V. *Organic Oximides.—A Research on their Pharmacology.*

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INTRODUCTION.

By the term "organic oximides" is understood the whole class of organic compounds whose molecular constitution includes the chemical group = N.OH.

Few questions have of late years interested the scientific chemist more than those relating to this class of carbon compounds. For the most part these bodies are of recent discovery, and are still at the present time yielding material for numerous contributions to the chemical journals, more especially in Germany, where the investigation of their chemical nature was initiated by Professor Victor Meyer and his pupils. Indeed the enthusiasm shown by chemists in the elucidation of the structure and reactions of these compounds is sufficient evidence of their importance as a class.

These bodies may be broadly divided into two groups :

(*a*) Those whose preparation involves the use of hydroxylamine. These are known as "oximes," whence the generic name oximide is derived.

(*b*) Those which are prepared independently of hydroxylamine. These latter may be obtained by the aid of nitrous acid, and have been termed "isonitroso" bodies.

This group = N.OH must be distinguished from the true "nitroso" group — NO.

The oxime group is bivalent, being regarded as a compound of trivalent nitrogen with the monovalent radicle hydroxyl. The true nitroso group is monovalent, two "affinities" of the nitrogen being taken up by oxygen.

Nitrites are usually regarded as true nitroso bodies. At the same time it appears doubtful whether nitrous acid may not be structurally composed of the oxime group saturated by oxygen. In this acid it may either be said that the two available "affinities" of the bivalent group = N.OH are satisfied by oxygen, or that the one available "affinity" of the monovalent group — NO is satisfied by hydroxyl. Indeed the presence of both these groups in nitrous acid might also be claimed.

The organic bodies containing this oxime group are found to exhibit acid characters, the hydrogen of the = N.OH being for the most part replaceable by bases. The

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same structural change may therefore be said to occur as in the formation of the salts of nitrous acid.

There is an essential structural difference, however, between the bodies forming the subject of this research, and the nitrites. In the nitrites the nitrogen of the oxime group is attached to oxygen, whereas in these other bodies the nitrogen of this group is attached to carbon, and the larger group C = N.OH may be considered present.

For example :—

Ethylaldoxime. Ethylnitrite.

It is this larger group C = N.OH which has been called the oximido group. Organic oximides may therefore be concisely defined as "bodies containing the bivalent group = N.OH attached to a carbon atom." (V. MEYER and JANNY, 'Ber. Deutsch. Chem. Ges.,' 15, 1164.)

There are several classes of these organic oximides :—

Aldoximes.
Ketoximes.
Ketoxime acids.
Isonitrosoketones.
Isonitrosoacetoacetic ether.
Isonitroso acids.
Nitrolic acids.

Some "paranitroso" bodies of the aromatic series probably also contain this same oximido group and are to be regarded as homologous to the ketoximes; thus, nitrosophenol is more correctly described as being quinonoxime.

Chemically, these bodies may be said to be typified by the presence of the oxime group = N.OH. The ultimate object of this research is to correlate this structural relationship with the pharmacology of these bodies, and to discover how far they may possess any pharmacological type which can be isolated and referred to the presence of this group in their structure.

With this object, representative members were selected for pharmacological investigation from several series of the oximido bodies. From the fatty aldoximes were taken ethylaldoxime, propylaldoxime, isobutyl-aldoxime, and œnanthaldoxime. Acetoxime was chosen to represent the ketoximes, isonitrosoacetone to represent the isonitrosoketones, benzaldoxime and salicylaldoxime to represent the aromatic bodies.

I had previously investigated the pharmacological actions of quinonoxime (nitrosophenol). (Thesis presented for doctorate in the Victoria University.)

These several classes of bodies differ structurally in the method of inclusion of the oximido group.

In all cases the nitrogen is joined to carbon and the group $=C=N.OH$ may be considered present. This union is effected in the case of isonitrosoketones by the replacement of two hydrogen atoms of a terminal methyl group in the corresponding ketone. Thus

$$\begin{matrix} R \\ R \end{matrix}\!\!>\!CO = \text{Isonitrosoketones.}$$
$$\quad\|$$
$$\quad N.OH$$

In both the classes of "oximes," that is to say, aldoximes and ketoximes, the group $=C=N.OH$ is attained by the replacement of oxygen in the corresponding aldehyde or ketone. Oximes are compounds resulting from the action of hydroxylamine on an aldehyde or ketone, water being separated.

For example, ethylaldoxime is formed from ethylaldehyde,

$$CH_3.CHO + NH_2OH = \underbrace{CH_3.CH=N.OH}_{\text{ethylaldoxime,}} + H_2O$$

and acetoxime from acetone,

$$(CH_3)_2CO + NH_2OH = \underbrace{(CH_3)_2C=N.OH}_{\text{acetoxime}} + H_2O$$

Aldoximes are to be distinguished from ketoximes.

In aldoximes the group $=C=N.OH$ is situated between an atom of carbon and an atom of hydrogen.

In ketoximes this same group is between two carbon atoms. Thus—

$$\begin{matrix} R \\ H \end{matrix}\!\!>\!C=N.OH. \qquad \begin{matrix} R \\ R \end{matrix}\!\!>\!C=N.OH.$$

aldoximes ketoximes.

In these formulæ the presence of a hydroxyl group is taken for granted. The mode of formation of the oximes would allow another idea of their structure (JANNY, 'Ber.,' 16, 176).

We could imagine their structure to be as follows—

$$>CO + \begin{matrix} H \\ HO \end{matrix}\!\!>\!NH = H_2O + >C\!<\!\begin{matrix} N-H \\ | \\ O \end{matrix}.$$

These formulæ, however, are not probable and certainly do not correspond with the structure of the ketoximes. The hydrogen atom of the oximido-group in ketoximes is replaceable by alkyl or acid radicles. In this way benzylacetoxime is formed. This on boiling with hydrochloric acid is split up into acetone and benzylhydroxylamine. The reaction of this benzylhydroxylamine with hydriodic acid shows that the benzyl radicle is joined to oxygen and not nitrogen. The formula of benzylacetoxime must therefore be $(CH_3)_2C:N.O.C_7H_7$, and there can be no reason for assigning to acetoxime itself any other constitutional formula than that corresponding to its benzyl derivative: $(CH_3)_2C:N.OH$.

The aldoximes of the lower members of the acetaldehyde series occur as clear colourless fluids, of slight smell, and can be distilled without decomposition.

Ethylaldoxime is miscible with water; as the molecular weight increases the solubility in water diminishes.

The lower ketoximes are also undecomposed by distillation and are soluble in water.

The oximes, in consequence of the presence of the hydroxyl group, have the nature of weak acids and are soluble in alkalis; but many also unite with acids. From acetoximes, for example, by passing hydrochloric acid gas through the ethereal solution, the salt $C_3H_7NO.HCl$ is obtained as a white precipitate.

On warming with acids the oximes split into hydroxylamine and the corresponding aldehyde or ketone.

$$>C:N.OH + H_2O = >CO + H_2N.OH.$$

Reducing agents convert the aldoximes as well as the ketoximes into primary amines, whilst the group $>C = N.OH$ becomes $>C\begin{matrix}NH_2\\H\end{matrix}$.

In describing the results of my researches on the physiological action of these bodies, it is my intention first to take the aldoximes, to describe the action of the lowest member, ethylaldoxime, at length, and subsequently to compare therewith more briefly the action of the higher members of the same group. After further description of the actions found to be possessed by acetoxime, taken as representing the ketoximes, and by isonitrosoacetone, taken as representing the isonitrosoketones, it will be possible to contrast the actions ascribed to these main classes of oximido bodies, and therefrom evolve some idea of the pharmacological bearing of the chemical group $= N.OH$.

(A.) ALDOXIMES.

These are for the most part easily prepared by mixing in the cold one part of the aldehyde with an aqueous solution of one part of hydroxylamine hydrochloride and half a part of soda. After some time the aldoxime is extracted from the mixture by shaking with ether.

In the case of those aldehydes which are insoluble in water a dilute alcoholic solution is used.

Ethylaldoxime.

Ethylaldoxime, more briefly named aldoxime, is a transparent colourless fluid, miscible in all proportions with water, alcohol, and ether, and possesses a slight though characteristic and not unpleasant smell.

The aldoxime used for my experiments was made by myself according to Petraczek's method ('Ber. Deutsch. Chem. Ges.;' 15, 2793).

An aqueous solution of hydroxylamine hydrochloride is acted upon by the calculated equivalent of sodium carbonate, and to the cooled mixture is added rather more than the theoretical quantity of ethylaldehyde diluted with water. The mixture is allowed to stand twelve hours and is then extracted with ether. The ethereal extract is dried with calcium chloride, and the ether then distilled off over a water-bath. There is left a fluid with a constant boiling-point of 114–115° C.

General Action on Frogs.

In these experiments male frogs of the species *Rana temporaria* were used. Good-sized animals were selected, their weight averaging about 30 grams. Both winter and summer frogs were injected, the time of the year being always noted with each experiment.

In compliance with the Vivisection Act, no frog was injected before the cerebral lobes had been destroyed. This, of course, greatly vitiates the value of these experiments, but, even under these circumstances, valuable information can be obtained, more especially when the hinder part of the brain, with the medulla, is left intact. The optic lobes, cerebellum and medulla, were interfered with as little as possible, though, in most cases, they would be more or less injured. Voluntary movements were, in every case, abolished.

After the brain had been pithed, the animal was left quiet for a quarter of an hour so that the immediate shock might be overcome. The skin reflex was then estimated by means of dilute sulphuric acid, and the respiratory movements, when present, noted.

The drugs were either injected pure, or dissolved in a 0·75 per cent. solution of pure salt in distilled water. The puncture was always made in the region of the dorsal lymph sacs.

EXPERIMENT.—Male frog, weighing 32 grams. Temperature of room, 16° C.

Time.	
2.45 P.M.	Brain pithed.
3.0 ,,	0·1 cub. centim. of ethylaldoxime injected subcutaneously into the dorsal lymph sac.
3.2 ,,	Respiratory movements shallow and irregular.
3.5 ,,	Skin reflex of hind legs retarded.
3.10 ,,	Very few respiratory movements.
3.12 ,,	Posterior limbs, if extended, are not at once drawn up.
3.15 ,,	Posterior limbs show little resistance to passive movements.
3.25 ,,	Limbs slowly withdrawn from acid solution.
3.45 ,,	Frog in much the same condition.
3.50 ,,	Posterior limbs offer more resistance to passive movements.
4.0 ,,	Limbs drawn up. Few respiratory movements seen.
4.15 ,,	Skin reflexes more active.
4.25 ,,	Legs at once drawn up if forcibly extended. Respiratory movements much the same as before injection.
4.45 ,,	Same condition.
5.5 ,,	Limbs again slowly withdrawn. Skin reflexes good.
5.15 ,,	The same.
5.30 ,,	Heart and muscles exposed. Heart found beating normally. Muscles and nerves respond well to electrical stimulation. Blood distinctly darker than normal, but shows no abnormal bands.

This was clearly not a lethal dose, and an unpithed frog might have recovered.

EXPERIMENT.—Male Frog, weighing 30 grams. Temperature of room, 16°·5 C.

Time.	
11.15 A.M.	Brain pithed.
11.30 ,,	0·25 cub. centim. of ethylaldoxime injected beneath skin of back.
11.32 ,,	Respiratory movements ceased.
11.35 ,,	Posterior limbs offer no resistance to passive extension, and only drawn up after a little time.
11.36 ,,	Skin reflexes much diminished.
11.40 ,,	Much stronger acid required to produce a reflex action. Pupils distinctly darker.
11.43 ,,	Posterior limbs remain motionless wherever placed. Some power still in fore limbs.
11.45 ,,	The same.
11.50 ,,	No skin reflex. Limbs appear completely paralysed. Skin is darker in colour.
11.51 ,,	Sectio. Heart found beating, the auricles normally. The ventricle does not contract completely in systole; seems to remain more or less distended with blood. Blood chocolate-coloured, and shows the bands of methaemoglobin.

The irritability of the muscles and nerves was then tested with the induced current from a Daniell's cell and Du Bois-Reymond's induction coil. The irritability of both muscle and nerve was found diminished. The minimum stimulus to cause any response required the secondary coil to be placed at 18·5 centims. for the muscle and at 14 centims. for the nerve. No movements of posterior limbs upon placing the electrodes over the spine. Spinal cord exposed and stimulated directly. Still no movements in muscles of posterior limbs.

EXPERIMENT.

This was a similar experiment, only the frog was left three hours before examination.

There was found to be no response to the strongest stimulation of the sciatics. The muscles only respond to stimulation with coil at zero. The auricles were still beating slowly and irregularly. The ventricle was quiescent in diastole.

The main points to be noted from these injection experiments were the general nitrite-like action and the marked depression of the spinal centres.

Voluntary Muscle.

In all my investigations on voluntary muscular tissue I have immersed the muscle, usually the gastrocnemius of the frog, in a solution of the drug, the solvent being either a 0·75 per cent. solution of common salt, or sheep's blood diluted with the same solution in the proportion of 1 to 2. The apparatus mostly used was that introduced by Dr. R. B. WILD ('Outlines of Practical Physiology,' Professor STIRLING, p. 202).

The frog is first pithed and the skin removed from the hind limb. The tendo Achillis, divided close to its attachment, is seized, and the gastrocnemius torn up from its connections. One end of a thin piece of brass wire is sharpened and bent over to form a hook. This hook is then passed through the tendo Achillis. The bones of the leg being grasped, a small double hook, made out of a pin, is passed well beneath the ligaments in front of the knee-joint; the femur is divided above its condylar extremity, and finally the tibia is also divided at its upper end, when we have left the knee-joint with the gastrocnemius attached. In cases where it is required, the sciatic nerve is first dissected down and left attached to the muscle. In this way neither the muscle nor the nerve need be directly handled.

An ordinary two-ounce phial is cut in two, and the sharp edges melted smooth. The upper half of the bottle is taken and a cork is fitted to the mouth. The piece of wire used for perforating the tendo Achillis must first have been made to pass through this cork, from end to end, and in such a way that the muscle hangs from the narrow end of the cork, which is then pushed down against the hook, and the tendo Achillis so held to the end of the cork.

The muscle is now dropped through the neck of the bottle and the cork following is pushed home, by which means the end of the bottle is blocked and rendered water-tight. The glass with the contained muscle is now inverted and fixed in a small wooden stage, the free part of the cork being wedged in a hole in the stage. This hole perforates the stage, so that the wire passing through the cork projects beneath. This wire is now connected with one pole of the coil. Connection with the other pole is obtained by means of another wire looped on to the hook in front of the knee-joint.

This latter wire is very thin, but made of copper and insulated with silk. It passes out through the upper open end of the glass vessel, and also serves to connect

the muscle with the short arm of a lever which is fixed to the stage and projects over the glass vessel. This lever is then loaded and can be made to describe its movements on a vertical revolving drum. The electrical apparatus used is a DANIELL'S cell and DU BOIS-REYMOND'S induction coil, the current being made or broken by means of a mercurial key.

Experiments were made with reference to the action of the drug upon the irritability, contractile power, extensibility and description of the curve of voluntary muscle.

(*a*) *Irritability.*—The irritability of muscle is depressed by aldoxime from the commencement of the action of the drug without any preliminary increase. At first it was thought that a preliminary increase of irritability did occur, since in several experiments the muscle was found to respond to a weaker induction shock after immersion in the aldoxime solution than when immersed in normal salt solution. This increase in irritability must however be referred to an action upon the nerve-endings, since it was never noticed if more than about half an hour had elapsed between killing the frog and stimulating the muscle; nor was it ever noticed in curarised muscle.

The method adopted to test the irritability of muscle was to pass the break induction shock through a frog's gastrocnemius arranged in the apparatus already described, the strength of the stimulus being regulated by moving the secondary coil.

In this way it was found that when a muscle is acted upon by a 2 per cent. solution of aldoxime, it ceased to respond in about three-quarters of an hour to any stimulus weaker than that produced with the secondary coil at 10 centims. distance. For example:—

EXPERIMENT.—Gastrocnemius of Frog. Temperature, 18° C. Load, 12 grms. Secondary coil at 10 centims.

At 3.30 P.M. the arc traced by the muscle contracting in normal salt solution under conditions as above, measured 22 millims.

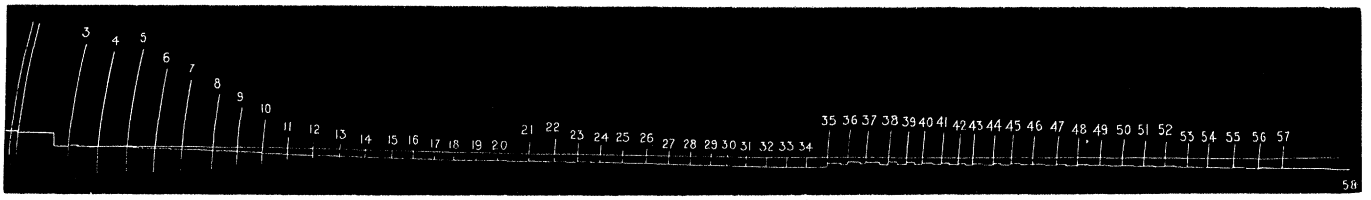
At 3.42 P.M. the normal salt solution was replaced by a 2 per cent. aldoxime solution.

The height of contraction then diminished as follows:—

Time.	Height of contraction.	Position of secondary coil.
	millims.	centims.
3·51	14	10
4·0	11	10
4·9	6	10
4·18	9	5
4·27	5	5
4·36	4	0
4·51	3	0

Fig. 1 is the tracing of an observation with a 1 per cent. solution of aldoxime. After 53 minutes' application of this solution the muscle had ceased to respond to stimulation with the secondary coil at 10 centims. distance.

Fig. 1.



ABSTRACT of Protocol (fig. 1):—Gastrocnemius of Frog. Temperature, 20°·5 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1 and 2	..	30
Application of aldoxime solution, 1 per cent.		
3	2	28
6	11	21·5
9	20	12
12	29	4·5
15	38	2
20	53	the slightest response.
Coil at 5 centims.		
21	56	6
27	74	4
33	92	3
Coil at 0 centim.		
35	96	10
57	162	6

Under the action of a 3 per cent. solution of aldoxime the muscle ceased to respond with the secondary coil at 10 centims. in twenty-four minutes.

The loss of irritability brought about by aldoxime was also traced sequentially by noting the minimum stimulus required to produce a muscular response.

For example, the following notes were taken in an experiment with a 1 per cent. solution of aldoxime.

The irritability of the muscle in normal salt solution was first noted, when the

minimum stimulus necessary to produce a minimum response in the muscle was that with the secondary coil standing at 28 centims.

The solution was then changed at 10.45 A.M. for the same salt solution now containing 1 per cent. of aldoxime.

The secondary coil had to be moved up as follows:—

Time.	Position of secondary coil.	Time.	Position of secondary coil.
10.47	28·7	12.5	18·2
10.50	28	12.10	17·2
10.55	28	12.15	16
11.0	28	12.30	9
11.10	27	12.35	8
11.15	26·8	12.40	7·3
11.30	23	12.45	7
11.45	21·4	12.50	5·6
11.50	21·4	12.57	5·0
11.55	20	1.0	4·0
12.0	19	1.5	3·5

The gastrocnemius of the opposite extremity was tested at the same time in normal salt solution and was found to have its irritability scarcely impaired. At 10.40 A.M., this muscle responded to minimum stimulus with secondary coil at 27·5 centims. At 1.6 P.M. it responded with secondary coil at 26 centims.

Extensibility and Elasticity.—By comparing the tracings of muscle contractions taken in normal salt solution with those of muscle contractions taken in solutions of aldoxime, a discrepancy in the latter at once becomes evident. This discrepancy is the varying relationship between base line and abscissa. In some cases the base line is abnormally low, and in other cases it rises high above the abscissa. The analysis of various tracings shows the circumstances corresponding with those differences. The tracing of a muscle in normal salt solution usually shows a fall of the base line below the abscissa owing to the gradual loss of tone in the muscle and its consequent yielding to the traction of the weight. The record of a muscle immersed in normal salt solution shows a gradual fall without any subsequent rise of the base line.

When the weaker solutions of aldoxime are used, this same fall of the base line again occurs, and it would almost seem, provided the stimulus be not too powerful, that with corresponding weights the fall is greater than when the muscle is simply immersed in normal salt solution. This is seen in fig. 3, which shows a steady fall whilst the secondary coil remained at 10 centims.—that is, until after contraction 19.

This fall, however, is not traced by muscles in stronger solutions nor even in weaker solutions under the influence of a stronger stimulus. As the solution is made stronger, or the secondary coil is pushed further home, the fall of the base line ceases, and a rise takes its place till the abscissa may be surmounted by some distance, showing the elasticity of the muscle to be diminished.

Fig. 2 shows the effect of a 2 per cent. solution of aldoxime in normal salt solution. The drug was applied between contraction 3 and 4. The usual fall of the base line which occurs when the muscle is immersed in normal salt solution had already commenced. This fall is at once arrested and gives place to a continuous slight rise, till, at contraction 19, the abscissa is passed by a clear interval. The secondary coil was now pushed up to 5 centims. distance, which sufficed to throw the muscle into a state of semi-rigor, the subsequent contractions remaining only partly relaxed.

Fig. 2.

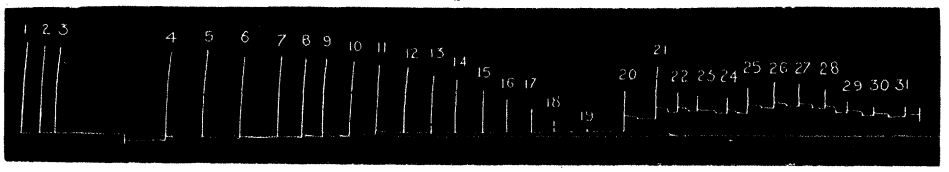
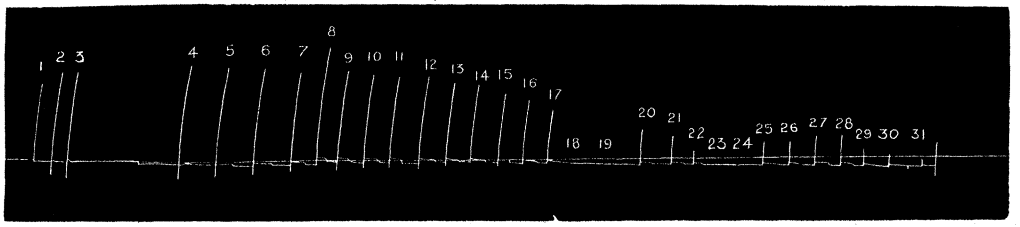


Fig. 3.



ABSTRACT of Protocol (fig. 2):—Gastrocnemius of Frog. Temperature, 18°·3 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2, and 3	..	18
Application of aldoxime solution, 2 per cent.		
4	3	18
7	14	16
10	23	15
13	32	12
16	41	7
19	50	1
Coil at 5 centims.		
20	53	8
31	113	3

The nature of this proneness to contracture is peculiar. It is by no means confined to this drug, but is a frequent pharmacological experience, and has been variously explained by different observers. In the similar condition produced by veratrine,

there was shown by BÖHM and FICK to be an increased formation of heat. It would appear therefore to be an active process associated with increased metabolism. This question will be again discussed in connection with the nerve endings in muscle.

Height and Range of Contraction.—Whether the base line rise or fall, all tracings of the action of aldoxime, on voluntary muscle, show one constant effect on the range of contraction varying only in degree with the strength of solution employed. In strong solution aldoxime is a muscle depressant. From the commencement of its action, a diminution in the total range of contraction is coincident, till the muscle is finally paralysed. True, some tracings have suggested a very transient initial stimulation, but this has been the exception, and has already been referred to the nerve-endings rather than to the muscle substance itself. This initial stimulation was never observed in curarised muscle, nor when blood was present in the immersing solution.

Still aldoxime cannot fairly be called a muscle poison. A very large dose is required to produce paresis, to say nothing of complete paralysis. A solution of the strength of one pro mille is without effect. A muscle immersed in a solution of the strength of 1 in 500 responds to stimulation for two hours as well as if simply immersed in normal salt solution, and, although a tracing of its contractions subsequently shows a diminishing range, as compared with the contractions of the fellow muscle in normal salt solution, yet the duration of life under these circumstances has been found to differ little in the two muscles.

In fig. 4 aldoxime was used in the proportion of one part in two hundred of normal salt solution. The poison in this observation was commenced at 10.16 A.M., and the same afternoon at 4.52 P.M. the muscle still showed a large response to stimulation.

ABSTRACT of Protocol (fig. 4):—Gastrocnemius of Frog. Temperature, 16°·2 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2, and 3	..	31
Application of aldoxime solution, 5 per cent.		
4	3	30
9	18	27
14	33	22
19	48	18
Coil at 5 centims.		
20	51	24
67	192	22

Fig. 4.

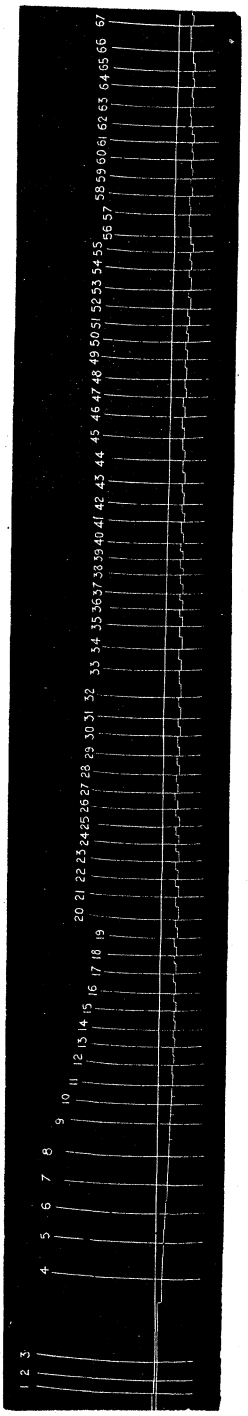
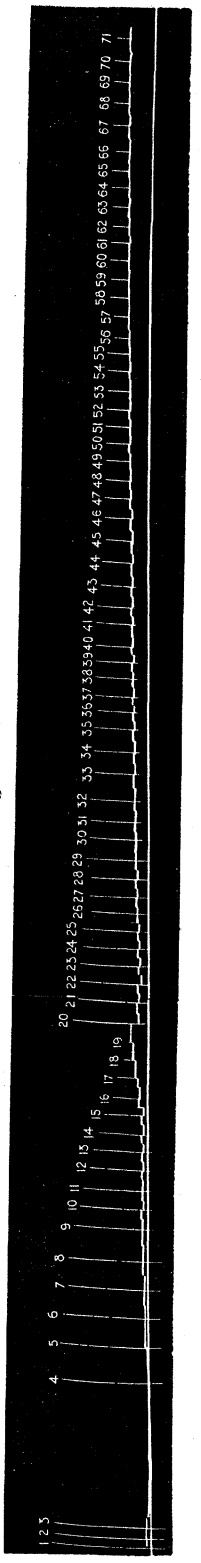


Fig. 5.



The contractions were recorded every three minutes. At contractions 26, 45, and 58, the increased height was due to moistening the upper muscular attachment and hook.

In fig. 1, as previously stated, a 4 per cent. solution of the drug was employed. The poison was commenced at 3.8 P.M. At 4.4 P.M., the muscle ceased to respond to stimulation with the secondary coil standing at 10 centims. In 96 minutes there was no response with the secondary coil standing at 5 centims. Still, although there was this diminution of irritability, the muscle was far from being paralysed, and at 5.52 P.M., after 2 hours 42 minutes application, it still responded fairly to stimulation with the secondary coil at zero.

In some tracings, when sufficiently strong solutions have been used, a deceptive appearance of increased range of contraction is produced by the ascent of the base line. The summit of a contraction is seen to be higher than that of its predecessor. Measurement, however, always shows the total range of contraction to be diminishing.

As we have seen, it is not easy to kill muscle with aldoxime. Strong solutions very soon show their influence by producing a paretic condition, but complete paralysis does not soon follow. For example—a 2 per cent. solution of aldoxime applied at 3.45 p.m., was found not to have entirely abolished contractility at 10 a.m. the next morning, although at first a rapid paretic effect had been manifest.

Paralysis can, however, be produced by still stronger solutions. A 10 per cent. solution of aldoxime completely killed a muscle in 43 minutes. A 3 per cent. solution had almost abolished response of the muscle after 90 minutes application.

Muscle Curve.—When the drum used in the frog muscle apparatus before described is allowed to revolve during the contraction of the muscle, the lever, instead of describing a vertical stroke, registers a curve, just as in the different forms of myograph. By a very slight alteration in the general schema of the apparatus, it can also be secured that the break induction stimulus shall each time enter the muscle at one and the same period of the drum's revolution, so that any change in the muscle curve is at once made evident.

The mercurial key is replaced by a trigger key.

A short projecting arm is affixed to the lower edge of the drum and the key is so placed as to be struck by this arm only when the key is vertical, that is, when contact is made. The arm on striking the trigger, consequently breaks the current, and so long as the relative positions of arm and trigger are allowed to remain the same, the induction shock must enter the muscle always at the same period of the drum's revolution.

Absolute uniformity in the speed of the drum's revolution is in all experiments assured by means of a metronome before placing the key in the vertical position.

The curves described by the lever will then follow the same line on the drum's surface, so long as the muscle contractions correspond with one another. Any change

in the contraction can, by a deviation of the pen from the normal line, be at once seen and analysed by comparison.

In this way it has been found that the essential characters of the muscle curve are not much affected by aldoxime. The primary and secondary curves continue to possess their main features. This fact is brought out plainly in fig. 7. This tracing shows the curve described by a muscle contraction after the muscle had been standing 33 minutes in a 2 per cent. solution of aldoxime. Fig. 6 shows the curve described by the muscle of the opposite extremity of the same frog after standing the same period in a 1 per cent. solution of aldoxime. They are both fairly normal tracings.

Fig. 6.

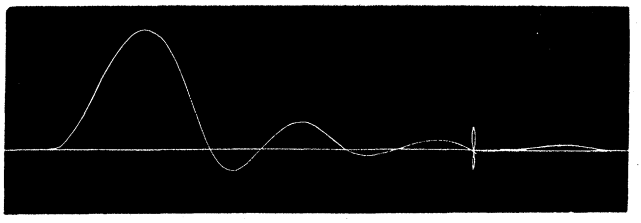
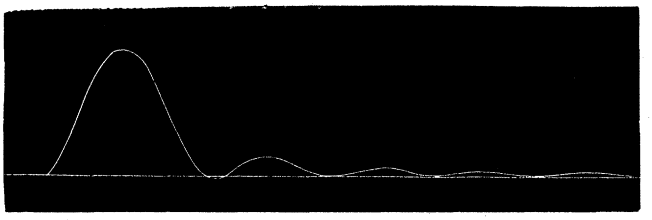


Fig. 7.



The difference between the two is confined to the period of relaxation. Under the effect of the stronger solution the lever does not fall below the base line. The elasticity of the muscle is lessened, and the secondary waves rendered shallow. This result corresponds with the ascent of the base line seen in the tracings of contractions on the stationary drum.

Fig. 8.

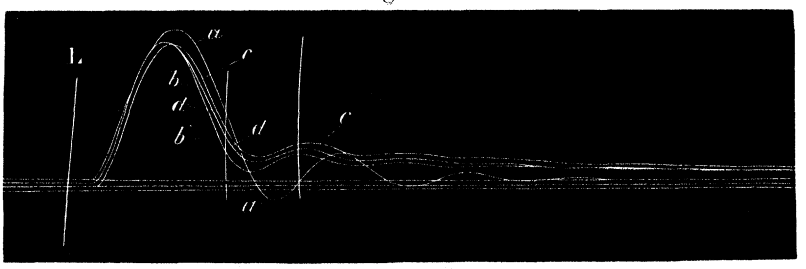


Fig. 8 serves to contrast a series of curves described by a muscle standing in a 2 per cent. solution of aldoxime.

a. Normal curve.

b. Curve 3 minutes after application of aldoxime 2 per cent.

c. „ 8 „ „ „ „ „

d. „ 13 „ „ „ „ „

The slow and incomplete fall of the lever and tendency to obliteration of the secondary curves are well seen. After each contraction the lever remains at a higher level, never again falling to the initial base line. At the same time the height of the primary curves is diminishing: the range of contraction is curtailed.

Action in presence of Blood.

The action of aldoxime on voluntary muscle is greatly modified by the presence of blood in the solution.

In the injection experiments, we find no note of any contracture of the limbs of the frogs; no record of any tonic or clonic spasm of the muscles. The limbs were simply paralysed. In like manner in the muscle contraction experiments, when blood is present in all but the strongest solutions of aldoxime, all evidence of contracture disappears; the base line never mounts above the abscissa, not even with the maximal stimulus.

This result was first supposed to depend upon a decomposition of the drug by blood. It was subsequently found that one of the products of the decomposition of aldoxime by blood has the same action upon muscle in producing contracture as that possessed by aldoxime itself. Indeed, this product of the decomposition of aldoxime acts more powerfully in producing contracture than does undecomposed aldoxime. Nor would it appear that the other product of the decomposition of aldoxime by blood has any action in preventing contracture in muscle.

Veratrine has an analogous action on muscle in producing a form of contracture. Relaxation after contraction is slow and incomplete.

This action of veratrine was shown by BRUNTON and CASH ('Journ. of Physiol.,' vol. 4) to be at once dispelled by the presence of a potassium salt.

In the same way I have found that a small quantity of potassium chloride added to the weaker solutions of aldoxime prevented the ascent of the base line.

It would therefore appear reasonable to suppose that the power of blood to antagonise the contracture effect of aldoxime may, at any rate partly, be ascribed to the salts of the blood.

Figs. 2 and 3 illustrate this antagonistic action of blood. The two tracings are those of the opposite gastrocnemii of the same frog. Each muscle was immersed in a two per cent. solution of aldoxime at the same time, and under the same conditions, with the exception that in fig. 3 the solution consisted of one part of defibrinated sheep's blood to two parts of normal salt solution.

The poison was in each case commenced at 11.20 A.M., between contractions 3 and 4. The two muscles were afterwards stimulated simultaneously at intervals of three minutes.

In fig. 2 the base-line is already above the abscissa at contraction 9, and rises considerably higher as a result of the stronger stimulus used for contraction 20.

In fig. 3, on the contrary, there is a gradual fall of the base-line without any rise, not even as a result of the stronger stimulus.

Another effect of the presence of blood is that the irritability of muscle is diminished more quickly. Thus, in the same two tracings,—the muscle of fig. 3, that is to say, the muscle in the solution containing blood ceased to respond in 45 minutes to the stimulus induced with the secondary coil at 10 centims. distance, whereas this same stimulus was, after the same interval, still provocative of response in the muscle of fig. 2, as shown by contraction 18.

In another quarter of an hour the muscle of fig. 3 had ceased to respond with the secondary coil at 5 centims. distance, whilst the muscle of fig. 2 continued to respond well with the secondary coil at that distance.

Complete paralysis of the muscle, however, does not appear to be hastened by the presence of blood.

Nervous System.

Efferent Nerve Trunks and End Plates.—The action of aldoxime on efferent nerve trunks and their endings in muscle was tested in various ways.

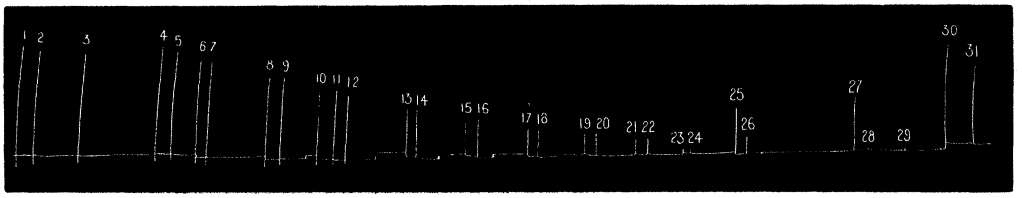
It was determined first to immerse the muscle and nerve in the same fluid, and compare the muscle response to direct stimulation with the response to stimulation of its supplying nerve. Should the nerve trunk, or its end plates, be affected by the poison more rapidly or more powerfully than the muscle, such an effect must, by this means, be made evident. Should the nerve trunk or its end plates be affected to the same or less extent than the muscle, such a method of experimenting must give negative results. The nerves employed were the sciatics of frogs. The whole nerve is dissected out down to its entrance into the gastrocnemius muscle.

Direct handling of the nerve is avoided by leaving a portion of the vertebræ attached to its proximal end. A piece of silk is tied to this vertebral handle, by which means the nerve can be easily moved about. A pair of electrodes is so arranged as to dip into the glass vessel containing the nerve-muscle preparation.

A Pohl's commutator is introduced into the schema described for muscle contractions, and an extra pair of wires made to connect the commutator with the nerve electrodes. The nerve is now placed on the electrodes, and the glass vessel filled with solution so as to completely cover the nerve. Each time it is desired to stimulate the nerve, enough solution is removed from the glass to leave the nerve uncovered, and so ensure the conduction of the stimulus along the nerve alone. The vessel is then again filled to cover the nerve.

A control experiment was performed, using simply normal salt solution. The course of events is seen in figure 9.

Fig. 9.



PROTOCOL (fig. 9):—Gastrocnemius of Frog with nerve attached. Nerve stimulated with separate electrodes. Temperature, 17° C. Load, 12 grms. Coil at 10 centims.

Time.	Muscle.	Nerve.
hrs. mints.		
	Application of normal salt solution.	
0 0	1 and 2	3
0 15	4	5
0 25	6	7
0 45	8	9
0 55	10 and 11	12
1 20	13	14
1 30	15	16
1 45	17	18
2 0	19	20
2 15	21	22
2 30	23	24
	Coil at 5 centims.	
2 45	25	26
4 55	27	28 and 29
	Coil at 0 centim.	
5 8	30	31

The first contractions were taken at 11.30 A.M. During the first two hours and a half, with the secondary coil standing at 10 centims., there was a gradual loss of irritability advancing *pari passu* in both muscle and nerve. At 2.15 P.M., that is to say in 2 hours 45 minutes, the secondary coil was pushed up to 5 centims. This stronger stimulus caused a much larger response when direct than when indirect. With the coil at 0 centim. there appears less discrepancy, and it is seen that five hours after commencement of the experiment the nerve was still fully irritable, and this stronger stimulus, when conducted along the nerve caused almost as large a muscular response as when passed directly through the muscle.

Employment of 1 and 1·25 per cent. solution has demonstrated the fact that a loss

of irritability in efferent nerve-fibres is distinctly a prior effect of the action of aldoxime to the loss of irritability in the muscle-fibres themselves.

The question arises, is this really due to a loss of irritability in the nerve trunk, or is it simply due to a loss of power of conduction either in the nerve trunk or end plates?

Irritability of Efferent Nerve Trunks.—Experiments were therefore made with a view to acting upon the nerve trunk alone.

For example, the skin having been removed from the lower half of a pithed frog, the two sciatic nerves are dissected out in their whole length, a small piece of the spine being left attached to each. The frog is then pinned down, and the proximal two-thirds of each nerve allowed to dip into a waxen trough containing normal salt solution. The muscle and remaining portion of nerve-trunk are kept moist by irrigation with the same solution. A pair of non-polarisable electrodes is arranged at the side of each trough, so that the nerves can be easily lifted on to them. The irritability of each nerve is then ascertained by means of one DANIELL'S cell and DU BOIS-REYMOND'S induction coil. The simple saline in one of the troughs is now replaced by the poisoned solution and the irritability of the two nerves again tested every few minutes.

The following is the result of one such experiment :—

EXPERIMENT.—Female Frog, weight 39 grms. Temperature, 17° C.

At 10.25 A.M., the portions of the nerve trunks selected for immersion were tested with varying strengths of current. The weakest stimuli necessary to call forth the smallest distinct muscular contractions, principally seen in movements of the feet, were found to be those with the secondary coil standing at the following distances :—

Left nerve.	Right nerve.
31	34

The left nerve was now allowed to dip into its trough containing normal salt solution. The trough for the right nerve was filled with a 1 per cent. solution of aldoxime at 10.30 A.M. The irritability of the nerves was then compared frequently, and at the expiration of 115 minutes the reading was

Left nerve.	Right nerve.
25·6 centims.	27·7 centims.

It is evident that in this observation the trunk of the nerve was very little affected by any local action of aldoxime. This was also the case in the majority of observations. Occasionally a decided effect was noted, and invariably so when a 3 per cent. solution of aldoxime was used. The following are the notes of an experiment with this stronger solution :—

EXPERIMENT.—Male Frog, weighing 40 grms. Temperature, 15°·7 C.

The two sciatics in normal salt solution required minimum stimuli as follows:—

Time.	Left nerve.	Right nerve.
11.15 A.M.	29	28·5

The left nerve was now acted upon by a 3 per cent. solution of aldoxime. The secondary coil had then to be placed for the two nerves successively, as here noted:—

Time.	Left nerve in 3 per cent. solution of aldoxime.	Right nerve in normal salt solution.
11.20 A.M.	30	28·5
11.25 „	28	28·5
11.30 „	27	28·5
11.36 „	27	28
11.40 „	25·5	27·5
11.45 „	25	27·4
11.52 „	24	27
12.0 „	24	27
12.5 „	22·9	26
12.10 „	22·6	26
12.20 „	22	26
12.30 „	21	26
12·45 „	18	24·8
1·0 P.M.	16·5	24
1.15 „	10·2	23

In this and one or two other experiments, a primary slight increase of irritability in the poisoned nerve was noted, though possibly not really due to any action of the drug.

Conductivity of Efferent Nerve Trunks.—The conductivity of nerves was tested with the same apparatus as that used for testing the irritability. The trough containing the poison was placed somewhat nearer to the muscle, and a good piece of the proximal end of the nerve was kept moist with normal salt solution on a pair of non-polarizable electrodes, resting on a glass plate and above the level of the poison.

Very contradictory results were obtained, but in the majority of cases, and in the most carefully-conducted experiments, it was found that a stronger stimulus was required to produce a muscular response when the electrodes were applied to the poisoned area than when they were applied to the non-poisoned proximal area, and that equal stimuli produced a much larger muscular response when applied to the non-poisoned proximal portion than when applied to the poisoned area.

Aldoxime, therefore, diminishes the irritability before the conductivity of nerve trunks.

The following are the notes of an observation showing a distinct primary increase in conductivity :—

EXPERIMENT.—Male Frog, weighing 38 grms.

The left sciatic nerve dissected out, and the frog pinned down as described.

Two pair of electrodes were used, and each time a portion of nerve was stimulated that portion was lifted on to its own pair of electrodes.

At 2.30 P.M. the two areas chosen gave a muscular response to the same minimum stimulation, with the secondary coil standing at 31 centims.

The middle portion of the nerve trunk, between the two pairs of electrodes, was now allowed to dip into the trough containing a 3 per cent. solution of aldoxime.

The irritability of the two areas then varied as follows :—

Time.	Poisoned area.	Normal area.
2.35 P.M.	30	32
2.40 ,,	29	32·4
2.45 ,,	29	33
2.50 ,,	28·5	32·6
2.55 ,,	28	32
3.0 ,,	27·1	31·3
3.5 ,,	26	31
3.15 ,,	24·5	30
3.30 ,,	23	28·9
3.35 ,,	22·3	27
3.45 ,,	20	25·2

There was a primary increase of irritability in the normal proximal portion of the nerve trunk, and as the irritability of this portion subsequently diminished, it remained greater than that of the poisoned portion. This is equivalent to saying there was a primary increase of conductivity with secondary decrease.

Motor Nerve Endings.—In the experiments upon muscle-nerve preparations, it has been seen that there is a more rapid loss of irritability in the nerve than in the muscle. In experimenting with similar solutions of aldoxime upon the nerve trunk alone, the muscle and nerve endings not being poisoned, no comparable loss of irritability has been noted. It seems a fair deduction therefore to suppose that the motor end plates are the main seat of this loss of irritability in the nervous path.

Any primary increase of irritability in these end plates could not be demonstrated. They cannot be stimulated apart from the muscle. I should like, nevertheless, to refer to these end plates a great part in the causation of that form of contracture noted as one effect upon muscle of strong solutions of aldoxime.

We know that as a consequence of increased irritability or excessive stimulation, nerve centres which are normally co-ordinated, such as those of the spinal cord, may overstep co-ordinating boundaries and communicate with each other, not only by the usual channels, but also by channels not normally used for such transmission. The result is a tetanus in co-ordinated muscles. Such a tumult in the spinal nerve-centres is seen in strychnine poisoning.

We also know that when a muscle is over-stimulated, it passes into tetanus which, being continued, passes into contracture and *rigor mortis*.

Now there must be a co-ordinating mechanism between the different fibres forming a muscle. This mechanism must be localised in the nerve end-plates. Should these end plates become hyper-æsthetic from any cause, the ordinary inhibition of co-ordination will be suspended, stimuli will be summated, and the muscle thrown into varying degrees of tetanus or contracture. In fact, contracture might be considered an epilepsy of the end plates.

The action of aldoxime upon curarised muscle is in favour of this view.

Curarised Muscle.—Curare greatly modifies the action of aldoxime. There is no longer the ascent of the base-line, no shortening of the muscle in the form of contracture. Aldoxime acts upon a fully-curarised muscle simply as a depressant. There is a gradual loss of irritability and slight fall of the base-line.

It is known that curare paralyses the terminations of motor nerves in muscle. It would appear, therefore, to be a natural corollary to suppose that the veratrine-like action of aldoxime upon muscle is closely connected with the motor end plates.

Afferent Nerves.—Observations upon cutaneous nerves, by local applications to the skin, have failed to adduce any evidence of their being certainly affected by aldoxime independently of the spinal cord. Aldoxime at least does not appear to depress afferent nerves, but at times a quickening of the cutaneous reflex in frogs was suspected. This, however, might have been due to a central action, since the possibility of some absorption of the drug was not entirely eliminated.

Spinal Cord.—The spinal cord is paralysed by large doses of aldoxime. After injecting frogs, as in one of the injection experiments before described, the posterior vertebral arches have been carefully removed and the cord stimulated directly. In this way, after full lethal doses, stimulation of the spinal cord has failed to elicit any muscular response, and that at times when the motor nerve trunks have been still irritable. I have not succeeded in paralysing the spinal cord by immediate application of the aldoxime solution, but when such a solution is perfused through the vessels, spinal paralysis invariably results.

A frog's brain is pithed, the right aorta is ligatured, and a cannula tied in the left aorta. The heart is then removed, and the poisoned solution entering by the cannula is allowed to perfuse through the vessels. In this way the spinal cord is always found paralysed before the muscles. Such paralysis is however not quickly produced, and requires the perfusion to be continued some time.

A quicker method was found in first tying low down the abdominal aorta, so cutting off the supply to the lower limbs, and concentrating the perfusion more in the vessels of the cord.

A 2 per cent. solution of the aldoxime so perfused was found to render the motor paths of the cord non-irritable in a little under three quarters of an hour.

Whilst using this latter method, spasmodic movements of the posterior limbs were noticed on one occasion, soon after commencing the perfusion.

Circulation.

The action of aldoxime upon the circulation has been investigated by means of experiments on the vessels of the Tortoise, by means of perfusions through fresh sheep kidneys, and also personally by means of the sphygmograph.

Such investigations have shown that aldoxime possesses little influence over the walls of the vessels when present in small proportions. This little influence has been found however, to be fairly constant and typical for equivalent proportions of the drug, though varying somewhat with different proportions of aldoxime employed.

Vessels of the Tortoise.—The small Water Tortoise was the species always used. The animal is first killed by decapitation. After allowing it to bleed as much as possible, any subsequent escape of fluid from the cervical vessels is prevented by a stout ligature made to include the whole root of the neck. The plastron is next sawn through, and its anterior half removed. The heart and great vessels can now be fully exposed by excising the scapulæ and opening the pericardium.

The systemic aortic arch on one side having been isolated, the remaining five aortic arches are occluded by ligature, and a glass cannula inserted into the selected systemic arch. The whole heart is now excised by cutting through the aortic arches below the common ligature, and by freely cutting through the sinus venosus.

The animal is now placed neck downwards in a glass funnel, beneath which a vessel collects all fluid flowing from the patent veins.

A system of branching tubes is made to connect the aortic cannula with two or three vessels containing the fluids to be circulated.

A graduated glass tube in communication with the common system, registers the level of the circulating fluid, and serves as the index for regulating the pressure. Alternation of the circulating fluids is easily secured by a series of stop-cocks.

The action of aldoxime upon the vessels, as observed in the Tortoise, differs somewhat according to the strength of solution circulated, and is well illustrated by the following three experiments.

These three observations also testify a modifying influence over the action of aldoxime possessed by the spinal cord.

So far as possible all experiments on the vessels of the Tortoise were performed under the same conditions. The fluids were circulated under a pressure of 25 centims.

The outflow from the veins was measured every three minutes, and from these measurements the flow per minute was each time deduced. No measurements of the outflow are made until the blood is well washed from the vessels.

The results of these circulation experiments are presented in diagrammatic projections which readily appeal to the eye. It will therefore be unnecessary to state more than the main points of the protocols.

In these projections the lighter shade signifies the circulation of the poisoned solution, whilst the normal fluid is represented by the darker colour.

The squares, when read horizontally, represent periods each of three minutes' duration. The vertical reading of the squares is given in figures to the left and shows the volume of fluid in cubic centimetres circulated during each interval.

EXPERIMENT (Chart 1).—Medium-sized Water Tortoise. Temperature, 15° C.; Pressure, 25 centims; Circulation of Ethylaldoxime, 1 in 500.

The flow of the normal fluid having become fairly constant at 7 cub. centims. for the three minutes, the poisoned fluid, that is to say, aldoxime 1 in 500 of normal salt solution, was then circulated 36 minutes, during which time the outflow is seen to have slightly decreased. The normal flow having been restored, the poison was again perfused 39 minutes. This time a primary slight constriction of the vessels was succeeded by an equally slight dilatation. This corresponds with many other experiments in which, the poison having been circulated longer, a primary constriction gives place to a secondary dilatation.

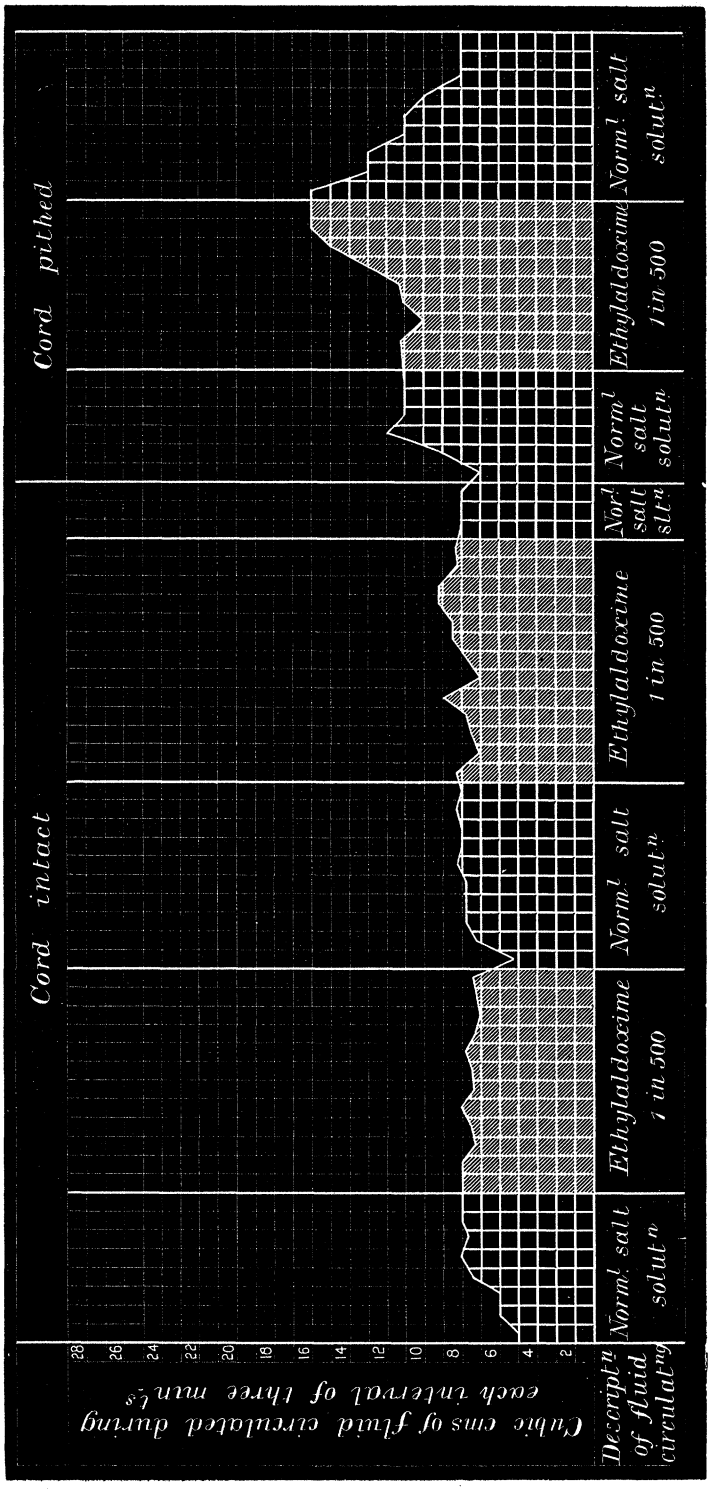
In this experiment the normal flow was again soon regained. The spinal cord was then pithed, and the consequent loss of tone in the vessels is seen on the chart, though much less than usual. The normal flow having again become steady, the poison was once more circulated 27 minutes, and a marked dilatation of the vessels was produced. This dilatation seemed then to be followed by a rapid death of the vessel walls.

This observation therefore points to a greater dilating influence of aldoxime over the vessel walls in the absence of the spinal cord than in presence of the intact cord. At other times, after pithing the cord earlier in the experiment, there has again been a primary constriction, but followed by a more marked dilatation. It would therefore appear that the vaso-constricting influence of aldoxime is at least partly exerted through the nervous system.

EXPERIMENT (Chart 2).—Water Tortoise. Temperature, 14°·5 C.; Pressure, 25 centims.; Circulation of Aldoxime, 1 in 1000.

In this experiment there was no constriction of the vessels either with the cord pithed or unpithed. On the contrary, the circulation of the poisoned solution was each time accompanied by a dilatation of the vessels. It is peculiar that this strength of solution was always found to dilate the vessels without any primary constriction, whereas either weaker or stronger solutions more often cause a primary constriction, with or without a secondary dilatation.

Chart 1,


Cubic cms of fluid circulated during each interval of three min.ts
28
26
24
22
20
18
16
14
12
10
8
6
4
2
Cord intact
Cord pithed
Decrpt.n of fluid circulat.g
Norm.l salt solut.n
Ethylaldoxime 1 in 500
Norm.l salt solut.n
Ethylaldoxime 1 in 500
Norm.l salt solut.n
Norm.l salt solut.n
Ethylaldoxime 1 in 500
Norm.l salt solut.n

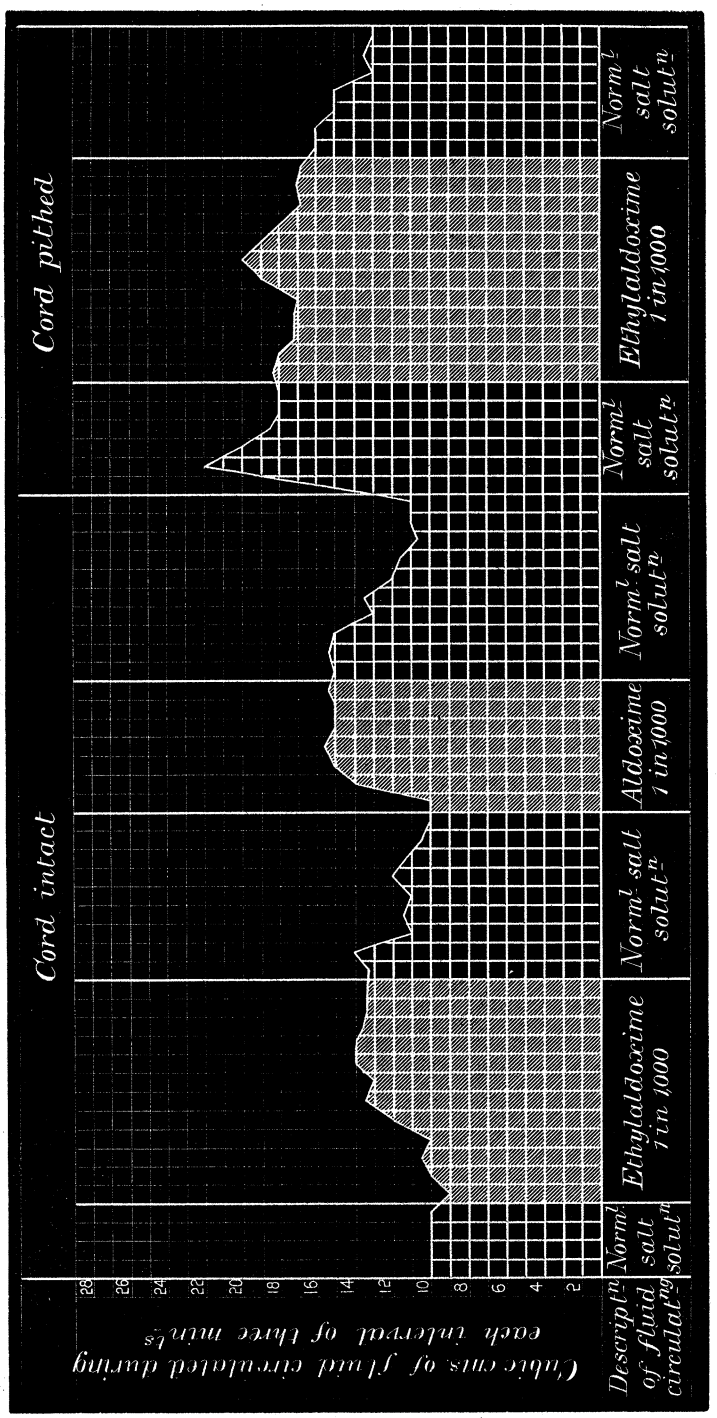

Cubic cms. of fluid circulated during each interval of three mins.
Cord intact
Cord pithed
Description of fluid circulating
Norml salt solution
Ethylaldoxime 1 in 1000
Aldoxime 1 in 1000
Norml salt solution
Norml salt solution
Ethylaldoxime 1 in 1000
Norml salt solution

Chart 2.

Excised Sheep Kidneys.—The action of aldoxime was repeatedly tried on excised sheep kidneys. The animal is killed in the usual way and the kidney together with its capsule of fat is quickly excised, care being taken to cut the renal vessels long. Cannulæ are inserted into both artery and vein, and there secured by ligature. No time is lost in placing the kidney in a specially arranged oven. There are two of these ovens. They are on the principle of those used by KOBERT, and consist of chambers surrounded on all sides except in front by hydrostatic compartments. In front each is closed by a glass door.

A constant temperature of about 40° C. is maintained by means of a gas jet, regulated by a mercurial governor. In one oven are placed the vessels holding the fluids to be circulated. These vessels are provided with inlet and outlet glass tubes. The inlet tube is short and terminates above the surface of the contained fluid. The outer end of this tube is connected by india-rubber tubing with an air-tight reservoir. Water under pressure is allowed to flow into the reservoir, and consequently the air is driven along the tubes into the perfusion vessels. The connection with these vessels can be interrupted by stop-cocks. These stop-cocks being closed, the air in the tubes and the reservoir then having no way of escape, becomes compressed by the in-flowing water. The volume of water entering the reservoir is regulated by means of a bib-tap, and the pressure of the air is recorded by a mercurial manometer interposed in the system of tubes connecting the reservoir with the perfusion vessels. The outlet tubes are long and nearly reach the bottom of the perfusion vessels.

The kidney remains in the second oven. The arterial cannula is connected with a glass tube which passes between the two ovens and perforates their opposed walls. On gaining the interior of the perfusion oven this tube branches. The branches are coupled on to the outlet tubes from the perfusion vessels, each branch being also provided with a stop-cock and a syphon for expelling air bubbles.

The side of the kidney oven is also perforated by a collecting tube which conveys the blood from the cannula in the renal vein.

The supply tube having been coupled with the perfusion vessels, the system of tubes is first completely filled with normal blood, and all air is carefully expelled by opening the syphons.

Perfusion can now be commenced by opening the stop-cock in the inlet tube of one of the vessels. Air, under pressure from the reservoir, immediately rushes in and drives the subnatant fluid up the outlet tube. The pressure is then regulated and kept constant at a fixed standard, generally that of 80 millims. of mercury.

The flow from the collecting tube is measured at fixed intervals, and the readings of the perfusions of different fluids then compared.

The normal fluid circulated was always defibrinated sheep's blood, and generally that of the same animal supplying the kidney. At other times the blood was taken from a previously killed sheep.

Experiments performed in this manner seemed at first most conflicting. The results differed not only with different preparations of aldoxime perfused, but they also differed in experiments in which the same percentage of aldoxime was perfused.

When the blood contained 1 part of aldoxime in 500 parts a slight contraction of the vessels usually resulted, a dilatation being rarely noted. One part of aldoxime in 1000 of blood more often dilated the vessels, just as observed in the Tortoise.

Weaker solutions sometimes dilated the vessels, sometimes contracted them, and at other times no influence whatever was to be seen.

For these apparently conflicting results a satisfactory explanation subsequently appeared.

Contraction of the vessels nearly always results when aldoxime is perfused in greater proportion than 1 in 1000 parts of blood. Any exception to this rule, as well as the various action of weaker solutions, is to be accounted for by a difference in procedure.

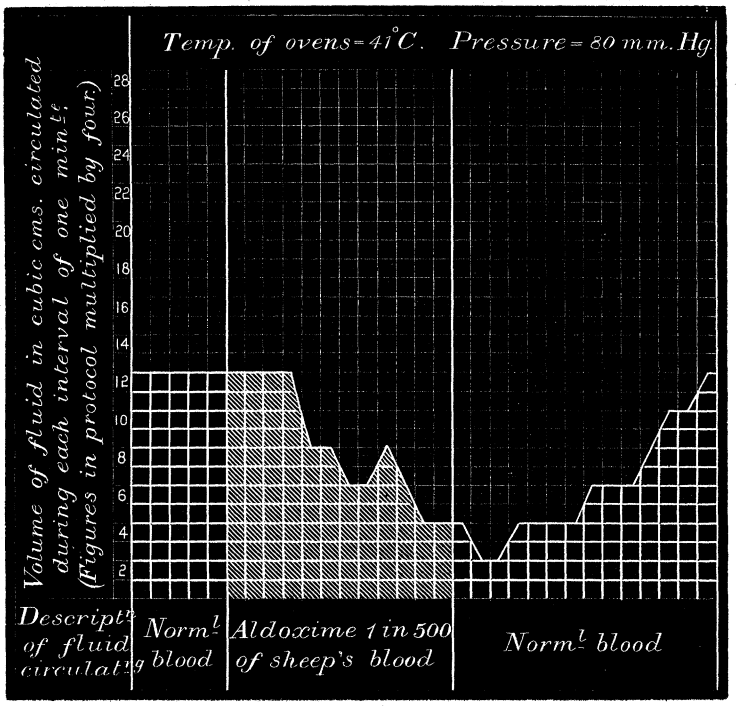
When aldoxime is mixed with the blood shortly before perfusing at least a primary constriction of the renal vessels is the invariable result.

If the mixing be performed some little time before perfusing, and the perfusion vessel be immediately closed, there is less constriction of the vessels; no action may be noted, or slight dilatation. If the poison be mixed with blood two or three hours before perfusion, and the vessel be left open, more especially when left open in the oven at 40° C. till the commencement of the experiment, then dilatation of the vessels invariably follows, a primary constriction being either slightly marked or entirely absent. This dilating action is most evident when 1 part of aldoxime is mixed with 1000 parts of blood and lessens with the weaker solutions.

Blood decomposes aldoxime; slowly at ordinary temperature, more rapidly at the body temperature. One of the products of decomposition dilates the vessels; the other product constricts them. This latter body is volatile and easily oxidised and so is more or less dissipated, provided there be free access of air to the mixture. Time, a warm temperature, access of air to the blood containing the aldoxime, must therefore each give the dilating factor more prominence, and a consideration of such circumstances provides the key to many apparent discrepancies of experiments. No doubt the undecomposed drug itself primarily constricts the vessels, and this accounts for the more constant vaso-constricting action of the stronger solutions, in which undecomposed aldoxime has still been present.

The following are a few typical results extracted from these circulation experiments. In each case the flow of the normal blood had become constant at the initial measurement noted before commencing the circulation of the aldoxime. The flow was usually measured every minute.

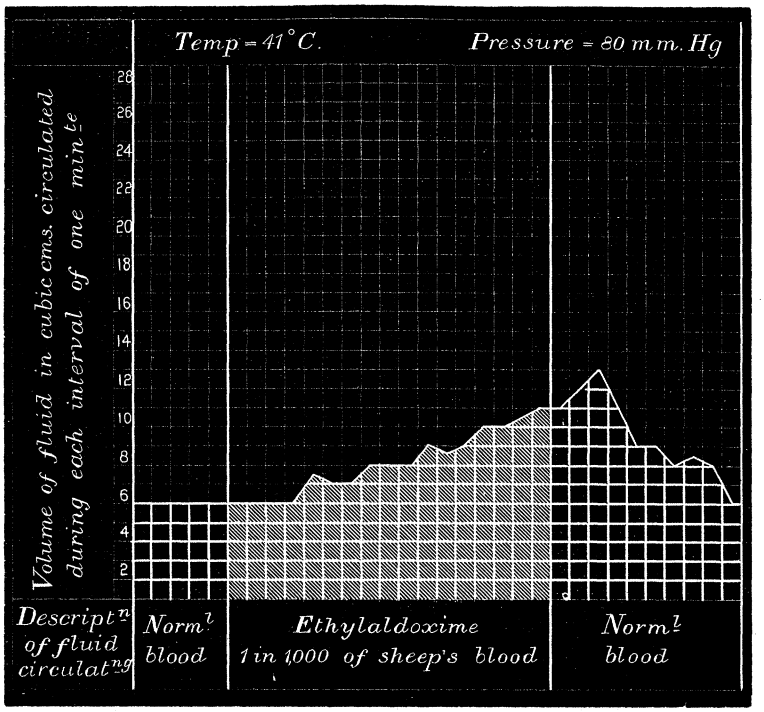
Chart 3.



EXPERIMENT.—Sheep's Kidney (Chart 3). Temperature of Ovens, 41° C. Pressure, 80 millims. of Mercury.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid circulating per minute.
11·18 A.M.	Normal blood	3
11·19 „	Aldoxime 1 in 500 of sheep's blood	3
11·20 „	. . . . .	3
11·21 „	. . . . .	3
11·22 „	. . . . .	3
11·23 „	. . . . .	2
11·24 „	. . . . .	2
11·25 „	. . . . .	1·5
11·26 „	. . . . .	1·5
11·27 „	. . . . .	2
11·28 „	. . . . .	1·5
11·29 „	. . . . .	1
11·30 „	. . . . .	1
11·31 „	Normal blood	1
11·32 „	. . . . .	0·5
11·33 „	. . . . .	0·5
11·34 „	. . . . .	1
. . . . .	. . . . .	. . . . .
11·44 „	. . . . .	3

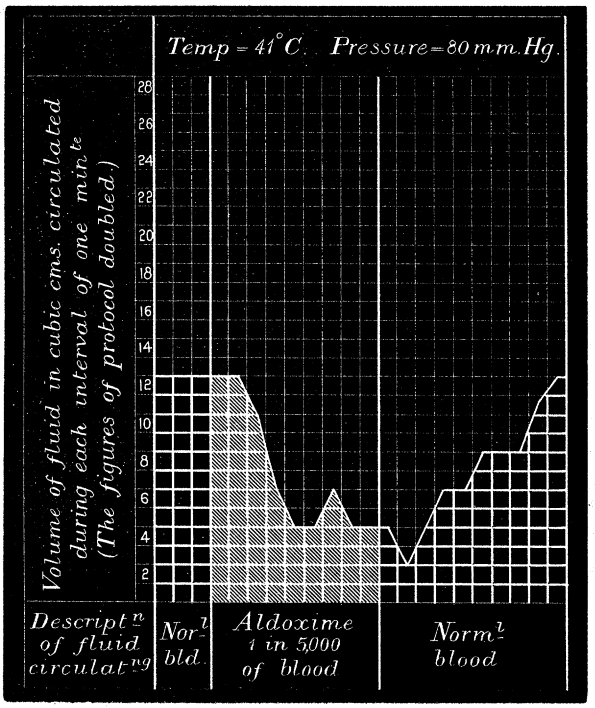
Chart 4.



EXPERIMENT.—Sheep's Kidney (Chart 4). Temperature of Ovens, 41° C. Pressure, 80 millims. Hg. Aldoxime 1 in 1000 of Sheep's Blood. Mixed only Short Time before Closing the Perfusion Vessel.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
3.20 P.M.	Normal blood	5
3.21 „	Aldoxime 1 in 1000 of sheep's blood	5
3.22 „	. . . . .	5
3.23 „	. . . . .	5
3.24 „	. . . . .	5
3.25 „	. . . . .	6·5
3.26 „	. . . . .	6
3.27 „	. . . . .	6
3.28 „	. . . . .	7
3.29 „	. . . . .	7
3.30 „	. . . . .	7
3.31 „	. . . . .	8
3.32 „	. . . . .	7·5
3.33 „	. . . . .	8
3.34 „	. . . . .	9
3.35 „	. . . . .	9
3.36 „	. . . . .	9·5
3.37 „	. . . . .	10
3.38 „	Normal blood	10
. . . . .	. . . . .	. . . . .
3.47 „	. . . . .	5

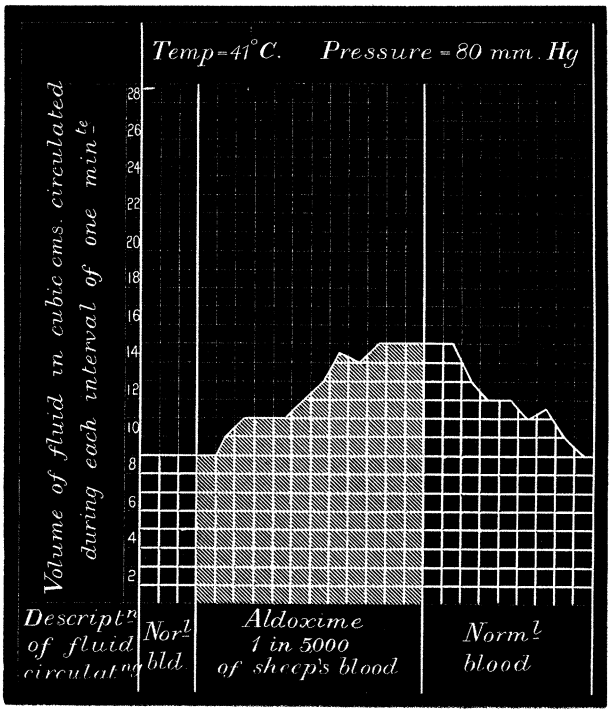
Chart 5.



EXPERIMENT.—Sheep's Kidney (Chart 5). Temperature of Ovens, 41° C. Pressure, 80 millims. Hg. Aldoxime 1 in 5000 of Sheep's Blood. Mixed and Vessel Closed Shortly before Commencing Experiment.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
4.54 P.M.	Normal blood	6
4.55 „	Aldoxime 1 in 5000 of blood . . .	6
4.56 „	. . . . .	6
4.57 „	. . . . .	5
4.58 „	. . . . .	3
4.59 „	. . . . .	2
5.0 „	. . . . .	2
5.1 „	. . . . .	3
5.2 „	. . . . .	2
5.3 „	. . . . .	2
5.4 „	Normal blood	2
. . . . .	. . . . .	. . . . .
5.13 „	. . . . .	6

Chart 6.



EXPERIMENT.—Sheep's Kidney (Chart 6). Temperature of Ovens, 41° C. Pressure, 80 millims. of Mercury. Aldoxime 1 in 5000 of Sheep's Blood. Mixed Half-an-hour in Open Vessel in Oven at 41° C., and Shaken.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
11.5 A.M.	Normal blood	8
11.6 „	Aldoxime 1 in 5000 of sheep's blood	8
11.7 „	. . . . .	9
11.8 „	. . . . .	10
11.9 „	. . . . .	10
11.10 „	. . . . .	10
11.11 „	. . . . .	12
11.12 „	. . . . .	13·5
11.13 „	. . . . .	13
11.14 „	. . . . .	14
11·15 „	. . . . .	14
11.16 „	. . . . .	14
11.17 „	Normal blood	14
. . . . .	. . . . .	. . . . .
11.25 „	. . . . .	8

Human Pulse.

Observations on the action of aldoxime in man have been limited. Three healthy individuals have taken the drug, and its effect on their radial arteries carefully watched by means of the sphygmograph.

Single doses of V–Xm have been taken without any apparent action.

Doses of XX-XXXm have invariably altered the sphygmographic tracings. This alteration has had a more cardiac than vascular character, as seen in a more ample and more frequent beat. A diminished pulse tension has also resulted from these larger doses, but not constantly. Some diminution of vascular tension was, however, a usual result of repeated doses; equivocal in the case of V–Xm doses; decided in the case of X–XXm doses.

Heart.

The action of aldoxime was experimentally investigated on the frog's heart. For this purpose various apparatus was used: Roy's Tonometer, Coats' apparatus, and that of Williams. Roy's Tonometer was found to give the most typical tracings, and from these, representative ones have been selected for description. The absolute power of the heart was measured by Coats' apparatus.

Aldoxime can no more be described as a cardiac poison than it can be said to poison voluntary muscle. On the contrary, when present in anything like moderate doses, aldoxime is a stimulant and tonic to the frog's heart.

In the experiments with Roy's Tonometer, the perfusion fluid used has been a mixture of one part of Ringer's fluid, or of normal salt solution with two parts of defibrinated sheep's blood.

When dissolved in this fluid, in proportions ranging from 1 in 500 to 1 in 5000, the action of aldoxime on the frog's heart has not been found to vary but in degree.

This action shows itself in an increased rate of beat and an increased heart tonus.

The systole of the heart is rendered more perfect and under the influence of the stronger solutions the heart dilates less in diastole.

Perfusions of the same quantitative solutions, by means of Coats' apparatus, have shown a primary increased contractile power in the heart, followed later by a diminution of such power.

A control experiment showed, however, that the ultimate loss of contractility is brought about just as soon when normal solution is alone perfused.

The action of stronger solutions of aldoxime has not been so constant. The variations noted are comparable with the varying action of aldoxime on voluntary muscle, and are explicable by reference to the presence of blood, as was also seen to be the case in perfusion through the vessels.

At times the heart is arrested in systole; at others in diastole. This difference

partly depends upon the strength of solution. Aldoxime in solutions exceeding 1 per cent. usually arrests the heart in firm systolic contracture.

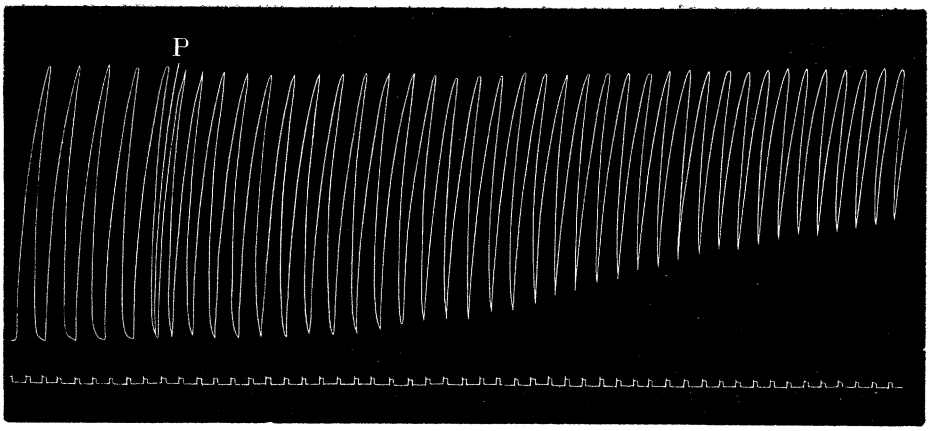
Solutions of one part of the drug to 200 of the normal fluid differ in their action according to the length of time which has elapsed since the mixing of the solution was performed. The longer the aldoxime remains in contact with the blood, the less is the tendency to systolic contracture, and the greater the tendency to diastolic paresis.

Two effects of aldoxime are to be seen in all cardiac tracings taken with Roy's tonometer, and these are accelerated speed and regularity of rhythm.

The action of aldoxime on the frog's heart is well illustrated by the accompanying tracings, which were all taken with Roy's tonometer. The normal fluid was in each case a mixture of normal salt solution and defibrinated sheep's blood.

Fig. 10. Perfusion of 1 part of aldoxime to 200 parts of normal fluid. The drug was mixed with blood immediately before commencement of experiment, and its perfusion replaced that of the normal fluid at P. Here the rhythm was at once

Fig. 10.



accelerated. The ventricle dilated less and less in diastole, reaching a partial condition of contracture.

This contracted condition soon passed off on resuming the perfusion of the normal fluid.

Figs. 11 and 12. These show the action of a similar solution, only this time the mixing of the aldoxime was performed at 9.45 A.M. and the perfusion was commenced at 10.45.

Fig. 11 is the normal tracing. Fig. 12 was traced after perfusing the aldoxime solution 15 minutes.

The rate of beat is again increased. There is a slight decrease in amplitude of beat due to increased tone of the ventricle. The heart was contracting perfectly, but dilated less in diastole. This increased tone is a minor degree of the contracture in

Fig. 11.

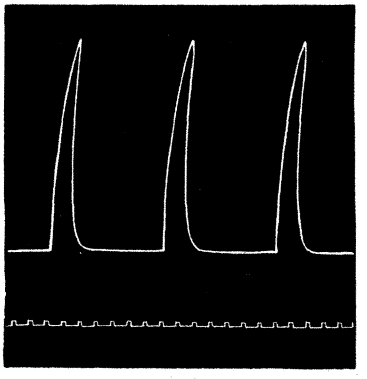
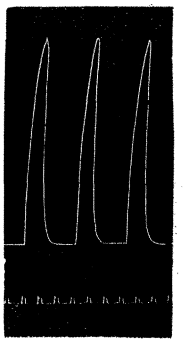


Fig. 12.



the preceding perfusion and was produced almost immediately. It reaches a certain degree and then advances no further, as shown by the length of time the solution was perfused.

Figs. 13, 14, 15, 16, and 17. These tracings typically represent the action of aldoxime on the frog's heart when the drug is mixed with the blood some time before perfusing. The action might be taken for that of a nitrite, except that the rate of beat is more markedly accelerated. There is no longer any contracture or even exalted tonus. There is a slight and gradual diminution of amplitude of beat, seen to be due not to imperfect relaxation of the ventricle, but to the opposite condition, to a greater diastolic dilatation and less complete systole. There is a gradual fall in the summits of the curves ; in fact, there is a slowly progressing paresis of the ventricle.

Fig. 13.

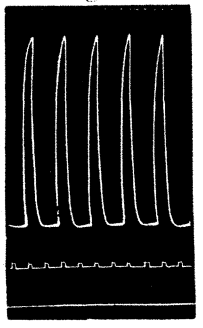


Fig. 14.

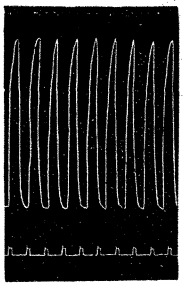


Fig. 15.

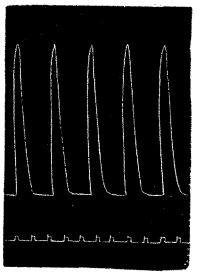
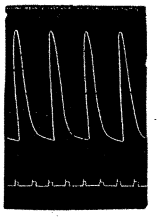


Fig. 16.

Fig. 17.



That aldoxime cannot be considered a cardiac poison is shown by the fact that the perfusion of this strong solution was continued three hours, and at the end of that time the heart was still beating fairly well (fig. 17). At the end of two hours the perfusion of the drug was suspended and the normal fluid continued, with the result that the normal beat was almost restored (fig. 15). The solution of aldoxime was again perfused and caused an immediate return of the accelerated rhythm and diminished tonus (fig. 16).

Figs. 18, 19, 20, and 21. These tracings again illustrate the comparatively non-

poisonous action of aldoxime on the frog's heart. A 1 per cent. solution in equal parts of lamb's blood and normal salt solution had been standing all morning in an open vessel. Perfusion was commenced at 2.16 P.M. Fig. 19 shows the tracing eleven minutes later. On comparison with the normal tracing (fig. 18), there is again found

Fig. 18.

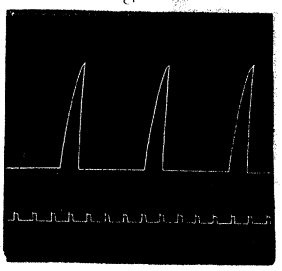


Fig. 19.

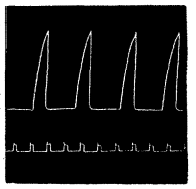


Fig. 20.

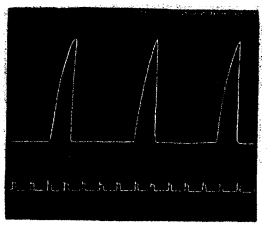
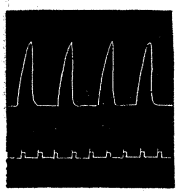


Fig. 21.



evidence of accelerated rhythm and less perfect systole. At 2.31, return was made to the normal fluid, and under its influence there is very soon a return to the normal beat (fig. 20).

At 2.37 the solution of aldoxime was once more perfused. Seven minutes later fig. 21 was traced.

Fig. 22.

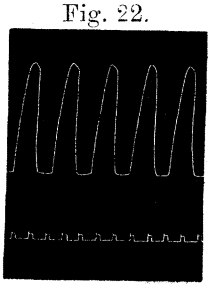
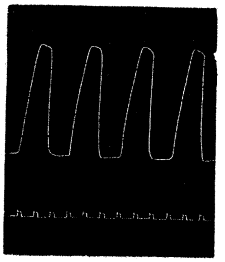


Fig. 23.



Figs. 22 and 23. These show the action of a weaker solution of aldoxime, viz., 1 in 400. The chief influence is again seen to be the acceleration of the rhythm. Fig. 22 is the normal tracing. Fig. 23 shows the tracing one hour later, the drug having been perfused during the whole of the interval.

Blood.

The analysis of the mutual actions of blood and aldoxime has been fruitful of results and has also shed light on the action of aldoxime on other tissues.

If 1 part of aldoxime be mixed with 500 parts of sheep's blood at ordinary temperatures, no effect is seen for some hours, when the colour of the blood darkens. This darkening of colour takes place more rapidly at higher temperatures.

Still, even at 40° C. the change takes quite an hour to develop. Stronger solutions darken more quickly. A 1 per cent. solution at 40° C. darkens in a quarter of an hour or twenty minutes.

Spectroscopic examination of the blood darkened by aldoxime reveals a band in the red, near FRAUNHOFER'S line C. This band is in the same position as that depicted by Dr. GAMGEE ('Physiological Chemistry,' vol. 1), and described by him as being characteristic of methæmoglobin. At the same time the blue end of the spectrum is also largely absorbed. This band was compared with that of acid hæmatin, and was found to be situated nearer D, and differed also from that of acid hæmatin by disappearing on the addition of ammonia.

The presence of methæmoglobin no doubt accounts for the darker colour of the blood, but it is not easy to at once see how aldoxime can produce methæmoglobin.

We know that methæmoglobin is a typical product of the action of nitrites, and the question arises: can nitrous acid be formed by the blood from aldoxime?

This seems both chemically and physiologically improbable, and the question raises the still disputed problem as to the nature of methæmoglobin.

Methæmoglobin was formerly described as a reduction product of oxyhæmoglobin. Later observers, more especially GIACOSA ('Zeits. f. Physiol. Chem.,' vol. 3, p. 54) have regarded it as a superoxidised oxyhæmoglobin in which the oxygen is more stably held than in simple oxhyhæmoglobin. This extra oxygen could not be obtained directly from aldoxime. Aldoxime is not split up by reduction. The molecule is reduced as a whole, into a primary amine.

In order to obtain nitrous acid from aldoxime there must be an oxidation process. Active processes of oxidation in the blood are paradoxical to the generally received physiology of to-day. It is a well proved fact that active processes of oxidation take place in the tissues, indeed we know that such is a necessary condition for the life of the tissue cells. I cannot see why it should therefore be argued that oxidation processes cannot take place in the blood. The blood is also a tissue containing living cells. These cells must consume oxygen in the same way as any other living cells. Active oxygen has not been found in extra-vascular tissues any more than in the blood. It is a fact that reducing substances cannot be found in normal blood; but according to the experiments of LUDWIG and ALEXANDER SCHMIDT (ALEX. SCHMIDT, 'Ber. über die Verhandl. der Sächs. Ges. der Wissensch. zu Leipzig, Math phys. Classe,' vol. 19, p. 99, 1867), the blood of animals, which have died of suffocation, contains only traces of oxygen or none at all, whilst it contains reducing substances in large quantities. AFANASSIEW (N. AFANASSIEW, 'Ber. der Sächs. Ges. der Wissensch.,' vol. 24, p. 253, 1872) showed later that these reducing substances could only be found in the corpuscles and none at all in the serum.

It would appear that these reducing substances are normally seized by the blood corpuscles, and by them immediately oxidised, but failure to supply oxygen caused them to be stored up in the bodies of the corpuscles.

The inability of the blood to oxidise substances is again argued from the fact that certain easily oxidisable substances pass through the blood and are excreted in the urine unchanged. It is quite possible that such substances are amongst those not

normally taken up by the cells. They have escaped oxidation because they have been rejected not only by the cells of the fixed tissues but also by those of the blood.

Other substances may escape oxidation from another cause. Thus, such easily oxidisable substances as pyrogallic acid (CL. BERNARD, 'Leçons sur les Propriétés Physiologiques, &c., des Liquides de l'Organisme,' vol. 2, p. 144, 1859) and pyrocatechin (BAUMANN and HERTER, 'Zeitschr. f. Physiol. Chem.,' vol. 1, p. 249, 1877) appear in the urine unchanged.

This can be explained by the fact of their not circulating in a free state, but, like all hydroxyl derivatives of the aromatic hydrocarbons, they combine with the sulphuric acid which is formed by the decomposition of albuminates. These dichotomised sulphuric acids are excreted as salts without further change. It would seem that sulphuric acid, not being capable of further oxidation, also protects the organic conjugate against oxidation.

None of these arguments therefore bear scrutiny, and it remains quite possible that active oxidation processes, though undoubtedly most active in extra-vascular tissues, may also be carried on by the blood corpuscles, provided the substances to be oxidised are actually taken up by the cells.

Failing such an active intervention of the corpuscles, it is also possible to imagine a passive oxidation taking place in the blood; a process in which the substances to be oxidised themselves become the active agents. If these substances happen to be powerful reducing agents, such as hydroxylamine, there seems to be no reason why they should not reduce the oxyhæmoglobin without any more intimate connection with the corpuscles. We know that such is the case outside the body, where we can at once reduce the oxyhæmoglobin by such substances as ammonium sulphide. Less powerful reducing agents, such as aldehyde, might also be imagined to carry on the same process, though more slowly. Such reduction in the circulating blood, exerted by a small proportion of substance, need not cause any asphyxial or other symptoms. The reduced hæmoglobin would be quickly re-oxygenated in the lungs.

Again, it is known that organic substances undergo oxidation much more easily in an alkaline than in an acid or neutral mixture. Such an alkaline fluid we find in the liquor sanguinis. Although the serum contains so little dissolved oxygen, what little there is might be taken up by such a substance as hydroxylamine, and the partial pressure of the gas in the lungs would quickly make good the loss.

It was, therefore, determined to ascertain what takes places when aldoxime is oxidised outside the body.

The amount of potassium permanganate required to completely oxidise 1 gramme of aldoxime into aldehyde and nitrous acid having been calculated, the two substances were mixed in half-a-litre of water slowly added. The solution was allowed to stand till almost colourless, and then filtered from the precipitated manganese dioxide. Nitrous acid was now tested for by the iodide of potassium and by the ferrous

sulphate tests, and was found to be present in large quantity, though in a quantity considerably short of the theoretical yield. The smell of aldehyde was doubtful, but by distilling with sulphuric acid, and also by obtaining acetic ether on addition of alcohol, the presence of acetic acid was amply proved.

Probably aldoxime under the influence of oxidising agents is first split up into its components aldehyde and hydroxylamine. These two products are then oxidised into acetic and nitrous acids.

Or, it may be that aldoxime is at once oxidised, nitrous acid being liberated without the intermediate formation of hydroxylamine.

Whether hydroxylamine is formed or not matters little pharmacologically. Hydroxylamine was shown by BINZ ("Toxicologisches über das Hydroxylamine," VIRCHOW'S 'Archiv') to act like nitrites, and he obtained the reaction of nitrites from the blood of animals poisoned by it.

RAIMONDO and BERTONI ('Annali Univ. di Med.,' vol. 259, 1882, p. 9) showed that hydroxylamine produced a chocolate-brown colour of the blood, and a change in its spectrum similar to that produced by nitrites.

BRUNTON and BOKENHAM also showed the similarity in action between hydroxylamine and nitrites ('Proceedings of Royal Society,' vol. 45).

That the blood acts upon aldoxime in the same manner as permanganate is almost certain. To assure myself that such is the case outside the body, blood rendered dark by aldoxime was dialysed and the dialysed liquor was found to yield the reactions of nitrites. The dialysed liquor also smelt of aldehyde, but the presence of acetic acid was not always proved. The smell of aldehyde is always developed after adding aldoxime to blood. Aldehyde is evidently less quickly oxidised by the blood than is hydroxylamine, and this fact would, perhaps, favour the view of a passive as opposed to an active oxidation.

The development of the aldehyde smell before the change of colour in the blood also points to the primary splitting up of the aldoxime molecule.

Judging by these experiments on blood, there seems, therefore, no reason to doubt that aldoxime is by that fluid split up into hydroxylamine and aldehyde, and that hydroxylamine is further oxidised into nitrous acid. The further oxidation of aldehyde is a much slower process, but that it may occur is shown by the presence of acetic acid being found in dialysed blood which has previously been treated with aldoxime and has stood several hours.

This oxidation might proceed at the same rate in any alkaline fluid exposed to the atmosphere. If the oxidation of aldehyde be as tardy in the living body, excretion will probably anticipate the change.

The physiological actions of aldoxime must then be explained in the light of those of nitrites and of aldehyde.

The pharmacology of nitrites has been well worked out, but that of aldehyde seems to be little known.

Bibliography records very little exact pharmacological work either on acetaldehyde or any other member of the aldehyde group, if we except paraldehyde, which, being a polymer of much higher atomic weight, is scarcely comparable.

O. Loew pointed out that aldehyde is a protoplasmic poison (O. Loew, Pflüger's 'Archiv,' vol. 35, p. 516).

From a pharmacological standpoint the only important work on aldehyde appears to be that recorded in a monograph, by Drs. Albertoni and Lussana, of Padua ('Trav. I. de Méd. Chir. et Pharmacol.,' Brux., 1887, vol. 34, p. 715). These observers however, confined themselves to the general action of the drug. They administered aldehyde to dogs by intravenous injection, by the stomach and by inhalation.

In order more fully to interpret the physiological actions of aldoxime, it seemed necessary to know more about aldehyde and its actions on individual tissues. The following investigations were therefore made:—

Ethylaldehyde. CH_3COH.

I have sought to ascertain the action of aldehyde on nerves, spinal cord, muscle, vessels, and the heart, adopting much the same methods as those described in the case of aldoxime. The results of these investigations I will briefly state, prefixing them with a précis of the general action of aldehyde on dogs, as stated by Drs. Albertoni and Lussana. The account given by these observers admirably upholds my own results on the individual tissues.

General Action on Dogs.

When from 3 to 5 grms. of aldehyde diluted with water are injected into the veins of a moderate-sized dog, the animal at once becomes comatose, with an almost instantaneous arrest of respiration. During the coma the heart's action is only slightly weakened, but the voluntary muscles are paralysed and sensation and reflex excitability are temporarily destroyed. As a rule the animals recover completely in a little while.

When injected in smaller proportions the coma is replaced by a narcotic condition, resembling that produced by alcohol, but there is an almost complete loss of sensibility. Respiration is markedly affected, being immediately accelerated by small quantities, and arrested by large quantities. The heart's action may continue as long as half an hour after arrest of respiration, and during this time the heart beats remain either normal, or slightly less frequent in number and somewhat increased in strength. After all respiratory movements have ceased for 10 or 15 minutes dogs may completely recover without any artificial aid. Aldehyde abolishes the cardio-inhibitory power of the pneumogastric nerves, and during the stage of asphyxia the irritation of these nerves has not the slightest influence on the heart's action.

When dogs are made to inhale the vapour of aldehyde their sensibility and power of motion are completely lost in about a minute. If the inhalation be continued, the pupils become widely dilated, respiration ceases, and the only sign of life is to be found in the contractions of the heart. Even now the dogs quickly recover if the inhalation be discontinued.

Given by the mouth aldehyde acts as an irritant.

Voluntary Muscle.

Irritability.—When in strong solution aldehyde acts upon voluntary muscle as an irritant poison. Weaker solutions show a primary stimulant followed by a secondary depressant action.

The primary stimulant action is well seen in tracings of single muscle contractions, and the increased irritability of the muscle is usually to be observed by comparison of the minimum stimuli required to promote a muscle contraction before and after the application of the drug.

The following protocol shows this effect.

The two gastrocnemius muscles of the same frog were arranged in the usual electrical apparatus and first immersed in normal salt solution. At 10.15 A.M. the minimum stimulus to produce a muscle response was for each muscle that induced with the secondary Du Bois-Reymond's coil at 27 centims.

The left muscle was now treated with normal salt solution containing 1 part of aldehyde to 300 parts. The following variations in the irritability of this muscle were then noted by reading the positions of the secondary coil corresponding to the minimum stimuli required each time to call forth the least evident muscle contraction.

Time.	Position of secondary coil, in centims.	Time.	Position of secondary coil, in centims.
10.7 A.M.	30	10.20 A.M.	29
10.10 ,,	31	10.22 ,,	28·5
10.12 ,,	31	10.24 ,,	26.3
10.14 ,,	31	10.26 ,,	26
10.16 ,,	30	10.28 ,,	25.5
10.18 ,,	29	10.30 ,,	25

The opposite muscle continued during this time to give a minimum response to stimulation with the secondary coil always at 27 centims.

The subsequent loss of irritability is produced more quickly than by solution of aldoxime of the same strength.

When a muscle is immersed in a solution of 1 part of aldehyde to 200 parts of normal salt solution, the muscle ceases to respond to the induced shock from one

Daniell's cell with Du Bois-Reymond's secondary coil, at any further distance than 10 centims., in about an hour and a half. In a 1 per cent. solution of aldehyde, this same quantitative loss of irritability was seen in a little over half an hour. A 2 per cent. solution of aldehyde killed a muscle in ten minutes.

Weak solutions, such as 1 part of aldehyde in 2000 parts, though generally showing a primary slight stimulant action, seem in no way to shorten the life of the muscle. Indeed the muscle lives in such a solution, I have thought, even a longer average period than when in simple normal salt solution.

The secondary impairment of irritability brought about by a solution of 1 part of aldehyde in 200 parts of normal salt solution is seen from the following observation :—

The two gastrocnemii from the same frog were put up in the usual way. At 10.50 A.M. the left muscle gave a minimum response with secondary coil at 28 centims. At the same time the right muscle required the secondary coil at 27 centims.

The poisoned solution was applied to the left muscle at 10.54 A.M. The sequence of events for this muscle was then as follows :—

Time.	Position of secondary coil, in centims.	Time.	Position of secondary coil, in centims.
10.55 A.M.	28	11.40 A.M.	21
10.57 ,,	29	11.45 ,,	19
10.59 ,,	30·1	11.50 ,,	18
11.5 ,,	28·5	12.0 ,,	15
11.10 ,,	27	12.15 P.M.	11·6
11.15 ,,	26	12.30 ,,	9
11.30 ,,	23	12.35 ,,	8·5
11.35 ,,	22		

At this time the right muscle, still in normal salt solution, contracted with the secondary coil at 24·5 centims.

Extensibility and Elasticity.—Tracings of single muscle contractions, when strong solutions of aldehyde are used, show the same ascent of the base line above the abscissa and the same loss of elastic reaction after contraction as observed in the case of aldoxime; only aldehyde causes both phenomena to appear in a much more marked degree.

A muscle immersed in a 2 per cent. solution of aldehyde passes into complete rigor in eight or ten minutes. A solution containing 1 part of aldehyde in 300 parts produces an ascent in the base line, followed by a descent, and this again by an ascent upon more powerful stimulation.

With weak solutions these effects are not seen; there is the usual exhaustion and stretching of the muscle.

Range of Contraction.—Solutions of aldehyde, the strength of which ranges from 1 part of aldehyde in 300 parts to 1 part in 2000 parts, produce in frogs' muscle a

primary and transiently increased range of contraction. The period of this increased contractile power corresponds with the increased irritability previously described. This increased range has not invariably been evident in tracings of single muscle contractions. The stimulus remaining constant, there follows a gradual diminution in range of contraction, varying in rapidity of development with the strength of solution employed, but always more rapid than that produced by aldoxime in solutions of equivalent strength.

Muscle Curve.—The contraction curves of frogs' gastrocnemii are greatly altered by aldehyde. There is seen a much nearer approach to the veratrine curve than was seen in the case of aldoxime. In fact, in the prolonged descent and alteration, or even obliteration of the secondary curves, the action closely resembles that of veratrine. In the ascent and height of the curve the likeness to veratrine is not found. On the contrary, the height in solutions of medium strength may be increased, and the ascent is always at first rendered more abrupt.

As the action of aldehyde proceeds, and the muscle becomes paralysed, the height of the curve decreases and the ascent again becomes more sloping.

Action in Presence of Blood.—The phenomenon of contracture evoked by aldehyde is largely dispelled by the presence of blood. It may be said that blood modifies the action of aldehyde upon voluntary muscle in the same way that it modifies the action of aldoxime.

The presence of blood entirely banishes the ascent of the base line from the contraction tracings of muscles immersed in weak solutions of aldehyde, such as a solution of 1 part of aldehyde in 500 parts of blood and saline.

Contractions traced by muscles immersed in stronger solutions of aldehyde still show signs of contracture, in spite of the presence of blood, only the contracture is much less pronounced than when aldehyde solutions of similar strength are used without blood. It seems that blood cannot counteract the contracture effect of more than a certain proportion of aldehyde.

Curarised Muscle.—The contracture effects of aldehyde are again always greatly lessened by curare, and usually the action has been completely antagonised, the muscle simply showing an advancing paresis.

The times when some contracture still appeared, strong solutions of aldehyde were used, and it is probable that the irritability of the end plates had not been completely abolished.

Nervous System.

Efferent Nerve Trunks and End Plates.—Experiments with muscle and nerve in the same solution, performed according to the method described under aldoxime, have revealed no more powerful depressant action of aldehyde on the nerve than on the muscle. The loss of irritability in the nerve advances *pari passu* with that in the muscle. Only when using strong solutions of aldehyde, such as 1 per

cent. solutions, has a stimulus when thrown along the nerve failed to provoke a muscular response whilst the muscle has still responded to direct stimulation. It has in such cases happened that when the coil has been pushed home the nerve has rapidly ceased to be irritable, whilst the muscle has continued to respond to an immediate shock. The idea suggests itself that the stronger stimulus to the already poisoned nerve finally determines the dislocation of the conducting paths. The observation would also go to show that aldehyde does not paralyse either muscle or nerve alone but both structures equally. In the action of aldoxime we have seen a prior paralysis of the nerve and have for the most part relegated the priority to the nerve endings rather than to the nerve trunk. The action of aldehyde is also exerted on the end-plates and not on the nerve trunks, for when care has been taken not to poison the muscle, experiments upon the irritability of nerve trunks have yielded nothing but negative results.

Experiments upon the comparative irritability of muscle and nerve have demonstrated the primary stimulation to be more marked in the nerve than in the muscle, and since the nerve trunks are not affected, this must mean a diminution of resistance in the nerve endings.

For example, a muscle-nerve preparation gave minimum response to stimulation with the secondary coil placed as follows :—

Time.	Muscle.	Nerve.
2.10 P.M.	29	30·5
The normal salt solution was then changed for the same solution containing 1 part of aldehyde in 300 parts. Then :		
2.12 P.M.	30	32
2.14 ,,	30	34
2.16 ,,	30	33
2.18 ,,	30·2	34
2.20 ,,	29·5	33
2.22 ,,	29	32·5
2.24 ,,	29	32
2.26 ,,	28	31
2.28 ,,	27·7	30·5

Conductivity of Efferent Nerve Trunks.—Aldehyde appears to be completely innocuous to efferent nerve trunks. Their conductivity has not been found depressed any more than their irritability. Under aldoxime was described an experiment suggesting an actual increase of conductivity. That is to say, the muscle responded to a weaker stimulation of the free non-poisoned end of the nerve, after than before the poisoned solution had been applied to the middle portion of the nerve trunk. This same curious result was also obtained with aldehyde. After learning the action of aldehyde on nerve endings in muscle, it seems to me that a critical observer would

again seek to make these end organs responsible, by pointing out the possibility of the poison reaching them by diffusion along the nerve trunk. It would certainly seem that such a chance is not entirely eliminated.

Spinal Cord.—Aldehyde first stimulates and then depresses the spinal cord.

EXPERIMENT :—Male frog, weighing 34 grms. Brain pithed. Right aorta tied. Cannula tied in left aorta. Heart removed. Abdominal aorta ligatured low down. Normal salt solution first perfused and all blood washed from the vessels.

2.0	P.M.	Skin reflexes tested. Pair of electrodes over spine, with secondary coil at 100 centims., produces strong movements in posterior extremities.
2.5	,,	Commenced to perfuse aldehyde 1 in 300.
2.7	,,	No alteration.
2.9	,,	The same.
2.11	,,	,, ,,
2.15	,,	Skin reflexes quickened.
2.20	,,	Stimulation of cord, with coil at 100 centims., produces tetanus in posterior extremities. Irritation of skin produces quick tonic spasms.
2.25	,,	The same.
2.30	,,	Skin reflexes much delayed and weakened. Electrodes over spine produce less powerful movements than at commencement of the perfusion.
2.35	,,	The same.
2.40	,,	,, ,,
2.50	,,	Electrodes over spine between the scapulæ produce no response with coil at 100 centims.
3.0	,,	Only slight skin reflexes. With coil at 50 centims., electrodes over spine just cause extension of posterior extremities.
3.15	,,	The same.
3.30	,,	No skin reflexes. No movements upon stimulation over spine with current at 50, movements with current at 37, but not till after removal of skin over spine.

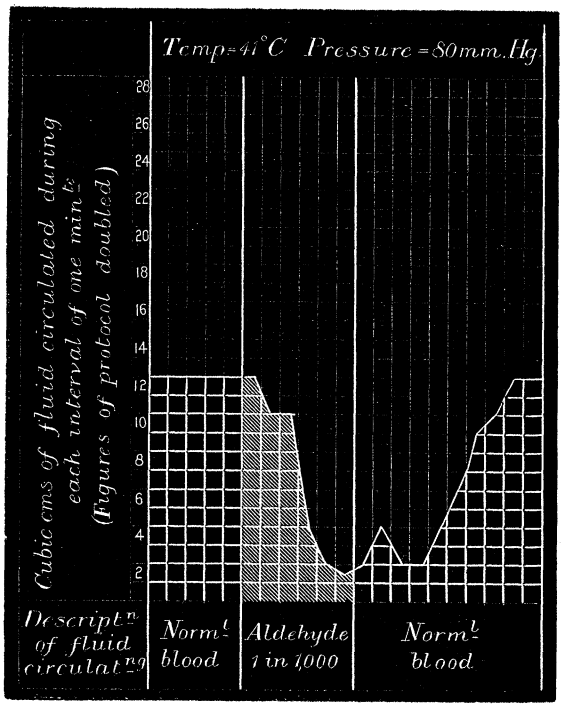
Sensibly the same reflex phenomena, indicating a primary stimulation and a secondary depression of the spinal cord, were always observed during the perfusion experiments with aldehyde on the vessels of the tortoise.

Circulation.

Aldehyde is a vaso-constrictor. This action has been constantly noted and verified in experiment on the renal vessels. Perfusions through the vessels of the tortoise have also demonstrated a constricting influence, only not so prominently. Stronger solutions have been found necessary to produce effects on the tortoise's vessels than those required to produce equal effects on the renal vessels. Dilatation of vessels, either as a primary or secondary influence, has never been observed.

Blood containing aldehyde was perfused through sheep kidneys in the same manner as that employed for aldoxime.

Chart 7.



EXPERIMENT.—Sheep's Kidney (Chart 7). Perfusion of Ethyl-aldehyde 1 part in 1000 parts of Blood from the same animal. Pressure, 80 millims. Hg.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
11.44	Blood	6
This same amount of flow had been noted last five minutes.		
11.45	Aldehyde 1 in 1000 of sheep's blood	6
11.46	. . . . .	5
11.47	. . . . .	5
11.48	. . . . .	2
11.49	. . . . .	1
11.50	. . . . .	0·75
11.51	Normal blood	1
. . . . .	. . . . .	. . . . .
12.0	. . . . .	6

EXPERIMENT.—Sheep's Kidney (Chart 8). Perfusion of Ethyl-aldehyde 1 part in 5000 parts of Blood from the same animal. Pressure, 80 millims. Hg.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
11.6	Normal blood	5
This flow had become steady.		
11.7	Aldehyde 1 in 5000 of sheep's blood	5
11·8	. . . . .	6
11·9	. . . . .	4·5
11.10	. . . . .	4
11.11	. . . . .	3
11.12	. . . . .	3
11.13	. . . . .	3
11.14	. . . . .	2·5
11.15	. . . . .	2·5
11.16	. . . . .	1·5
11.17	. . . . .	1·5
11.18	. . . . .	1·5
11.19	Normal blood	2
11.20	. . . . .	2
11.21	. . . . .	3
11.22	. . . . .	3
11.23	. . . . .	3·5
11.24	. . . . .	4
11.25	. . . . .	5
11.26	Aldehyde 1 in 2000 of sheep's blood	4
11.27	. . . . .	5
11.28	. . . . .	4·5
11.29	. . . . .	4·5
11.30	. . . . .	3
11.31	. . . . .	3
11.32	. . . . .	2·5
11.33	. . . . .	2
11.34	. . . . .	1
11.35	. . . . .	1
11.36	. . . . .	1
11.37	Normal blood	2
. . . . .	. . . . .	. . . . .
11.48	. . . . .	5

Three different strengths of aldehyde solution were used in the experiments just described, and it is to be noted as somewhat peculiar that the resulting constriction of the vessels could scarcely be said to vary in degree. Indeed the 1 in 5000 solution acted almost as powerfully as that containing 1 part of aldehyde in 1000 parts.

Chart 8.

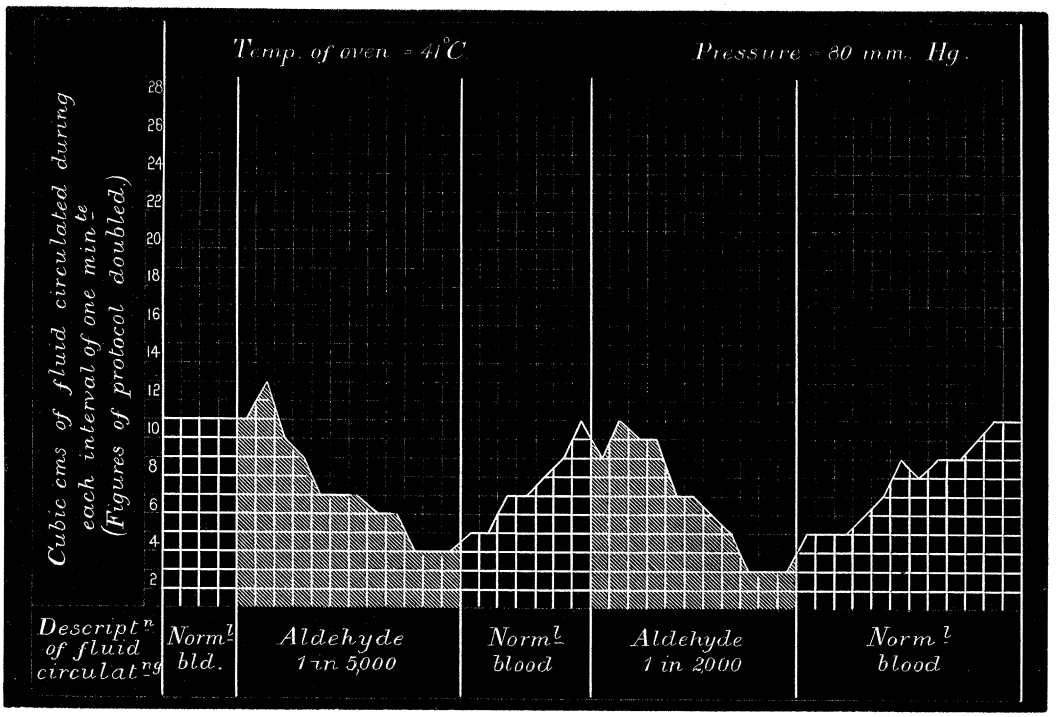
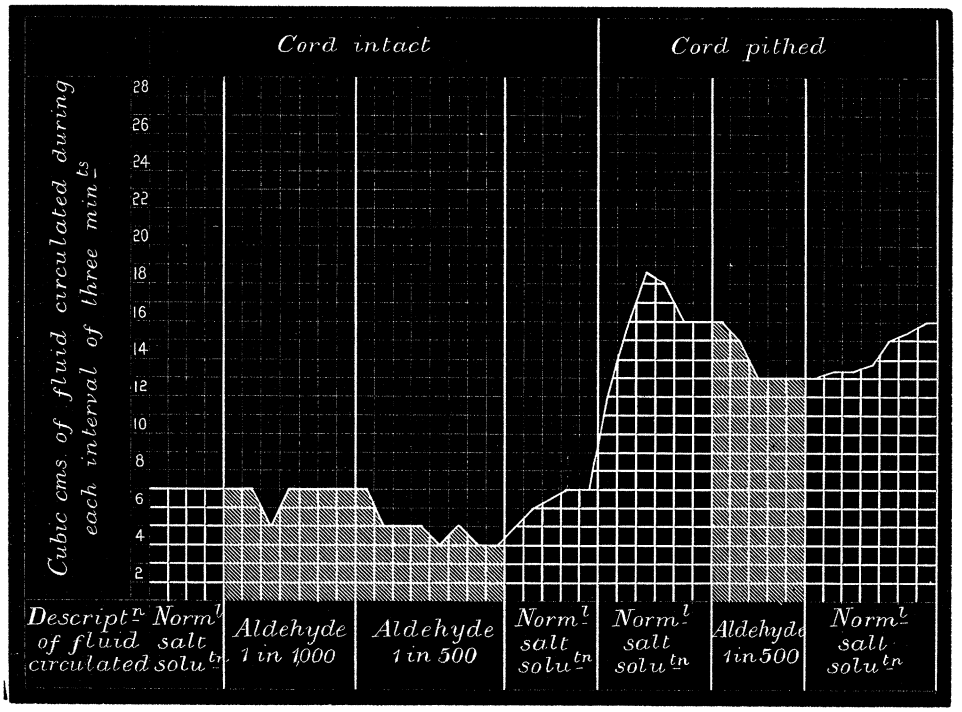


Chart 9.



EXPERIMENT.—Small Water Tortoise (Chart 9). Perfusion of Aldehyde 1 part in 1000 parts of Normal Salt Solution. Pressure, 25 centims.

Time.	Fluid circulating.	Cub. centims. of fluid circulated during interval.	Cub. centims. of fluid circulating per minute.
	(A) Cord intact.		
12.1 12.4	Normal salt solution .	6	2
This flow had been closely maintained during nine minutes.			
12.7	Aldehyde 1 in 1000 .	6	2
12.10	. . . . .	6	2
12.13	. . . . .	4	1·3
12.16	. . . . .	6	2
12.19	. . . . .	6	2
12.22	. . . . .	6	2
12.25	. . . . .	6	2
12.28	Aldehyde 1 in 500 .	6	2
12.31	. . . . .	4	1 3
12.34	. . . . .	4	1·3
12.37	. . . . .	4	1·3
12.40	. . . . .	3	1
12.43	. . . . .	4	1·3
12·46	. . . . .	3	1
12.49	. . . . .	3	1
12.52	Normal salt solution .	4	1·3
12.55	. . . . .	5	1·6
12.58	. . . . .	5·4	1·8
1.1	. . . . .	6	2
1.4	. . . . .	6	2
	(B) Spinal cord pithed.		
1.10 1.13	Normal salt solution .	11	3·6
1.16	. . . . .	15	5
1.19	. . . . .	17·5	5·8
1.22	. . . . .	17	5·6
1 25	. . . . .	15	5
1.28	. . . . .	15	5
1.31	Aldehyde 1 in 500 .	15	5
1.34	. . . . .	14	4·6
1.37	. . . . .	12	4
1.40	. . . . .	12	4
1.43	. . . . .	12	4
1.46	Normal salt solution .	12	4
. . . . .	. . . . .	. . . . .	. . . . .
2.4	. . . . .	15	5

In this last, as in other experiments on the tortoise, a solution containing 1 part of aldehyde in 1000 parts had no apparent action on the vessels.

A solution containing 1 part of aldehyde in 500 parts contracted the vessels, but usually not so powerfully after as before destruction of the spinal cord. On one occasion

the constriction of the vessels was as proportionately great after pithing the cord as it was with the cord intact.

It seems to me that these results can only be interpreted by reference to the action of the drug on the spinal cord. This action we found to be a primary stimulation and secondary depression.

Aldehyde has evidently a local constricting action on the vessel walls, and it would appear that this action may be reinforced by a like influence exerted through the spinal centres during the period of exalted sensibility of the cord. As the cord becomes depressed this central constricting influence is abolished or even replaced by an influence antagonistic to the local constrictory action. This is the only way it seems possible to account for the constriction of the vessels reappearing after pithing the cord in the last experiment.

Heart.

In dilute solution, aldehyde is a cardiac tonic, increasing the amplitude of the beat by producing a more perfect systole, and also increasing the contractile power.

Observations with COATS' apparatus show a marked increase of contractile power on perfusing through a frog's heart a solution of one part of aldehyde in 5000 parts.

This more powerful systole is also shown in tracings taken with a ROY'S tonometer by an increased height of curve, whilst the diastole continues to be traced along the same abscissa.

This action is seen from figs. 24 and 25. This was an experiment with a frog's heart in a ROY'S tonometer. Fig. 24 was traced at 12.27 p.m., after the normal fluid had perfused 16 minutes. The perfusion of ethylaldehyde was commenced at 12.30, the strength of solution being one part of aldehyde in 5000 parts of blood and normal salt solution. This solution was continued 8 minutes, when fig. 25 was traced, and the only effect of the aldehyde is seen to be the greater amplitude of beat due to the increased height of the curves.

Fig. 24.

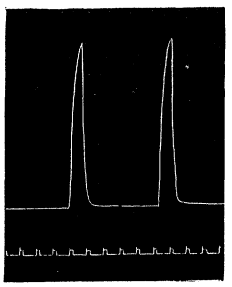
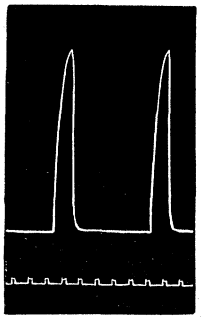


Fig. 25.



The tonic effect of such a solution is not succeeded by any more paralysis than ultimately occurs during the perfusion of the normal fluid. A secondary depressant

action does result from the perfusion of stronger solutions, culminating with the strongest solutions in arrest in systole, and with those of medium strength in arrest in diastole.

Fig. 26 shows the depressant action of a solution twice the strength of the last. The poison was commenced at (P). Almost immediately the curves become less in height. The poison was perfused 4 minutes when the normal fluid was resumed and $3\frac{1}{2}$ minutes later the height of the curves was again restored.

Fig. 26.

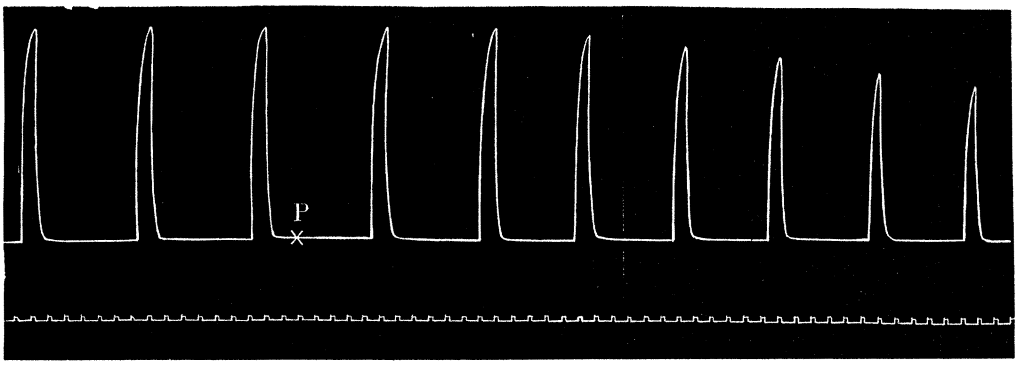
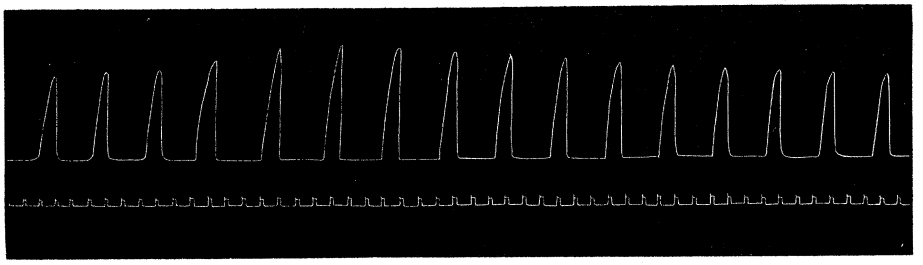


Fig. 27 shows the transient tonic effect of a solution of one part of aldehyde in 2.000 parts of the normal fluid. The resulting increased altitude of curve is succeeded by a gradual diminution in height.

Fig. 27.



The acceleration of rhythm so marked an action of aldoxime is not to be seen in any aldehyde tracing.

Summary.

Having thus gained some little idea of the action of ethylaldehyde, we are in a better position to analyse the physiological actions attributed to ethylaldoxime.

It has been shown that in all probability the blood splits up aldoxime into nitrous acid and aldehyde. Should the blood in this respect fail or be too tardy in its action, there still remains the likelihood that in the interaction between living tissues and

chemical bodies there is a disseverance of a more complex molecule into its component and simpler molecules. The question resolves itself into the nature of the affinities between tissue cells and their mutual surroundings, in fact into the life processes of cells. In any case it seems more scientific in investigating the physiological action of any complex chemical body to look rather for a combination of the ascertained actions of its component parts, than endeavour to pourtray any action peculiar to the whole.

With this object it will be well now to reiterate succinctly the physiological actions attributable to aldoxime, and while so doing to judge how far they reflect the combined actions of a nitrite and of aldehyde.

Muscle.—It was found that aldoxime depressed the irritability of voluntary muscle, and that, in some few experiments, there was a suspicion of a very transient primary stimulation. This depressant action is also possessed by nitrites and by aldehyde. Aldehyde has also a primary stimulant action, but this, in the aldoxime molecule, may be antagonized by the oxime group.

Strong solutions of aldoxime diminish the extensibility and elasticity of muscle, actions also possessed by aldehyde.

Aldoxime, aldehyde, and nitrites all diminish the range of contraction. Aldoxime has sometimes produced an initial increased range of contraction, which initial increase is a usual effect of aldehyde, but would be for the most part counteracted by nitrites.

Nerve.—Aldehyde has no action on nerve trunks. Neither are nitrites generally supposed to affect nerve trunks. I have made many experiments to satisfy myself on this point, and have found that, while nitrites do not appear to influence nerve endings, at least, not before the muscle substance itself, they certainly do diminish the irritability of nerve trunks. The action is neither powerfully nor quickly exerted, but is always noticed. I have also observed that, though causing this depression of irritability in motor nerve trunks, nitrites do not affect their conductivity, or not to the same extent. These results fit in exactly with the action of aldoxime, which also was found to cause some depression of irritability without depressing the conductivity of efferent nerve trunks. This action of nitrites also explains the quicker loss of irritability in the nervous path compared with the loss in the muscle, observed in muscle-nerve preparations immersed in solutions of aldoxime.

In several of these muscle-nerve experiments with aldoxime, a primary stimulation was noted in the nervous path, and since such primary stimulation has not been found in the nerve trunks, the nerve endings in the muscle must be the seat of its localization.

A still greater primary increase of irritability in the nervous path was noted in the case of aldehyde, and here we can again eliminate the nerve trunks. This increased irritability is therefore to be referred to the nerve end-plates. The functional activity of these end-organs is exalted, and, since nitrites have no such action, the exaltation must be accounted for by the action of aldehyde.

It was found that the presence of blood greatly altered the action of aldoxime on muscle. The tendency to contracture was lessened or disappeared in the actions of all but the strongest solutions; the primary increase of irritability was absent; the diminution of irritability came on more quickly.

If we are so far to accept our conclusions, this influence of blood must be interpreted as a sedative or co-ordinating action on the motor end-plates, antagonizing the stimulant action of the aldehyde moiety of the aldoxime molecule, and such a view we have previously seen strongly confirmed by the quite similar action of curare.

Spinal Cord.—Passing now to the spinal cord, the action of aldoxime was shown to be depressant with a questionable initial stimulation. Aldehyde undoubtedly first stimulates the cord, but such an action must be largely antagonized by nitrites, which are depressant *in initio*.

Vessels.—The fact of the vaso-dilating action of aldoxime being so feeble seemed at first to militate against the presence of any nitrite-like body. This can now be explained by the vaso-constrictory influence of aldehyde, and by the excessive weight of aldehyde present in the aldoxime molecule.

The fact that a mixture of blood and aldoxime, after standing, acquires a greater dilating influence is to be accounted for, I take it, by the disappearance of part of the aldehyde, either by oxidation or evaporation. Nitrous acid will not be lost. It will be present in the form of sodium nitrite, which salt we know is not easily oxidizable.

Heart.—Finally, in its action on the heart, we find the tonic effect of aldoxime typified in aldehyde, the acceleration of rhythm in nitrites, and the secondary depressant action in both bodies.

Higher Aldehydes and Aldoximes.

The aldoximes selected for further investigation were propyl-, isobutyl-, and œnanthaldoxime from the fatty compounds; benzaldoxime and salicylaldoxime from the aromatic compounds.

A close pharmacological relationship between these several aldoximes might perhaps have been fairly predicated without experimental proof. Analogy between chemical structure and physiological action is not yet, however, acceptable as a convincing argument, and the elucidation of the pharmacological relationships of the oximido group seemed to demand the examination of aldoximes other than the ethyl compound.

The opportunity appeared a good one since the molecules of these several oximides each include the same volumetric equivalent of the oximido group and differ only in their aldehyde moiety. But the physiological effect of increased molecular weight in

the aldehydes themselves, that is to say, the equation between their toxicity and the number of their included carbon atoms has never been demonstrated.

The toxicity of different alcohols has been investigated in a general way by several observers, notably by RABUTEAU ('Compt. Rend. Soc. de Biol.,' 1878), by DUJARDIN-BEAUMETZ and AUDIGE ('Recherches expérimentales sur la puissance toxique des alcools,' Paris, 1879), and by R. WURTZ ('Compt. Rend. Acad. Sci.,' Paris, 1888).

The outcome of these various contributions is to show that the toxicity of the alcohols increases as the atomic weight, exceptions within certain limits being provided by the highest and lowest alcohols.

This law, I have found, holds good also for the aldehydes, for before proceeding to the study of aldoximes I first shortly investigated the action of the aldehydes corresponding with my selected aldoximes. I will not attempt to detail these experiments. The general type of action was found to be that of acetaldehyde already described. It will therefore suffice for the present purpose to point out briefly how the action exerted by the aldehydes varies as the atomic weight increases.

Propylaldehyde. $CH_3.CH_2.COH$.
Isobutylaldehyde. $(CH_3)_2:CH.COH$.
Heptylicaldehyde. $C_6H_{13}.COH$.

Voluntary Muscle.—The increasing toxicity of these fatty aldehydes is evidenced by voluntary muscle chiefly in two ways—more violent contracture—quicker loss of irritability and contractility. The primary stimulation is always seen in observations with minimal stimuli, but becomes more and more transient as the series of aldehydes is ascended. In muscle tracings a primary increased height of contraction continues to be seen when dilute solutions are used; but the dilution has to be increased with the atomic weight of the aldehyde.

This same variation of action is also reflected in the muscle curves, where the abrupt ascent and increased height, whilst continuing to be seen as initiatory effects, are found to become more transient. At the same time the descent continues to show the rigidity of contracture.

Figs. 28 and 29 are good illustrations of the action of an aldehyde on voluntary muscle.

Fig. 28.

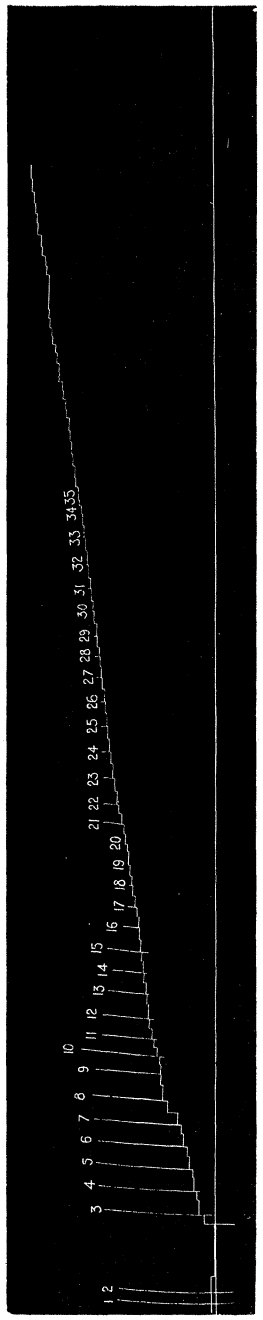
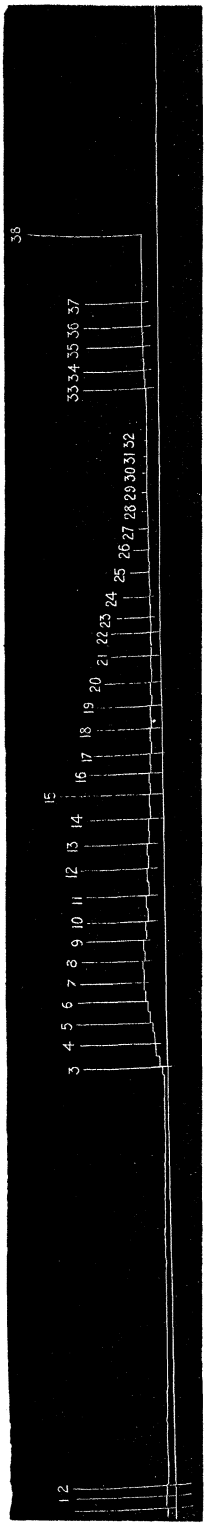

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35

Fig. 29.


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38

ABSTRACT of Protocol (fig. 28).—Gastrocnemius of Frog. Temperature, 16°·6 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1 and 2	..	25
Application of isobutylaldehyde, 1 per cent.		
3	1	27
4	2	26
6	4	24
9	9	18
12	15	12
15	21	9
18	27	1·5
Coil at 0 centim.		
21	33	6
24	39	3
27	45	2

ABSTRACT of Protocol (fig. 29).—Opposite Muscle of same Frog as that of fig. 28. Same conditions as fig. 28. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1 and 2	..	24·5
Application of isobutylaldehyde, ·5 per cent.		
3	1	21
4	3	20
6	7	18
9	13	16
12	19	17
15	25	23
18	31	15
21	37	10·5
24	43	7·5
27	49	2·5
30	55	1·5
Coil at 0 centim.		
33	61	17
36	67	15

The lever was left against the drum all night. The number 38 marks the position of the lever next morning, the muscle being in firm *rigor mortis*.

Motor Nerves.—As the group of aldehydes is ascended, muscle-nerve preparations show a gradually increasing loss of irritability in the nervous path, both absolutely and also slightly in comparison with the loss of irritability in the muscle. The primary exaltation of irritability in the nervous path also becomes a little more evident, and since the nerve trunks continue to show no such action the nerve endings must remain the seat of such primary stimulation.

Spinal Cord.—Here again the primary increase of irritability becomes more intense, but of shorter duration, and the secondary depression follows more quickly. This is true with modification. Thus, the intensity of the primary stimulation of the cord seems scarcely to vary in the action of the lower three members, that is to say, ethyl-, propyl-, and isobutylaldehyde, whereas the potency of their secondary depressant action advances with their increasing weight. Œnanthol causes a more marked primary stimulation than would inferentially be expected, and may cause reflex convulsions in the frog.

Vessels.—Both propyl- and isobutylaldehyde constrict the vessels of the excised sheep's kidney. This action varies inversely as the atomic weight. Isobutylaldehyde constricts the vessels less than propylaldehyde, and the latter less than ethylaldehyde. Œnanthol first constricts and then dilates the same vessels. In the tortoise the action of propylaldehyde has not been found to differ in any way from that of its ethyl homologue. Isobutylaldehyde dilates the tortoise's vessels slightly and the action increases somewhat as the circulation is continued.

The effect of pithing the cord in the tortoise has varied with the strength of solution circulated, and with the length of time the circulation has been continued. Generally speaking, the dilating influence of isobutylaldehyde is less evident after pithing the cord than it is whilst the cord is intact, but should the pithing be performed early in the experiment, the degree of dilatation caused by this drug is as great or even greater after than it is before the destruction of the cord.

Judging by my notes, it would appear that isobutylaldehyde acts locally on the vessel walls to dilate them, that this action is at first either uninfluenced by or slightly antagonized by the spinal cord; and that later a vaso-dilator influence is also exerted through the spinal centres.

Œnanthol also dilates the vessels of the tortoise, but provided the spinal cord be intact, by no means so markedly as the vessels of the excised kidney. Pithing the cord balances the comparison, for then the tortoise's vessels are dilated by œnanthol to as great a degree as those of the excised sheep's kidney. It would thus appear that œnanthol has its local vaso-dilating action antagonized by a central action exerted through the spinal cord.

Heart.—All these aldehydes have essentially the same action on the heart, the difference between them being simply one of degree. They all tend to slow the

cardiac rhythm and have a primary tonic and secondary depressant action. As the atomic weight of the aldehyde increases, weaker solutions are required to show the tonic effect, and the arrest in diastole is more quickly reached.

Benzaldehyde. C_6H_5-COH.

Salicylaldehyde. OH-C_6H_4-COH.

These aldehydes have the same type of action as their fatty homologues, but differ from them in the greater dominance of irritation, which is more especially seen in their action on the spinal cord and voluntary muscle.

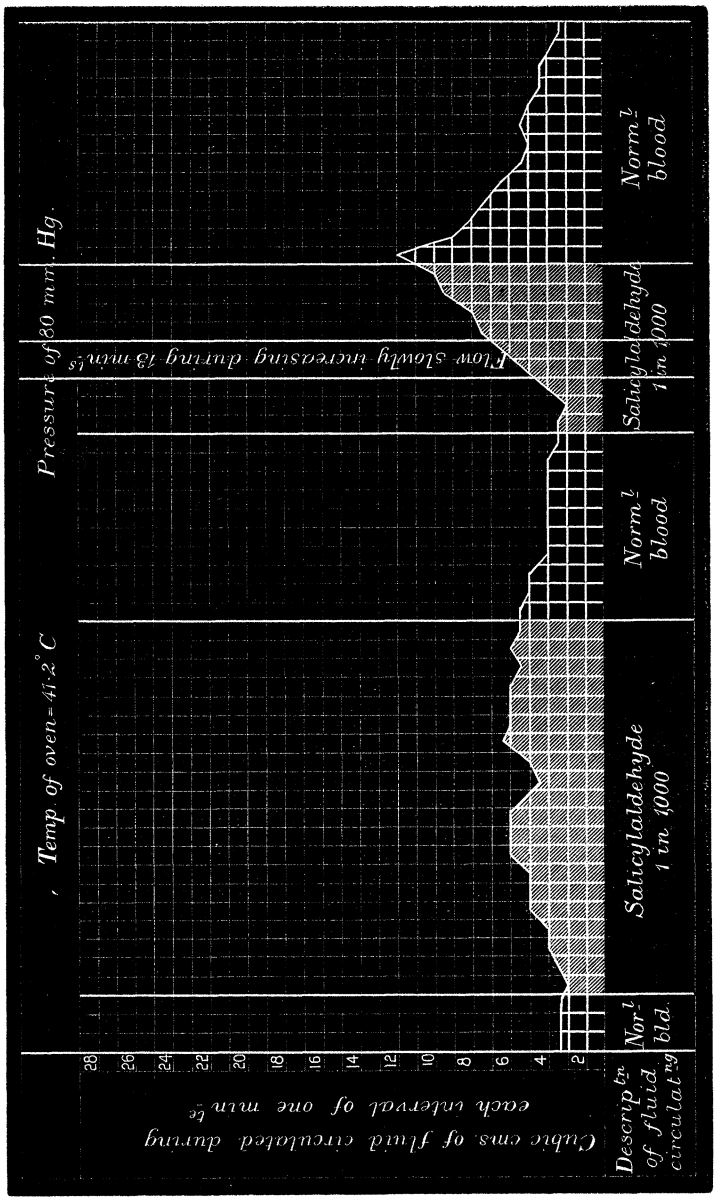
Voluntary Muscle.—Tracings of frog muscles immersed in solutions of these aldehydes when contrasted with the tracings of muscles poisoned with the fatty aldehydes show more powerful contracture, and a more distinct primary increase in height of contraction. Muscles immersed in a solution containing one part of either of these two aromatic aldehydes in 1000 parts, are killed in complete rigor in less than half-an-hour.

Motor Nerves.—These aromatic aldehydes again cause a prior loss of irritability in the nervous path compared with the loss in the muscle substance. There is also the primary increase of irritability traceable to the end-plates, seen even in very dilute solutions. This latter action is more noticeable than in the case of the fatty aldehydes. When solutions of greater strength than 1 in 1000 are used, the comparative increase of irritability in the nervous path is either not seen at all or is very transient.

Spinal Cord.—In a very few minutes after injecting a frog with either benzaldehyde or salicylaldehyde, the skin reflexes are found quickened and exaggerated. This spinal irritability increases; the slightest touch of the skin or impact of a current of air soon suffices to cause a convulsive movement, till finally the posterior limbs become rigid in extension. Later, this rigidity passes off, and shortly the cord is found quite insensitive.

Vessels.—Both these aldehydes dilate the vessels of the excised sheep's kidney. Still, having regard to what we know of other salicyl compounds, it is surprising how feeble is the vaso-dilating action of salicylaldehyde.

Chart 10.


Cubic cms of fluid circulated during each interval of one min.te
Descrip.tn of fluid circulat.g
Nor.l bld.
Salicylaldehyde 1 in 1,000
Norm.l blood
Salicylaldehyde 1 in 1,000
Norm.l blood
Temp of oven = 41·2° C
Pressure of 80 m.m. Hg.
Flow slowly increasing during 13 min.s

EXPERIMENT.—Sheep's Kidney (Chart 10). Temperature of Oven, 41°·2 C. Pressure = 80 millims. Hg. Perfusion of Salicylaldehyde, 1 in 1000 of Blood from the same animal.

Time.	Fluid circulating through kidney.	Cub. centims. of fluid flowing per minute.
3.39	Normal blood	2·5
This flow had become steady.		
3.40	Salicylaldehyde 1 in 1000	2
3.41	. . . . .	2·5
3.42	. . . . .	3
3.43	. . . . .	3
3.44	. . . . .	4
3.45	. . . . .	4
3.46	. . . . .	4
3.47	. . . . .	5
3.48	. . . . .	5
3.49	. . . . .	5
3.50	. . . . .	4
3.51	. . . . .	3·5
3.52	. . . . .	4
3.53	. . . . .	5·5
3.54	. . . . .	5
3.55	. . . . .	5
3.56	. . . . .	5
3.57	. . . . .	4·5
3.58	. . . . .	5
3.59	. . . . .	4·5
4.0	Normal blood	4·5
. . . . .	. . . . .	. . . . .
4.9	. . . . .	2·5
4.10	Salicylaldehyde 1 in 1000	2·5
4.11	. . . . .	2
4.12	. . . . .	3
The flow then gradually increased.		
4.25	. . . . .	6·5
4.26	. . . . .	7
4.27	. . . . .	8·5
4.28	. . . . .	9
4.29	Normal blood	11
4.30	. . . . .	8
4.31	. . . . .	7
4.32	. . . . .	5·5
. . . . .	. . . . .	. . . . .
4.41	. . . . .	2·5

The poison was again circulated, but the vessels did not again dilate to the same extent, the flow not surpassing 6 cub. centims. per minute.

Heart.—A solution of either of these aldehydes so weak as 1 part in 30,000 parts has a marked action on the frog's heart. The rhythm is slowed, whilst the amplitude of beat gradually diminishes and the heart becomes arrested in diastole. Solutions

stronger than 1 part in about 30,000 parts cause imperfect dilatation of the ventricle during diastole with final arrest in systole. In no strength has any solution of either drug been found to strengthen the heart or to cause any increased amplitude of beat.

Propylaldoxime. C_3H_6:N.OH.
Isobutylaldoxime. C_4H_8:N.OH.
Œnanthaldoxime. C_7H_{14}:N.OH.

Propylaldoxime.—This is a fluid very like ethylaldoxime, differing, however, from its lower homologue in having a higher boiling-point (130°–132°), and though soluble, in not being miscible with water in all proportions.

Isobutylaldoxime.—This, again, is a colourless fluid. It is much less soluble in water than the two preceding aldoximes, and has a boiling-point about 139° C.

Œnanthaldoxime.—This body is a solid, occurring in white, waxy tabellæ, with a disagreeable smell of rancid oil. The tabellæ melt at 50° C. and boil at 195° C. This aldoxime is with great difficulty soluble in cold water, but easily soluble in alcohol or ether.

The pharmacological actions of these three fatty aldoximes are closely allied, and as in the case of the corresponding aldehydes, may be conveniently described together.

General Action in Frogs.—The general action of these drugs when injected in pithed frogs scarcely differed from that of ethylaldoxime. No convulsive movements were ever observed after injecting either propyl- or isobutylaldoxime. The period of exalted reflexes in the action of these two bodies is short and the depressant action more marked. In this respect œnanthaldoxime acts differently, producing more exaltation of reflexes than even ethylaldoxime, and a tendency to convulsive response.

Voluntary Muscle.—These fatty aldoximes differ amongst themselves in their action on voluntary muscle exactly as do the corresponding aldehydes. As the series is ascended, the action on voluntary muscle becomes more toxic, as seen firstly in the increasing degree of contracture, and secondly, in the quicker loss of irritability.

Referring back to figs. 4 and 5, we there find compared the effects on frog's muscle of ethylaldoxime and propylaldoxime in solutions of the same strength, that is to say, 1 part of the drug to 200 parts of normal salt solution. The muscles used were the two gastrocnemii of the same frog. In each case the conditions were the same. The poisoned solutions were added at the same time, and the contractions of the two muscles were taken simultaneously.

Contrasting first the loss of irritability in the two cases, it is seen from fig. 5 that the muscle which was immersed in the solution of propylaldoxime barely responded at stimulation 19. The stimulus employed was that of one DANIELL'S cell, with the

secondary coil placed at 10 centims. distance. The time of induction of this stimulus was 48 minutes after addition of the poison. The opposite muscle of the same frog under the action of ethylaldoxime still responded well at contraction 19.

The coil was then put at 5 centims. distance. The tracings were continued on another paper, and, four hours and twelve minutes after commencement of the poison, the muscle in propylaldoxime was dead. Two hours and a half later still, the opposite muscle, under the influence of ethylaldoxime, continued to respond well.

The same two tracings also illustrate the greater power possessed by propylaldoxime to produce contracture. Whilst the secondary coil remained at 10 centims. the base line of fig. 4 gradually fell. No fall is seen in fig. 5. On the contrary, propylaldoxime caused the base line to ascend from the very commencement of its action, and, at contraction 19, the base line is already seen well above the abscissa.

In the action of neither drug is there any evidence from these tracings of a primary increased range of contraction. With a constant stimulus the range in both cases is gradually diminished.

As just stated, the muscle immersed in a 5 per cent. solution of propylaldoxime (fig. 5) ceased to respond in 48 minutes to the shock induced with the secondary coil at 10 centims. distance. In an experiment with a solution of isobutylaldoxime of the same strength it was seen that the muscle ceased to respond to the same stimulus in 18 minutes, and was, at the same time, also irresponsive to stimulation with the coil at 5 centims. In 47 minutes, this muscle in the solution of isobutylaldoxime had become insensitive even with the coil at zero. This muscle, therefore, was killed by a solution of isobutylaldoxime in 47 minutes, compared with 4 hours and 12 minutes, the time taken to kill a muscle by the same volumetric solution of propylaldoxime.

There is also an interesting point in the contracture produced by isobutylaldoxime. Contracture comes on more quickly, and is at first more marked in the muscle acted upon by isobutylaldoxime than in a muscle acted upon by either of the two lower aldoximes ; but, having reached a certain point, the lever begins again to fall, and, as will presently be seen, the interval between the application of the solution, and the commencing fall of the base line, closely corresponds with the time required by such a solution to annul the irritability in the nervous path in muscle-nerve preparations.

In figs. 30 and 31 two stronger solutions of propylaldoxime and of isobutylaldoxime are compared. In each case a 1 per cent. solution of the drug was employed. Again, we see the more rapid loss of irritability, as well as the immediate onset of contracture brought about by the isobutyl compound. Under the influence of this stronger solution both muscles retain their contracture, there being no return of the base line towards the abscissa.

Fig. 30.

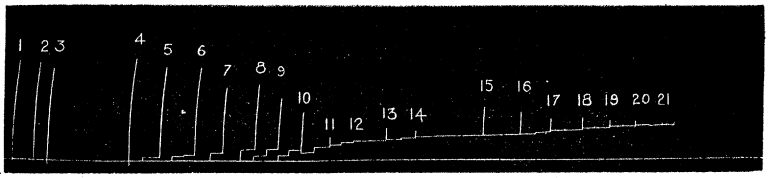
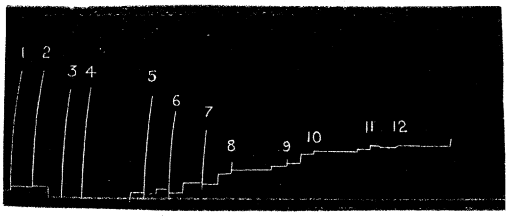


Fig. 31.



ABSTRACT of Protocol (fig. 30).—Gastrocnemius of Frog. Temperature, 16°·1 C. Load, 12 grms. Coil at 10 centims.

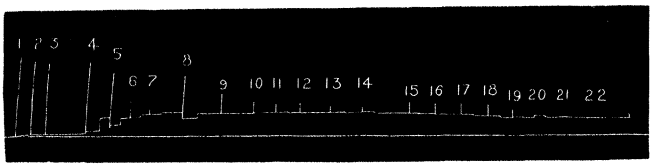
Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2, and 3	..	19
Application of propylaldoxime, 1 per cent.		
4	3	21
6	11	19
8	20	16
10	32	8
Coil at 5 centims.		
13	50	3
Coil at 0 centims.		
15	62	6
17	74	3
19	86	2
21	98	

ABSTRACT of Protocol (fig. 31).—Opposite muscle of same Frog used in preceding observation. Same conditions as fig. 30. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
	Application of normal salt solution.	
3 and 4	..	22
	Application of isobutylaldoxime, 1 per cent.	
5	3	19·5
6	6	16
7	9	11
8	15	2
	Coil at 5 centims.	
9	18	1·5
	Coil at 0 centims.	
11	24	1
12	27	
	No response in half-an-hour.	

Œnanthaldoxime, owing to its little solubility, is a difficult drug to work with. In the observation from which fig. 32 is taken, there was employed a saturated solution of œnanthaldoxime, that is to say, 1 part of the drug in about 1200 parts of normal salt solution.

Fig. 32.



ABSTRACT of Protocol (fig. 32).—Gastrocnemius of Frog. Temperature, 16°·6 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2, and 3	..	15
Application of Œnanthaldoxime (saturated solution).		
4	1	15·5
5	4	10
6	7	5
7	10	2
Coil at 5 centims.		
8	13	9
9	19	4
14	34	1·5
Coil at 0 centim.		
15	37	2·5
22	67	no further response.

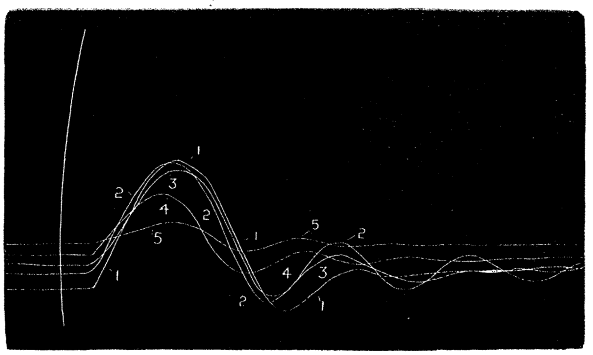
Considering the weakness of the solution, the loss of irritability brought about by the drug is seen to be developed very rapidly, and when, by the aid of alcohol, stronger solutions are used, and their action compared with that of similar solutions of the lower fatty aldoximes, œnanthaldoxime is seen to destroy muscle irritability much more quickly than these lower homologues. Its power to provoke contracture is also greater as witnessed by the same tracing. Equally weak solutions of the lower aldoximes show no signs of contracture.

Muscle Curve.—The curves are simply affected in the descent by contracture, a phenomenon exactly similar to that observed in the action of ethylaldoxime. In fact, whatever difference there is to be seen in the curves of muscles poisoned with any of these aldoximes simply depends again upon the amount of contracture, and the rapidity with which irritability is lost. One tracing will suffice for all.

Fig. 33 represents the curves described by a muscle in a 1 per cent. solution of propylaldoxime. An interval of three minutes was allowed to elapse between the registrations. No. 1 is the normal curve, immediately after which the propylaldoxime solution was applied.

The muscle was the gastrocnemius of a Frog. Temperature, 16°·1 C. Load, 12 grms. Coil at 10 centims.

Fig. 33.



Curarised Muscle.—Curari modifies the action of these aldoximes exactly in the same way as it was found to modify the action of ethylaldoxime. All contracture is abolished. This fact is illustrated by figs. 34 and 35. Both muscles were first curarised, and then the one was immersed in a 1 per cent. solution of propylaldoxime, and the other in a ·5 per cent. solution of isobutylaldoxime. There is no evidence of contracture. Throughout both tracings there is a gradual fall of the base line, just as is seen in a muscle simply immersed in normal salt solution.

Fig. 34.

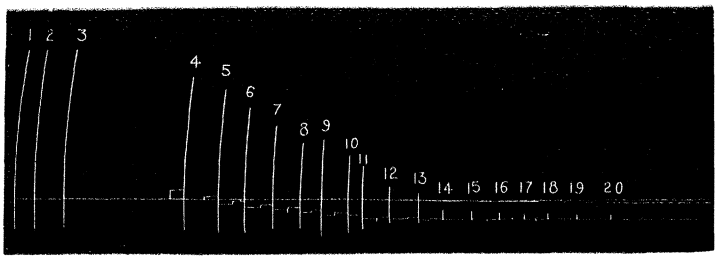
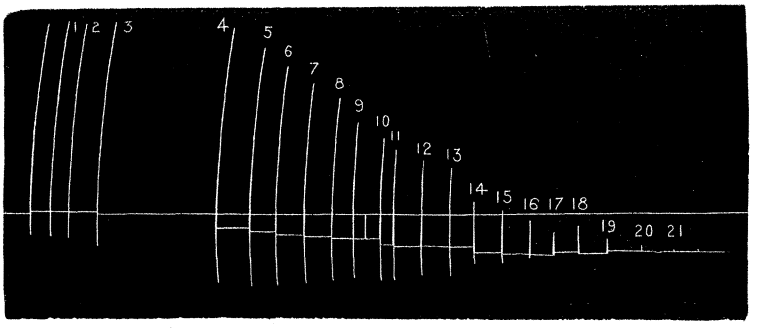


Fig. 35.



ABSTRACT of Protocol (fig. 34).—Gastrocnemius of Frog, curarised. Temperature, 16°·3 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2, and 3	..	30
Application of propylaldoxime, 1 per cent.		
4	3	25
6	9	20
8	15	14
10	21	12
12	27	7
14	39	2·5
20	57	no response after 60 minutes.

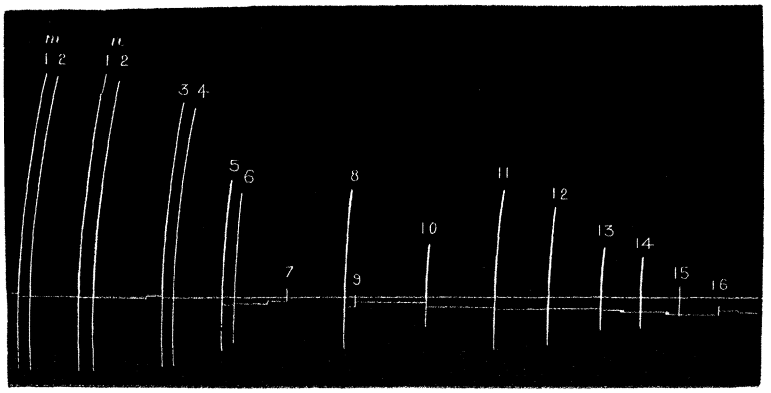
ABSTRACT of Protocol (fig. 35).—Opposite Gastrocnemius (curarised) of same Frog as that used in observation (fig. 34). Same conditions.

The first three contractions were the normal tracing. Isobutylaldoxime ·5 per cent was then applied at the same time as the application of the poison to the opposite muscle, and the subsequent contractions were in each case registered simultaneously. The two muscles were killed in almost the same period, this one in the solution of isobutylaldoxime ceasing to respond in 63 minutes.

Action in Presence of Blood.—The presence of blood acts also in the same way as was found in the case of ethylaldoxime. The effect is again that of curari; all contracture is abolished.

Fig. 36 was described by a muscle immersed in a ·5 per cent. solution of isobutylaldoxime in equal parts of sheep's blood and normal salt solution. The base line is seen to have continuously fallen.

Fig. 36.



ABSTRACT of Protocol (fig. 36).—Gastrocnemius of Frog with nerve attached. Temperature, 16°·6 C. Load, 12 grms. Coil at 10 centims.

Muscle stimulation.	Duration of application.	Nerve stimulation.
	minutes.	
Application of normal salt solution.		
1 and 2	..	1 and 2.
Application of isobutylaldoxime, ·5 per cent. in equal parts of sheep's blood and normal salt solution.		
3	2	4
5	9	6
7	14	no response
Coil at 5 centims.		
8	15	9
10	19	no response
Coil at 0 centim.		
11	20	no response
16	44	
no response	49	

Efferent Nerves.—Muscles with their supplying nerves dissected out and left attached were examined in the same way as that adopted in the investigation of ethylaldoxime. It has invariably been found that the loss of irritability is greater in the nerve; that is to say, stimulation of the nerve always fails to provoke a muscle response before such failure is recorded by direct stimulation of the muscle. This loss of irritability in the nervous path becomes more marked an action as the series of aldoximes is ascended. Propylaldoxime does not differ much in this respect from the ethyl compound, but the action is more marked in the case of isobutylaldoxime. Thus, in fig. 36, stimulation of the nerve ceased to produce any contraction of the muscle in 14 minutes after commencing the poisoned solution, and 5 minutes later there was no muscular response even to maximal stimulation of the nerve. The muscle is seen to have responded half-an-hour longer to direct stimulation.

Experiments on nerve trunks, as before pointed out, are not very trustworthy, since it would seem that no matter how carefully the experiment be performed, capillary currents along the nerve-trunks may carry some poison to the end-plates. Again, it would appear difficult to reach the axis-cylinder by means of solutions directly applied to the continuity of medullated nerve-trunks. Such experiments have, however, in the action of the drugs, shown some depression of irritability, and that before conductivity just as was observed in the action of ethylaldoxime. This

has more especially been the case with isobutylaldoxime, even more so than with œnanthaldoxime.

Still, the depression of irritability in efferent nerve-trunks has never been seen anything like that observed in the nervous path in muscle-nerve preparations, when the two structures are together immersed in the same solution.

The poison used in fig. 36 we saw to have been dissolved in equal parts of blood and normal salt solution, and that, therefore, no contracture was evidenced. The nerve ceased to convey stimuli in 19 minutes. Now, comparing this result with that of other experiments in which solutions of isobutylaldoxime of similar strength were used in the absence of blood, the fact is brought out that the loss of irritability in the nervous path in the one case corresponds in time with the relaxation of contracture and return of the base-line to the abscissa in the other case. This comparison suggests cause and effect. We have seen that the nervous loss of irritability cannot be due to the action of the drug on the nerve-trunks ; it must, therefore, be referred to the end-plates. It seems then that the failure of conductivity through these end-plates is synchronous with the relaxation of contracture.

This may perhaps be another argument in support of my contention, that contracture, at least in the case of these drugs, is due to their action on the nerve end-plates.

It will be at once objected that this return fall of the base line does not always take place. I would answer that this is probably due to the tetanic condition of the muscle having been so great or maintained so long, that some actual *rigor mortis* has already commenced, and may then continue to progress in spite of the end-plates having become paralysed. The same picture is seen on the large scale, in the rapid onset of *rigor mortis* after strychnine poisoning, when the primary seat of the chaos is the spinal centre instead of the muscle end-plate.

Spinal Cord.—Intralymphatic injections of these higher aldoximes in frogs when conducted with special reference to their action upon the spinal cord, have demonstrated a paralysing action on that structure, with an intensity varying with the molecular weight of the aldoxime. There has also been observed an initial period of spinal irritability. This primary phase in the action of the lower three aldoximes has varied inversely as the molecular weight, and not only does the duration of the phase lessen with the increase of weight, but also its intensity.

It is in this primary action that œnanthaldoxime has been found to depart from the general rule. Although œnanthaldoxime is certainly more toxic to the spinal centres than either of the three lower homologues, yet in comparison with their action the duration of the stimulant phase of œnanthaldoxime is found to bear a greater proportion to the duration of the whole action. And not only the duration, but also the intensity of the phase is greater, as shown by reflex convulsive movements. In fact, with œnanthaldoxime, this primary stimulant action on the spinal cord ceases to

Chart 11.

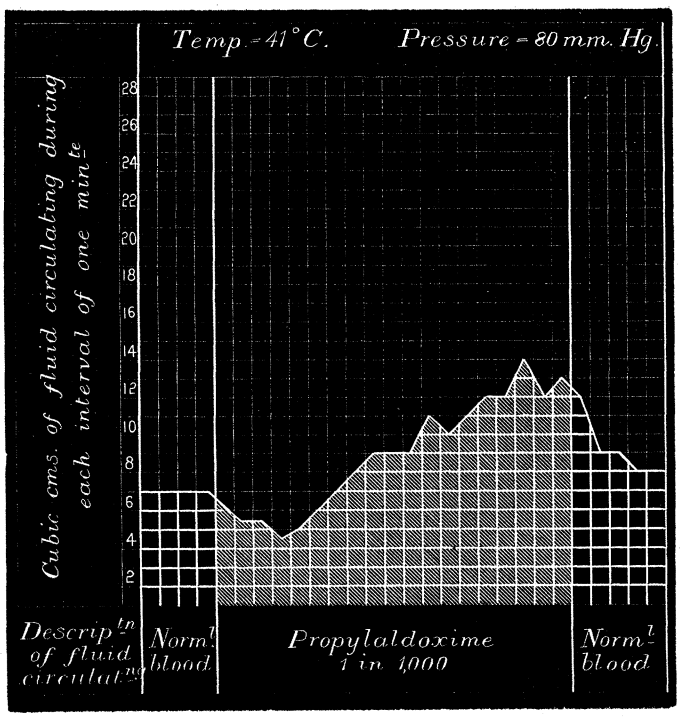
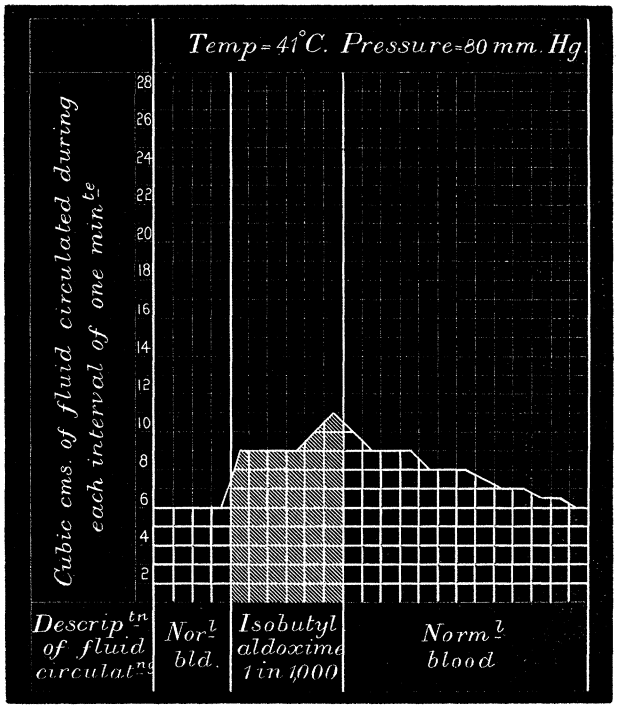


Chart 12.



be the vanishing quantity it was found to be in the case of the lower three aldoximes, and again becomes a main feature for consideration.

Vessels.—The actions of propylaldoxime and of isobutylaldoxime on the vessels of the excised sheep kidney are subject to variation by the same influences as those found to affect the action of ethylaldoxime. That is to say, the result of circulating a solution in blood of one of these drugs depends upon the time the solution has been standing, upon the facility for evaporation, and upon the temperature.

If the solution to be circulated be mixed in the ordinary course, the blood used being taken from the same animal as that providing the kidney, and the experiment being performed as soon as convenient, then the actions of these aldoximes, when compared with the action of ethylaldoxime, under the same conditions, show a diminishing vaso-constrictory influence and an increasing vaso-dilatory influence. Thus, when circulated under these conditions in ovens at the body temperature, propylaldoxime produces a primary constriction and a secondary dilatation, whilst isobutylaldoxime dilates the vessels without, as a rule, any primary constriction being manifest. The following two abstracts of experiments are in illustration :—

EXPERIMENT.—Sheep's Kidney (Chart 11). Temperature of Ovens = 41° C. Pressure = 80 millims. of Hg. Propylaldoxime, 1 in 1000 of Blood from the same animal.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid circulating per minute.
11.1 A.M.	Normal blood	6
11.2 „	Propylaldoxime 1 in 1000 of sheep's blood	5
11.3 „	. . . . .	4·5
11.4 „	. . . . .	4·5
11.5 „	. . . . .	3·5
11.6 „	. . . . .	4
11.7 „	. . . . .	5
11.8 „	. . . . .	6
11.9 „	. . . . .	7
11.10 „	. . . . .	8
11.11 „	. . . . .	8
11.12 „	. . . . .	8
11.13 „	. . . . .	10
11.14 „	. . . . .	9
11.15 „	. . . . .	10
11.16 „	. . . . .	11
11.17 „	. . . . .	11
11.18 „	. . . . .	13
11.19 „	. . . . .	11
11.20 „	. . . . .	12
11.21 „	Normal blood	11
11.22 „	. . . . .	8
11.23 „	. . . . .	8
11.24 „	. . . . .	7
11.25 „	. . . . .	6

EXPERIMENT.—Sheep's Kidney (Chart 12). Temperature of Ovens, 41° C. Pressure, 80 millims. of Hg. Isobutylaldoxime, 1 in 1000 of Blood from the same animal.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
11.0 A.M.	Normal blood	5
11.1 „	Isobutylaldoxime 1 in 1000 of sheep's blood	8
11.2 „	. . . . .	8
11.3 „	. . . . .	8
11.4 „	. . . . .	8
11.5 „	. . . . .	9
11.6 „	. . . . .	10
11.7 „	Normal blood	9
11.8 „	. . . . .	8
. . . . .	. . . . .	. . . . .
11.19 „	. . . . .	5

Œnanthaldoxime has been found to possess a very powerful action on the vessels. The influences affecting the actions of the lower three aldoximes are not noticed to affect the action of the œnanth compound, which action is always seen in a dilatation of the vessels, no constriction, however transient, having in any experiment been attributable to this body. The same powerful vaso-dilator action has been noted in all cases. For example—

EXPERIMENT.—Sheep's Kidney (Chart 13). Temperature of Oven, 41° C. Pressure, 80 millims. of Hg. Œnanthaldoxime, 1 in 2000 of Blood from same animal.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
11.7 A.M.	Normal blood	4
11.8 „	Œnanthaldoxime 1 in 2000 of blood	4
11.9 „	. . . . .	5
11.10 „	. . . . .	42
11.11 „	. . . . .	45
11.12 „	Normal blood	37
11.13 „	. . . . .	22
11.14 „	. . . . .	11·5
11.15 „	. . . . .	7
11.16 „	. . . . .	5
11.17 „	. . . . .	4

When circulated through the vessels of the tortoise the action of propylaldoxime is that of vaso-dilatation from the commencement. There is never seen the primary

constriction noted in the renal perfusions. The dilatation of the vessels is much greater than that brought about by ethylaldoxime, and the influence of the spinal cord is in no way to check the action.

Chart 13.

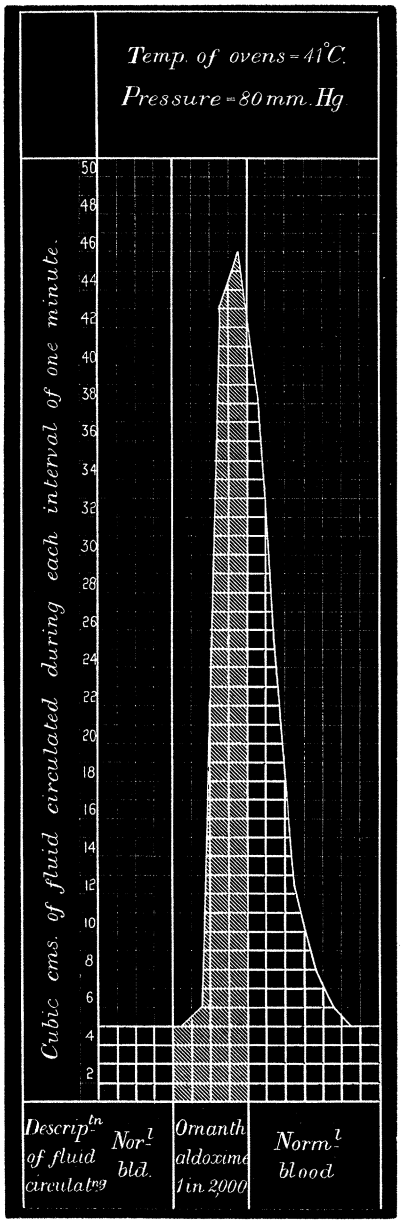
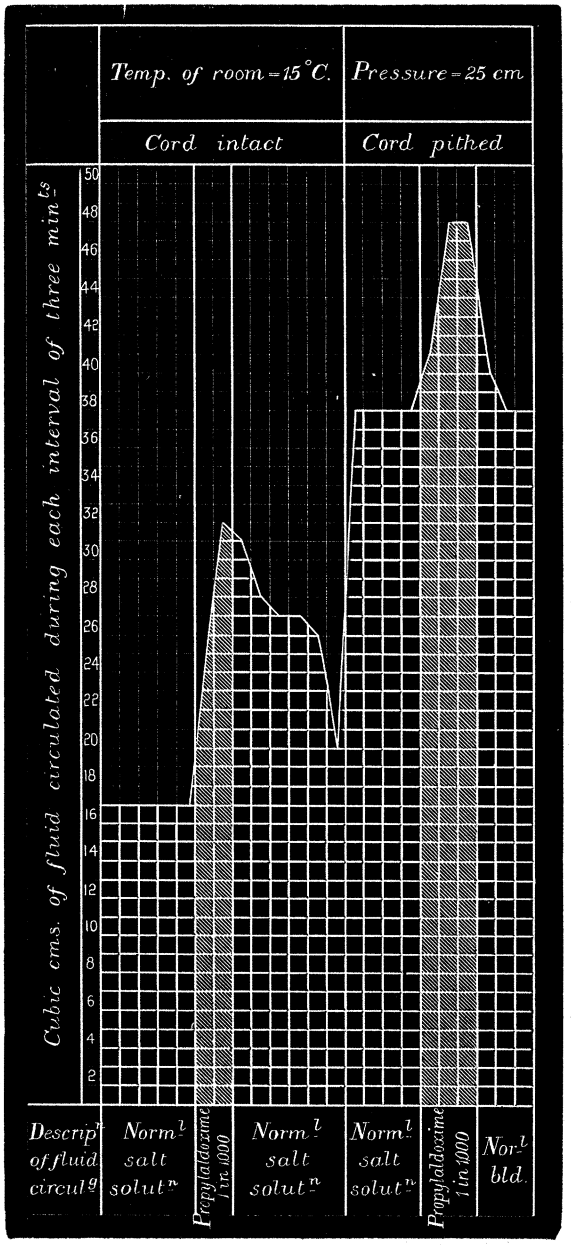


Chart 14.



The following abstract of a protocol will suffice to illustrate this action of propylaldoxime.

EXPERIMENT.—Water Tortoise (Chart 14). Temperature of Room, 15° C. Pressure, 25 centims. Propylaldoxime, 1 in 1000 of normal salt solution.

Time.	Fluid circulating.	Cub. centims. of fluid circulated during interval.	Cub. centims. of fluid flowing per minute.
	(A) Cord Intact.		
11.55 A.M. to 11.58 „	Normal salt solution . .	16	5·3
12.1 P.M.	Propylaldoxime 1 in 1000	24	8
12.4 „	. . . . .	31	10·3
12.7 „	Normal salt solution . .	30	10
12.10 „	. . . . .	27	9
12.13 „	. . . . .	26	8·6
12.16 „	. . . . .	26	8·6
12.19 „	. . . . .	25	8·3
12.22 „	. . . . .	19	6·3
	(B) Cord Pithed.		
1.29 P.M. to 1.32 „	Normal salt solution . .	37	12·3
1.33 „ to 1.36 „	Propylaldoxime 1 in 1000	40	13·3
1.39 „	. . . . .	47	15·6
1.42 „	. . . . .	47	15·6
1.45 „	Normal salt solution . .	39	13
1.48 „	. . . . .	37	12·3

Isobutylaldoxime acts upon the tortoise vessels in the same way as propylaldoxime, the only difference being that equal effects are produced by weaker solutions.

Much weaker solutions of œnanthaldoxime suffice, apparently, to produce complete dilatation of the vessels of the tortoise, since the same maximal flow is attained both before and after destroying the spinal cord.

In very dilute solutions, however, œnanthaldoxime differs from both propyl- and from isobutylaldoxime by the fact that a greater relative degree of vaso-dilatation is produced after than before pithing the spinal cord. In this the œnanth- agrees with the ethyl- compound, and in both cases the explanation is found in the action of the drug on the spinal centres.

Heart.—In their action on the heart all these aldoximes agree in producing an accelerated rhythm. The primary tonic influence seen to be possessed by ethyl-aldoxime is exerted to a less extent by propylaldoxime. Such tonic influence is entirely absent from the action of the isobutylaldoxime and also from that of œnanthaldoxime. An acceleration of rhythm is the only cardiac action of weak solutions of the two latter drugs. This is well seen by reference to figs. 37, 38, 39. These tracings are the records of an experiment with ROY'S Tonometer, in which isobutyl-

aldoxime was perfused in the proportion of 1 part to 1200 parts of a mixture of blood and normal salt solution. A slightly depressant action is the only accompaniment of the accelerated rhythm, as shown by fig. 38.

Fig. 37.

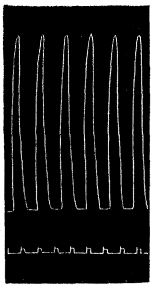


Fig. 38.

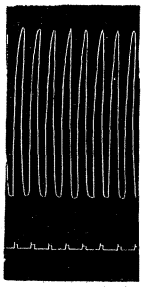
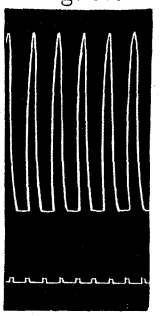
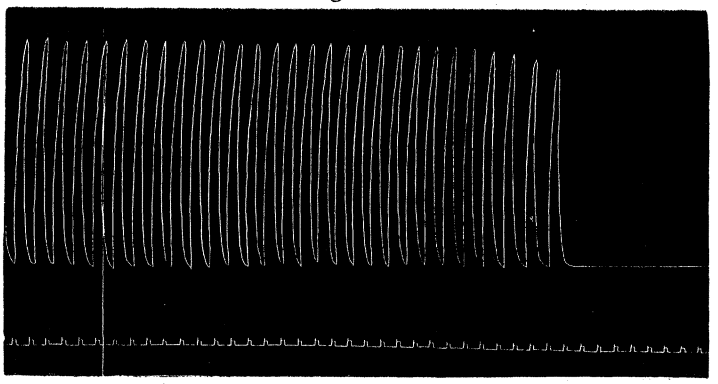


Fig. 39.



Stronger solutions of isobutylaldoxime depress the heart, and cause arrest in diastole, as seen from the tracing in fig. 40.

Fig. 40.



The accelerated rhythm is best seen in figs. 41 and 42. In this experiment the perfusion fluid contained 1 part of isobutylaldoxime in 400 parts, and the duration of the diastole was lessened in forty minutes from 15″ (fig. 41) to 2″ (fig. 42). Four minutes after resuming the perfusion of the normal fluid the duration of the diastole was again 15″.

Fig. 41.

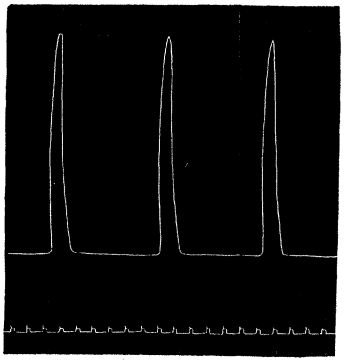
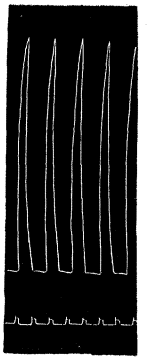


Fig. 42.



Much stronger solutions of propylaldoxime are required to produce depression of the heart's action. Thus a solution of 1 part of propylaldoxime in 200 parts has no more depressant influence than was shown to be exerted by a solution of 1 part of isobutylaldoxime in 1200 parts.

Fig. 43.

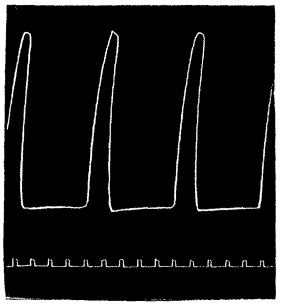


Fig. 44.

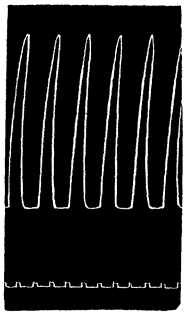
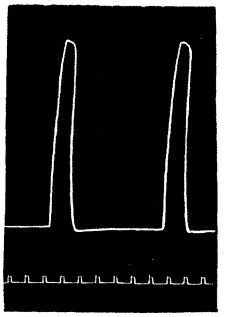


Fig. 45.



This fact is illustrated by figs. 43, 44, and 45. In this experiment the acceleration of rhythm was very marked, but though the poisoned solution was perfused three hours, it is seen that, upon reverting to the normal perfusion, the systole became as strong and complete as at the commencement of the experiment.

Blood.—The interactions between blood and these higher aldoximes are essentially the same as those between blood and ethylaldoxime. After addition of the drugs at ordinary temperatures, the blood darkens in colour more quickly if it be propylaldoxime than is the case with ethylaldoxime, and more quickly still if it be the isobutyl compound. At the body temperature the change takes place much more rapidly. In fact, on the addition of isobutylaldoxime to blood at 40° C., the colour almost immediately darkens. Strong solutions of these two aldoximes also decompose the blood, with extrusion of the colouring matter from the corpuscle. This latter process can be watched under the microscope, when there is presented the appearance of the red blood corpuscles shrinking, and so causing the pigment to be squeezed out in granular lumps.

Œnanthaldoxime again departs somewhat from the current character, and instead of acting still more powerfully on blood, it produces no change whatever in the blood's colour at ordinary temperatures. At 40° C., however, the blood is darkened by œnanthaldoxime quite as readily as by isobutylaldoxime, or even more so.

In all three cases spectroscopic examination has again shown the dark colour to be associated with the spectrum of methæmoglobin. There is no doubt that blood decomposes these bodies in exactly the same manner as it decomposes their ethyl homologue. They have each been found to yield nitrous acid on treatment with potassium permanganate, and the dialysed liquor of blood, to which they have been added, also yields nitrite reactions.

Aromatic Aldoximes.

Benzaldoxime. $C_6H_5.CH:NOH$.

Oil of bitter almonds is mixed with a watery solution of hydroxylamine hydrochloride with excess of soda, and enough alcohol is added to produce a clear solution. This is accomplished in an atmosphere of carbonic acid to avoid oxidation of the oil. After twenty-four hours the mixture is extracted with ether. The ether is distilled off and the remaining oil is dried over sulphuric acid in vacuo.

This benzaldoxime boils with partial decomposition at above 200° C.; little soluble in water; freely so in alcohol or ether.

Salicylaldoxime. $C_6H_4\begin{cases}OH\\CH:NOH.\end{cases}$

This substance is a solid in the form of white crystalline prisms. Slight aromatic odour. Quite soluble in alcohol, ether, and benzol; slightly in cold water, and insoluble in petroleum spirit. The crystals melt at 57° C., and are decomposed by distillation.

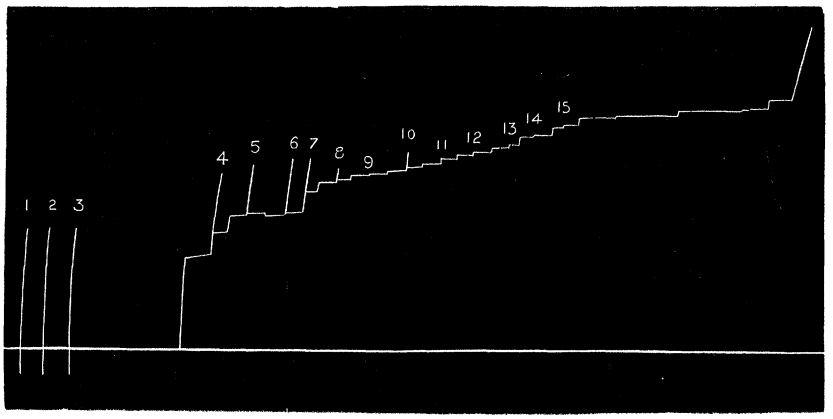
The method of preparation is to mix an alcoholic solution of twenty grammes of salicylaldehyde with a concentrated solution of fifteen grammes of hydroxylamine hydrochloride and the necessary amount of soda. After standing twenty-four hours the mixture is made strongly acid with hydrochloric acid, and then extracted with ether. The ethereal solution is evaporated, and the residue is pressed and recrystallized from a mixture of benzol and petroleum spirit.

There has been found such similarity of action in these two aromatic aldoximes that the one description applies almost equally well to both substances.

General Action in Frogs.—Frogs in which the brain was pithed, but in which the spinal cord had been left intact, were injected with solutions of these aldoximes in the region of the dorsal lymph sacs. A very powerful action is evinced by such injections. The action is essentially irritation of the spinal centres. A quantity of the drug corresponding to the $\frac{1}{600}$ part of the body weight of the frog is sufficient to produce such irritation. The skin reflexes become more and more exalted. Soon, a reflex response takes the form of a tetanic stretching of the hind limbs. Larger doses cause a rigid extension of the hind limbs independently of any apparent reflex stimulus. After a time the rigidity passes off, and no reflexes can then be obtained. The spinal cord is now found to be completely insensitive, even to direct application of the electrodes. If immediate sectio be made in such a case, the heart is found still beating, and the nerves and muscles still irritable. Later, the ventricle stops in diastole before the auricles cease to beat.

Voluntary Muscle.—Both these aromatic aldoximes repeat the type of action on voluntary muscle possessed by the fatty aldoximes. In their toxicity, they are in the same ascending scale, their intensity of action being even greater than that of œnanthaldoxime. Progressive contracture and loss of irritability are again the main features, and are to be seen recorded in a high degree in fig. 46. In this experiment, contractions 1, 2, and 3, were obtained whilst the muscle remained in normal salt solution. At 11.25 A.M. the muscle was immersed in a solution of 1 part of salicylaldoxime in 500 parts. Shortening of the muscle immediately took place, causing the lever to rise. Three minutes later, the drum having been first moved on a piece, contraction 4 was recorded and the drum was again moved round a short distance, thus causing a base line to be described which is already on a level with the summits of the normal contractions. Contraction 10 was the response to stimulation with the secondary coil at zero, and was practically the last response obtained, the later effects of stimulation being simply to increase the contracture. So that the muscle lost contractile power in fifteen minutes, though the idiopathic shortening still caused the lever to ascend as shown by the remainder of the tracing. This was an instance of contracture passing into *rigor mortis*. The muscle remained shortened, hard and opaque.

Fig. 46.



ABSTRACT of Protocol (fig. 46).—Gastrocnemius of Frog. Temperature, 16°·6 C. Load, 12 grms. Coil at 10 centims.

Application of Normal Salt Solution.

Contractions 1, 2, and 3.

Application of Salicylaldoxime 1 in 500.

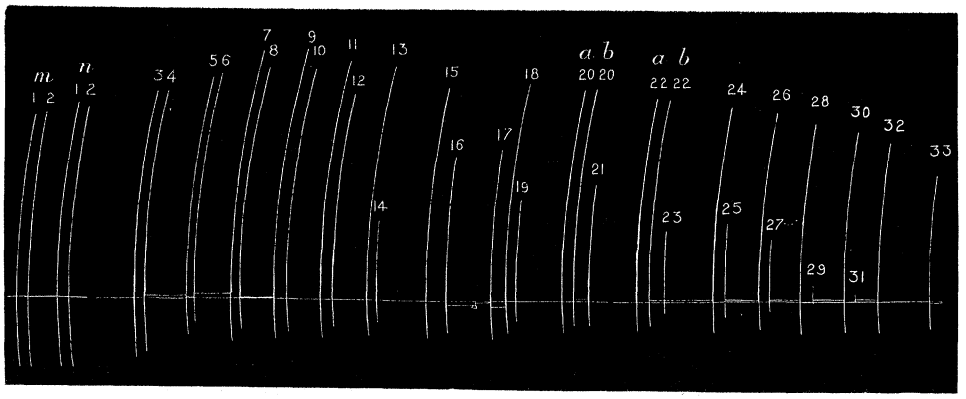
The muscle was then stimulated at intervals of three minutes. Coil placed at 0 centim. after contraction 9.

Any primary stimulation of voluntary muscle was shown to be doubtful in the action of the fatty aldoximes. There is no doubt of such an action in the case of these aromatic aldoximes. In nerve-muscle preparations this primary stimulation is

seen equally well, should the stimulus be thrown along the nerve or directly into the muscle fibres.

This action is well in evidence in fig. 47. In this experiment the immersing solution contained 1 part of salicylaldoxime in 2000 parts. The poisoned solution was commenced at 11.5 A.M. between contractions 2 and 3. During the next ten minutes the contractile power of the muscle is seen to have gradually increased, contraction 11 being the first to show the advent of the secondary depression.

Fig. 47.



ABSTRACT of Protocol (fig. 47).—Gastrocnemius of Frog with nerve attached. Direct and indirect Stimulation. Temperature, 17°·2 C. Load, 12 grms. Coil at 10 centims.

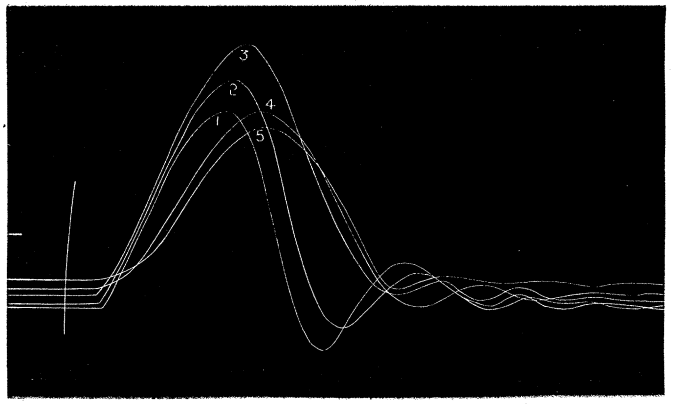
Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
(A) Muscle. Application of normal salt solution.		
1 and 2	..	48
Application of salicylaldoxime, 1 in 2000 of equal parts of blood and normal salt solution.		
3	2	55
5	5	58
9	15	67
11	20	63
15	30	56
17	35	40
Coil at 5 centims.		
18	35	57
22*a* and 22*b*	45	53
33	85	34

The muscle remained in the solution and ceased to respond two hours and a half later.

This tracing also illustrates the action of blood in preventing contracture.

Muscle Curve.—Figure 48 is in illustration of the action of salicylaldoxime on the muscle curve. The solution employed was a weak one, only containing 1 part of the drug in 4000 parts. The curve increases in height for some time, corresponding with the primary stimulant action of the drug. Then follows depression, and it is now that the curve becomes abnormal. This abnormality is chiefly seen in the descent, which reflects the slow and irregular relaxation of the muscle after contraction.

Fig. 48.



Curve 1 is the normal. Salicylaldoxime 1 in 4000 was then applied, and the other four curves were traced at intervals of six minutes. The muscle was the gastrocnemius of a frog. Temperature, 15° C. Load, 12 grms. Coil at 10 centims.

Efferent Nerves.—Fig. 47 was described by a muscle with its nerve attached.

The primary increase of muscular contractile power is testified equally well both in response to direct stimulation of the muscle and also in response to stimulation of the nerve. Depression of irritability is again most rapid in the nervous path.

No constant action was noted on efferent nerve trunks.

ABSTRACT of Protocol (fig. 47). (B) Nerve. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1 and 2	..	51
Application of salicylaldoxime, 1 in 2000 of equal parts of blood and normal salt solution.		
4	2	55·5
6	5	60
10	15	61
12	20	54
14	25	21
no response	30	
Coil at 5 centims.		
16	31	38
no response	35	
Coil at 0 centim.		
19	35	27
27	55	17
no response	70	

Spinal Cord.—The results of subcutaneous injections of these two aldoximes, in frogs, have shown their action on the spinal cord to be paramount. The reflex irritability of the spinal cord is greatly increased until the muscles of the limbs are thrown into tetanic convulsions. That this condition is really of spinal origin is shown by its non-appearance in a limb to which the nerve supply has been interrupted. This condition of increased irritability later gives place to paralysis.

Vessels.—Circulation experiments with either of these drugs show them to be vaso-dilators. Their action however is peculiar in one respect, and that is, that when circulated in weak solution a primary slight dilatation passes off and may be succeeded by vaso-constriction. This reaction is seen both in the excised kidney and in the vessels of the tortoise.

Chart 15.

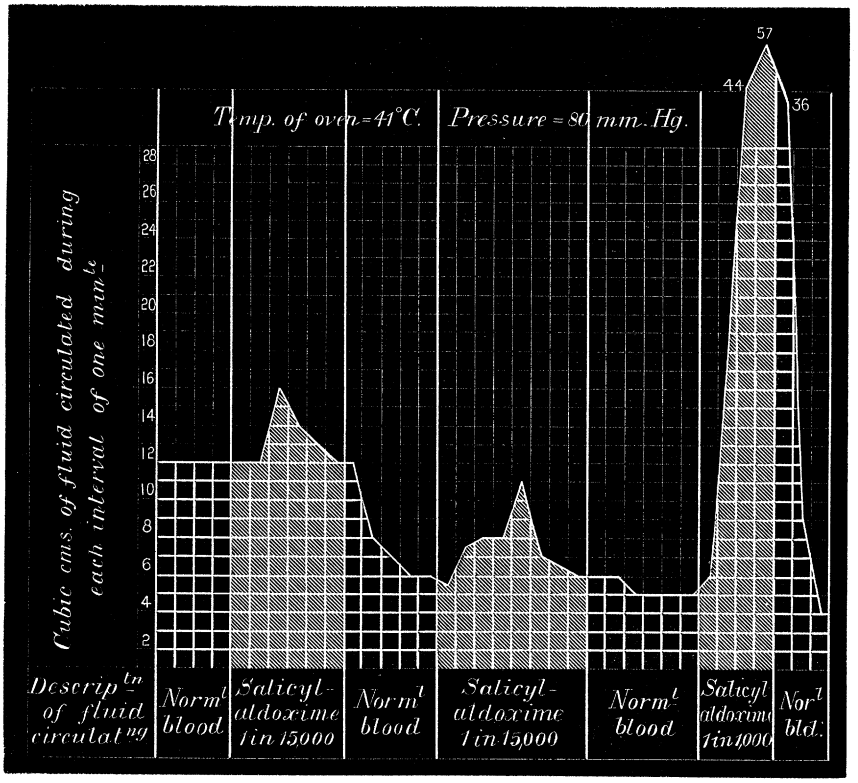
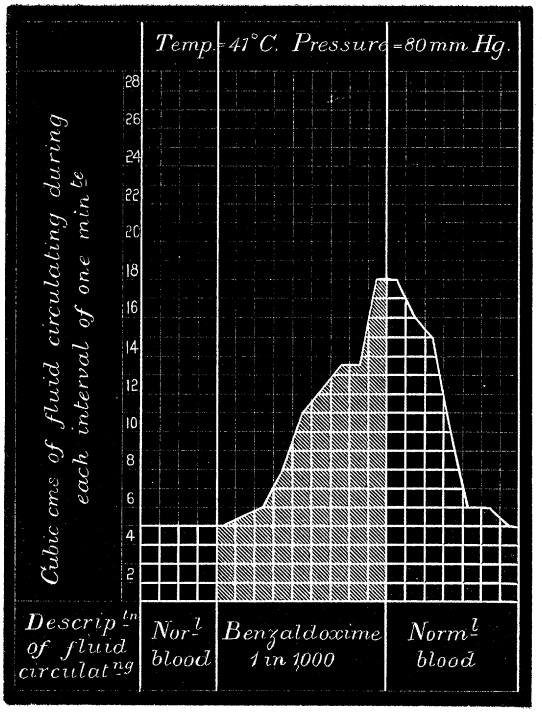


Chart 16.



EXPERIMENT.—Sheep's Kidney (Chart 15). Temperature of Ovens, 41° C. Pressure, 80 millims. Hg. Salicylaldoxime, 1 in 15,000 of Blood from the same animal.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
12.0 P.M.	Normal blood	11
12.1 „	Salicylaldoxime, 1 in 15,000	11
12.2 „		11
12.3 „		15
12.4 „		13
12.5 „		12
12.6 „		11
12.7 „	Normal blood	11
12.8 „		7
12.9 „		6
12.10 „		5
12.11 „		5
12.12 „	Salicylaldoxime, 1 in 15,000	4·5
12.13 „		6·5
12.14 „		7
12.15 „		7
12.16 „		10
12.17 „		6
12.18 „		5·5
12.19 „		5
12.20 „	Normal blood	5
12.21 „		5
12.22 „		4
12.23 „		4
12.24 „		4
12.25 „		4
12.26 „	Salicylaldoxime, 1 in 1000	5
12.27 „		19
12.28 „		44
12.29 „		57
12.30 „	Normal blood	36
12.31 „		8
12.32 „		3

From this experiment it is seen how powerful is the vaso-dilating action of a strong solution of salicylaldoxime. The solution, containing 1 pro mille, acted immediately, and must have removed all tonus from the vessel walls.

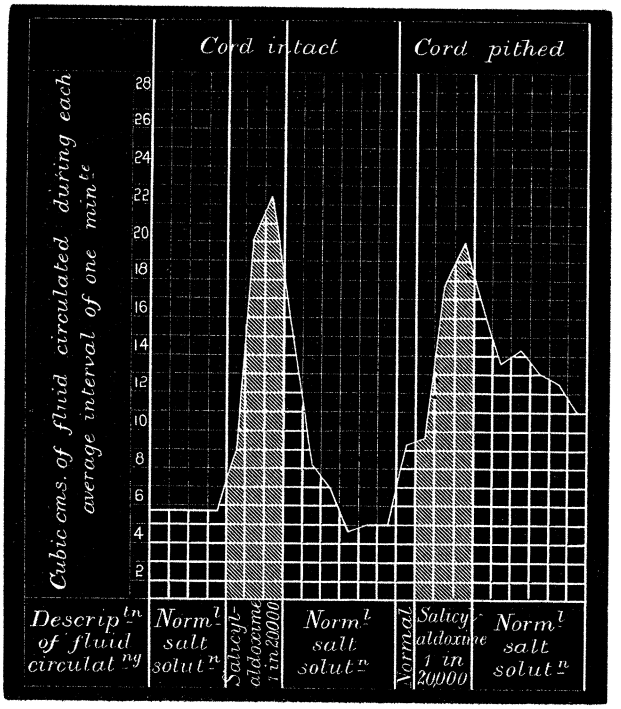
Benzaldoxime acts much less powerfully, as seen from the following protocol :—

EXPERIMENT.—Sheep's Kidney (Chart 16). Temperature of Ovens, 41° C. Pressure, 80 millims. Hg. Benzaldoxime, 1 in 1000 of Blood from the same animal.

Time.	Fluid circulating through the kidney.	Cub. centims. of fluid flowing per minute.
11.31 A.M.	Normal blood	4
11.32 „	Benzaldoxime 1 in 1000	4
11.33 „	. . . . .	4·5
11.34 „	. . . . .	5
11.35 „	. . . . .	7
11.36 „	. . . . .	10
11.37 „	. . . . .	11
11.38 „	. . . . .	12·5
11·39 „	. . . . .	12·5
11.40 „	. . . . .	17
11.41 „	Normal blood	17
11.42 „	. . . . .	15
11.43 „	. . . . .	14
11.44 „	. . . . .	8
11.45 „	. . . . .	5
11.46 „	. . . . .	5
11.47 „	. . . . .	4

The vessels of the tortoise react still more readily to these drugs. For example :—

Chart 17.



EXPERIMENT.—Small Water Tortoise (Chart 17). Temperature of Room, 16° C. Pressure, 25 centims. Salicylaldoxime, 1 in 20,000 of normal salt solution.

Time.	Fluid circulating.	Cub. centims. of fluid circulated during interval.	Cub. centims. of fluid circulated per minute.
	(A) Cord intact.		
11.57 A.M. } 12.0 P.M. }	Normal salt solution . .	17	5·6
12.3 ,,	Salicylaldoxime 1 in 20,000	27	9
12.6 ,,	. . . . .	57	19
12.9 ,,	. . . . .	64	21·3
12.12 ,,	Normal salt solution . .	43	14·3
12.15 ,,	. . . . .	22	7·3
12.18 ,,	. . . . .	18	6
12.21 ,,	. . . . .	14	4·6
12.24 ,,	. . . . .	12	4
12.27 ,,	. . . . .	12	4
	The vessels were then again dilated and brought back to normal.		
	(B) Cord pithed.		
1.37 P.M. } 1.40 ,, }	Normal salt solution . .	25	8·3
1.43 ,,	Salicylaldoxime 1 in 20,000	26	8·6
1.46 ,,	. . . . .	50	16·6
1.49 ,,	. . . . .	57	19
1.52 ,,	Normal salt solution . .	47	15·6
1.55 ,,	. . . . .	38	12·6
1.58 ,,	. . . . .	40	13·3
2.1 ,,	. . . . .	36	12
2.4 ,,	. . . . .	35	11·6
2.7 ,,	. . . . .	30	10

Heart.—So far, the ascertained actions of benzaldoxime and salicylaldoxime have, for the most part, conformed with the actions of their fatty homologues. We now, in the action of these aromatics on the heart, for the first time meet with a departure from the ethylaldoxime type.

Tracings of frogs' hearts, perfused with solutions of either of these aromatic aldoximes, no longer show the characteristic acceleration of rhythm. No primary tonic effect has ever been noticed. Cardiac depression is the unvarying action, and is seen from the influence of so dilute a solution as one containing one part of the drug in 30,000 parts.

The final arrest may occur in diastole, but more usually the heart has been observed to pass into systole shortly before stopping.

The cardiac rhythm cannot be said to be in any way affected by the action of either benzaldoxime or of salicylaldoxime. There is neither acceleration nor retardation.

It is only when the heart is finally passing into contracture that some acceleration of rhythm is usually apparent.

Blood.—The relations of these substances to blood are exactly the same as those obtaining in the relations of the fatty aldoximes. Nitrous acid can be obtained from both substances by oxidation. Salicylaldoxime is however not decomposed by blood in the cold, though readily so at 40° C.

(B.) KETOXIMES.

Acetoxime. $(CH_3)_2 = C = N.OH$.

Ketoximes are bodies containing the group $= C = N.OH$ between two carbon atoms. The body now to be considered is dimethylketoxime, or acetoxime, the lowest member of the series. It is a solid substance in the form of hard, white, very volatile prisms. These prisms are freely soluble in water, ether, alcohol and petroleum spirit. They melt at 59–60° C., and can be distilled without decomposition at 134°·8 C. The substance has a neutral reaction and a pleasant smell recalling both acetic acid and chloral.

To prepare the body an aqueous solution of hydroxylamine hydrochloride is mixed with acetone. The reaction takes little time, the smell of acetone very soon disappearing. This solution is then extracted with ether, and on evaporation the prisms are deposited.

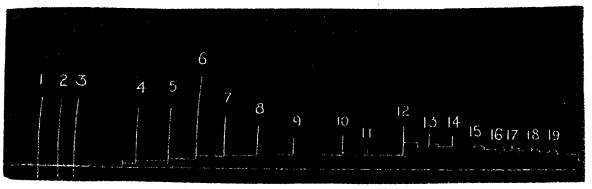
I have investigated the physiological actions of this substance by the same methods as those employed for the previously described bodies, and have found these actions to entirely correspond with those of the fatty aldoximes, more especially propylaldoxime. In the presence of this fact it is interesting to observe that the molecular weight of acetoxime is exactly equivalent to that of propylaldoxime. It will therefore be unnecessary to do more than merely point out the salient features.

General Action.—The general action of acetoxime in frogs resolves itself into depression of the spinal cord. Reflexes become abolished, and the limbs finally hang limp whilst the heart is still beating.

Voluntary Muscle.—In the action of acetoxime on muscle elevation of the base line and depression of irritability occur to approximately the same degree as in the action of propylaldoxime. With solutions of equal strength, however, the loss of irritability is a little more quickly produced by acetoxime, and the contracture is a little less marked.

Fig. 49 illustrates the toxic action on frog's muscle of a 2 per cent. solution of acetoxime.

Fig. 49.



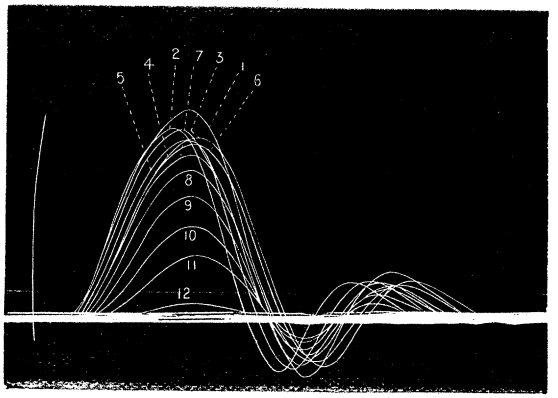
ABSTRACT of Protocol (fig. 49).—Gastrocnemius of Frog. Temperature, 18°·3 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2, and 3	..	14
Application of acetoxime, 2 per cent.		
4	3	12
5	6	10
7	12	8
9	21	3
no response	24	
Coil at 5 centims.		
10	25	5
Coil at 0 centim.		
12	33	6
14	42	2
no response	60	

Muscle Curve.—Fig. 50 shows the curves described by a muscle immersed in a 1 per cent. solution of acetoxime.

The curve is not really altered. The progressive loss of contractile power is well seen, and the thick base line shows the amount of contracture.

Fig. 50.



ABSTRACT of Protocol (fig. 50).—Gastrocnemius of Frog. Temperature of Room, 15° C. Load, 12 grms. Coil at 10 centims. 1 is the normal curve. Application of acetoxime, 1 per cent.

Number of curve.	Duration of application.
	minutes.
2	3
4	9
6	15
8	22
10	34
12	46

Efferent Nerves.—In nerve-muscle preparations the irritability disappears from the nervous path before it is lost in the muscle, and the degree of priority is about the same as in the case of propylaldoxime.

Vessels.—In its action on the vessels acetoxime is a vasodilator of about the same activity as propylaldoxime.

EXPERIMENT.—Male Tortoise (Chart 18). Temperature, 16°·6 C. Pressure, 25 centims. Acetoxime, 1 in 1000 of normal salt solution.

Time.	Fluid circulating.	Cub. centims. of fluid circulated during intervals.	Cub. centims. of fluid circulating per minute.
11.55 A.M. to 11.58 „	Normal salt solution. . .	33	11
11.59 „ to 12.2 P.M.	Acetoxime 1 in 1000 . .	39	13
12.5 „	. . . . .	43	14·3
12.8 „	. . . . .	43	14·3
12.11 „	. . . . .	43	14·3
12.14 „	Normal salt solution. . .	38	12·6
12.17 „	. . . . .	37	12·3
12.20 „	. . . . .	32	10·6
12.23 „	. . . . .	35	11·6
12.26 „	. . . . .	32	10·6
12.29 „	Acetoxime 1 in 1000 . .	35	11·6
12.32 „	. . . . .	40	13·3
12.35 „	. . . . .	48	16
12.38 „	. . . . .	51	17
12.41 „	. . . . .	53	17·6
12.44 „	. . . . .	53	17·6
12.47 „	Normal salt solution. . .	45	15
12.50 „	. . . . .	43	14·3
12.53 „	. . . . .	38	12·6

Chart 18.

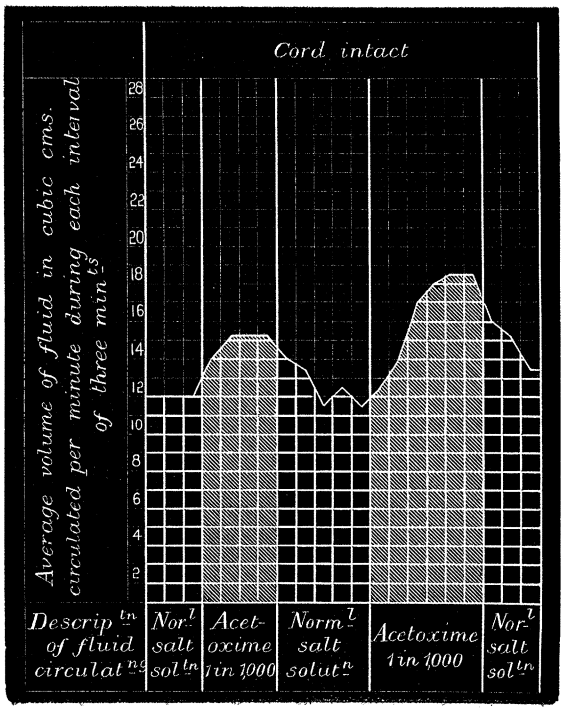
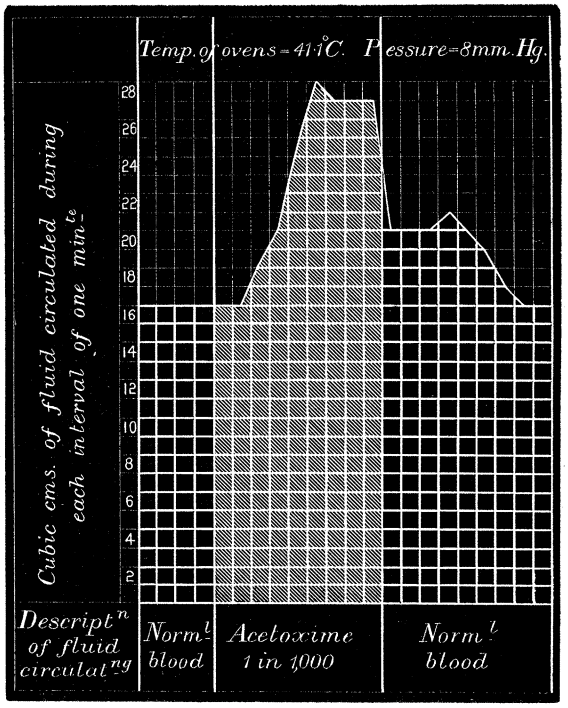


Chart 19.



EXPERIMENT.—Sheep's Kidney (Chart 19). Temperature of Ovens, 41°·1 C. Pressure, 80 millims. Hg. Acetoxime, 1 in 1000 of Blood from the same animal.

Time.	Fluid circulating through kidney.	Cub. centims. of fluid circulated per minute.
3.24 P.M. } 3.25 „ }	Normal blood	16
3.26 „	Acetoxime 1 in 1000.	16
3.27 „	. . . . .	16
3.28 „	. . . . .	18
3.29 „	. . . . .	20
3.30 „	. . . . .	24
3.31 „	. . . . .	28
3.32 „	. . . . .	27
3.33 „	. . . . .	27
3.34 „	. . . . .	27
3.35 „	Normal blood	20
. . . . .	. . . . .	. . . . .
3.43 „	. . . . .	16

Heart.—Acetoxime has no very powerful action on the heart. Strong solutions produce cardiac depression in the sense of weakened systole and final arrest in diastole. At the same time, as in the case of the fatty aldoximes, the rhythm is always accelerated. This acceleration is the only effect of more dilute solutions.

Figs. 51 and 52 show the toxic action of the drug when perfused in a solution containing 1 part of the drug in 400. Fig. 51 is the normal tracing, and fig. 52 shows the tracing after the acetoxime had been perfusing 4 minutes. The acceleration of rhythm is again unmistakable, and there is now also evident depression of contractile power.

Fig. 51.

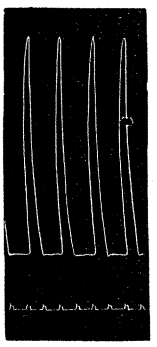


Fig. 52.

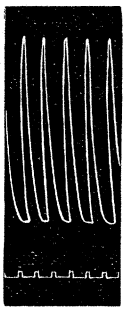


Fig. 53.

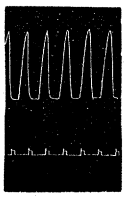


Fig. 54.

Figs. 53 and 54. These figures are given to illustrate toleration, a cardiac phenomenon observed several times whilst experimenting with these oximides. The solution

contained 1 part of the acetoxime in 200 parts of the normal fluid. In fig. 53 the poisoned solution had been perfusing 5 minutes, and a considerable degree of toxic action had been exerted, when power began to return to the heart, and 25 minutes later fig. 54 was traced, that is to say, after the drug had been perfused half-an-hour.

Blood.—The addition of acetoxime to blood is very soon followed by the development of methæmoglobin, and for the most part the reactions of this body follow lines parallel to the changes brought about by mixing the aldoximes with blood, acetone taking the place of aldehyde. Acetone and nitrous acid are the main products of the decomposition of acetoxime by blood. At times, along with acetone, there have been found indications pointing to the presence of a ketonic acid.

Traces of such an acid have been yielded by the ethereal extract of dialysed blood. This acid has not always been found, and its nature is doubtful.

Oxidation of acetoxime by potassium permanganate has also led to the formation of such an acid in small quantities. The acid so formed has the smell of pyroracemic acid, and its ethereal solution gives a precipitate with phenyl-hydrazine. It is difficult to see how such a body can arise under the circumstances. Acetone cannot be the source since the oxidation of acetone yields carbonic and acetic acids. It is probably formed at the time of disruption of the acetoxime molecule.

At such a time the presence of nitrous acid may very possibly lead to the formation of some of the aldehyde corresponding to isonitroso-acetone, that is to say, pyroracemic aldehyde, which body would be immediately oxidized to pyroracemic acid.

Acetone. $(CH_3)_2:CO$.

Since acetone is a product of the decomposition of acetoxime by blood, it now becomes necessary to know how far the actions of acetoxime may be referred to this product of its decomposition. The literature of acetone has for the most part been written in connection with diabetes and the auto-intoxication of the system in that disease. The general action of the drug has, however, been experimentally investigated by a few well-known observers.

Kussmaul gave 6·0 grams of acetone to men without any effect. Administered subcutaneously to rabbits in a few rapidly repeated doses of 1 c.c. each, symptoms were developed pointing to intoxication and anæsthesia ('Deut. Archiv f. klin. Med.,' vol. 14, 1).

Frerichs gave as much as 20 to 25 grams, both to men and to dogs, without any apparent action ('Zeitschr. f. klin. Med.,' vol. 6, 1).

It was further shown by Kussmaul that acetone is rapidly excreted by the lungs. Guided by this knowledge, Penzoldt conceived the idea that by limiting excretion the toxic action of the drug would be made manifest. Penzoldt, therefore, placed under a bell-glass a rabbit which he had subcutaneously injected with 1·0 gram of pure

acetone. The result was narcosis, loss of motor power, and finally complete anæsthesia ('Deut. Archiv f. klin. Med.,' vol. 34, 2).

TAPPEINER, in 1879, made dogs inhale acetone by means of MÜLLER'S valves and took observations of the blood-pressure, pulse, and respiration. TAPPEINER noted two stages in the action of acetone—1st, excitation characterized by heightened blood-pressure, with acceleration of pulse and respiration; 2nd, depression, with relaxation of muscles, loss of reflexes, and complete anæsthesia. The blood-pressure sinks, pulse and respiration frequency diminish, and the body temperature falls up to death, which occurs from paralysis of respiration ('Deut. Archiv f. klin. Med.,' vol. 34, 4).

I have myself cursorily examined the actions of acetone on the isolated tissues and organs and have found that, except in the case of voluntary muscle, these actions differ in little from those of propylaldehyde.

Nervous depression is the cardinal feature of the general action of acetone on the frog. Injections have paralysed the spinal cord.

In muscle-nerve preparations acetone quickly depresses the irritability of the nervous path.

It is in its action on muscle that acetone diverges most from the aldehydes. Pure acetone causes no contracture in muscle, and the muscular irritability is depressed rather than the contractility. Thus, a muscle which has ceased to respond to stimulation with the secondary coil at 10 centims. will often respond during a lengthened period to a stronger stimulus as well as it did at first to the weaker stimulus.

On the vessels of the tortoise and excised sheep's kidney acetone has not been found to possess any action, beyond at times an equivocal constriction.

Acetone is quite innocuous to the frog's heart in all but very strong doses, when the only action is depressed systole with arrest in diastole.

(C.) ISONITROSOKETONES.

ISONITROSOACETONE. $CH_3.CO.CH:NOH$.

Isonitrosoacetone is produced by the action of potassium nitrite on aceto-acetic ether. A solution of 2·1 grams of potash in 80 cub. centims. of water is mixed with 4·5 grams of aceto-acetic ether. To this mixture is added 2·5 grams of sodium nitrite dissolved in 10 cub. centims. of water. The whole is acidified with sulphuric acid and then saturated with potash. This mixture is now left to stand two or three days and is then reacidified with sulphuric acid and the compound extracted with ether.

The following reaction takes place:—

$$CH_3.CO.CH(NO).CO.OC_2H_5H_2O = CH_3.CO.CH:NOH + CO_2 + HO.C_2H_5.$$

Isonitrosoacetone is freely soluble. The crystals melt at 65° C. and decompose at a higher temperature.

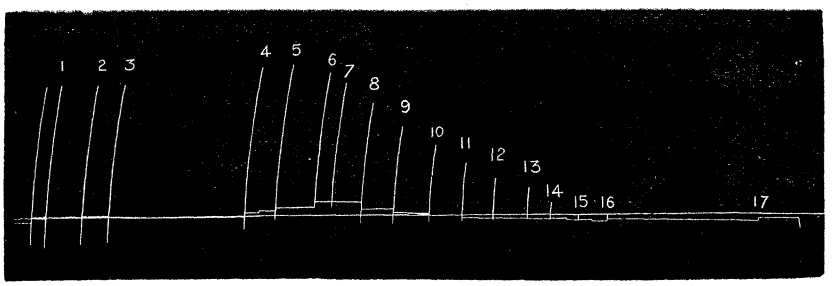
General Action.—The general actions of the fatty aldoximes are again repeated in isonitrosoacetone. The structural difference is not borne out pharmacologically, and just as acetoxime finds its parallel in propylaldoxime, so isonitrosoacetone may be assigned a parallel intermediate between propylaldoxime and isobutylaldoxime, in some of its actions approaching the former, but on the whole being nearer to the latter. In molecular weight isonitrosoacetone finds its exact equivalent in isobutylaldoxime. In respect, however, to hydrocarbon, the isonitrosoacetone molecule compares better with that of propylaldoxime, since the two contain the same number of carbon atoms, the extra weight of isonitrosoacetone being due to its ketone oxygen.

Voluntary Muscle.—Parallel observations on voluntary muscle with isobutylaldoxime and isonitrosoacetone show the toxicity of the two drugs to be closely allied. There is evidence in each tracing of corresponding contracture and depression of irritability. The only difference is that the final loss of irritability produced by isobutylaldoxime is reached somewhat earlier than that produced by isonitrosoacetone.

As previously pointed out, the inverse relationship exists between isonitrosoacetone and propylaldoxime, and whilst thus occupying a position between these two aldoximes, the toxicity of isonitrosoacetone more nearly approaches that of the isobutyl compound. This latter fact may be further illustrated by fig. 55.

The tracing shows the action on a frog's muscle of a 1 per cent. solution of isonitrosoacetone and may be compared with fig. 30, which shows the action of a 1 per cent. solution of propylaldoxime. The muscle immersed in the solution of isonitrosoacetone lost irritability in three quarters of an hour, and the muscle in the propylaldoxime solution lost irritability in an hour and thirty-eight minutes.

Fig. 55.



ABSTRACT of Protocol (fig. 55).—Gastrocnemius of Frog. Temperature of Room, 16°·6 C. Load, 12 grms. Coil at 10 centims.

Number of contraction.	Duration of application.	Height of contraction.
	minutes.	millims.
Application of normal salt solution.		
1, 2 and 3	..	26
Application of isonitrosoacetone 1 per cent.		
4	3	30
6	9	27
8	15	20
10	21	14
12	27	8
14	33	4
16	39	
Coil at 0 centim.		
17	45	Slight rise of lever with no fall. No response with coil at 5 centims.

Muscle Curve.—The action of isonitrosoacetone on the description of the muscle curve in no way differs from that of the fatty aldoximes.

Nervous System.—On the spinal cord and nerve endings isonitrosoacetone is purely depressant and to fully the same degree as isobutylaldoxime.

Vessels.—Isonitrosoacetone is again a vaso-dilator, and to this action the vessels of the tortoise seem peculiarly susceptible, far more so than the vessels of the sheep's kidney.

EXPERIMENT.—Water Tortoise (Chart 20). Temperature, 15°·8 C. Pressure, 25 centims. Isonitrosoacetone, 1 in 1000 of Normal Salt Solution.

Time.	Fluid circulating.	Cub. centims. of fluid circulating during interval.	Cub. centims. of fluid flowing per minute.
	(A) Cord intact.		
11.2 A.M. } 11.5 „ }	Normal salt solution . .	17	5·6
11.7 „ } 11.10 „ }	Isonitrosoacetone 1 in 1000	35	11·6
11.13 „	. . . . .	71	23·6
11.16 „	Normal salt solution . .	35	11·6
11.19 „	. . . . .	13	4·3
11.22 „	. . . . .	13	4·3
11.23 „ } 11.26 „ }	Isonitrosoacetone 1 in 1000	24	8
11.29 „	. . . . .	67	22·3
11.32 „	Normal salt solution . .	43	14·3
11.35 „	. . . . .	15	5
11.38 „	. . . . .	13	4·3
11.41 „	. . . . .	13	4·3
	(B) Cord pithed.		
12.4 P.M. } 12.7 „ }	Normal salt solution . .	25	8·3
12.8 „ } 12.11 „ }	Isonitrosoacetone 1 in 1000	25	8·3
12.14 „	. . . . .	52	17·3
12·16 „ } 12.19 „ }	Normal salt solution . .	35	11·6
12.22 „	. . . . .	25	8·3
12.25 „	. . . . .	25	8·3

EXPERIMENT.—Excised Sheep's Kidney (Chart 21). Temperature of Oven, 41° C. Pressure, 80 millims. Hg. Isonitrosoacetone, 1 to 1000 of Blood from same animal.

Time.	Fluid circulating.	Cub. centims. of fluid flowing per minute.
11.42 A.M. } 11.43 „ }	Normal blood	7
11.44 „	Isonitrosoacetone 1 in 1000 . . .	7
11.45 „	. . . . .	8
11.46 „	. . . . .	8
11.47 „	. . . . .	9
11.48 „	. . . . .	11
11.49 „	. . . . .	15
11.50 „	. . . . .	20
11.51 „	. . . . .	20
11.52 „	. . . . .	20
11.53 „	Normal blood	15
11.54 „	. . . . .	10
11.55 „	. . . . .	8

Chart 20.

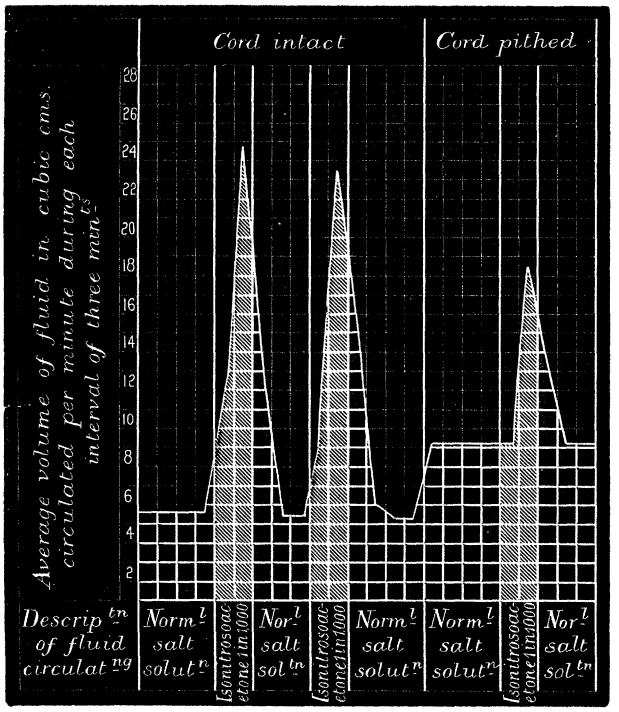
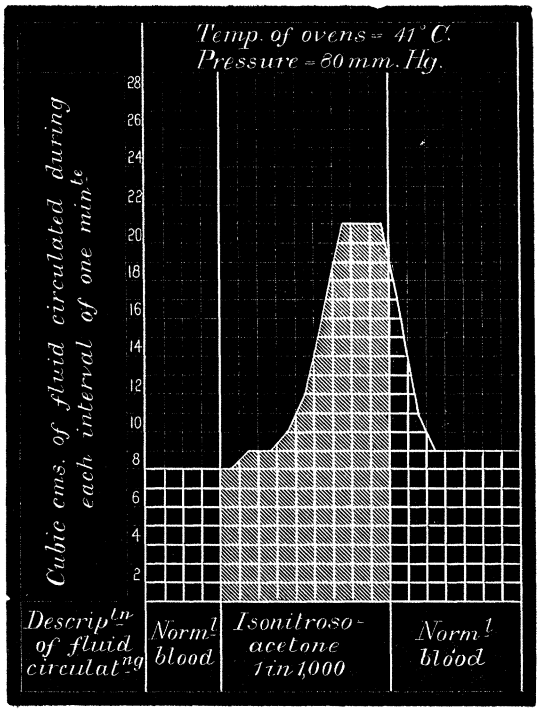


Chart 21.



Heart.—In its action on the frog's heart isonitrosoacetone repeats almost exactly the action of isobutylaldoxime.

Figs. 56, 57, and 58 illustrate the action of a solution containing 1 part of isonitrosoacetone in 800, when perfused through the frog's heart. Fig. 56 is the normal tracing. Fig. 57 was traced after the isonitrosoacetone solution had perfused 6 minutes; fig. 58 after the same solution had perfused 20 minutes.

Acceleration of rhythm is practically the only result.

Fig. 56.

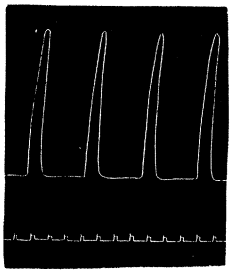


Fig. 57.

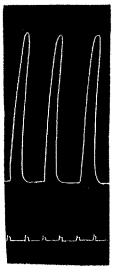
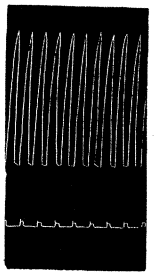


Fig. 58.



Figures 59 and 60 show the depressant effect of a stronger solution, namely, one containing 1 part of isonitrosoacetone in 200 parts. Fig. 59 is the normal tracing. Almost immediately after the perfusion of the isonitrosoacetone solution had been

Fig. 59.

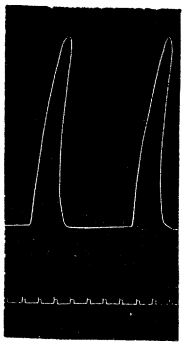
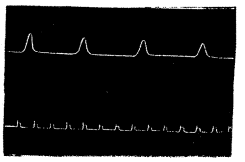


Fig. 60.



commenced, the amplitude of the systole decreased, and in less than 1 minute fig. 60 was traced. The normal perfusion was then resumed, when the heart began to revive, and regained its normal beat as quickly as it had been lost.

Blood.—When mixed with blood at ordinary temperatures, isonitrosoacetone has not caused any change in the colour of the blood. At 40° C. there is a development of methæmoglobin just as with the other drugs. This drug is again decomposed by blood with the production of nitrous acid. The nature of this decomposition is seen by oxidation apart from blood. Isonitrosoacetone is oxidised by permanganate of potash in alkaline solution with the development of nitrous acid in abundance. If the solution be then acidified with sulphuric acid, a body is liberated which can be

dissolved out by ether. This body is acid and has the typical smell of pyroracemic acid. The ethereal solution yields a crystalline precipitate with phenyl-hydrazine, and the melting point of this precipitate has again pointed to pyroracemic acid.

Oxidation of isonitrosoacetone leads therefore to decomposition on the same lines as the decomposition of the aldoximes. In all probability an aldehyde is first formed, namely, acetyl-formic aldehyde CH_3—CO—COH. This aldehyde is unstable and must immediately take up oxygen to yield its corresponding acid.

CH_3—CO—COOH, pyroracemic or acetyl-formic acid.

Conclusion.

Seeing, therefore, the resemblance in action found to exist between a ketoxime and an aldoxime, and also between isonitrosoacetone and an aldoxime; seeing, further, the resemblance in action between the involved aldehydes and ketone, it must follow, as a corollary, that the influence of the oxime group is in each case the same. This influence is that of a nitrite, as it was also found to be in the case of the aromatic aldoximes. The only discrepancy arises in the actions of acetoxime and of isonitroso-acetone on voluntary muscle. They both give rise, when present in strong solution, to the development of some contracture, a phenomenon which cannot be ascribed to acetone.

During the course of this research it has been sought to explain the nature of muscle contracture, and it has been determined that the phenomenon is probably due to direct irritation of the nerve end plates, the irritant in the case of these oximido-bodies, being an aldehyde, or, perhaps, more accurately, the COH group.

In support of this contention several facts may be here adduced.

It is an active process associated with an increased formation of heat.

The development of contracture is prevented by curare.

A primary increase of irritability in the nervous path of muscle-nerve preparations can be traced to the end plates.

This irritability, better expressed as exalted conductivity of the end plates, becomes more marked as the power of the aldehydes to cause contracture increases.

The decline of contracture is synchronous in its onset with the loss of conductivity through the end plates.

Experiments on the oxidation of acetoxime and isonitrosoacetone have led to the detection of an aldehyde. This formation of aldehyde, should it take place in the tissues, would then be a sufficient explanation for their giving rise to contracture. On the other hand, it might be argued that the oxime group, whilst in all other respects giving rise to actions identical with those of nitrites, yet exerts a primary stimulant action on nerve centres and on the muscle end plates. Such an action this investigation has not disproved.