ALLYL SULPHIDE: SOME ASPECTS OF ITS PHYSIOLOGICAL ACTION WITH AN ANALYSIS OF THE COMMON LEEK (*ALLIUM PORRUM*)

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INTRODUCTION

The plants of this family are very widely distributed over the five continents, and distinct races of men in all quarters of the globe have used them largely as condiments without having any knowledge of their close relations. In Spain and Portugal onions are everyday articles of food, and onions, garlic and shallot are extensively used as foods and condiments in Russia, France, and all other European countries. The alliaceous diet of the peninsula was probably acquired from the Northern coast of Africa.

Over the whole of Northern Africa—from the Mediterranean to the Nile—garlic and the onion are highly esteemed as seasoners of the usual food. We are told that ‘Arab, Moorish, and Ethiopian tribes equally delight in them; and this taste is of very remote origin. The Israelites, during their sojourn in the wilderness, murmured, saying, “We remember the cucumbers and the melons, the leeks, the onions, and the garlic.”’

‘Among the ancient Egyptians themselves the onion formed an object of worship: and the modern Egyptians assign it a place in their paradise. To the present day the onion of the Nile borders possesses a peculiar excellence and flavour.’¹

Plants of this class have considerable nutritive value when used as food, but it is to the presence of a volatile oil that they owe their importance as condiments; this oil is allyl sulphide (C_3H_5)₂S, a yellow liquid possessing a characteristic odour of garlic. Com-

1. Johnson and Church, *Chemistry of Common Life*, p. 450.

mercially it is sold as oil of garlic, being prepared by the steam distillation of garlic. In this process 1 oz. of oil is obtained from 30 to 40 lbs. of garlic. Allyl sulphide occurs in variable but small amounts in the following plants:—The common onion (*Allium cepa*), cultivated garlic (*A. sativum*), leek (*A. porrum*), shallot (*A. ascalonicum*), common ramson (*A. ursinum*), chive (*A. schænoprasum*), rocambole (*A. scorodoprasum*), Indian onion (*A. leptophyllum*), *Thlaspi arvense alliaria officinalis* (*A. moly*).

The strength of the flavour depends mainly on the relative amount of oil present. Whether the universal selection of these plants as condiments is due to the physiological effect of the essential oil, or whether they have attracted attention through the psychological effect of their characteristic odour, it is impossible to say.

In the different varieties of mustard seed substances exist which are capable of forming another allyl derivative when under suitable conditions.

These two substances are potassium myronate and a ferment myrosin.¹ When a solution of myrosin or an extract of white mustard is added to an aqueous solution of potassium myronate the latter decomposes into mustard oil (allyl isothiocyanate), acid potassium sulphate and glucose.

Hence myronic acid and its salts are glucosides.

It is impossible to say whether in the alliaceous plants examined the allyl sulphide exists entirely preformed, or whether under appropriate conditions it arises from a glucoside precursor. At all events, the majority of it exists preformed, and if any is formed subsequently the amount is very slight.

On account of the close similarity of these plants, one was taken as a type of chemical composition, viz., the leek. This was used on account of the ease of obtaining it in a fresh condition.

For the investigation of the physiological effect, onions (the strongest procurable), garlic, and allyl sulphide itself were used.

1. *Jour. of Pharm.*, XCVI, 39.

CHEMICAL ANALYSIS

(By C. LOVATT EVANS)

Johnson and Church¹ give as the composition of the onion :—
 Water 91.0, flesh formers 1.5, starch² 4.8, fat 0.2, ash 0.5, other
 substances 2.0 = 100.

Our results with the analysis of leeks according to Dragendorff's
 method³ were as follows :—

Water and volatile oil	...	...	...	...	88.00
Fixed oil (and glucoside ?)	...	...	...	...	0.65
Resinous substance	...	...	...	...	0.48
Organic acids, colours, etc., precipitable by lead acetate	...	...	...	...	1.10
Sugars (and extractives, etc., not precipitated by lead acetate)	...	...	...	...	2.24
Gums and pectous substances soluble in water	...	...	...	...	2.20
Proteins, etc.	...	...	...	...	1.55
Pectous substances soluble in dilute NaOH	...	...	...	...	1.69
Cellulose	...	...	...	...	0.77
Soluble in Br. NH ₄ OH	...	...	...	...	0.46
Soluble Ash (= Cl, SO ₄ and P ₂ O ₅ of K and Na)	...	...	...	...	0.72 (5% Cl)
Insoluble Ash ⁴	...	...	...	...	0.14
					<hr/>
					100.00

Sugars and Gums are the only constituents that call for special
 mention.

A certain amount of a reducing sugar (dextrose) is present
 normally in the plant, but on boiling with water the reducing power
 of the solution is increased considerably. This is due to the fact
 that a gummy substance is hydrolysed by the action of the hot water
 and the acid juice, with the formation of a sugar.

The sugar so produced yields a crystalline osazone (M.P. =
 196° C.).

The gum itself was found to be a reducing one, even after repeated
 precipitation with alcohol and with hydrochloric acid and lead acetate.

1. *Ibid.*, p. 89.

2. This is really 'carbohydrate.'

3. Allen, *Commercial Organic Chemistry*, Vol. I, p. 429.

4. The composition of this ash is as follows :—SiO₂ 55.0, Fe₃(PO₄)₂ and Al₃(PO₄)₂ 13.1, CaO 7.4,
 CO₂ 1.25, SO₃ 2.3

It is readily extracted even from the fresh leek or onion by cold water, and it reduces, even when freed from sugar as above. The gum yields a slightly alkaline solution, which is precipitated as follows :—

Readily precipitated by basic lead acetate, lead acetate and ammonia, baryta water, and alcohol.

Less readily precipitated by lead acetate, lime water, dilute hydrochloric acid, sulphuric and phosphotungstic acids, acetic and tannic acids, acetic acid and potassium ferrocyanide, hydrochloric acid and potassium mercuric iodide, picric acid.

*It also yields the following reactions :—*Xanthoproteic—very slightly ; iodine—a pale brown colour ; strong mineral acids—brown on boiling.

The *Volatile Oil* was allyl sulphide (C_3H_5)₂S. No trace of allyl isothiocyanate was found in the fresh onion or leek. The actual amount of allyl sulphide in even the strongest onions or in garlic is very small (not exceeding 0·1 to 0·2 per cent. in garlic). Traces of allyl oxide are not infrequently present.

PHYSIOLOGICAL PROPERTIES

1. *Absorption.*—The oil is absorbed unchanged, since experiments show that it is unaltered by prolonged gastric and pancreatic digestion. The absorption is a slow process, and often takes place with difficulty from the mucous membrane of the intestines and perhaps, to a certain extent, from the stomach also. It may also be absorbed through the skin, as in manipulating allyl sulphide in the laboratory, and after the application of a garlic poultice, in which cases its absorption in traces is indicated by its presence in the breath after a short time.

2. *Excretion.*—That the odour of allyl sulphide persists in the air expired is a well known fact, which shows that the lungs are a channel for its excretion, and also that the act of excretion is rather slow—a day or two being necessary to eliminate quite a small quantity. Its excretion in the milk excreted by cows eating alliaceous plants is a source of much annoyance to many dairy farmers.

Excretion by the skin is a common though not an invariable result of eating garlic or onions.

Lastly, it is never completely absorbed from the intestine, or, what is less likely, it is absorbed and re-excreted, so that it is almost constantly present in the faeces of persons eating alliaceous plants.

According to Johnson and Church¹ the odour of these plants is so persistent that it is said to be recognisable 'in the excreta of persons who have consumed the oil in the form of a sauce into which a chive or onion has been dipped.'

We have never been able to obtain evidence pointing to the excretion of allyl sulphide by the kidneys, though on many occasions it was searched for. For example, 50 grammes of strong English onion was eaten raw at 3.45 p.m., and the urine collected for seventeen hours afterwards. Volume, 575 c.c.; specific gravity, 1021; reaction, acid. Though the large amount taken caused the skin to smell of the sulphide, no traces of it could be discovered in the urine.

PHYSIOLOGICAL EFFECTS

3. *General*.—The first effect of a moderate dose is an excitation of the central nervous system, followed by the usual compensation, viz., depression.

This we believe to be the most marked physiological property of allyl compounds in general, the extent of the excitement varying slightly with different compounds.

Thus allyl thiocyanate 'appears to exert a poisonous action, inasmuch as on working with the substance for some time headache, nausea, and nervous excitement are noticed.'² We have ourselves noted a similar effect with allyl iodide.

Allyl sulphide taken in the form of garlic, onions, or leeks, immediately before retiring at night may produce either an excited or depressed state of the nervous system, or both in succession, according to the dose.

1. *Ibid.*, p. 449.

2. Roscoe and Schögebeumer, Vol. III, Pt. ii, p. 389.

Upon persons of a neurotic tendency, garlic or onions, even in small quantities, cause extreme excitation, accompanied in some cases by vomiting, and in others by profuse salivation during sleep, followed by the extreme of depression. Allyl compounds and alliaceous plants all evidently owe their physiological effects to an action on the brain—chiefly upon the medullary centres in causing the physical effects, and on the cerebral regions in causing the psychical ones.

Supposed Solvent Action for Urates.—Allyl sulphide was found to exercise practically no solvent action upon either uric acid or urates. Whatever other therapeutic properties this compound may possess, therefore, it is certainly of no value in this relation.

SPECIAL PHYSIOLOGICAL EFFECTS AS TESTED ON LIVING ANIMALS

(By E. WACE CARLIER, M.D.)

The experiments were performed upon rabbits and one cat. The animals were first completely anaesthetised under a bell jar either with ether or with chloroform, and subsequently in all cases a tube was inserted into the trachea, through which the anaesthetic was administered in such a way that the anaesthesia could be regulated to a nicety, the animals thereby kept perfectly motionless, and artificial respiration easily maintained.

The operative procedures consisted in inserting cannulae into the carotid artery and jugular vein, or in merely inserting the point of the hypodermic needle into the latter and holding it in position with an artery clamp. The respiratory movements were recorded either by encircling the lower part of the thorax with a thin rubber band, to which a silk thread working over pulleys upon an elastically-supported lever was attached, or by Head's method.

The time was electrically recorded in seconds.

Owing to the difficulty of obtaining allyl sulphide from plants in sufficient quantity for these experiments, synthetically made allyl sulphide was purchased and used undiluted and in 1 per cent. and 5 per cent. solutions in normal saline. The solutions in all cases gave

rather anomalous results, due, no doubt, to the fact that the oil does not form good emulsions with salt solution; so that although the mixtures were administered with care, it was quite impossible to be certain of the exact amount of the drug present in each minim used. With the undiluted drug the case was very different, the results obtained being constant.

Allyl sulphide acts directly upon both the respiratory mechanism and the blood pressure, but only indirectly upon the heart, probably as a result of asphyxiation, though the inhibitory action of the vagi as tested by the inductorium is diminished by about one-half, but was never found to be entirely abolished.

Effect on Respiration and Blood Pressure.—The following experiment may be taken as a type :—

In a rabbit weighing 2685 grammes, 15 minims (0·89 c.c.) of a 1 per cent. solution in normal saline was injected into the jugular vein, and produced a slight fall in blood pressure amounting only to 6 mm. of mercury. The pressure began to fall $4\frac{1}{2}$ seconds after injection, reached a minimum at the 42nd second, and thereafter rose steadily to a maximum of 16 mm. of mercury 598 seconds after the injection, crossing the normal line at the 127th second. This was followed by a fall to normal at the 778th second. This small dose, therefore, caused a disturbance of the blood pressure lasting nearly thirteen minutes.

The respiration was likewise affected by this amount, being reduced from 51 to 39 per minute during the fall of pressure, and continuing to diminish both in rate and amplitude despite the subsequent pressure rise. At the 100th second the respirations had fallen to 30 per minute, became irregular in amplitude, and continued thus to the 200th second, when they again became regular, though small, with a rate of 33 to the minute, and remained so to the 480th second, when they again became irregular for ten seconds, and began to increase in rate and amplitude. They regained their normal rate and amplitude at the 560th second. The respiratory disturbance, therefore, lasted some nine minutes—i.e., a shorter time than that of the blood pressure.

About a quarter of an hour later 1 minim of the pure allyl sulphide was injected, and was followed by an immediate fall of blood pressure of 47 mm. of mercury in $25\frac{1}{4}$ seconds, the fall reaching to within 15 mm. of zero. This was soon succeeded by a gradual rise, which lasted until artificial respiration was resorted to; after which the pressure again fell somewhat.

The respiratory movements diminished in amplitude immediately after the drug was administered, and their record was reduced in 100 seconds to a mere sinuous line, and, therefore, the aeration of the blood rapidly became inefficient, by which the rise in blood pressure already noted was probably produced. Even these sinuosities in the tracing disappeared a little later, and, as the heart was beating strongly, artificial respiration was resorted to and maintained for about 20 minutes, after which the animal began to breathe normally though feebly. Three-quarters of an hour later the animal had quite recovered from the drug, and was killed by opening the carotid.

(The tracing of this experiment was taken on a fast moving drum, and is too long for publication, and, therefore, a similar one with slow motion has been given in Fig. 1.)

One minim of allyl sulphide was, therefore, a fatal dose for this animal, and, generally speaking, it was found that the intravenous injection of $\frac{1}{2}$ minim (0.3 c.c.) per kilo. of body weight was always fatal unless artificial respiration was performed.

This drug, therefore, kills by asphyxia brought about by paralysis of the respiratory centre in the medulla.

Another interesting point in the action of this drug is that when an animal has fully recovered from a non-fatal dose a second dose of the same strength and amount has practically no effect either on the respiration or blood pressure, a considerably stronger dose being required to produce any effect at all, the first having caused a considerable amount of immunity.

Effect of Large Doses on the Blood Pressure.—The injection of 5 minims (0.3 c.c.) of pure allyl sulphide not only arrests the respiratory movements, but at once, or within 15 seconds, causes a fall of blood pressure to zero, yet the heart keeps on beating forcibly for a much

FIG. 1.—Effects upon the blood pressure and upon the respiration of the injection intravenously of 1 minim (0.06 c.c.) pure allyl sulphide in a medium-sized rabbit. This and all the other tracings are to be read from right to left. Scale of 2 : 5.

FIG. 3.—Effect of successive $\frac{1}{4}$ minim (0.015 c.c.) doses of allyl sulphide injected into a rabbit weighing 2600 grams, upon the respiration and blood pressure. Scale of 2 : 5.

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longer time, as may be seen from Fig. 2. No attempt was made to recover the animal from this dose with artificial respiration.

Effect of Repeated Small Doses on the Blood Pressure.—The effect of repeated small doses on the same animal is also interesting.

In a large rabbit $\frac{1}{4}$ minim (0.015 c.c.) of the drug was injected as above, and produced on the blood pressure an immediate depressor effect, rapidly followed by a lesser pressor, which in turn is followed by a fall.

FIG. 2—Carotid trace in a rabbit of 2300 grams showing the effect of a 5 minim (0.3 c.c.) dose of allyl sulphide upon the blood pressure. Scale of 2 : 3.

Shortly afterwards another $\frac{1}{4}$ minim was injected, and followed as before by a depressor effect, though less rapidly produced, the subsequent pressor effect being more marked. Another $\frac{1}{4}$ minim resulted in a less depressor effect followed by a pressor rise to slightly above the normal. Another $\frac{1}{4}$ minim had a similar result with less depressor and still greater pressor after-effect, and another $\frac{1}{4}$ minim increased the after pressor effect still more, but the depressor effect was never abolished.

The $\frac{1}{4}$ minim doses were now given in rapid succession; the second being administered as the pressor effect of the first began to appear, and so with the third dose, with the result that a heaping up of the blood pressure to a considerable height was obtained. As shown by the tracing (Fig. 4) each pressor effect was checked, but a cumulative rise was obtained. At the top of this stair the heart began to fail, and the respirations quickly after died out, which resulted in death.

FIG. 4—Effect of three rapidly repeated doses of $\frac{1}{4}$ minim (0.015 c.c.) allyl sulphide upon the same rabbit as in fig. 3, and subsequent to the injections there illustrated. The humped condition of the blood pressure trace is well shown.

Though the total amount of the drug given had amounted to $2\frac{3}{4}$ minims (0.16 c.c.), the respirations had been little affected, gradually diminishing, but never ceasing until after the last dose had been administered. This immunisation seems, therefore, to apply to the respiratory rather than to the vaso-motor mechanism.

Experiment to Determine the Seat of Action of the Drug upon the Blood Pressure Mechanism.—To determine whether the vaso-motor centre was the seat of action of the drug a cat was chloroformed, pithed, and decerebrated; artificial respiration established, and the usual operations for a blood pressure experiment performed. Five minims (0.3 c.c.) of pure allyl sulphide were injected into the jugular vein, and produced somewhat tardily a slight depressor effect amounting only to 7 mm. of mercury. A further injection of 10 minims (0.6 c.c.) was then given, which caused a further fall of 3 mm. So that 15 minims (0.89 c.c.) of pure drug only resulted in a fall of 10 mm. mercury, which is less by 6 mm. mercury than that produced by a stimulation of the vagus before administration of the drug.

This is very different from the result obtained with even small doses of the drug on rabbits with intact medulla, presenting no comparison with the fall obtained by 5 minims (0.3) in the rabbit that yielded Fig. 2. No doubt the small depressor effect manifested was due to the action of the drug upon the supplementary vaso-motor centres present in the spinal cord, and we must conclude, therefore, that allyl sulphide acts on the vaso-motor centre and not on the musculature of the vessels, which was indeed to be expected from previous experiments with the drug on frogs' muscles, all of which gave negative results.

The vagus was again stimulated with the same strength of current as before, and produced arrest of the heart beat, and a stimulus with a current of double the strength gave the same result, but unaccompanied in both cases by any fall of blood pressure.

(The cat was used in this experiment because pithing in a rabbit results in a fall of blood pressure almost to zero owing to the paralysis of the great vessels of the abdominal cavity that supervenes, rendering it quite unsuitable for such experiments.)

Effect of the Drug on the Heart and other Muscles.—When allyl sulphide is dropped upon or injected into the myocardium of pithed frogs no alteration is produced thereby either in the rate, amplitude, or rhythm of the contractions, yet in a few cases large doses diminished the rate and increased the force of the contractions, and caused

FIG. 5.—Cat weighing 2340 grams. shewing the effect of injection of 5 minims (0·3 c.c.) and then of 10 minims (0·6 c.c.) of pure allyl sulphide upon the blood pressure after destruction of the vaso-motor centre in the medulla, and also the effect of vagal stimulation upon the heart and blood pressure before A and after B the injection of allyl sulphide. Scale of 1 : 2.

FIG. 6.—Carotid tracing in a rabbit weighing 2670 grams. The left vagus was stimulated before injection of three minims (0·18 c.c.) of allyl sulphide and again after the drug had produced a considerable fall in the blood pressure. Scale of 1 : 2.

some irregularity, even arresting the heart in diastole in one case ; but this is quite exceptional, and due probably to the experiments having been done in winter. Mr. Cranston Walker, at my request, repeated these experiments upon a number of frogs, and in one case only was any change in the heart beat recorded.

With the mammalian heart in both rabbit and cat, injection into a vein of even fatal doses of the drug produced no direct effect upon it, as judged by the pressure tracings obtained from the carotid artery, except such as are normally present in death from asphyxia.

Only one experiment was performed in this relation upon a rabbit, in which the thorax was opened after the establishment of artificial respiration, and the heart so exposed made to record the beating of its auricles and ventricles over separate pulleys. In this case injection of the drug into a vein remained without effect, as did also direct injection of it into the myocardium.

In the case of the pithed cat the thorax was opened at the end of the experiment, and allyl sulphide dropped on the heart without effect, and even a considerable dose (a hypodermic syringe full) injected into the myocardium also failed to alter the beat in any way.

We may, therefore, safely conclude that the drug has no direct effect upon the heart.

Similarly, when injected into the skeletal muscle of the frog (gastrocnemius) no change is produced thereby in the force of the contractions, response to electrical stimuli, or the onset of fatigue, which is also borne out in the ergograms of one of us after large doses of leeks and onions eaten with the food as compared with those taken on other days on a regular diet.

Effect on the Inhibitory Activity of the Vagus on the Heart as Ascertained by the Inductorium.—In all cases in which the effect of vagal stimulation upon the heart beat and blood pressure was tried a marked decrease in vagal inhibition was demonstrated after injection of the drug into a vein in considerable doses, its depressor effect being reduced by one-quarter, or even, in some cases, by one-half,

that produced by the same strength of current before its administration, but whether the heart ganglion cells or the termination of the inhibitory fibres on the muscle are the seat of this phenomenon was not specially determined.

In the pithed cat the fall of blood pressure, well marked before the allyl sulphide had been administered, was not obtained upon stimulating the vagus after the drug had taken effect, though the heart was distinctly retarded and even arrested thereby.

CONCLUSIONS

1. Allyl sulphide acts chiefly upon the respiratory centre in the medulla, paralysing it rapidly when large doses are intravenously administered.

2. The drug acts to a less degree upon the vaso-motor centre, diminishing its effect in the first instance, but followed, especially when small doses are given, by a subsequent rise of pressure that may persist for a considerable time.

3. When administered in small doses its effects upon the vaso-motor centre are more lasting than upon the respiratory, the contrary being the rule with large doses.

4. The drug diminishes to some extent the inhibitory action of the vagus upon the heart.

5. The drug has no direct effect upon the heart or upon skeletal muscle.

6. One-half minim of the pure drug per kilo. of body weight may be taken as a lethal dose, death resulting from asphyxia owing to paralysis of the respiratory centre, but if artificial respiration is had recourse to, recovery is complete within an hour.

7. After the effects of a non-lethal dose have passed off the animal is thereby immunised for a time against a similar and even a considerably larger dose.

8. Owing to its powerful action on the respiratory centre it cannot be recommended as a therapeutic agent for internal administration.