a number of years in succession. For months together the results may be discouraging in the extreme; at another time, under the same conditions of operation and nursing, recovery will be the rule rather than the exception. One house-surgeon commences his experience with a dozen fatal results, whilst another has five or six recoveries running. Success in tracheotomy for diphtheria depends very largely on the treatment after operation.

In a depressing disease like diphtheria it is most important to keep up the powers of the patient, and nasal feeding is far more efficient than the giving of nutrient enemata. Much of the treatment advocated in textbooks is apt to be overdone, particularly the routine employment of the tent bed and steam spray.

It is quite pitiable to see children fighting for their lives under such enervating conditions. The air of the room should be kept pure and at an even temperature of 65°; above all, the bed should not be placed near a hot fire, with the spray from a kettle constantly playing over the face and body. A sponge kept warm and moist should be always over the tube, and the inner tube changed every hour, or even oftener, whilst the discharges are thick. A great deal of harm may be done by a too zealous nurse, especially by the constant introduction of a feather to clear the tube, and by attempts to thus extract membrane from the trachea. If actual obstruction takes place it is better for the surgeon to take the tracheotomy tube out altogether, and examine the trachea before replacing it.

When membrane is present on the fauces or pharynx, the use of perchloride of mercury by means of a hand spray appears to be more beneficial than solutions of bicarbonate of soda, borax, or phosphate of soda.

At the Great Ormond Street Hospital a mercury solution, of the strength of 1 in 1,000, has been employed by Dr. Collier in some seventy cases, without producing any signs of irritation or evidence of mercurialism. Concerning the details, he writes to me as follows:—"In using the hand spray it was found necessary to use a tongue depressor, because, however willing the patient was, the solution did not thoroughly reach the posterior pharyngeal wall unless the tongue was depressed. Each spraying procedure lasted from two to four minutes, including a pause for a few seconds at the end of each half minute, and the quantity of solution used was about 3j. While membrane continued to be evident, the application was made every three hours; it was then continued for a day or two, at intervals of six hours.

"In nasal cases the nose was douched with warm boracic solution every three hours, and was sprayed with mercury solution after each douching.

"The tracheotomy wounds were sprayed every two hours with the mercury solution, care being taken that no solution entered the tube."

Emphysema is not so common a complication after tracheotomy, since the high operation has become the established practice, and the wound is left freely open.

When the opening was made in the lower part of the neck and the more separated layers of fascia opened up, emphysema, by spreading to the anterior mediastinum, was sometimes a serious complication, both by its mechanical effects and by preparing the way for a diffuse inflammation.

Diphtheritic invasion of the wound may lead to extensive sloughing, both of the soft parts and the tracheal rings, the tube should then, if possible, be dispensed with and warm antiseptic dressings applied. If recovery take place it is likely to be attended with troublesome stenosis of the trachea from after-contraction of the cicatricial tissue.

Extensive hæmorrhage after tracheotomy for diphtheria is now fortunately of rare occurrence. The old fashioned, greatly curved tube, inserted low down in the trachea, frequently caused ulceration of its anterior wall, and the large vessels in the neighbourhood were endangered.

(To be continued).

WE are requested to state that the inspection of the London companies of the Volunteer Medical Staff Corps under Surgeon-Lieutenant-Colonel Norton will take place at Chelsea Barracks, on Saturday, July 15th, at 5.30 P.M. The inspection will be held by the Principal Medical Officer of the Home District.

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.

By D. J. LEECH, M.D.LOND., F.R.C.P.,

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LECTURE III.—THERAPEUTIC USES OF THE NITRITES AND NITRATES.

In considering the bearing of the pharmacological action of the nitrites on their therapeutic application there are three points worthy of note. The first is the minute quantities which may influence the vascular system, and, as a consequence, certain functions of the body. An eighth of a grain of sodium nitrite, a small but uncertain fraction of a minim of ethyl nitrite, or the sixteenth-hundredth of a grain of nitro-glycerine will in many distinctly affect the circulation.

A second point is that, notwithstanding their potency, even large quantities of the nitrites and nitro-glycerine do not readily cause death. Although unpleasant and even alarming results have been known to follow comparatively small doses, there has been, as far as I know, only one case recorded in which a fatal result has been attributed to their medicinal use. This is the more worthy of notice since these drugs have been commonly given in serious cases. I do not know of an instance in which ethyl nitrite or sodium nitrite have proved fatal, though very large doses of the latter have been administered. Amyl nitrite has been swallowed by the dessertspoonful, yet recovery has, I believe, always occurred, and severe though the symptoms are which follow its inhalation no harm has ever accrued from its employment, save in one instance, a case of phthisis, where death followed the inhalation of 7 drachms. Considerable quantities of nitro-glycerine have been taken with impunity, so far at least as concerns a fatal result; only in few instances have very large amounts, taken accidentally or for suicidal purposes, caused death.

A third point which it is important to bear in mind is the evanescence of nitrite action. When nitrites advantageously alter functions their direct influence for good usually soon ceases; on the other hand, their evil effects are also short lived; there is no cumulative influence.

The pharmacology of the nitrites and nitro-glycerine indicates the class of cases in which these drugs will be of the most utility—namely, those in which the heart is embarrassed in its work owing to a want of due relationship between its power and the calibre of the vessels through which it transmits blood.

Angina pectoris is the most conspicuous ailment of this class. It would be out of place here for me to discuss its pathology and its various forms, but there are one or two points to which I must allude, because they are intimately connected with the use of nitrites. *Angina pectoris* has been defined by Sir Richard Quain as an affection of the chest accompanied by severe pain, faintness, and anxiety, occurring in paroxysms connected with disorders of the pneumo-gastric and sympathetic nerves and their branches, and frequently associated with organic disease of the heart.

It is manifest that for the production of angina as thus defined, a variety of pathological conditions may suffice. Alterations in the cardiac nerves and plexuses due to intrinsic structural changes, or to their involvement in diseased conditions of adjacent organs, may lead to periodic neuralgic attacks similar to those which we see in other parts of the body when nerves or plexuses are similarly affected. Neurægic pains referred to the heart may be the outcome of

reflected irritation originating elsewhere, as, for example, in the abdominal organs. Hysterical pains may be felt in the cardiac region as well as in other parts. All these causes may perhaps lead to paroxysmal pain apart, or almost so, from circulatory changes connected with alteration in tension. But clinical observations do, I think, indicate that a large proportion of anginal attacks are directly caused by a rise in tension, and there seem to me good grounds for believing that this rise is due to a temporarily decreased calibre of the systemic or pulmonary vessels, and a consequent suddenly increased call on the propelling action of a heart the walls of which are more or less altered in structure.

In some cases, as Dr. Douglas Powell has so well pointed out,¹ the call may be made upon a diseased heart (angina pectoris gravior); in others there is more or less cardiac reserve power and integrity (angina pectoris vaso-motora); but in both forms the symptoms are due to the fact that the heart is unequal to the work it is called on to perform.

With a view of removing the high tension ensuing from this contraction, Dr. Brunton first made trial of amyl nitrite in angina pectoris, and discovered its wonderful power of relieving the cramp-like pain which accompanies this ailment. Of late, however, doubts have been raised as to whether high tension is really the cause of pain; and it has been suggested that nitrites relieve, not because they lower tension, but because they act as analgesics, and remove the pain which causes high tension. It seems to me that for this theory there is but little foundation; experiments, as I have said, give no indication that nitrites are direct analgesics; in poisonous doses, indeed, they depress the functions of all portions of the nervous system, but the afferent portion is the last which is affected. So powerful an analgesic as morphine not infrequently fails to relieve the pain which a minute dose of amyl nitrite at once removes, and there is, I hold, no warrant for the assumption that nitrites or nitro-glycerine have a special analgesic influence on the cardiac plexus. I cannot see sufficient ground in what has so far been advanced, for calling in question the opinion that increased tension is the cause of suffering in a large proportion of cases in which paroxysmal pain is referred to the heart; and that in the treatment of angina pectoris it is important, in the first place, to lower this tension as speedily and efficaciously as possible.

In the reduction of tension by nitrites we have three objects in view: (1) to relieve pain as rapidly as possible, (2) to avert a fatal termination, (3) to prevent the recurrence of pain. The second object is for the time attained when the pain is removed.

The pain of angina varies greatly in duration; generally it is short in the earlier stages of the disease and abates quickly when the immediate cause, usually some movement, has ceased. Not infrequently, especially towards the termination of a longstanding case, atrocious pain is present for many minutes, sometimes for many hours. But, whether the duration of pain be short or long, those nitrites are manifestly, in the first instance, called for which act most quickly.

What I have stated with regard to the time at which the influence of the various nitrites on the circulation is first distinctly perceptible points clearly to the drugs which may most advantageously be used during anginal pain. It has been shown that propyl, isobutyl, and amyl nitrites reduce the tension in a few seconds, whilst sodium nitrite takes from two to five minutes to act, and ethyl nitrite about the same time. Even nitroglycerine, which affects the circulation in from forty seconds to two minutes, acts much less rapidly than do the fatty nitrites when they are inhaled.

Manifestly then to relieve urgent pain and its concomitant danger, the fatty nitrites should be inhaled. Hitherto an impure nitrite has been chiefly used for this purpose. The nitrite of amyl of the *British Pharmacopœia* is a mixture of many nitrites, and contains likewise amyl alcohol, and oxidation products such as valeric aldehyde, valeric acid, and amyl valerate. Dunstan and Woolley, in one specimen found less than 40 per cent. of the amyl nitrite, and in another 50 per cent., but in addition 10 per cent. of isobutyl nitrite.²

Even the impure amyl nitrite now used is a most valuable drug, but considering the importance of the influence required, it seems desirable that a more-definite compound

should if possible be introduced. Of late isobutyl nitrite has been employed occasionally as a substitute for amyl nitrite. Cash finds isobutyl and secondary propyl nitrites somewhat more active in reducing tension than the amyl compound. It has appeared to me, too, that isobutyl nitrite more certainly relieves anginal pain than does the official amyl nitrite.

The inhalation of amyl nitrite sometimes fails to relieve the pain of angina pectoris; this failure may arise from several causes:

(1) The paroxysms may be due to neuralgia of local origin, or it may be reflected or hysterical, and circulatory changes may take but little part in its production. In such conditions nitrite inhalations can do no harm, yet they may fail to relieve pain.

(2) In some cases the nitrite does not remove pain because of the short duration of its action. It does not break the spell of the vessel contraction. There may be relief, but it is not complete, and when in a minute or two the effect of the drug passes off, the wave of contraction returns, and with it the pain.

(3) Some are curiously insusceptible to the influence of amyl nitrite. In such people full inhalations may succeed when slight ones fail, though this is not very common. If a certain measure of success is not obtained with ordinary inhalation, it is not often that a more copious use of amyl nitrite completely removes anginal pain.

(4) Lastly, in very advanced cases where the attacks of pain continue long, amyl nitrite may entirely fail to relieve the pain, though in an earlier stage it proved useful for this purpose.

If from any of these causes amyl nitrite does not remove pain, one of the nitrites whose effects are more persistent should be tried. Of the official preparations, nitro-glycerine is by far the best. On referring to the table it will be seen that it reduces tension more quickly than sodium nitrite, more quickly, too, than ethyl nitrite. Beginning with one drop of liquor trinitrini, the dose may be gradually increased until either the pain is relieved or unpleasant physiological effects as throbbing in the head or palpitation show that no more can be borne. In pain of hysterical or reflected origin this physiological limit is often quickly reached; in other cases very large doses may be given before relief is obtained.

Dr. Murrell, to whom we owe the introduction of nitro-glycerine as a remedy for angina pectoris, has given, as I have said, 110 minims eight times daily. Some are very insusceptible to nitrites, especially when passing through a dyspnoic attack, and it is worthy of note that the same individual may be more susceptible at one time than another.

A patient, L., from whom several of the tracings I show have been taken, came into the infirmary with intense dyspnoea and cyanosis, and some cardiac dilatation. The nitrites of amyl and ethyl seemed to have no effect in relieving the dyspnoea, and the ordinary effect of the amyl compound he did not feel. Nothing was of service except free venesection, which at once relieved him. The next day even, his pulse was somewhat refractory to nitrites, ordinary doses of sodium and amyl nitrites only affecting his circulation slightly. The pulse tracing, taken a month later, showed that he was then fairly susceptible to 2 grains of sodium nitrite; then he commenced to take the nitrites regularly, and in another month I found the tension of his pulse but little influenced by this dose, though by stronger doses it was readily brought down. As I have before said, people with high tension are less affected by nitrites than those with low tension. I have several times had occasion to gradually raise the dose of liquor trinitrini to 20 minims; it not infrequently happens that larger doses are required as a case progresses, and I believe it is far safer to employ somewhat large doses of nitro-glycerine than to resort to morphine injections, which in the later stage of angina pectoris generally fail to give relief, and I suspect, at times, hasten the fatal termination. Let me say here that I look on the injections of morphine in severe paroxysmal cardiac pain as by no means devoid of danger. It is quite true that they often give relief in anginal attacks, and are not usually followed by dangerous symptoms, but I have myself twice seen death occur shortly after subcutaneous injection of morphine in a prolonged anginal attack, and in the experience of others I find a fatal termination so frequently a sequence of an injection of morphine that it

savours strongly of cause and effect. From the use of nitrites I can find no evidence that fatal results appear to follow, notwithstanding the large doses in which they have been given, and the critical condition of many of the patients who have taken them. On the other hand, I have several times seen reason for believing that life has been shortened owing to the want of nitrites or their use in too niggardly a fashion, and on more than one occasion it has seemed as if the immediate cause of death has been an unrepentless nitrite bottle.

Every person who suffers from angina pectoris, and who has derived relief from nitrites, should have immediately at hand amyl nitrite, or the tabellæ or liquor trinitrini.

To prevent the recurrence of anginal attacks amyl nitrite is, of course, of no service, but nitro-glycerine is as useful in preventing attacks as in relieving them. A sufficient dose should be given a few minutes before an exertion which is likely to cause an attack of pain. The amount which is sufficient can only be determined by the effect on the patient; sometimes one drop will suffice to ward off attacks for two or three hours; oftener larger doses are required. One patient, for example, finds not less than twenty-five drops necessary in order to enable him to perform light work for some hours, and for six months has, by the aid of this dose once or twice daily, been enabled to live and earn a livelihood in fair comfort. Danger, I believe, arises not from the size of the dose or from its frequent repetition, but from too great fear of the drug.

In those in whom the anginal pains are connected with serious cardiac degeneration the time at length arrives when severe cardiac pain, which may be long continued, comes on without apparent cause; the end is then usually near at hand. Here the frequent use of large doses of liquor trinitrini will not suffice either to prevent or ward off all pain, but it is the most effective means we possess, and if it does not prevent suffering, it at least mitigates it without adding to danger. Nitro-glycerine is so quickly absorbed in the stomach that subcutaneous injection is, as a rule, not necessary; but in cases of urgency, where there is fear that the absorptive power of the stomach is in abeyance, it may be resorted to. At times nitro-glycerine is not well borne, owing to the headache which it causes; sodium or ethyl nitrite may then be tried, especially for the purpose of preventing paroxysms. The sodium compound may be used, beginning with 2-grain doses, but I do not think it usually agrees so well with patients as nitro-glycerine when large doses are required. A 2½ per cent. solution of ethyl nitrite in absolute alcohol I have often used, giving doses of one or two teaspoonfuls. The solution should be mixed with water immediately before being taken, otherwise the nitrite rapidly escapes.

Of late I have employed the ethyl nitrate, which has distinctly a longer lasting influence in reducing tension than the nitrite, and in some ten or twelve cases in which I have used it the testimony in favour of its prolonged beneficial action has been satisfactory. A medical man, who has been under my care for angina pectoris, has at my request compared on himself the effects of various nitrites, and places the nitrate of ethyl distinctly above the others in the length of time it wards off the attacks. In another case a woman, aged 28, who had suffered from anginal attacks for three or four months, and who found relief during the attacks both from nitro-glycerine and the inhalation of amyl nitrite, I found nitrate of ethyl give more continuous relief than nitro-glycerine. For two or three days she took 3-minim doses of the ethyl nitrate at intervals of three or four hours; in this quantity the attacks, though not prevented, were lessened in frequency. As the heart's action seemed quickened, she returned to the occasional use of the nitro-glycerine, but soon afterwards the attacks became more frequent and less amenable to relief by this drug. One morning, in the absence of one of my colleagues, I saw her, and found her with severe cardiac pain, which had lasted an hour, and which nitrite of amyl and nitro-glycerine in small doses had failed to relieve. A drachm of a 10 per cent. solution of nitrate of ethyl, the last I happened to have at the time, was then given to her. In ten minutes the tension was lowered as shown by the tracing, and the pain entirely disappeared.

A few hours later it recurred. Nitro-glycerine gave slight

relief, but only for a very short time, nitrite of amyl failed entirely to remove the pain. A subcutaneous injection of morphine guarded by atropine was now cautiously given, only two doses of the eighth of a grain being injected with an interval of half an hour. Hardly the slightest relief followed, the pain continued for three hours. Then she became cyanotic, and died somewhat suddenly. At the *post-mortem* examination the aortic valves were insufficient; one of the coronary arteries was found small, and the other almost obliterated. My experience of the use of nitrate of ethyl in angina pectoris and other ailments is not sufficiently large to enable me to form a definite opinion as to its value as compared with nitrites, but the long period during which it lowers tension in healthy subjects, and its very definite effects in the few cases of angina in which I have tried it lead me to think it may prove of value. The nitrate of propyl, isobutyl, and isoamyl are as effective in lowering tension as nitrate of ethyl, but the tendency to cause headache, which is I think even more marked with the nitrate than the nitrite of ethyl is a still more prominent feature in the action of the propyl, isobutyl, and isoamyl compounds, and I have not used them medicinally.

Although I regard the nitrites and the organic nitrates as of the greatest value in relieving and preventing anginal attacks, and in helping to ward off the fatal result in which any attack might terminate, I cannot rank them high as curative agents.

Doubtless, when attacks of angina are warded off and rendered less severe by the use of tension depressors, recovery does at times take place, as Dr. Murrell has well shown in some of the cases which he has so graphically described in his book on *Nitro-glycerine*. The relief from pain and suffering may tend to prolong life, and when regularly given the heart's work may be so decreased that its nutrition may improve. Perhaps, too, the vessel walls gain some advantage from the fact that under the influence of the nitrites their continued contest with the blood current is somewhat lessened. But I am by no means satisfied that the recoveries from angina pectoris which have been reported after nitrites and nitro-glycerine are really due to these drugs. Their employment is only one element, though an important one, in the treatment of angina. It should be accompanied by the use of those agents calculated permanently to improve the condition of the vascular system, among which I believe iodide of potassium and arsenic hold a foremost place.

Cardiac Dyspnoea.—Next to the relief of angina the nitrites are of most service in the prevention of dyspnoea connected with other forms of cardiac and with pulmonary disease. The theories which have been broached to account for cardiac dyspnoea are many in number, but hyperdistension of the pulmonary vessels is regarded in most cases as the immediate cause of the continued shortness of breath associated with cardiac dilatation and valvular lesions. The heart is at times unable to send the blood on its way through the system, because, owing to the weakening of its walls or the narrowing of the vessels, there is a disproportion between the power of the heart and the obstacle it has to overcome; from these causes or from a defective valve the pulmonary vessels may be kept constantly overful.

The dyspnoeal paroxysms may depend immediately on many causes, but most frequently they are due to sudden increase in the difficulty which the heart experiences in driving the blood onwards through the systemic system, either from a passing increased narrowness of the arterioles or from a temporary failure of cardiac power. Paroxysms of dyspnoea in cardiac disease may likewise occur from exacerbations of pulmonary hyperæmia and oedema. Unfortunately it is not always possible to determine whether attacks of dyspnoea with which we have to deal are due to heart failure, vascular contraction, or some other cause; often, indeed, more causes than one are present, hence the difficulty of coming to any conclusions as to the cases in which tension reducers may be of service, but in certain forms of cardiac trouble they are usually of special value.

In the dyspnoeic attacks which so often accompany cardiac dilatation connected with alcohol, gout, etc., I have seen nitrites of ethyl and sodium and nitro-glycerine give much relief. By dilating the vessels for a time they enable the

heart to do its work, and thus relieve the congestion of the lung vessels. The question arises, If the dyspnoic attacks are connected with cardiac failure, can they do harm in virtue of their cardiac depressant influence? I believe large doses might work evil, but in small quantities, such as 1 to 2 drops of nitro-glycerine, 1 to 2 drachms of the $2\frac{1}{2}$ per cent. solution of nitrite of ethyl, or 2 grains of sodium nitrite, the action is always in favour of the heart. These small quantities can powerfully dilate the vessels, but they do not, in an important measure, depress the heart. Experiments on animals, as I have pointed out, show that very small quantities increase rather than decrease the amount of work a heart can do. I have given the doses I have named in a very large number of cases, and never seen the slightest indication pointing to possible evils. The amount administered may be cautiously increased without any risk if the relief be insufficient, or the efficacy first noticed seems afterwards to fail.

In the case of nitrites, increase of danger is not proportioned to increase of dose. When relief is not obtained by a small dose, and when no physiological effects follow, such as throbbing in the head or palpitation, I find it quite safe to repeat the dose in half an hour. It is desirable, when the larger doses are given, or when the drug is given more frequently, that the patient should rest. Discomforts which have arisen after small doses of the nitrite, such as 3 grains of sodium nitrite, have for the most part occurred in those who have been pursuing their ordinary avocations.

I am not deterred from giving nitrites in dyspnoea by irregularity or weakness of the pulse, for I find that in dyspnoea they do not tend to cause syncope or lead to heart failure. Dr. Sansom has published a case in which a patient with an extremely weak and irregular heart's action was in the habit of taking six to twelve nitro-glycerine tablets daily without medical advice. I have met with one or two similar instances in which people with very dilated hearts have found such relief from nitro-glycerine tablets that they have continued to take them for months, and I have no doubt that many sufferers take them habitually without advice. I can easily conceive that grave mischief might arise, but, so far, I have met with no record of it. Fortunately, there seems to be a special tolerance of nitrites in such cases. When with cardiac dilatation moist sounds at the base give evidence of bronchitis or lung oedema, the nitrites generally fail to relieve but by no means always. Partial relief is indeed not uncommon, and a few doses of a nitrite are always worthy of trial.

In the paroxysms of dyspnoea which occur in many valvular diseases of the heart the nitrites are sometimes of great service. But here, as in simple cardiac dilatation, they often fail when there are abundant moist sounds at the bases of the lungs. They will fail to remove dyspnoea, too, as all other remedial agents fail, in very advanced conditions of cardiac disease, yet even in the most unpromising cases they are at times of the greatest value in the relief of distress, so much so that patients will often beg for the repetition of the dose which has given so much comfort.

The nitrites are naturally most useful in mitral disease, since here paroxysmal dyspnoea is more frequent than in aortic troubles, but aortic incompetence is no bar to the use of nitrites in small quantities when the breathing is oppressed. In valvular disease as in simple dilatation, weakness and irregularity of the heart's action need not be taken into account in giving small doses of the nitrites for dyspnoic attacks; such doses do no harm even if they do no good. In a few cases, as I have already said, I have known irregularities cease under their employment.

Against the utility of nitrites in cardiac dyspnoea it might be urged that as their vascular influence is but transitory, so also will be the relief they give, and this is true; but here, as in the case of other remedies, we find that relief is not limited to the period during which the medicine directly acts. When unduly contracted arteries are dilated, they do not forthwith resume their contracted condition as soon as the effect of the nitrite on the vessel wall has passed away. Whether the dilatation of the pulmonary vessels by nitrites is one factor in the relief they give in cardiac dyspnoea we cannot say, but the very marked effect they can be shown experimentally to produce in dilating these vessels seems to render it likely that, besides increasing the calibre of the

systemic vessels and easing the left heart, they at the same time, by widening the lung vessels, relieve the strain on the right heart.

Since paroxysmal cardiac dyspnoea has many causes, some of which are not influenced at all by vascular dilatation, it follows that sometimes no relief is obtained from nitrites, but, as a routine remedy for this dyspnoea, I believe there is nothing better.

For the past two or three years nitrites have been resorted to habitually in my wards of the infirmary at Manchester in all forms of dyspnoea. Comparing their effects with those obtained from ether and ammonia in paroxysmal attacks of cardiac dyspnoea, I have no hesitation in saying that the nitrites are by far the most beneficial. I have used a solution of nitrite of ethyl in absolute alcohol, but nitro-glycerine or nitrite of sodium with alcohol might be in some respects perhaps better since they are more stable.

For the permanent short-breathedness of cardiac disease the nitrites are, I believe, less useful than for dyspnoic attacks. Occasionally the measure of relief may be given to the heart's work by them which is doubtless beneficial to this organ, but I do not think it possible to keep the tension permanently low, either by nitrites or nitro-glycerine, for by persistent administration at short intervals their vascular dilating power lessens somewhat, and, with large continuous doses, methæmoglobin might be produced. I have found some patients with weak dilated hearts, and suffering from dyspnoea on slight exertion, experience great relief from a few small doses daily of nitro-glycerine, and I think I have seen some permanent advantage derived from this treatment. In some other special conditions connected with cardiac disease the nitrites have been found of service, as, for example, in aortic insufficiency with hypertrophy and severe headache.

We often meet with patients just past the middle period of life, stout, and with some evidence of fatty cardiac change, who feel a sense of discomfort on any exertion and are therefore unable to take exercise, and who at times have somewhat smart attacks of dyspnoea from slight causes. In these cases I think the nitrites not only useful in the attacks, but also in giving comfort when taken regularly. A tablet or two of nitro-glycerine, when taken twice daily, will often remove long-standing discomforts due to the readiness with which dyspnoea is excited, and a permanent improvement at times ensues, because, with the aid of the nitro-glycerine, patients are able to take a certain amount of exercise.

Even in advanced fatty changes I have no hesitation in giving small doses of the nitrites, both to relieve and prevent dyspnoea. I question whether the heart in this condition is weakened by them at all, but of this I am quite sure it is much relieved and aided in its work.

Syncope and Cardiac Failure.—A difficult question to decide is whether nitrites should be used in syncope and cardiac failure.

The flushed face produced by amyl nitrite led to the idea that it might be of service in syncope, for which purpose indeed it was proposed in the first paper on its action, by Guthrie in 1859. In 1871 Dr. Goodhart again suggested its use in sudden failure of the heart's action, and in the same year Dr. Talfourd Jones gave it with apparent advantage to a patient who had fainted. Since this time it has often been recommended and given in cases of apparent heart failure from various causes, including cardiac failure due to chloroform, and so far as I am aware no evil consequences have ever appeared to result from its employment; on the contrary, distinct and immediate improvement in the patient's condition is said to have followed its use.

Nitro-glycerine, too, has been given in syncope and collapse, and in one case of collapse during the passing of gall stones; and when the patient was pulseless it is recorded that ten drops of a 1 per cent. solution of nitro-glycerine were injected with advantage.

Reichert especially has claimed the nitrites as valuable cardiac stimulants, and in support of his contention has marshalled a series of cases of heart failure, in which they seemed to prove useful. As I have indicated when speaking of the pharmacology of the nitrites, there is ground for thinking that the initial influence of small doses of nitrites on the circulation is a stimulant one, notwithstanding that

they are so capable in large doses of weakening the heart's action. Syncope is the result of a failure of the heart to supply the cerebrum with a due amount of blood, and to this failure arterial dilatation and lowered tension sometimes contribute. When this is the case it would appear that the administration of nitrites might be gravely dangerous since they so powerfully lower tension. But spasmodic contraction of the arterial vessels is probably in some cases one cause of the insufficient supply of blood which leads to syncope, and here for increasing the cerebral supply, nitrites would be of service.

When, too, sufficient blood is not driven into the brain, owing to deficient power in the heart itself, nitrites may be useful by their direct influence on this organ, and indirectly by dilating the vessels, and thus relieving the heart of some portion of its work.

Whilst then in some forms of syncope harm might be done, and even a fatal result brought about by full doses of nitrites, it seems very probable that in others good results will follow from their employment, and since no bad effect has yet been recorded from the use of nitrites in syncope, whilst in many cases great advantage have followed their use, the employment of small doses of nitrites in syncopal conditions seems to be well justified.

In cardiac failure, too, there is evidence that good results have followed both from the use of amyl nitrite and nitro-glycerine, and it seems to me that these are grounds for the use of the drugs in small quantities. A failing heart will under their influence beat more quickly, and will be relieved of a certain portion of its work by the dilatation of the vessels. But the difficulty is to graduate the amount of nitrite to the necessities of the heart. If any nitrite were by inhalation thrown into the blood in large quantities, it might stop the action of a failing heart.

Pulmonary Dyspnoea.—For the relief of dyspnoea due to asthma and bronchitis, the nitrites and nitro-glycerine have been occasionally used since Dr. Talfourd Jones, in 1871, recorded the beneficial effects of the inhalation of amyl nitrite during an asthmatic paroxysm. Five years ago Professor Fraser published the results of his investigations on the influence of the nitrites of amyl, ethyl, and sodium in the dyspnoea connected with asthma and bronchitis.³ He found that in asthmatic paroxysms the inhalation of these nitrites was capable of completely relieving the respiration, and removing the adventitious lung sounds. Usually the rhonchi returned when the effect of the nitrites passed away; at times the relief was permanent. With the nitrites of ethyl, sodium, and nitro-glycerine he generally noted in half a minute a decrease of the adventitious sounds, and lessened dyspnoea, and relief in three to five minutes. As might be expected, the effects were more prolonged than after nitrite of amyl. In 61 observations made on 25 patients suffering from bronchitis, in some cases accompanied with dyspnoeic paroxysms, the nitrite in 48 removed every vestige of rhonchus or sibilus for various periods of time. In 10 the sounds were lessened, but they were not altogether silenced; in 3 the effects were slight or negative, and in these the dyspnoea was not relieved. I cannot say my experience of the use of nitrites in asthma and bronchitis has been as favourable as that recorded by Fraser. Nevertheless, I have seen a large measure of relief afforded in pulmonary dyspnoea by them. In typical asthma I have often seen complete and rapid relief afforded, yet in some cases hardly the slightest benefit arises either from inhalation of amyl nitrite or from the administration of large doses of the other nitrites. In the less severe asthmatic attacks, which are apt to come on from time to time in nervous people subject to slight bronchitis, the attack is almost always cut short by nitrites; and where marked bronchitis symptoms are permanently present and asthmatic exacerbations also occur, the nitrites give relief to the urgent dyspnoea in a large proportion of the cases, yet by no means in all. The disappearance of the rhonchi in bronchitis under the influence of the nitrites I have often seen, but it does not in my experience occur so frequently as in the cases observed by Fraser.

Where abundant moist sounds are present owing to a large amount of secretion in the bronchial tubes, the nitrites generally are of little service. But in dyspnoea with bronchitis,

indicated by abundant sibilant and sonorous rhonchi, and also in asthmatic paroxysms, amelioration is at least the rule; at times paroxysmal dyspnoea is cut short by a single dose of one of the nitrites, and may not recur for hours. In bronchitic dyspnoea the duration of the relief varies, but usually lasts as long as the influence on the circulation. From this Fraser thinks that the nitrites produce their effect by relaxing the muscles of the bronchial tubes, in the same manner as they relax the contraction of the blood vessels, and that this effect is the essential cause of the relief nitrites give in dyspnoea. From the marked effect of nitrites in some cases of asthma and bronchitis, and from the evidence we have of the influence which nitrites exert on involuntary muscle fibre, it certainly seems probable that they are capable of increasing the lumen of bronchial tubes when narrowed by contraction of muscular fibre which surrounds them; but it by no means follows that such contraction is the sole cause of asthmatic paroxysms or the exacerbations of dyspnoea in bronchitis. There is a want of uniformity in the action of nitrites which I should hardly expect if paroxysmal dyspnoea depended entirely upon contraction of the bronchial muscles alone. Moreover, dyspnoeic attacks are at times relieved by nitrites without any marked alteration in the auscultatory signs.

It seems to me likely that some alteration takes place in the bronchial mucous membrane more or less coincident with spasmodic contraction of the bronchial muscles.

Sir Andrew Clark⁴ has suggested as a cause for asthmatic paroxysms a sudden hyperæmic swelling of the mucous membrane of the bronchial tubes comparable to the changes which occur in the skin in urticaria. Fraser is of opinion that the relief afforded by the nitrites in asthma is opposed to such a theory, because the dilating action on the vessels which he supposes occurs in the bronchi, as in all the other vessels of the body, would increase or prolong the paroxysms instead of controlling or checking it. With this view I cannot coincide. For if the tumidity of the mucous membrane connected with asthmatic attacks resembles that which occurs in urticaria, it is probable that it is associated with spasm; at least in urticaria antecedent spasm is held as probable. It is not likely that vascular dilatation would be present at any one time over the whole mucous membrane affected; it is more probable that spasm and dilatation would coexist in different portions of the mucous membrane. Such a condition the administration of nitrites would tend to relieve. By decreasing spasm they would tend to restore the mucous membrane to its normal condition. It is just possible, too, that the dilating influence exerted on the pulmonary vessels by the nitrites may to some extent relieve the bronchial vessels.

As a rule nitrites are well borne by dyspnoeic patients, and large doses may be safely given if experience shows they are needed. I have administered 1 drachm of a 2½ per cent. of ethyl nitrite solution every ten minutes, until 3 or 4 drachms have been taken. Sodium nitrite is at times borne better in pulmonary dyspnoea than ethyl nitrite, and sometimes the reverse is the case.

The spiritus ætheris nitrosi of the *Pharmacopœia* would be equally serviceable if it always contained a definite amount of the ethereal nitrite, but the rapid deterioration in the strength of this ingredient, which at times takes place, renders it uncertain in its influence. Perhaps the best preparation would be liquor trinitrini combined with a small quantity of rectified spirit. Headache, however, seems to me more common after trinitrine than after nitrites. Of late I have used ethyl nitrate in doses of from 5 to 10 minims, and find that it is quite as efficacious as ethyl nitrite, and that its influence lasts longer. Amyl nitrite acts for too short a time to be of service.

The nitrites must not be looked on as curative agents in bronchitis; they are capable often of relieving dyspnoea, and by dilating the vessels of the lung they may possibly temporarily relieve the right heart. But in the ordinary forms of bronchitis their regular administration does not, as a rule, prove very advantageous. It is for the relief of dyspnoeic conditions they should be reserved, and even then they often fail when abundant moist sounds indicate that the difficulty of breathing is connected with accumulation of bronchial mucus rather than with spasm of the tubes or vessels. By

some the nitrites have been used in pneumonia, lung œdema, and many other lung ailments. It is quite possible that they may give relief at times, but I question whether they can be looked on as curative.

Uræmic Dyspnœa.—In uræmic dyspnœa I have been at times disappointed in the use of nitrites. Scattered through the journals are many records of the utility both of nitro-glycerine and amyl nitrite in this condition. I also have found them advantageous, yet they have often failed. They are indeed well borne in large doses, but the relief they give is usually transient. Perhaps it may be that uræmic dyspnœa owns another cause besides those which are the chief factors in cardiac and pulmonary lesions. Huchard is of opinion that even in that altered condition of the arterial walls which often so long precedes renal disease (and which may indeed terminate life by the cardiac troubles it induces, apart from renal disease), toxic products may accumulate in the blood, because the kidney is unable from the changes in its vessels to eliminate them. He adduces in support of his views the non-toxic effect of the urine in these cases, and he looks on the dyspnœa which occurs as the result of the reaction on the body of toxins which would have been eliminated had the kidney been perfectly healthy. In Bright's disease this toxic material must be often present, and it seems possible that in some cases it may exert its influence so strongly as to neutralise the effects of the nitrite molecule, as I have shown barium neutralises it outside the body. There must be great variations in the amount of toxic material present at various times, and it may be this variation accounts for the different effects produced by nitrites under apparently the same conditions. Nitrites and nitro-glycerine cannot be relied upon to combat the high tension which is often present long before renal disease declares itself. They act quickly, but not continuously, for they are easily eliminated. There is reason to believe, too, the tissues get accustomed to them if they are given frequently, and become less influenced by them; hence I believe their frequent administration is not desirable in this condition, which, as Huchard and others have pointed out, should be met by milk diet and eliminants. But to relieve some of the discomforts arising from high tension—as headache, heaviness, and dyspnœa—the administration of liquor trinitrini or the nitrites is often of great service, and in the dyspnœic paroxysms which accompany the heightened tension from arterial changes when cardiac dilatation has commenced, these drugs are of the greatest value if given in sufficient doses.

Let me lay stress on the word "sufficient." The doses in these cases must usually be large, and an amount which will dilate the vessels ordinarily very fully may have too slight an effect to be of service in chronic Bright's disease. Yet, even in this ailment, full doses at times produce alarming symptoms, and even moderate amounts may give rise to discomforts. It is never wise to commence the administration of nitrites and nitro-glycerine with large doses.

Cheyne-Stokes Respiration.—Filehne many years ago noticed that the inhalation of amyl nitrite will remove the Cheyne-Stokes respiration, and attributed its result to its effect on the vasomotor mechanism. Gibson, however, finds that though it has this effect in some cases, owing, he thinks, to its stimulating effect on the central nervous structures, it produced no influence in others.⁵

Migraine and Headache.—For the relief of headache the nitrite and nitro-glycerine have been much employed, and considerable success has been recorded from their use. Amyl nitrite has been specially credited with the power of relieving migraine, and sometimes curing it. That it will at times cut short an attack, no one who has used it extensively as I have done can doubt, but in my hands its failures have far outnumbered its successes. Even if, as has been suggested, the immediate cause of suffering in some forms of migraine is connected with local vascular contraction, it is not likely that a very temporary dilatation of the vessels could be relied on to restore a normal condition. We know, however, how suddenly tension may fall, and inhalation of amyl nitrite coming at the right time may be the final cause of relief, the dilatation which it causes not being followed by contraction. But perhaps, as Pick long ago suggested, it is sometimes probably a kind of "surprised influence," which immediately takes

away the pain when nitrite of amyl is inhaled, just as any other influence, physical or mental, may have the same effect. It not infrequently happens that after amyl nitrite inhalation has succeeded once or twice, it subsequently quite fails to give relief. The drug, indeed, has not maintained its promise, the utility attributed to it in the account of earlier reporters has not been borne out by frequent use. It does not seem likely that nitrite of amyl can permanently cure migraine.

Nitrite of amyl has been used to combat slight forms of headache; and here, too, it is sometimes successful in giving relief, but, as it at times greatly intensifies the pain, its general employment has fallen into disrepute. Nitro-glycerine is probably a far more effective remedy than amyl nitrite. Dr. Hammond and many others have borne strong testimony to its utility in migraine. It is naturally most useful in those attacks in which the face is pale and the radial artery tense. A drop or two of nitro-glycerine in these conditions I have sometimes seen give rapid and long lasting relief, yet this effect is by no means always seen, and in neurotic patients and those with low tension and an easily excitable circulation discomforts may be considerably aggravated. I believe, however, that nitro-glycerine might with advantage be more frequently used for the relief of migraine and headache generally, if care were taken to employ it only where the circulatory conditions point to some degree of high tension. That migraine and other forms of headache have permanently disappeared under its use I do not doubt; it is by no means so certain that this effect has followed because of its use. The dose of nitro-glycerine given for the relief of headache should always be in the first place small. Even a single drop, if the case be not suitable, may prove very unpleasant for the patient. It is sufficient in doubtful cases, at least, to commence with half a drop of liquor trinitrini. If slight relief or no relief ensue in half an hour, a drop may be given, and later on, if necessary, larger doses.

REFERENCES.

- ¹ *Practitioner*, vol. xlvii, p. 255. ² *Pharm. Journ.*, 1888, p. 489. ³ *Trans. Ed. Med.-Chir. Soc.*, vol. vi. ⁴ *Int. Journ. of Med. Sci.*, 1886, p. 105. ⁵ *Practitioner*, vol. xxxviii, p. 86.

THE FORFARSHIRE MEDICAL ASSOCIATION.—Dr. Rorie, the President of the Forfarshire Medical Association, delivered an address at the thirty-fifth annual general meeting of this Association, recently held at University College, Dundee. His thesis was a defence of the theory of vitalism in opposition to the chemico-physical theory of mere metabolism, which he contended was insufficient to explain the phenomena of life. The officers for the year were then elected: Dr. Russell, of Arbroath, being chosen President; Dr. Rorie and Dr. Dickson, Vice-Presidents; and Dr. McGillivray, Treasurer. The following local secretaries were appointed: Drs. Key (Montrose), Laing (Arbroath), Cable (Forfar), and Leishman (Brechin). Dr. Mackie Whyte, the retiring treasurer, was cordially thanked for his services during his seven years of office. A donation of five guineas was voted to the British Medical Benevolent Fund. The members subsequently dined together, and among the guests were Professor Fraser (Edinburgh), Professor M'Call Anderson (Glasgow), Professors Frankland, D'Arcy Thompson, and Geddes (University College), Dr. Douglas, (Cupar), Dr. Murray (H.M.S. *Unicorn*), and Mr. Walter Campbell.

MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—The following officers for the year 1893-94 were elected at the recent annual general meeting of this Society:—**President:** Dr. Hector C. Cameron. **Section of Medicine:** *Vice-President:* Dr. Middleton; *Councillors:* Dr. Auld and Dr. W. A. M'Lachlan; *Secretary:* Dr. C. O. Hawthorne. **Section of Surgery:** *Vice-President:* Dr. W. J. Fleming; *Councillors:* Dr. Dalziel and Dr. MacPhail; *Secretary:* Dr. John Barlow. **Section of Pathology:** *Vice-President:* Dr. Charles Workman; *Councillors:* Dr. John Brown and Dr. T. K. Monro; *Secretary:* Dr. R. M. Buchanan. **Section of Obstetrics:** *Vice-President:* Dr. M. Cameron; *Councillors:* Dr. Lapraik and Dr. Jardine; *Secretary:* Dr. Lawrence Oliphant. *Treasurer:* Mr. Henry E. Clark. *General Secretary:* Dr. Walker Downie.