SOME FURTHER EXPERIMENTS ON THE PHYSIOLOGY OF THE ALLYL COMPOUNDS

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Owing to the difficulty of determining whether the effects of allyl-isothiocyanate upon respiration and blood pressure, previously recorded by me,¹ were due to the allyl or the isothiocyanate moiety of the compound, it appeared advisable to perform similar experiments with at least one other isothiocyanate as well as with various allyl compounds.

With this end in view it was determined to investigate the action of phenyl-isothiocyanate C_6H_5NCS upon deeply-anaesthetised rabbits.

As in the case of the allyl compound, 10 per cent. and 20 per cent. solutions of the substance in olive oil were used, but produced so little effect that in subsequent experiments undiluted phenyl-isothiocyanate was alone employed.

Phenol-isothiocyanate

Only one experiment with this substance needs to be recorded in detail. Fig. 1.

1 minim (0.06 c.c.) of the drug was injected into the jugular vein of a deeply-etherised rabbit, weighing 1950 grams and registering a blood pressure of 75 mm. mercury.

Eleven seconds after the commencement of the injection the blood pressure began to rise, and attained to 82 mm. in 20 seconds; this was followed by a depressor effect to 67 mm. at the 60th second. Seven seconds later it rose again to 70 mm.; this slight recovery was succeeded by a slow fall, which reached as low as 31 mm. at the 480th second, after which a slow rise commenced that had attained to 79 mm. at the 1070th second.

No marked effect upon the respiratory movements was observed until the 63rd second after injection, when a deep gasp occurred followed by respirations rapidly diminishing in amplitude to the 95th second, after

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which they quickly increased, almost but not quite reaching their initial amplitude at the 120th second. At the 170th second a slight decrease set in, followed at the 193rd second by a sudden fall to one-fourth the initial

FIG. 1. The effect of 1 minim (0.06 c.c.) Phenyl-isothiocyanate injected into the Jugular Vein of a Rabbit.

All Figures to be read from right to left.

amplitude accompanied by a slowing of rhythm; from this recovery was slow, reaching only one-third the original size at the 1076th second. A marked feature of this recovery was the occurrence, at fairly regular

intervals, of a gasping inspiration, the first of which took place at the 210th second, the second at the 274th, followed by others at the 340th, 403rd, 471st, 530th, 580th, 636th, 675th, 717th, 753rd, 801st, 836th, 873rd, 910th, 950th, 980th, 1012th, 1047th, . . . second.

Very little change in the force and rate of the heart beat appears in the tracing.

The temperature of the animal, as ascertained by placing the bulb of a thermometer in the vagina from the 210th to the 274th second, was 35° C.

Some time later, when the respiratory movements had become equal to half their initial size, another minim (0.06 c.c.) was injected into the vein, with similar though less-marked results, except for respiratory gasps which were repeated every twenty to thirty seconds. The animal was killed twenty-two minutes after the second injection.

In other experiments 2 minims (0.132 c.c.) and 3 minims (0.198 c.c.) doses were injected into the jugular vein, and produced similar results on the pressure, but caused more marked and more lasting respiratory spasms. The 3 minims (0.198 c.c.) dose proved fatal in 190 seconds, at which moment the blood pressure fell to zero, the heart having ceased beating ten seconds earlier. Nevertheless the respiratory movements continued, increasing in amplitude and rate till the 240th second when they suddenly failed. The heart, therefore, stopped quite fifty seconds sooner than the respiration.

Post mortem examination showed that intra-vascular clotting had taken place.

Effect of small doses.— $\frac{1}{10}$ minim (0.006 c.c.) in olive oil when injected into the circulation produces a temporary slight fall in the blood pressure. $\frac{1}{5}$ minim (0.012 c.c.) dose causes an initial slight rise followed by a fall, which is still more marked by a $\frac{1}{2}$ minim (0.03 c.c.) dose.

To affect the respiration a 1 minim (0.06 c.c.) dose is necessary, and a dose of $1\frac{1}{2}$ minims (0.09 c.c.) to alter the heart beat. Three minims (0.198 c.c.) may be taken as a fatal dose for a full sized rabbit weighing 2200 grams. This is approximately $1\frac{1}{2}$ minims (0.09 c.c.) per kilogram of body weight.

Phenyl-isothiocyanate, though a poison, is much less fatal than allyl-isothiocyanate, the lethal dose of which is $\frac{1}{5}$ minim (0.012 c.c.) per kilogram of body weight.

The phenyl compound acts upon the circulatory system more powerfully than upon the respiratory; probably, therefore, the very

poisonous action of allyl-isothiocyanate upon the respiratory centre is due to the allyl moiety; its action on the circulation may or may not be due in some measure to the isothiocyanate moiety.

Two substances analogous to allyl sulphide were experimented with: ethyl sulphide and ethyl hydrogen sulphide. Ethyl sulphide ($C_2H_5)_2S$ differs from allyl sulphide ($C_3H_5)_2S$ only in containing two atoms of carbon less in its molecule. Ethyl hydrogen sulphide or mercaptan is C_2H_5HS .

Ethyl Sulphide ($C_2H_5)_2S$

Ethyl sulphide in saturated solution has but slight effect upon the frog's heart.

Five minims (0.33 c.c.) injected into the ventricle of a pithed frog diminished the force of the heart to half the normal for a beat or two only, the heart completely recovering from this dose in five beats. A similar dose injected into the right auricle produced no alteration in the heart's action. A 10 minim (0.66 c.c.) dose, slowly injected into the ventricle produced a more marked effect, arresting its contractions for forty seconds, after which the ventricle began to beat again, feebly and slowly at first, but rapidly increasing in force and frequency, with very strong contractions at intervals; it regained first its normal rhythm and some time later, at the 390th second, its initial force. The auricles continued beating throughout the experiment, though with diminished rapidity during the ventricular stasis.

Fifteen minims (0.99 c.c.) injected into the ventricle produced a similar change in the heart's action lasting 410 seconds, but its effect was rather one of duration than of amount.

Owing to the feeble action of this drug on the frog's heart no experiments upon rabbits were made with it.

Ethyl mercaptan, C_2H_5HS

Two minims (0.12 c.c.) injected into the right auricle of a pithed frog resulted at once in the loss of one heart beat, followed by considerable increase in the force of the contractions for eleven beats. This was followed by a sudden diminution in force lasting for twelve beats, from which it returned again to normal eleven beats later. The effect of the dose lasted in all through thirty-five heart beats, occupying seventy-four seconds. The injection of 2 minims (0.12 c.c.) (Fig. 2a)

into the ventricle immediately produced a diminution in the rate and force of its contractions, which gradually became smaller during twenty-four beats. Recovery began at the 39th beat and was achieved at the 74th. From the moment of injection to the completion of recovery 125 seconds had elapsed. At no time was there complete cessation of either auricular or ventricular movement and the diminution in rate was trivial and transitory, the beats succeeding each other more rapidly as the heart's contractions diminished.

FIG. 2a. Injection of 2 minims (0.12 c.c.) Ethyl mercaptan into Frog's Ventricle.

An injection into the ventricle of 3 minims (0.18 c.c.) (Fig. 2b) resulted in a gradual diminution of the heart beat, until the auricles alone remained in action. Complete recovery eventually occurred, but not until the 789th second after injection.

Five minims (0.30 c.c.) introduced into the ventricle stopped that chamber in sixteen beats, but succeeded only in slowing the auricular rhythm. After a time the ventricle started to beat again, and quickly not only regained but surpassed its normal force, but with much slower rhythm.

When 10 minims (0.60 c.c.) were slowly injected into the ventricle, spasms of the skeletal muscles occurred with arrest of the heart for thirty-six seconds, both auricles and ventricle ceasing to beat. At the 36th second a feeble contraction took place, followed at intervals by several stronger ones, then, after a pause, a number of rapid beats were registered in succession, followed by a pause of a few seconds' duration; after which the heart rapidly recovered its strength but not its speed, which remained diminished as long as the experiment lasted.

These experiments prove that in the frog ethyl mercaptan acts more powerfully upon the ventricle than upon the auricles; that in some cases it can produce heart block, but the dose required to effect this is large

and the duration of the blocking short. Small doses accelerate the rhythm to some extent, whilst large doses retard it for a considerable time. In no case was the dose administered sufficiently large to permanently arrest the heart.

FIG. 2*b*. Injection of 3 minims (0.18 c.c.) Ethyl mercaptan into Frog's Ventricle.

Read from right to left.

A number of experiments with ethyl mercaptan were performed on deeply etherised rabbits; the solutions used varying in strength in different cases. As with allyl sulphide the best diluent was found to be olive oil.

The injection of 5 minims (0.30 c.c.) of a 20 per cent. solution into the jugular vein of a large rabbit weighing 2250 grams produced a slight fall in blood pressure, followed 40 seconds later by a slight rise above the normal. The highest pressure was recorded 130 seconds later, and was maintained for 90 seconds; then a gradual fall set in which reached the normal in 260 seconds.

An injection of 15 minims (0.90 c.c.) of the same solution was then made, producing a sudden rise followed by a continuous slow rise lasting 310 seconds.

When 20 minims (1.20 c.c.) of a 20 per cent. solution were introduced into the jugular vein a slight fall from 86 to 81 mm. mercury at once occurred, followed by a rapid rise to 93 mm. in 25 seconds. Then there was a sudden fall to 85 mm. in 2 seconds, after which a gradual rise to 89.2 mm. set in and occupied 163 seconds. At this moment the pressure suddenly fell to 89 mm. and continued to fall slowly to normal, which was reached in 135 seconds.

These small doses produced no visible alteration either in the heart beats or in the respiratory movements.

One minim (0.06 c.c.) of undiluted mercaptan introduced into the jugular vein of a rabbit (Fig. 3) produced, 10 seconds after its injection, a rapid fall in blood pressure from 79 mm. mercury to 74 mm. in 13 seconds, succeeded by a further fall to 50 mm. in the next 29 seconds. Thereafter the pressure began to rise and attained to 76 mm. 423 seconds after injection. Coincident with the beginning of the pressure fall a great respiratory effort was made, followed by increased respiration, lasting 60 seconds. The amplitude of these movements then began to diminish, but at the 130th second another deep breath occurred, followed by increased breathing, which continued so to the end of the experiment. At the 310th second a very deep inspiration was registered, after which slight Traube-Herring curves appeared in the pressure trace.

At the time of the pressure fall, the heart became weakened without change of rhythm, and remained affected for some time though it completely recovered its strength towards the close of the experiment.

The injection into the jugular vein of a rabbit of 3 minims (0.18 c.c.) of undiluted drug caused at the end of 10 seconds a deep inspiration, and at the end of 29 seconds a rapid fall in blood pressure. The pressure fell from 69 mm. mercury to 48 mm. in 22 seconds, followed by a sudden drop to 28 mm. in 1 second. At the 80th second recovery began, but after reaching 38 mm. at the 103rd second began again to fall rapidly. At the 150th second the pressure was only 10 mm., and at the 293rd it had died out altogether.

The respiratory mechanism was much affected by this dose. The deep inspiration at the 10th second was followed by normal breathing until the 40th second, when suddenly the movements trebled in size for four seconds, after which they grew rapidly more and more shallow,

without alteration in speed, until the 70th second. After that their frequency as well as their force became less, until they failed entirely at

FIG. 3. 1 minim Ethyl mercaptan injected into the Jugular Vein of a Rabbit.

the 124th second. Artificial respiration proved of no avail, though it was continued to the end of the experiment.

The force of the heart began to diminish at the same time as the blood pressure began to fall and the heart almost stopped when the sudden fall in pressure was registered; it, however, recovered for a time, but again became feeble just before the respiration ceased. Thereafter the beats were minute, and the heart finally stopped at the 293rd second after the injection.

Three minims (0.18 c.c.) of ethyl mercaptan introduced into the circulation of a rabbit appears to cause death by respiratory paralysis, whether it is administered in one dose or injected in two doses with a short interval between.

The fatal dose for the rabbit works out approximately at $1\frac{1}{4}$ minims (0.075 c.c.) per kilogram of body weight.

Injection into Serous Cavities

Three minims (0.18 c.c.) of ethyl mercaptan were injected into the pericardial cavity of a deeply-etherised rabbit weighing 2800 grams. Its blood pressure, which registered 98 mm. mercury, rose in 260 seconds to 126 mm., at which it was maintained for 90 seconds, then muscular tremors set in, producing a slight fall, but when they ceased the pressure increased to 146 mm. This high pressure was not long maintained, but was followed by a fall, rapid at first, then gradually becoming slower, it reached to 124 mm. Next a gradual rise set in to 138 mm., followed by a slower fall to 108 mm.

In this experiment the respirations increased in amplitude somewhat, especially just after the muscular tremors ceased, but returned again to their initial size long before the blood pressure had fallen to 108 mm. The heart's action was not appreciably affected.

When the blood pressure had remained stationary at 108 mm. for some time, 1 minim (0.06 c.c.) of allyl sulphide was introduced into the pericardial sac, with the result that in 13 seconds the blood pressure began to fall and reached 96 mm. in 17 seconds. Fifty-five seconds later it had again returned to 108 mm.

No change was observed in either respiratory or cardiac movement.

Two minims (0.18 c.c.) of allyl sulphide were now slowly injected into the pericardial cavity (Fig. 4) and produced considerable variation in blood pressure, due no doubt to the fluid pressing on the heart. Ten seconds after the injection a rapid fall in pressure occurred to 84 mm. succeeded by a slower fall to 44 mm., which was reached at the 35th second and at which it remained until the 50th second. A slight pressor

FIG. 4. 2 minims (0.12 c.c.) of Allyl Sulphide injected into the Pericardial Cavity of a Rabbit.

effect then set in which reached 50 mm. at the 70th second, followed by a depressor movement which ended at 0 mm. at the 420th second. The respiratory mechanism was at first somewhat depressed, and from the 31st second began to fail rapidly. At the 51st second hyperpnoea supervened and lasted thirty seconds, after which respiratory movements became gradually feebler and failed altogether at the 270th second, thus failing much sooner than the heart. This is a typical action of allyl sulphide.

One minim (0.06 c.c.) of ethyl mercaptan was injected into the pericardial cavity of a deeply-etherised rabbit weighing 1850 grams. The initial blood pressure was 85 mm. mercury. Eight seconds after injection the pressure began to fall, reaching 56 mm. at the 24th second, a rise then began and reached 68 mm. at the 77th second. This was succeeded by another fall which attained to 63 mm. at the 107th second, at which level it remained until the 217th second, when a new pressor movement set in and reached 78 mm. by the 517th second.

Respiratory movements were but slightly diminished in amplitude, without change of rhythm, and the heart remained quite unaffected by this dose.

Two more minims (0.18 c.c.) were then slowly introduced into the pericardium. Nine seconds later the blood pressure began slowly to fall and reached 60 mm. in 175 seconds, this was followed by a gradual rise to 68 mm., which was reached 150 seconds later. At this time the respiratory movements were becoming weaker though the heart was beating normally. Four minims (0.24 c.c.) were now slowly injected into the pericardial sac and produced no effect for 126 seconds, when respiratory spasms occurred and lasted 20 seconds. They produced a slight rise in blood pressure, but it returned again almost immediately to 68 mm. The animal was then killed.

Allyl Acetate

One minim (0.06 c.c.) (Fig. 5) of allyl acetate was injected into the jugular vein of a deeply-etherised rabbit weighing 2300 grams. Ten seconds after injection the blood pressure began to fall from 98 mm. to 70 mm. in 16 seconds. The pressure then began to rise again, slowly at first, then more rapidly and attained to 100 mm. at the 51st second. A U-shaped depression was thus produced in the pressure trace. This dose produced considerable alteration in the respiratory movements, reducing their amplitude by one-third in the first twelve seconds. Slight

FIG. 5. 1 minim (0.06 c.c.) Allyl Acetate injected into the Jugular Vein of a Rabbit.

FIG. 6. 2 minims (0.12 c.c.) Allyl Acetate injected into the Jugular Vein of a Rabbit.

recovery then set in, but at the 19th second they again became smaller and remained so to the 58th second; from this moment the movements increased until they finally slightly surpassed their initial size. At the 88th second a deep inspiration was recorded. During the whole experiment no change in the respiratory rhythm or alteration in the cardiac movements occurred.

Two minims (0.18 c.c.) (Fig. 6) were next injected into the vein, producing similar results, beginning from the 8th second and being more intense and prolonged than with the previous dose. Another 2 minims (0.18 c.c.) were introduced into the vein, with the result that the blood pressure began to fall from the 8th second, but did not fall so low as on the previous occasion, and on again rising did not attain a higher level than 93 mm., at which it remained to the end of the experiment.

These results show that allyl acetate is very feeble when compared with allyl sulphide, but that its action is similar in that it affects the respiratory mechanism first, leaving the heart practically unaffected by the small doses exhibited. No doubt larger doses would have altered the cardiac action also, but the supply of the drug failed.

The lethal dose of allyl acetate was not determined.

Allyl Alcohol, C_3H_5OH

To ascertain the action of this substance upon the vascular and respiratory mechanisms it was deemed advisable to dilute it, otherwise intravascular clotting was to be feared soon after its introduction into the circulation. One minim (0.06 c.c.) of a ten per cent. solution in normal saline was injected into the jugular vein of a deeply-etherised rabbit weighing 2750 grams, with the result that the blood pressure fell from 105 mm. mercury to 96 mm. in 79 seconds. The heart beat and respiration remained unchanged, and therefore 4 minims (0.24 c.c.) of the same solution were introduced, which sent the blood pressure up to 98 mm. in 31 seconds. A fall to 90 mm. at the 42nd second followed and was succeeded by a rise that attained to 97 mm. at the 66th second. This was not maintained, the pressure falling to 90 mm. at the 82nd second, after which it again started to rise. This alternate rise and fall of the pressure continued until the 222nd second, when another injection was made. During the whole of this time the heart beats and respiratory movements remained unaltered.

Five minims (0.30 c.c.) were introduced, as just stated, at the 222nd second, and produced a fall of pressure to 87 mm. 19 seconds later,

followed by a steady rise to 108 mm., which was reached in another 131 seconds. As before, the respiration remained unaffected, but the force of the heart was increased by one-half, without alteration in rhythm. The introduction of another 5 minims (0.30 c.c.) produced a similar result.

When this dose was doubled the blood pressure rose to 122 mm. in 190 seconds, but the respiratory and cardiac mechanisms were not further altered by it.

Three minims (0.18 c.c.) of undiluted allyl alcohol were next injected into the vein, with the result that the blood pressure fell to 79 mm. in three seconds, and was followed by a rise to 84 mm. at the 21st second. Then another fall began, reaching 69 mm. at the 32nd second followed by a second rise to 88 mm. at the 47th second. Thereafter a slower fall commenced, reaching as low as 65 mm. by the 93rd second and remained at that level until a new injection was attempted at the 300th second, which was found impossible owing to a long clot extending from the syringe to the thoracic veins. The only effect produced by this dose upon the respiration was to cause two deep inspiratory movements, but the force of the heart beat was increased by half its initial amount, its rhythm remaining the same.

Forty minims (2.4 c.c.) of a twenty per cent. solution in normal saline, equivalent to 8 minims (0.48 c.c.) pure allyl alcohol (Fig. 7), were introduced into the jugular vein of a deeply-etherised rabbit weighing 2270 grams, the injection taking 86 seconds.

From the very commencement of the injection the blood pressure began to rise from 108 mm., and reached 116 mm. in 11 seconds; then it began to fall more gradually to 100 mm., taking 14 seconds to reach that point, only to again rise gradually to 110 at the 51st second; followed by another fall to 98 mm. at the 66th second. Again it rose to 108 mm. at the 174 second only to fall to 46 mm. at the 1100th second. This was followed by a rise to 66 mm. at the 1900th second, when suddenly violent convulsions occurred that put a stop to further experiments.

This dose had an effect upon the respiration, causing at first a temporary decrease in the amplitude of the respiratory movements, followed by an increase with sundry fluctuations until the movements had nearly doubled at the onset of the convulsions. A marked feature of its action was the occurrence of a number of sudden very deep inspirations, beginning at the 258th second and recurring at intervals of about 70 seconds until the end of the experiment. The heart was but little affected.

FIG. 7. 40 minims (2.4 c.c.) of a 20 % solution of Allyl Alcohol in normal Saline injected into the Jugular Vein of a Rabbit.

In the rabbit, therefore, allyl alcohol acts chiefly upon the blood pressure, but in large doses affects the respiration also, resembling phenyl-isothiocyanate in producing deep inspirations at intervals. Its effect upon the heart is slight, merely increasing its force.

The lethal dose was not ascertained.

Though allyl alcohol appears to have little action on the mammalian heart when injected into the circulation, the case is very different when it is applied directly to the amphibian heart, as will be apparent from the following experiments:—

A drop of pure allyl alcohol allowed to fall upon the surface of the ventricle of a pithed frog at once diminished the force of the contraction by one-third. This depressed condition gradually passed off, the beat attaining to three-fourths of its initial amplitude in 140 seconds.

Two drops allowed to fall on the ventricle diminished the heart beats by one-half; from which they recovered somewhat, but attained only two-third their original amplitude in 230 seconds.

One minim (0.06 c.c.) of a twenty per cent. solution in normal saline injected into the left auricle (Fig. 8) produced cessation of the ventricular contraction in 15 seconds, though the auricles continued to beat as before. Ninety seconds later the ventricle started to beat again, but not with normal force; 320 seconds later the beats had regained only three-fourths of their normal size.

When one minim (0.06 c.c.) of the same solution was injected into the cavity of the ventricle (Fig. 9) the whole heart ceased contracting in 10 seconds and remained motionless for 120 seconds. The auricles then resumed beating, feebly at first, but gaining in strength they continued to contract for 750 seconds, their contractions succeeding each other more slowly than before the injection. The ventricle never contracted again.

From a number of such experiments performed upon large healthy frogs it may be concluded that allyl alcohol does act upon the heart, both auricles and ventricles being affected by it; but its action is much more profound upon the latter chamber than upon the auricles.

Some experiments, by way of contrast, were performed upon the hearts of pithed frogs with ethyl alcohol (C_2H_5OH) with the object of ascertaining whether or no the results obtained with alcohol were due to dehydration or to coagulation of the muscular substance.

One minim (0.06 c.c.) ethyl alcohol placed on the surface of the ventricle, at once brought the heart to a standstill, but this lasted only ten seconds, after which the whole heart started beating again with normal force and rhythm.

FIG. 8. One minim (0.06 c.c.) of a 2 % solution of Allyl Alcohol in Normal Saline injected into Frog's Auricle.

FIG. 9. One minim (0.06 c.c.) of a 20 % solution of Allyl Alcohol injected into Frog's Ventricle.

FIG. 10. 3 minims (0.18 c.c.) of a 20 % solution of Ethyl Alcohol injected into Frog's Ventricle.

A single drop placed on the auricles caused the heart to stop at once for 17 seconds, then, after slowly contracting twice, it resumed its normal beat.

In both cases the effect was suddenly produced and as suddenly recovered from.

Three minims (0.18 c.c.) of a twenty per cent. solution in normal saline injected into the ventricle (Fig. 10) stopped the heart in diastole for 120 seconds, the auricles then resumed their beating, somewhat feebly at first, but steadily gaining in strength. The ventricle resumed beating 140 seconds later, at first feebly with numerous interruptions, but gradually increasing in strength, the beats had attained to one-half their original amplitude when a second injection was made. This only increased the duration of the period of rest and delayed recovery.

This is again an example of the lethal effect of allyl as compared with ordinary alcohol. One minim (0.06 c.c.) of a twenty per cent. solution of the former was sufficient to permanently arrest the ventricle whilst 3 minims (0.18 c.c.) of the same strength of ethyl alcohol did not prove fatal to the heart's action. Both alcohols have this in common, that they affect the ventricle more profoundly than the auricles.

CONCLUSION

From all these experiments it may, I think, be concluded that the poisonous action of the allyl compounds is due to the allyl they contain, though in some cases, no doubt, its activity may be increased, and in others diminished by the substances with which it happens to be combined.

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