The cases noted sufficiently illustrate the dangerous and fatal effects of cardiac and pulmonary thrombosis. Others have occurred in my experience of which I have kept the notes, but it seems needless to multiply them. It is to be noted that however much or little these cases may be referable to malarial causes, septic conditions were then very rife in Indian hospitals.

THE CROONIAN LECTURES ON THE PHARMACOLOGICAL ACTION AND THERAPEUTIC USES OF THE NITRITES AND ALLIED COMPOUNDS.

Delivered at the Royal College of Physicians of London.

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LECTURE IV.

THERAPEUTICS OF THE NITRITES AND NITRATES.

Neuralgia.—In neuralgia, especially of the fifth nerve, the administration of nitrite of amyl and nitro-glycerine has been followed by relief. Considering the trivial circumstances which seem at times both to bring on and to remove neuralgic pain, we can hardly be surprised that agencies which so powerfully affect the circulation should have a distinct influence in this ailment. In the majority of cases both amyl nitrite and nitro-glycerine have in my hand failed to give relief, and it has appeared to me probable that where they have removed pain their success has been due to circulatory influence, to what I have called a "surprise" effect, or to suggestion.

Strychnine Poisoning and Tetanus.—Dr. H. C. Wood has proved that amyl nitrite depresses the reflex influence of the cord, and it has been suggested that this power might be utilised in strychnine poisoning. Experiments have been made which seem to show that in the rabbit nitrite of amyl antagonises to some extent the lethal influence of strychnine;¹ but, as Dr. H. A. Hare points out,² to be of service its full physiological action must be continuously present, and inhalation will not suffice. I do not see how this drug can be of any practical use in strychnine poisoning in man, nor is it likely that in tetanus it will prove an available remedy, although some cases have recovered after its use. The long-lasting effect of the tetanus poison cannot, it seems to me, be effectively antagonised by the fleeting action of nitrite of amyl or other nitrites.

Epilepsy.—In epilepsy nitrites of amyl and sodium have been extensively tried, but the testimony as to their value is by no means uniform. Their employment rests to some extent on pharmacological grounds, for the nitrites in large doses depress the functions of the cerebral cells; they likewise dilate these vessels, the contraction of which is a concomitant—and some have thought a cause—of epileptic seizures. Moreover, it has been shown by Sir J. Crichton-Browne that when the brain of a rabbit rendered epileptic by artificial means is stimulated, convulsions will not follow in the usual manner if amyl nitrite be inhaled.³ In favour of the utility of nitrite of amyl we have had the testimony of Sir J. Crichton-Browne and Dr. Weir Mitchell. The former found it specially serviceable in the "status epilepticus." Others say they have seen nitrite of sodium advantageous, whilst Osler thinks he has used nitro-glycerine with a certain amount of success. But many capable observers believe that the nitrites are of no avail in epilepsy. It seems to me unlikely that substances having such temporary influence on functions and tissues as the nitrites can be of any great benefit. Personally I have not seen good arise from their

employment, though I have given them a fair trial. It is, however, possible that the inhalation of amyl nitrite, when an attack is immediately impending, may ward it off. In the case of nitro-glycerine and sodium nitrite, dilatation of the vessels does not, if ordinary doses be given, last more than two or three hours, and even during much of this time the arteries are contracting after their dilatation. Unless, then, nitrites are given at very short intervals, the protective effect must be transient. I do not anticipate that the nitrites will ever play an important part in the treatment of epilepsy.

Tinnitus Aurium.—Some evidence has been given that both nitrite of amyl and nitro-glycerine are at times of benefit in tinnitus aurium. I have seen some relief given by nitrites in this ailment, but have not had sufficient experience of its use to speak definitely of its advantages.

Bright's Disease.—I have already given my views as to the diuretic value of nitrites when speaking of their pharmacology; I propose now to allude to their employment in Bright's disease. In acute Bright's disease it is very difficult to determine the effects of a diuretic. Spontaneous increase in the urine flow is as much a part of the natural history of the disease as is the termination of pneumonia by defervescence. In ten cases of acute nephritis, the course of which was not influenced by medicine, I found that in all diuresis set in between the ninth and twenty-first day. I have certainly seen a great increase in the urine flow follow the administration of the nitrites of ethyl and sodium and of nitro-glycerine in many cases of acute nephritis. But, on the other hand, this result by no means always follows, and I know of no means by which it can be determined whether, when a diuresis occurs in acute nephritis after a nitrite, it is *post hoc* or *propter hoc*. General impressions are not of great value, but it certainly has seemed to me that a minim of liquor trinitrini or two grains of sodium nitrite every four hours occasionally expedites the advent of the diuresis which precedes recovery. Such medication, too, may tend to decrease headache and other discomforts present in acute Bright's disease, and I believe there is the advantage that it is incapable of doing harm. No evidence has yet been given that nitrites can inflict any injury even on an inflamed kidney. As I have not found diuresis follow in a very early stage of acute Bright's disease, I do not give them in the earliest stage unless symptoms are present which seem to render their administration desirable; but in the doses I have mentioned they may be useful as adjuncts to other methods of treatment if, after a week or more has elapsed, no critical diuresis supervenes.

In the large white kidney and in mixed forms of chronic nephritis the difficulty of judging of the value of a remedy, though not so great as in acute Bright's disease, is still considerable, for here, too, we not infrequently meet with spontaneous diuresis which is apt to be put down to any medicine that has been given. It has been claimed that nitrites in chronic Bright's disease decrease the total amount of albumen passed whilst they increase the amount of water passed. I have been unable to determine the regular decrease in albumen which some have seen, though decrease at times occurs, nor have I been able to note so great an alteration in the amount of water passed as would lead me to believe that they have a pronounced effect on its excretion. I have indeed at times known profuse diuresis occur under their use. But as in acute Bright's disease I have not always been satisfied that it has taken place because of their use. I have indeed often observed a temporary increase lasting a day or two, and comparing the amount of urine excreted during the periods in which nitrites have been given with the amount passed before and after the administration of nitrites, I find in a series of cases in which the data are fairly reliable, a slight increase in the amount of urine excreted under nitrites. It has seemed to me that under the influence of small doses of nitrites three or four times a day patients have been on the whole more comfortable, the skin acting better, and dyspnoic discomforts, if present, becoming less prominent.

My impression, then, is in favour of a use of nitrites in Bright's disease; I do not hold them to be curatives, but they seem to give relief.

In the contracted form of chronic Bright's disease, the

¹ St. Clair Gray, *Glasgow Medical Journal*, 1871, p. 166.

² *Boston Medical Journal*, vol. cxi, p. 481.

³ *West Riding Lunatic Reports*, vol. iii, p. 168.

nitrites are often of great value, especially in the later stages. In the earlier stages, when the chief symptoms are failing health and high tension, I have not seen them of service, but when there is dyspnoea, and the heart's action begins to fail somewhat, a minim of trinitrin solution given three times daily will often add greatly to the patient's comfort, and I believe tend to prolong life, even though it may fail to subdue dyspnoeic storms. It is said to be of service in uræmic convulsions; I have not seen definite advantage from it in the few cases in which I have employed it.

Other Diseases of the Genito-urinary Organs.—In dysmenorrhœa nitro-glycerine has been found of service, and it is certainly worthy of a trial. In *post-partum* uterine contractions there are records of advantages gained by its use, but its vascular influence renders it a remedy of doubtful value in these cases.

Sea-sickness.—In the relief of gastric disturbances the nitrites can play but little part; utility has been claimed for them in enteralgia, and they have been given in sickness and the vomiting of pregnancy, like every other conceivable remedy. But it is not easy to see how they can be of service in gastro-intestinal irritation, for neither nitrous acid nor nitro-glycerine are sedatives. The claim of nitrite of amyl and nitro-glycerine for the relief of sea-sickness seems to stand on firmer ground; giddiness from anæmia of the brain is one of the troubles of *mal de mer*, and this may be relieved by nitrites. The pathology of sea-sickness is not sufficiently known to enable us to say that the nitrite influence on the circulation is likely to combat the conditions which give rise to nausea and sickness; only experience can determine their value. It seems to me, however, that the balance is in favour of the occasional efficacy of vaso-dilators, and one or two tabellæ of nitro-glycerine are worthy of trial. The inhalation of amyl nitrite seems to be the most objectionable form in which nitrites can be given for sea-sickness.

I do not propose to deal further with the numerous ailments in which the nitrites and nitro-glycerine have been employed. They are credited with the cure of ailments differing very widely in character, as for example ague, cholera, chorea, and whooping-cough, but a knowledge of their pharmacological properties makes it probable they can only relieve certain symptoms connected with circulatory conditions which may be present in these ailments.

Administration and Dosage.—Before I finish with the therapeutics of the nitrites I should like to make a few remarks on the employment of the official compounds, and especially with regard to the spiritus etheris nitrosi. When nitrite of sodium was first employed medicinally it was found to be very impure, sometimes containing more than 50 per cent. of the inert nitrate, even now impure specimens are occasionally dispensed. It is important therefore that the purity of the drug used should be inquired into if it does not give the relief sought for. With regard to dose, I believe it is well to begin with 2 grains. I have myself never seen discomforts from even 3 grains. But severe throbbing of the head has been recorded after this amount, and when given regularly, in a very few instances slight blueness of the lips has been reported. Much larger doses may be given if neither physiological effects nor relief follows from the smaller doses; I have raised the dose to 3 or 4, rarely to 6 grains, without seeing evil follow, but occasionally even small doses cause slight stomach discomforts. Solutions of sodium nitrite in the form of mixtures seem to keep fairly well.

The tabellæ trinitrini and the liquor trinitrini are excellent preparations of nitro-glycerine. It should be remembered, however, that nitro-glycerine will under some conditions decompose. In distilled water it undergoes no change, but in the presence of alkalies, nitrite of the alkalies is formed, and when any salt is present some decomposition may occur. It is best therefore to order the liquor trinitrini in distilled water. One minim forms an average dose to commence with, but may be gradually raised without fear of injury to 20 minims or more, provided no discomforts follow from its use. A small dose of nitro-glycerine may be repeated if it fail in ten or fifteen minutes to produce a perceptible effect, for in that time its full influence has been usually exerted. A somewhat longer time should be allowed to elapse after sodium nitrite. Nervous and hysterical people

often feel throbbing in the head, or even severe headache after small doses of either compound. It is rarely necessary to resort to subcutaneous injections, since nitrite of amyl acts so quickly when inhaled, and nitro-glycerine when taken by the mouth. On one occasion, however, I saw a patient, after severe and prolonged anginal pain, lapse into semiconsciousness. After the failure of amyl nitrite relief seemed at once to follow the injection of 2 minims of liquor trinitrini. I find that nitro-glycerine is preferable to sodium nitrite for subcutaneous injection.

Concerning the value of spiritus etheris nitrosi there is much difference of opinion. As a household remedy it is much believed in and largely used; as a medicine it is employed usually rather as a routine remedy than because much faith is placed in its action. When in proper strength it contains an amount of nitrite of ethyl sufficient to enable it to reduce tension, yet its proneness to decomposition renders it an unreliable remedy for the purpose. The lack of appreciation of its value is, however, to some extent due to the method in which it is ordinarily employed; it consists of rectified spirit containing in solution about 2 to 2½ per cent. of nitrite of ethyl, an uncertain amount of aldehyde, and minute proportions of ethyl nitrate and other compounds.

I shall point out shortly that aldehyde possesses properties which are in some measure antagonistic to those of ethyl nitrite; it contracts vessels, whilst nitrites, as we have seen, dilate them. Ethyl nitrate acts in the same direction as ethyl nitrite, but it is to the latter compound that spirit of nitrous ether owes its influence to the circulation. Now spirit of nitrous ether, when not exposed to the air, does not undergo rapid change in constitution, but kept, as it often is, for dispensing purposes, it rapidly loses some of its nitrite element. I found, for example, a half-filled bottle, which, on the day I first examined it contained the official amount of ethyl nitrite, lost in thirteen days 16 per cent.

Many cases have been mentioned in which spirit of nitrous ether has been found to contain less than one-tenth of normal amount of nitrite. But, owing to the method in which it is usually given, it becomes still more unreliable as a remedial agent. Under any circumstances, a considerable portion of the nitrite of ethyl which it contains (about 50 per cent.) is at once dissipated, but, on keeping the mixture, the loss continues until all the ethyl nitrite is dissipated or decomposed. If, for example, half an ounce of spiritus etheris nitrosi is mixed with 4 ounces of water, about half of the active ingredient—the nitrite of ethyl—is usually at once dissipated. But it will be found that on the next day 30 to 50 per cent. of what was left has gone, and on the third day the mixture will probably contain a very small amount of the ethyl nitrite. The rapidity of disappearance varies greatly according to temperature and other circumstances, but it is manifest that, under these conditions, mixtures containing spirit of nitrous ether soon lose any medicinal value which when first dispensed they may have. To be effective, spiritus etheris nitrosi should be taken immediately it is mixed with water. A mixture becomes less effective with each dose taken.

An alkali, or the acetate or citrate of ammonia, prevents, to a large extent, this loss of nitrite. It is on this account, perhaps, that the old-fashioned fever mixture, containing acetate of ammonia and spirit of nitre, has justly maintained for so long a time its reputation as a diaphoretic and diuretic.

In combining spirit of nitrous ether, or the nitrites, with other medicines the short period of their activity must be remembered. It has been suggested that the contraction of the vessels due to digitalis might be counteracted by combining it with the nitrites. Undoubtedly the contraction caused by digitalis may for short periods of time be annulled, but the prolonged action of digitalis on the vessels cannot be fully antagonised by substances like the nitrites.

THE NITRO-COMPOUNDS.

The group $\text{N} \begin{smallmatrix} \diagup \text{O} \\ \diagdown \text{O} \end{smallmatrix}$, in which nitrogen is probably a

pentad, as it is in the nitrate group, is capable of replacing a molecule of hydrogen in both fatty and aromatic

compounds, and it seems of interest to determine whether this group plays an active part in the compounds into which it enters like the nitrate group ($O-N=O$) with which it is isomeric, or a more passive part like the nitrate group

I have examined the action of the following paraf-

finic nitro-compounds on muscles, on vessels, and on the heart: Nitro-methane CH_3NO_2 , nitro-ethane $C_2H_5NO_2$, nitro-propane $C_3H_7NO_2$, and nitro-pentane $C_5H_{11}NO_2$. The nitro-paraffins are colourless compounds boiling above 212° , slightly soluble in water, and very stable. They break up in the presence of alkaline carbonates, nitrites of the metals being formed.

Professor Dunstan¹ has pointed out that when nitro-ethane is mixed with potassium carbonate half its nitrogen appears as nitrite of potash; it is decomposed by the carbonates even in the cold. The higher compounds are much less easily decomposed by alkalis than the lower.

Action on the Muscles.—I find that nitro-methane has but little effect in interfering with the contractile power or life of muscle. If one part be added to 500 of normal salt solution the contractions do not seem in any way interfered with. Nitro-ethane is equally free from toxic effects, a muscle put up in a normal salt solution containing 1 in 500 of nitro-

Fig. 21.—Effect of nitro-methane on vessels. After dilating twice with nitro-methane solution, sodium nitrite caused much greater dilatation. (As before, the horizontal figures represent number of minutes during which fluid was perfused, the vertical figures the number of c.c. flowing through, the darkly shaded part the period during which the poisoned blood was flowing.)

ethane was contracting well at the end of 290 minutes. In 1 in 1,000 a muscle was living and would contract to stimulation after twenty-six hours. Nitro-propane is slightly more toxic than nitro-ethane; 1 part of nitro-propane in 1,000 parts of normal salt solution causes the contractions to fall somewhat at the end of 270 minutes, but the muscle will live twenty-four hours. One part of nitro-pentane is not soluble in 1,000 parts of salt solution, but is distinctly more toxic, for the muscle will not contract in a saturated solution more than six hours. Moreover, a certain amount of contracture is sometimes produced, as in the case of many of the amyl compounds.

Fig. 22.—Effect of nitro-ethane on vessels; the same strength was perfused twice.

Action on Vessels.—In a strength of 1 in 1,000 nitro-methane always dilates the vessels of the tortoise slightly. In a typical experiment a flow of 11 c.c. through the vessels was increased to 15, an increase of 36 per cent. (see Fig. 21).

With nitro-ethane I got some rather contradictory results. In one case, from causes which I cannot explain, contraction occurred; on other occasions always dilatation. But the amount of this dilatation varied; sometimes it was not greater than with nitro-methane, in other cases the flow increased to more than 100 per cent. (see Fig. 22).

On the whole, the dilating power of nitro-ethane was distinctly greater than that of nitro-methane. Nitro-propane always very markedly dilated the vessels, the increased flow exceeding 100 per cent. (see Fig. 23). Nitro-pentane is very

Fig. 23.—Effects of nitro-propane on vessels. After two perfusions of nitro-propane saline pure saline was allowed to run through vessels, but no measurements were taken until the following morning.

insoluble in water, the very minute quantity which is soluble (probably not more than 1 in 5,000) dilates the vessels, but not so much as nitro-propane.

On the heart of the frog nitro-methane in the strength of 1 in 1,000 has practically no effect. It may, perhaps, beat a little more quickly, but this is the only influence exerted. Nitro-ethane quickens the heart's action, and renders the

Fig. 24.—Tracing taken from excised frog's heart with Kronecker's "Froschherzmanometer."

beat less forcible. Nitro-propane, 1 in 1,000, often doubles the speed of the heart beat, and weakens it considerably. It is impossible, as I have said, to dissolve 1 in 1,000 of nitro-pentane, for it is more insoluble than the other nitro-compounds, but a saturated solution both quickens and weakens the heart's action.

Effects on Circulation.—The effects I have so far noticed on the vessels, muscles, and heart are due directly to the nitro-compounds themselves. The saline solution in which the muscles have been contracted, and the fluid which has passed through the vessels in the perfusion experiments, have always been tested for nitrites before and after each experiment but no trace of nitrites has been found, nor has the blood used for the heart experiments shown by the presence of methæmoglobin that nitrites have taken any part in the production of increased rapidity and decreased power. No nitrite is formed immediately when nitro-compounds are mixed with weak alkaline solutions in the cold, but when heat is applied nitrites are in time produced. On mixing, for example, one part of each of the four nitro-compounds with 50 of a 5 per cent. solution of sodium carbonate I detected no nitrite immediately, nor did I find any after keeping the mixture at 38° for 40 minutes, but in a few hours the presence of a nitrite was detected in all.

¹ *Journal of Chemical Society*, 1891.

When nitro-ethane is mixed with blood at ordinary temperatures, methæmoglobin is not formed until decomposition sets in, but if the mixture be kept at 38° it appears after some hours.

As in the case of nitrates, it seems possible that nitrites are more readily produced after absorption into the circulation, at least an effect on the tension, somewhat like that caused by nitrites, follows. When 15 minims of nitro-ethane is given by the mouth and the tracing is continuously watched, no distinct change is perceived for about a quarter of an hour, then a slight lowering of tension occurs. In 30 minutes this is distinct, hence onwards for nearly four hours the lowered tension continues, but I have not found the same extent of fall produced as after either nitrites or nitrates; on the other hand the fall is much more prolonged, and may not reach its lowest point until three or four hours after the drug has been given (see Fig. 25). Sometimes at

Fig. 25.

the end of five hours the tension is still lowered, at other times it has risen to its normal height in four hours.

Nitro-propane, in a dose of 15 minims, has much the same effect as nitro-ethane; for a short time it seems to have but little influence on the pulse, but in three or four hours the tension has become distinctly lowered, and it is five or six hours before the pulse regains its normal condition. After 10 minims of nitro-pentane I noticed the first fall of tension about thirty minutes, but it was seventy minutes before any distinct fall took place. Between three and four hours after the drug had been taken the tension reached its lowest point, and the pulse had not quite regained its normal condition in six hours. (See Fig. 26.) Very slight effect is produced on the frequency of the pulse by the fatty nitro compounds; sometimes, but not always, during the lowered tension it is raised 5 to 10 beats per minute. No headache has been complained of by those who have taken these drugs, and no subjective symptoms have been noticed, but my experience of their effects is not yet sufficiently wide to say that headache and palpitation may not in some be produced.

I have not so far proved that in the living body nitro-compounds can be decomposed and nitrites produced; the changes which take place both when nitrates and nitro-compounds are mixed with blood is a subject I propose to investigate further; but either from the gradual development of nitrites, or from the action of the whole molecule itself, the fatty nitro-compounds possess a power of slowly depressing tension and keeping it down for a lengthened period, which may be found useful in therapeutics provided no bar to their utilisation appears. For the relief of angina pectoris, of course, they can be of no service; to prevent attacks in this ailment, and for the relief of some conditions connected with rise in tension, they may prove of value.

The NO_2 group does not give a toxic influence to the fatty compounds into which it enters. It differs completely in this respect from the ONO group, and resembles the ONO_2 group. Dr. Brunton has made experiments to determine its action in nitro-benzene, in which compound NO_2 replaces an atom of hydrogen. When benzene, C_6H_6 , is injected into the frog it causes some lethargy, and renders the spinal cord more excitable, as shown by tremor on movement, eventually paralysing it. Nitro-benzene, $\text{C}_6\text{H}_5\text{NO}_2$, caused the same sym-

ptoms; the tremor secured a little greater and the reflexes were abolished a little earlier, but the experiment showed that, so far as the aromatic compound benzene was concerned, the nitro-group plays almost as passive a part as it does in the compounds of the fatty series.

NITROSAMINE GROUP.

In the nitrosamine group ($=\text{N}-\text{N}=\text{O}$) an atom of nitrogen replaces one of the atoms of oxygen in the nitroxyl group, and has two links left free for junction with two other groups. It seemed interesting to determine what effect this group would have as compared with the group $-\text{O}-\text{N}=\text{O}$, when joined to fatty radicles. The effect of the junction is to produce a series of liquids extremely unpleasant to smell and taste, soluble in alcohol, and also slightly in water.

I have experimented with the dimethyl-nitrosamine, diethyl-nitrosamine and di-isobutyl-nitrosamine compounds. The action of the NNO group in no way resembles that of the ONO group, and, notwithstanding their nauseous smell and taste, the nitrosamines are not poisonous to the tissues.

Dimethyl-nitrosamine, $\text{CH}_3-\text{N}(\text{CH}_3)-\text{N}=\text{O}$, is not fatal to muscle in the strength of 1 in 1,000, and the diethyl-nitrosamine is equally innocuous, but when the butyl element takes the place of methyl or ethyl the resulting compound, di-isobutyl-nitrosamine, will, in the strength of 1 in 1,000, kill the muscle in about two hours.

The diethyl- and dimethyl-nitrosamines have no influence on the vessels; in the strength of 1 in 1,000 they do not

Fig. 27.

either contract them or dilate them (see Fig. 27). They slightly quicken the isolated heart, and then weaken it in the strength of 1 in 1,000, but this organ bears the presence of the ethyl and methyl compounds quite well.

I have not tried the effect of the nitrosamine compounds on the general circulation; their nauseous character renders it manifest they can never be of practical therapeutic importance, and whilst I have had volunteers willing to take nitrate, nitrite, and nitro-compounds, no one after once tasting the nitrosamines desired to go further. The chief point of interest in connection with their action on the various tissues is their harmlessness. The butyl compound killed muscle rapidly, but this is to be expected where there are two butyl molecules.

THE HYPONITRITE GROUP.

In most books on chemistry the existence of hyponitrites is alluded to, and hyponitrous acid is represented as having the formula HNO , the sodium salt being represented as NaNO .

It would have been highly interesting, had this been the case, to have ascertained the difference of the influence of the group NO and ONO in the respective compounds they form with sodium and the fatty radicles. Zorn, however, from his investigations on hyponitrous ether, has come to the conclusion that the hyponitrites are, as I have said in my first lecture, diazo-compounds, consisting of two molecules of the group NOH , the nitrogens of which are united by a double link. It seemed to me, nevertheless, of interest to determine, if possible, the comparative effect on tissues even of this double group as compared with the group ONO . Unfortunately the sodium hyponitrite is extremely unstable, solutions readily decomposing free soda being left in the solution, which becomes very alkaline. It is very difficult, therefore, to judge how far the effect produced by sodium

hyponitrite is due to the hyponitrite molecule or to free soda. I find that 1 of sodium hyponitrite in 1,000 of normal salt solution will kill the gastrocnemius of a frog in an hour. When perfused through the tortoise the vessels contracted so strongly as entirely to stop all fluid passing through them. The beats of the heart were rendered irregular and slow when 1 of sodium hyponitrite in 1,000 of blood was passed through it. The experiments I have made are, however, of doubtful value, because of the free alkali present. The solution neutralised by hydrochloric acid of the hyponitrite saline solution altered the shape of the muscle tracing, which, with the alkaline hyponitrite solution, had the appearance usually seen after alkaline solutions, but did not materially diminish toxicity.

THE OXIME GROUP.

Of late years a large and chemically interesting group of compounds have been produced called "oximes," which contain the group NOH united by a carbon element either to two fatty radicles or to one fatty radicle and

hydrogen. Aldoxime $\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}=\text{NOH} \end{array}$ is one of the best known examples of this group.

If CH_3 is replaced by ethyl C_2H_5 , propyl aldohime is formed. Isobutyl and other homologous oximes can in the same manner be produced by replacing C_2H_5 by higher members of the fatty series. At my suggestion two years ago Dr. Pomfret, at that time one of the Berkeley Fellows in Pharmacology, investigated in my laboratory at Owens College the effect of a series of these oxime bodies with a view of ascertaining how far they possess any pharmacological type which can be referred to the presence of this group in their structure. I propose to refer briefly to the action of three of them in order to illustrate the influence of the NOH group.

Aldohime or ethyl aldohime is a colourless fluid miscible in all proportions with water; it is remarkably free from all poisonous action on skeletal muscle. The gastrocnemius of a frog will live in a mixture 1 part of aldohime in 200 of normal salt solution for twenty-four hours. In solution of more than 1 per cent. contracture is produced, but even in 1 in 50 a muscle will live more than two hours. Propyl aldohime ($\text{C}_3\text{H}_7\text{NOH}$) acts on skeletal muscle like ethyl aldohime, but contracture is produced by more dilute solutions. It is also more toxic. In a solution of 1 in 200 a muscle lived over four hours.

Isobutyl ($\text{C}_4\text{H}_9\text{NOH}$) aldohime is still more toxic to muscle. A muscle dies in 1 part of this compound to 200 of normal salt solution within an hour. Contracture comes on more quickly, and is more marked than with either the ethyl or propyl compounds.

On the blood vessels of the tortoise the effects of ethyl aldohime vary with the strength of the solution: 1 in 1,000 always increases its flow; stronger or weaker solutions usually cause a primary contraction followed by slight secondary dilatation.

Propyl aldohime invariably dilates the vessels. The dilatation is much greater than that brought about by ethyl aldohime. Isobutyl aldohime in weak solutions also dilates the vessels. In the perfusion of organs of warm-blooded animals Pomfret noted that a different effect is produced on the vessels according to the time which elapses between adding aldohime to the blood and perfusing it. When blood is mixed with aldohime shortly before perfusion a primary contraction of the vessel is invariably obtained. If the blood and aldohime stand in an open vessel for two or three hours dilatation at once results. This fact led him to make an examination of the effects of aldohime on blood, and he then found that though on adding aldohime to blood no change at first takes place, after standing for a few hours the blood darkens, and the spectroscopist shows that this darkening is due to the presence of methæmoglobin. At the temperature of the body methæmoglobin is produced in 15 to 20 minutes. From further examination he found that aldohime, when mixed with blood, breaks up into hydroxylamine and aldehyde. Hydroxylamine has been shown to form in alkaline fluids a nitrite of the alkaline metal, and thus the addition of aldohime to blood leads to the formation in it of aldehyde

and nitrite of sodium. Pursuing his research he investigated the physiological properties of the aldehyde group, and discovered that aldehydes have a directly opposite effect to that of the nitrites; they stimulate muscles and contract vessels. When the perfusion of warm blood containing aldohime through an organ takes place soon after the aldohime is mixed with the blood, the presence of aldehyde causes the vessels to contract. If some time is allowed to elapse the aldehyde, being volatile, escapes, and the nitrites which have been formed dilate the vessels.

The action of propyl and isobutyl aldohime on the vessels of warm blooded animals does not materially differ from that of aldohime. On the heart aldohime has very little effect; there is an increased rate of beat and an increased heart tonus. Strong solutions sometimes arrest the heart in systole, sometimes in diastole, the varieties being due to the same decomposition which has been noticed in the perfusion of blood. The longer the aldohime remains in contact with the blood, the less is the tendency to systolic contraction, the greater the tendency to diastolic arrest. The other oximes, propyl and isobutyl, also produce acceleration of the rhythm, but have slightly depressant action. Strong solutions, 1 in 200 of propyl aldohime did not diminish the amplitude of beat after three hours. Isobutyl aldohime was much more poisonous.

On the circulation generally aldohime has but a slight effect. The increased tone which is produced by it in the isolated heart of the frog is not seen in warm-blooded animals because of the formation of hydroxylamine and nitrites, but instead a slight lowering of tension is seen about twenty to thirty minutes after the drug has been taken.

The NOH molecule also joins with or enters into aromatic groups. Dr. Pomfret has investigated the action of quinoxime ($\text{C}_6\text{H}_4\text{ONOH}$) of salicyl aldohime ($\text{C}_6\text{H}_4\text{OHCHNOH}$) and benzaldohime ($\text{C}_6\text{H}_5\text{CHNOH}$). He finds that the effect of the group NOH in producing contraction of the muscle is seen in these aromatic groups, and that all dilate the vessels.

I have given a very brief account of the results obtained from an examination of the fatty compounds containing the NO, N—NO, and NOH groups, because though what has been noted concerning them is interesting as giving an indication of their influence, the compounds themselves are not likely to prove of any therapeutic value. It is quite possible, however, that amongst the aromatic compounds which contain the oxime group, we may find substances of some utility, but these I have not myself examined.

Summary.—The investigations I have so far made with the view of determining the influence of the groups containing nitrogen and oxygen are, as I said in my first lecture, only preliminary. To determine accurately the action of a group of molecules, we must compare the effects of a large number of compounds containing them, both in the fatty and aromatic series, and we must compare these effects too, not only on muscles, vessels, and heart, but on all the tissues and organs of the body. This is a work which involves very large expenditure of time. I have ventured, however, to bring forward the results so far obtained.

It has long been known that the influence of certain elements in a compound varies according to the number of affinities by which they are united with other elements in the compound, and the groups I have alluded to seem to furnish an example of this.

For reasons into which I need not enter here, chemists are of opinion that in the nitroxyl or nitrite group nitrogen is a triad element, whilst in the nitrate and nitro groups it is pentad. It may be to this, as well as to the different manner in which two oxygens combine with the nitrogen in the nitrite and nitro groups respectively, that we must attribute the marked difference in their effects. It will be noted that there is some evidence that the hyponitrite group, in which nitrogen also plays the part of a triad, is distinctly toxic, like the nitrite group. The instability of the two triad nitrogen groups may enter to some extent into the causation of their toxicity, but for reasons which I have given it seems to me that, in the case of the nitrite group at least, the molecules of the group itself in some way or other play a definite part in the physiological effect which the compound containing them produces. The addition of another nitrogen to the group NO completely changes the influence which the

group NO has by itself, or when associated with another atom of oxygen. The addition of a hydrogen element to the NO group seems equally to modify its influence. The nitrosamines, so far as they have been examined, affect the tissues very slightly. The oximes, at least those of the fatty series, are singularly free from poisonous properties, but the NOH group shows a peculiar influence on muscle contraction. Throughout the experiments the increasing toxicity of the fatty series as the weight of the molecule increases has been very marked. The toxic action of the pentane and butane compounds has been always distinct.

A very remarkable feature has been the influence which compounds containing propyl have in dilating vessels. Nitrate of propyl has singular power in this respect; nitropropane dilates more than any other of the nitro-compounds, and Dr. Pomfret found that of the aldoximes, propyl aldoxime was the most efficient vessel dilator. Butyl and amyl compounds, if used in the same strength as the propyl compounds, contract instead of dilating vessels; they seem to act as irritants to muscular tissue unless in very dilute form, and the contracture which I have noticed as often occurring with amyl compounds shows that an analogous effect is produced on voluntary as well as on involuntary fibre.

In conclusion, let me say it has not been in any way my purpose to search for new remedial agents, but it seems possible a use may be found for some of the compounds I have examined. I allude to the nitrates and the nitro-compounds. They resemble in their powers the nitrites which we have so long been accustomed to use; probably, indeed, their influence is due to the development of nitrites from them. Yet if they possess the pharmacological properties which, from the examination I have so far made, they seem to have, they may possibly be advantageously employed when we want to influence the vessels more or less markedly for a long time.

It has been said with truth that what is now wanted is not a further supply of new remedies, but a better knowledge of the way in which to use the old ones. It seems to me, however, that if therapeutic knowledge is to advance, we must acquire more information than we now possess as to the exact method in which these older remedies act, we must know how they break up in the body, and we must know, too, the new and often simpler combinations they are capable of forming and how these act. The exact method in which the complex compounds of the organic kingdom influence the body we have not yet sufficient knowledge to comprehend; it is with the simpler compounds we must commence investigations, but a wider and deeper knowledge of the effect of these simpler compounds will surely open the way for the acquirement of further information with regard to the more complex ones. At present, even concerning the simple ones our knowledge is very small. It was with the hope of making some slight addition to this knowledge that the work on which these lectures I have had the honour of being invited to give was commenced. For this honour let me again thank you.

AN inquest was held at Hunmanby, near Bridlington, on July 12th, on the body of Mr. Henry Hick, aged 31, surgeon, practising at Hunmanby, who died on the previous day from the effects of opium poisoning. It appeared that the deceased had previously been unwell and depressed. The jury returned a verdict of "Death from opium poisoning during temporary mental derangement."

PROFESSOR VIRCHOW'S SEVENTIETH BIRTHDAY.—The committee appointed to carry out the arrangements for the celebration of Professor Rudolph Virchow's 70th birthday, which fell on October 13th, 1890, has recently published an account of its stewardship. The total amount subscribed was 42,311 marks (about £2,115). Of this sum 20,622 marks (about £1,030) was expended on a large gold medal 180 millimetres in diameter, and weighing 2.3 kilogrammes, presented to the professor, a reproduction of it in silver for his wife, and sixty-eight in bronze for members of his family and others. The balance was handed to Professor Virchow to be applied as he might think fit, and he has added it to the fund for the endowment of research which bears his name. The report of the committee includes a list of the subscribers, more than 2,000 in number.

ABSTRACT OF LECTURES

ON

THE SURGERY OF THE AIR PASSAGES AND THORAX IN CHILDREN.

Delivered at the Royal College of Surgeons of England.

By BERNARD PITTS, M.A., M.C.CAMB., F.R.C.S.,

Assistant Surgeon to St. Thomas's Hospital, and Surgeon to the Hospital for Sick Children, Great Ormond Street.

LECTURE II.

INTUBATION.

INTUBATION is invaluable as a help in the treatment of chronic stenosis, and O'Dwyer's tubes are undoubtedly the best adapted for the purpose. Intubation may also be of value in cases where the condition of acute obstruction is likely to be of short duration, and when there is no reason to think previous ulceration of the larynx existed. It may be of use also as a means of diagnosis when it is uncertain whether the dyspnoea arises from obstruction in the upper air passages, or to some condition affecting the tubes lower down, for example, pressure from mediastinal tumour, bronchitis, etc.

Intubation for laryngeal diphtheritic obstruction does not seem to make much progress in general favour in England. It is not my intention to go through the oft repeated arguments as to the respective merits of intubation and tracheotomy, but rather to point out some of the causes which have prevented intubation from a more extensive trial in this country. The treatment of diphtheria (in its surgical aspect) in our hospitals is for the most part carried out by the resident staff, and every six months or a year this staff is changed. Students are taught nothing about intubation in most of the textbooks; not unnaturally the operation of tracheotomy, concerning which they have heard and thought a good deal, presents many attractions. How many tracheotomies have you done? is a common question asked of the outgoing house-surgeon, and it is generally thought not kind or fair to add: And with what result?

In America and in many parts of the Continent, however, intubation has been very largely tried by the medical officers in continuous charge of the diphtheria hospitals, and with results which certainly command grave attention. The operation of passing an intubation tube in a young child without chloroform, with a swollen and inflamed condition of the parts is not an easy one, and requires constant practice, and much thought and attention to detail. Without special study tracheotomy is undoubtedly the safer operation. It is not however the difficulty, but rather the want of familiarity with the use of the instruments which often determines the hospital resident against intubation. In young children the epiglottis is not always easy to feel, but the arytenoid cartilages can always be defined. When intubation first began to be practised it was thought that it might be tried in all cases; and if the progress was unsatisfactory tracheotomy could be substituted, and in fact converted into an easy operation, with the intubation tube as a guide to cut down upon.

The mortality after such secondary tracheotomies was so terrible that not unnaturally operators became discouraged and wished they had performed tracheotomy in the first instance; and this has had a great deal to do with the present lack of confidence in intubation. It does not, however, by any means follow that this mortality is consequent on the previous intubation, but rather on the fact that cases which are sufficiently progressive or malignant as to be unrelieved by intubation are pretty certain to die under any circumstances. At St. Thomas's Hospital out of 18 cases of intubation followed by tracheotomy, only 2 recovered.

Taking the fatal results: in 6 tracheotomy was done within a few hours of first intubation, and in 10 after an interval varying from one to nine days; so that all died, when intubation was at first followed by improvement, and tracheotomy was performed later.