly and somewhat suddenly at the twelfth second after the commencement of the injection. Soon the respiratory efforts, though still rapid, increase in amplitude, becoming now and again convulsive, despite which they show a tendency towards recovery from the fifty-seventh second, which practically corresponds to the time at which the carotid curve is nearing its first pressure maximum. Thereafter the movements become less extensive and less frequent and finally attain their normal rate and magnitude about the 800th second after injection.

Allyl isothiocyanate, like allyl sulphide, produces a certain measure of immunity in the animal after it has recovered from a first dose, and therefore 3 minims (0·18 c.c.) of the same solution was administered in seven seconds by injection into the jugular vein of the same animal after it had completely recovered from the effects of the first, i.e., after half-an-hour, complete anaesthesia beng maintained during the whole time.

The carotid pressure at the moment of injection was 78 mm. Hg, but before the injection was over a slight fall in the tracing was observed, which was followed at the thirteenth second by a more rapid fall that

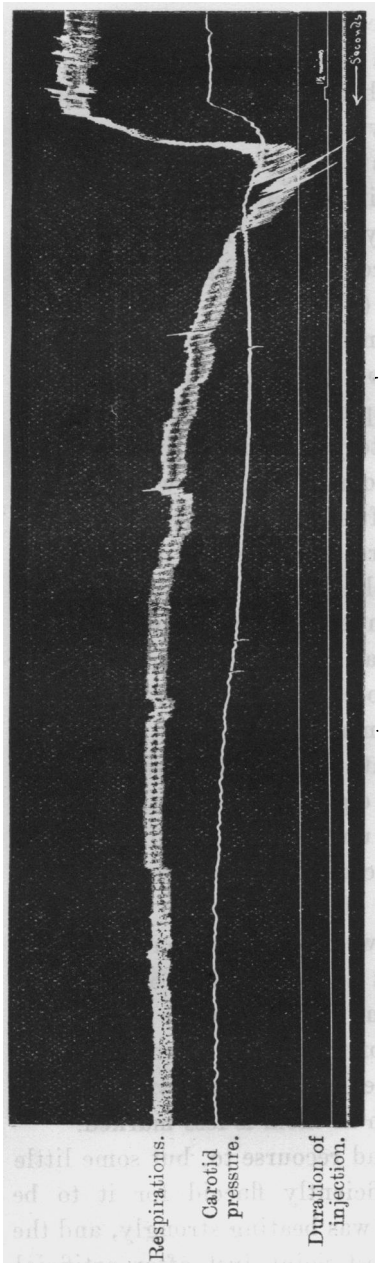

FIG. 1. Effects of injection into the jugular vein of 1·5 minims (0·09 c.c.) of a 20 % solution of allyl isothiocyanate in olive oil.

FIG. 2. Effects of injection into the jugular vein of a rabbit of 3 minims (0·18 c.c.) of a 20 % solution of allyl isothiocyanate in olive oil.

reached a minimum of 55 mm. Hg at the twenty-sixth second. From that moment a rapid rise commenced, crossing the normal line at the thirty-fifth second, and continuing in a series of humped curves to a maximum of 98 mm. at the seventy-second second, thereby attaining a height of 20 mm. above the normal. (Such a rise never occurs with a first dose.) This rise is followed by a very slow fall to 92 mm. at the 290th second, at which point there was a marked change in the respiration, accompanied by an abrupt fall in pressure to 83 mm. With the exception of a slight rise followed by a slight fall, the pressure gradually sank to 82 mm. at the 800th second, reaching the normal as the effects of the drug slowly passed away. (Fig. 2.)

With this dose, which would have been fatal to a fresh rabbit, the breathing became quicker and shorter from the moment the carotid pressure commenced to fall, the chest very rapidly became inflated and the tracing falling almost suddenly, the respiratory movements increasing in amplitude, despite their rapidity, as the bottom of the curve was reached; the tracing then rose somewhat, but at the fiftieth second spasms moderate in force and duration supervened, and were succeeded by a few small respiratory efforts that quickly grew in amplitude, the respiration finally settling down to a steady and regular rhythm, about three times less rapid than before the injection, passing into normal about the 320th second.

The animal having again recovered, a dose of 6 minims (0·36 c.c.) was administered in ten seconds in the same manner as before. This produced a fall of 7 mm. in the pressure curve in twenty seconds, followed by a rise to 16 mm. above the initial pressure some eighty-five seconds after the injection, from which point it began to sink until the animal died.

On the respiratory mechanism it produced first a quickening of the breathing with diminished amplitude, and at the twentieth second the usual sudden fall in the trace occurred followed by convulsions, in which the whole body participated. Tremors first appear in the abdomen and thorax, then in the hind limbs, which become rigid, with the toes widely separated and fully extended; the muscles of the spinal column are next attacked and lift the animal quite off the table in rigid opisthotinos, finally the fore limbs become affected, but the spasm in them is less marked.

At this stage artificial respiration was had recourse to, but some little time elapsed before the chest became sufficiently flaccid for it to be effective. During the whole spasm the heart was beating strongly, and the blood pressure kept up, reaching its highest point just after artificial respiration became effective, at which time the spasm also began to subside

in the hind limbs, though it continued in the paws and passed to the head and neck, producing convulsive movements of the jaw muscles and wheel-like movements of the eyeballs.

The animal was now killed by stopping the respiratory pump and opening the thorax, having been kept in the deepest anaesthesia during the whole course of the experiment.

The heart when exposed was beating well, the drug apparently in no way affected its muscle fibres, though this large dose of the drug produced violent and convulsive contractions of the skeletal muscles, the extensors being chiefly affected by it.

Allyl isothiocyanate is, therefore, a much more powerful poison than allyl sulphide. It attacks the respiratory system more powerfully than the vaso-motor, though its effects pass off more quickly from the former than from the latter. Poisonous doses kill by paralysing the respiratory centre, as with allyl sulphide. The expiratory centre seems more affected than the inspiratory, resulting in considerable chest inflation.

A tolerance is set up for the drug on the administration of repeated doses of the same strength, so that a stronger dose has to be given each time to produce an equal effect. By the first dose the vaso-motor centre is depressed and recovers but slowly, but from subsequent doses it not only recovers more quickly, but is less affected and becomes stimulated, so that the blood pressure rises high above the normal. This may be due partly to the muscular tremors that invariably occur with moderate doses, causing a more rapid return of the blood from the compressed veins towards the heart, but that is not the only cause, for considerable rises in pressure can be obtained by administering repeated small doses that do not produce visible tremors. With small doses the depressor effect alone is marked, with larger ones a pressor effect is subsequently developed, and with large, i.e., fatal doses, a pressor effect alone may be registered. The vaso-motor centre seems more sensitive than the respiratory centre to small doses, though with medium and large doses the reverse is the rule. (Fig. 3.)

With a small dose the respirations may be only quickened and somewhat reduced in excursion without any chest inflation, which is such a constant occurrence with medium ones.

The minimum fatal dose was not accurately determined, but it approximates to 1 minim (0·06 c.c.) of a 20 per cent. solution per kilo. of body weight, i.e., one-fifth minim (0·012 c.c.) of normal oil, and therefore this drug is two and a half times more fatal than allyl sulphide.

Even with fatal doses, if the animal be kept alive by artificial respiration, the vaso-motor system remains efficient, because every

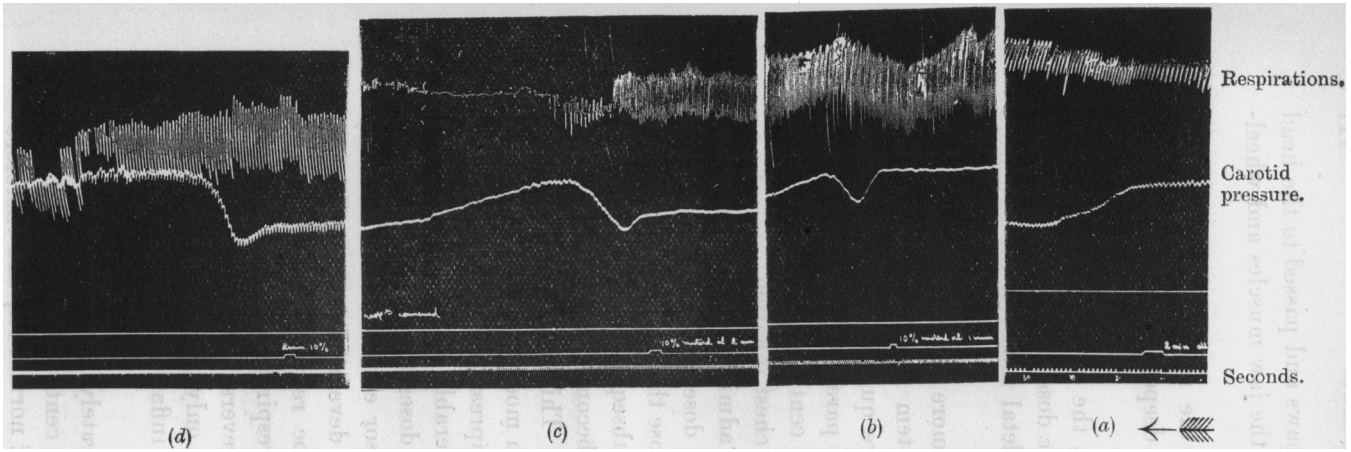

FIG. 3. Showing the effect of repeated small doses of 10 % allyl isothiocyanate on the carotid pressure of the same animal.

(*a*) Depressor effect alone marked.
(*b*) Depressor and pressor effects about equal.
(*c*) Depressor effect far surpassed by subsequent pressor effect.
(*d*) Depressor effect slight, with subsequent great and sustained pressor effect.

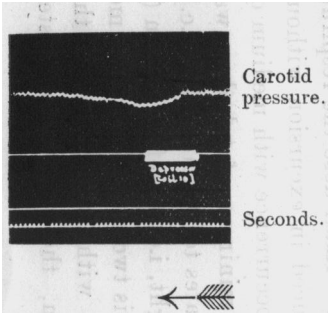

FIG. 4. Effect on the carotid pressure of stimulating the depressor nerve in a rabbit that has been injected with a strong dose of allyl isothiocyanate.

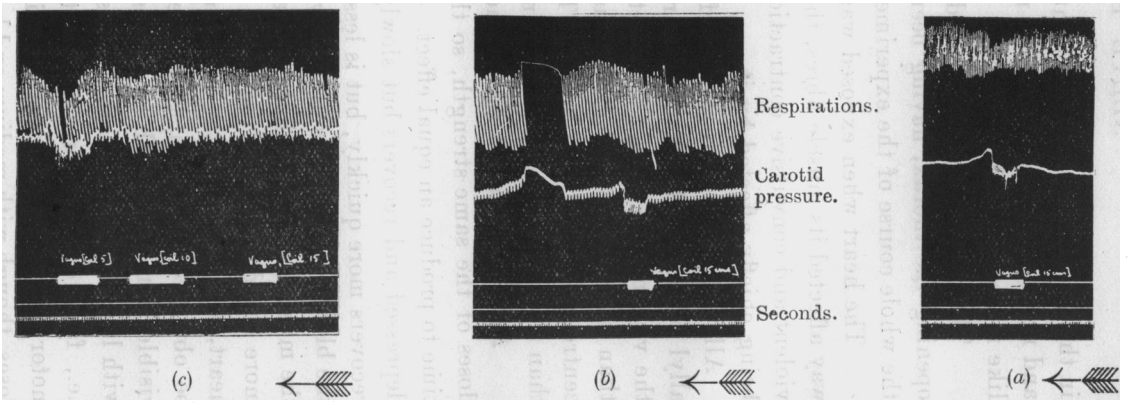

FIG. 5. Effect on the carotid pressure of stimulation of the peripheral end of the divided vagus, as the dose of the drug is increased.

(*a*) 1 mm. = 0·06 c.c. 10 % allyl isothiocyanate.
(*b*) 3 mm. = 0·18 c.c. 10 % allyl isothiocyanate.
(*c*) 7 mm. = 0·42 c.c. 10 % allyl isothiocyanate.

cessation of the ventilation is followed immediately by a rise in blood pressure, which passes off immediately the air-pump is restarted, and because when the depressor nerve was stimulated electrically in the only case in which its efficiency was tested, there was a slow fall of pressure succeeded by a slow rise after cessation of its excitation. (Fig. 4.)

With the vagus nerve things are different, it loses its efficiency upon the heart as the strength of the dose increases, failing to reduce the blood pressure, though it can still impede the heart beat to some extent; in this the action of the isothiocyanate closely resembles that of allyl sulphide. (Fig. 5.)

On skeletal muscles the drug acts powerfully, producing spasm, the extensor groups being more affected than the flexor. Its action in small doses on cardiac muscles is slight and of short duration; beginning early, it passes off in about 150 seconds and amounts to no more than a slight decrease in the rate of the heart beats, with lengthening of the systole.

With the frog's heart phenomena occasionally seen with allyl sulphide are well marked with the isothiocyanate, more especially so with winter frogs. In all cases pithed and decerebrated frogs were used, and the records obtained by placing the frog on a Pembry myograph, exposing the heart, inserting a hook in the apex of the ventricle, from which a thread passed to the lever of the apparatus. The drug, either pure or diluted with olive oil, was passed directly into an auricle by means of a hypodermic syringe.

A dose of 1 minim (0·06 c.c.) of the pure drug stops the heart at once, but a dose of half that quantity only takes effect after thirty seconds, the ventricle muscle passing into delirium before finally ceasing to beat. The auricles, however, continued to beat synchronously, though jerkily, for a considerable time longer.

One minim (0·06 c.c.) of a 33 per cent. solution produces some diminution both in amplitude and rate, followed suddenly some sixty seconds later by a marked change in speed with increase of amplitude, which gradually declines as the speed again increases for a while This is followed by marked slowing just before the sudden arrest of ventricle comes on, some 280 seconds after the injection. The auricles beat normally throughout, and continue so doing for another seventy seconds at least, after which their speed very gradually diminishes. Though arrested, the ventricle is not permanently stopped but resumes beating again with occasional stops, that become shorter as time wears on, until, by the end of fifteen minutes, the whole heart so far recovers as to beat quite rhythmically though slowly and with diminished force.

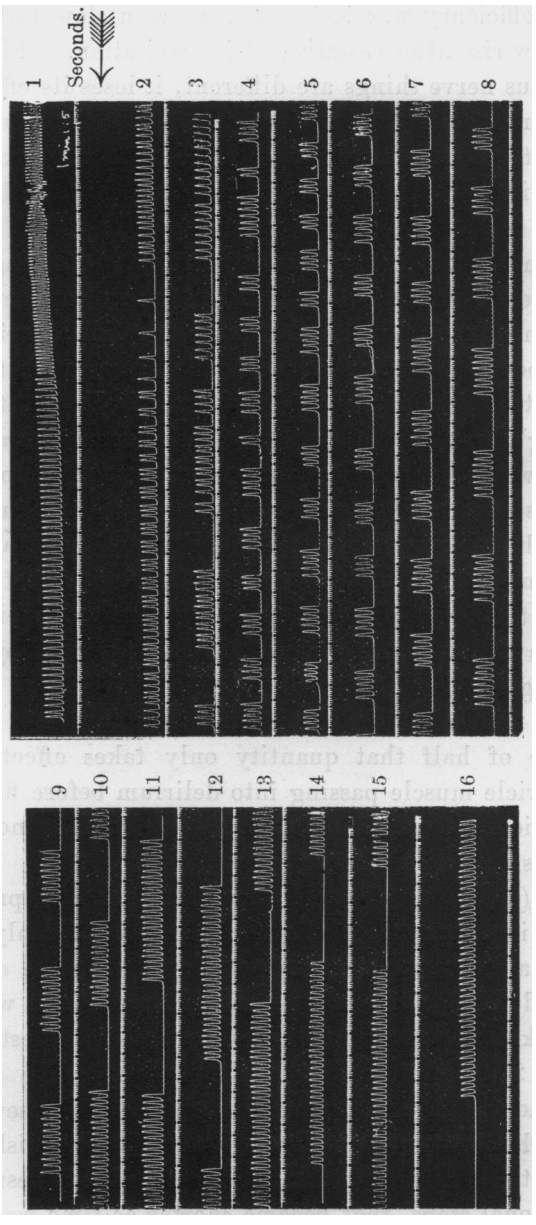

FIG. 6. Showing the effect produced upon the frog's heart by injection into one auricle of 1 minim = 0·06 c.c. of a 20 % allyl isothiocyanate solution. The phenomenon of heart block is clearly shown, and also the relative durations of the periods showing blocking and those free from it.

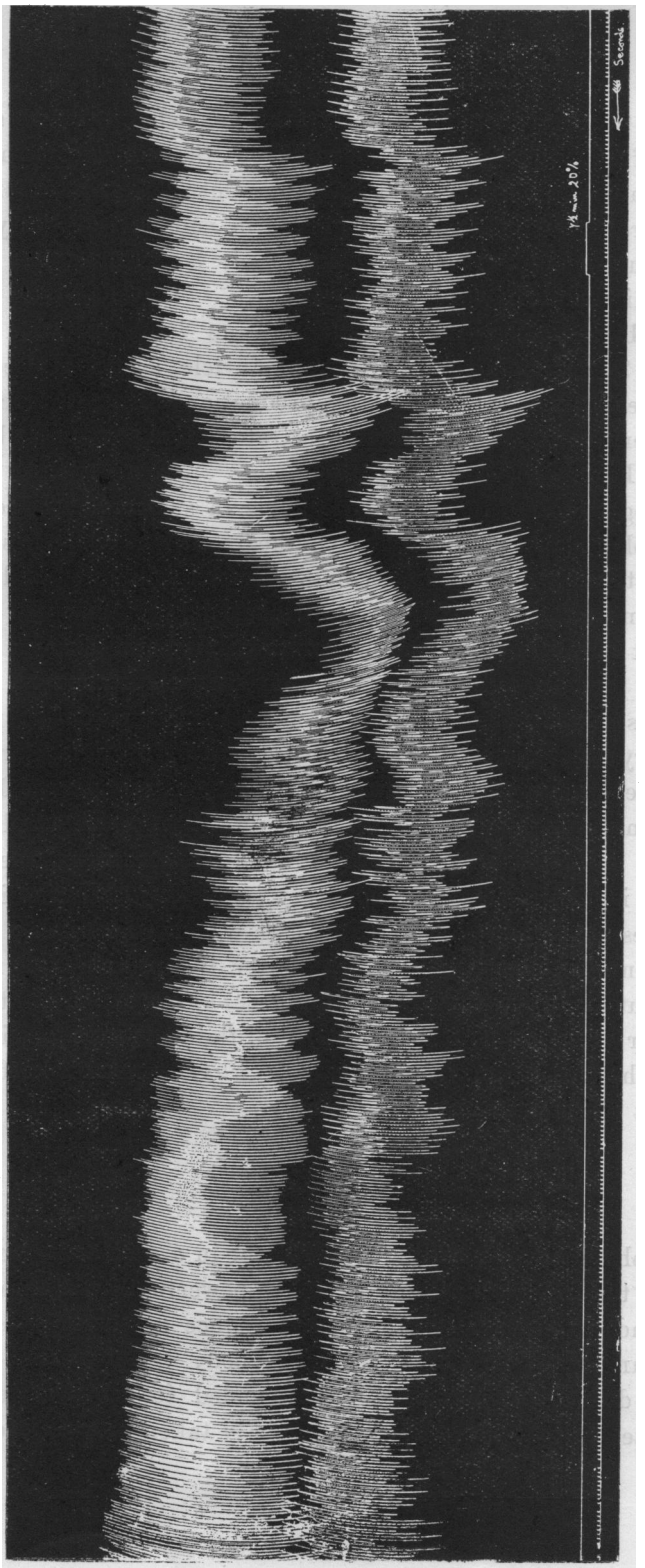

FIG. 7. Showing the effect upon the heart of the injection of 7½ minims (0·45 c.c.) of a 20 % solution of allyl isothiocyanate into the jugular vein of a rabbit, artificial respiration being maintained throughout the experiment. Levers—writing over pulleys—were attached by hooks: the upper in the auricle, and the lower in the ventricle muscle.

With this dose the results naturally vary somewhat with the size and vigour of the frog used; with small weak frogs the heart is permanently arrested, the auricles always outlasting the ventricle for a considerable time; with large and vigorous frogs partial or complete recovery in the rhythmic sequence is customary; the speed, however, seems always permanently diminished.

I have obtained the best results with an injection of 1 minim (0·06 c.c.) of a 20 per cent. solution into the auricle, as may be seen from the tracing here given, in which the production of heart block, with gradual recovery therefrom, is better illustrated than is possible by mere description. (Fig. 6.)

When frogs, taken fresh from the fields in summer, are treated as above, heart block rarely supervenes, the heart either stopping suddenly as a whole with large doses, or becoming gradually slower and feebler with smaller ones, until it finally ceases to beat altogether.

The effect of the drug upon the mammalian heart may be studied in the rabbit, provided artificial respiration is had recourse to, because the large doses required are very much more than sufficient to paralyse the respiratory mechanism. In all cases the ventricles are more profoundly affected than the auricles; with a dose of $7\frac{1}{2}$ minims (0·45 c.c.) of a 20 per cent. solution injected into the jugular vein the amplitude of the heart beat is first lessened, this is followed by diminished speed with some increase in amplitude, but the heart is finally paralysed in about twenty minutes. (Fig. 7.) Only in one case was some blocking noticed, towards the end of the experiment and after the animal had received several consecutive and increasingly larger doses of the drug. In this case three auricular beats corresponded with one of the ventricles. With these large doses the auricles occasionally fail a few seconds before the ventricles, but this is not the general rule.

Conclusion

Allyl sulphide and allyl isothiocyanate act in a similar manner upon the organism, the latter drug being the more powerful; both paralyse the respiratory and vaso-motor centres, both produce muscular spasms and affect the heart beat, and both lower the body temperature, as most essential oils do. Neither can be recommended for internal administration, despite the fact that they are commonly taken in minute quantity with food.