THE BRADSHAW LECTURE

ON

SOME NEW VASO-DILATORS.

Delivered before the Royal College of Physicians of London.

By J. B. BRADBURY, M.D., F.R.C.P.,

Downing Professor of Medicine in the University of Cambridge; Physician to Addenbrooke's Hospital.

[AFTER an expression of thanks for his selection for the office of Bradshaw Lecturer and a reference to the terms of the foundation, Professor Bradbury continued as follows:]

Having recently undertaken, in my capacity as Downing Professor of Medicine in the University of Cambridge, to teach and advance to the best of my ability the subjects of pharmacology and therapeutics, it occurred to me that I could not do better on the present occasion than address you on a subject in this department of medicine; and here I wish to express my obligation to my assistant, Mr. Marshall, who has rendered me invaluable aid in conducting the experiments mentioned in the lecture.

I propose, then, to ask your attention to certain vessel dilators which, so far as I am aware, have not previously been brought before the notice of the profession.

The vaso-dilating action of nitrites and nitro-glycerine has long been known, and the whole subject of their action was ably reviewed and further extended by Professor Leech in the Croonian Lectures of 1893. These compounds possess a powerful though more or less evanescent action; and as in some conditions it would be advantageous to possess a drug having a more prolonged though less powerful effect, it has been the endeavour of pharmacologists to discover such a substance. Professor Matthew Hay¹ experimented with ethyl-nitrate, nitro-cellulose, and allied bodies, but came to the conclusion that these were of no practical value. Later Dr. Leech, investigating the action of the nitrates of the fatty series, found that all these bodies possessed a dilating effect, generally of a prolonged kind.² He suggested them as remedial agents, but at the same time pointed out their liability to cause headaches. Still more recently Dr. Lauder Brunton has experimented with hydroxylamine hydrochlorate, but he found this compound liable to produce gastric disturbance.³

As all the alcoholic nitrates previously examined had been found to be vaso-dilators, and as nitro-glycerine, the only multivalent nitrate used, has a powerful influence in this direction, it seemed not improbable that the drug in quest might be found among the nitrate derivatives of the higher-valent alcohols or their allies. The nitrates of erythrol, mannitol, and some of the sugars were therefore examined; later, the series was extended; but it is mainly to the results of the examination of the bodies just mentioned, and their possible bearing on therapeutics, that I ask your consideration.

Chemically, nitrates consist of an NO₂ group united to a radicle by a bond of O, thus R—O—N $\begin{smallmatrix} \diagup O \\ \diagdown O \end{smallmatrix}$. True nitro bodies, on the other hand, consist of an NO₂ group, united to a radicle by the N atom directly, that is without the intervention of an O atom—for example,

Preparation.—All the substances I have experimented with were obtained by nitrating the alcohols or corresponding compounds by means of a mixture of nitric and sulphuric acids at a low temperature. The product obtained was well washed with water and dilute alkaline solution until free from acid, and was subsequently dried. The solid nitrates

¹ *The Practitioner*, vol. xxx, p. 321.

² *BRITISH MEDICAL JOURNAL*, 1893, vol. ii, p. 56.

³ *St. Bartholomew's Hospital Reports*, xxx, p. 189.

⁴ Although I may occasionally use the expression nitro compounds, all the bodies we are dealing with are in reality true nitrates. Unfortunately, the term nitro in reference to these bodies has become so familiar from long use that it is difficult to discard it altogether.

were afterwards crystallised from ethylic alcohol or ether. From the alcohols the following series was prepared:

Methyl Nitrate	...	...	...	CH ₃ ·ONO ₂
				CH ₂ ·ONO ₂
Glycol (Ethylene) Dinitrate	...	...		CH ₂ ·ONO ₂
				CH ₂ ·ONO ₂
Glycerol Trinitrate (Nitroglycerine)				CH·ONO ₂
				CH ₂ ·ONO ₂
				CH ₂ ·ONO ₂
Erythrol Tetranitrate	...	...	...	(CH·ONO ₂) ₂
				CH ₂ ·ONO ₂
(Arabinol Pentranitrate)				CH ₂ ·ONO ₂
Mannitol Hexanitrate	...	...	...	(CH·ONO ₂) ₄
				CH ₂ ·ONO ₂

Arabinol pentanitrate, which would occupy the place intermediate between the erythrol and mannitol compounds, has not yet been prepared.

Among the sugars the nitrates of dextrose, levulose, and saccharose have been investigated. Constitutionally these bodies differ from the alcoholic nitrates in containing an aldehyde or ketone group, and fewer nitrate (NO₂) groupings. Other nitrates—those of cellulose and starch—have also been examined, but as these have no bearing on therapeutics I shall not deal with them further.

The composition of the nitrates used was determined by means of a Lunge's nitrometer. This gives off all the nitrogen in these compounds as nitric oxide (NO), from which the number of NO₂ groups in the body can be determined.

Properties.—Of the nitrated alcohols the first three are liquid at the ordinary temperature of the air, the others are solid and crystalline. When pure they are colourless, and if kept in a dark and moderately cool place are stable. Exposed to sunlight and warmth they gradually decompose, turning yellow, and giving off nitrous fumes. Heated rapidly, or subjected to percussion, they explode. Methyl nitrate distils at 65° C.; but the boiling points of the glycol and glycerol nitrates have not been determined, as these bodies rapidly decompose as their boiling points are approached. Erythrol nitrate melts at 61° C., and the mannitol compound, according to Socoloff, at 113° C. All these nitrates are more or less soluble in water, their solubilities showing a gradual transition from the methyl—the most soluble—to the mannitol, the least soluble. In all cases the solubility in water is slight, but in alcohol and ether they are readily soluble.

The nitrated sugars, as I have obtained them, are white or slightly yellow tenacious masses, decomposing readily, and difficult to prepare in the pure state. Like the corresponding alcoholic esters they are readily soluble in alcohol and ether, and slightly so in water. All the nitrates when heated with alkalis give the nitrite reaction, that is, they liberate iodine from a slightly acidified solution of potassium iodide, and produce certain colour reactions (the meta-phenylene diamine test, etc.).

PHARMACOLOGICAL ACTION.

All soluble organic nitrates of the composition R·ONO₂, hitherto examined dilate blood vessels and change the normal spectrum of the blood. Their activity, however, varies within wide limits, and appears to be due to their different solubilities and liability to decomposition. The latter is, perhaps, the more potent factor,⁵ as methyl nitrate—the most soluble compound—has a comparatively slight vaso-dilating effect. On the other hand, glycol dinitrate—the least stable—has a powerful action closely resembling that of nitro-glycerine. Its effect, however, is more transient. The erythrol and mannitol nitrates and the nitro-sugars, being less soluble than the other compounds, have a correspondingly weaker effect, but, as we shall see, their action is more prolonged.

The vaso-dilating action of these bodies has been determined by means of perfusion experiments on both warm- and cold-blooded animals, and the duration of this action by their effect upon the blood pressure in animals and the pulse in man. Nitro-glycerine has been largely experimented with, but as the vessel-dilating effect of this drug is now so well known I shall say little further about it.

Perfusion Experiments.—The method of perfusion through excised organs, which we owe to the genius of Ludwig, demonstrates absolutely the direct effect of drugs upon blood vessels. In such experiments there is no question of nervous action except it be a purely local one. But whether the effect of an agent be upon the terminal nerve fibrillæ and intramural nervous ganglia or upon the muscular tissue of the vessel walls is of little moment. For all practical purposes it is sufficient to know that a drug acts either directly or indirectly, that is chiefly upon the peripheral vessels or upon the vasomotor centre.

For determining the action of these agents upon the vessels

⁵ See also Hay, *loc. cit.*, p. 329.

Fig. 1.—Glycol dinitrate 0.0125 g. per kilo. body-weight in 33 per cent. alcohol, injected through catheter into stomach at 4.31 P.M. The time in this and other tracings marks seconds.

of warm-blooded animals the kidney of the sheep, as being the most readily procurable, was used. For the effect on cold-blooded animals frogs and water-tortoises were employed. But in all the general effects obtained were the same, and I shall therefore confine myself to my experiments on the former.

In all the experiments, with the exception of those of methyl nitrate, a presumable strength of 1 of drug in 10,000 of blood was used.⁶ By means of ovens the excised organ and blood were kept at the normal temperature (37° to 38° C.) and the blood was perfused under a constant pressure (70 mm. Hg.). The outflow of blood from the vein was measured at intervals of a minute, first during the passage of normal blood and subsequently during the flow of nitrated blood. Methyl nitrate in the strength of 1:10,000 has scarcely any dilating effect. In 1:10,000, however, it transformed a normal venous flow of 23 c.cm. a minute to one of 33 c.cm. a minute. After the perfusion of normal blood the venous outflow again reached its former level. A second and a third time vascular dilatation was produced by the nitrated blood, and each time was followed by contraction when normal blood was perfused. The other nitrates are much more powerful. Dinitrate of glycol perfused in the strength of 1:10,000 increased the outflow from 9 c.cm. a minute to 23 c.cm. a minute, and nitro-glycerine in the same strength converted a normal outflow of 9 c.cm. into one of 19 c.cm. a minute. In both cases contraction immediately followed the perfusion of normal blood, and a second and third time marked dilatation was produced by nitrated blood. Erythrol and mannitol nitrates also caused marked dilatation, the former increasing the venous outflow from 13 c.cm. to 35 c.cm. a minute, the latter from 6 c.cm. to 11 c.cm. a minute. A nitrate of dextrose containing four NO₃ groupings, and therefore corresponding to a tetranitrate, when perfused increased a normal outflow of 14 c.cm. to one of 26 c.cm. a minute. Similar results have been obtained with the other nitrated sugars.

There can, therefore, be no doubt as to the capability of these bodies to dilate blood vessels; but, as I have previously intimated, what we want to know for therapeutic purposes is the duration of their action. This is shown in the blood pressure and pulse tracings.

BLOOD-PRESSURE TRACINGS.⁷

The blood-pressure tracings were mostly taken from rabbits which were kept under the influence of urethane, a drug exerting scarcely any effect upon the blood pressure.

In the case of the glycol and glycerol nitrates, an amount of drug corresponding to 0.0125 gramme per kilogramme of the body-weight was introduced. In this dose methyl nitrate had scarcely any effect, and therefore a dose of four times this amount—namely, 0.052 c.cm. per kilo. body-weight—was used. Even in this dose, the effect was slight and transient. With the solid bodies, doses of 0.025 gramme and 0.05 gramme per kilo. body-weight were used, but, as part of the substance could be extracted from the contents of the stomach after the completion of the experiment, this does not represent the amount absorbed. In the case of the liquid bodies, the substance was dissolved, and in the case of the solid bodies, in part dissolved and in part suspended in weak ethylic

⁶ I say "presumable," because in a few instances, notably those of the nitrates of mannitol and the sugars, complete solution of the drug may not have occurred.

⁷ I take this opportunity of thanking Professor Schmiedeberg, of Strassburg, for allowing my assistant the use of his laboratory for this purpose.

alcohol, the mixture being injected through a catheter into the stomach.

Both glycol dinitrate and glycerol trinitrate (nitro-glycerine) have a powerful action. The former (Fig. 1) in 1 minute reduced the blood pressure from 112 mm. Hg. to 85 mm., and in 4 minutes to 42 mm. The pressure then gradually rose, and 14 minutes after the administration stood at 106 mm. Hg. Later the blood pressure again fell, probably owing to further absorption of the drug, and later still commenced to rise again. Under similar circumstances nitro-glycerine produced an almost identical effect. In 1 minute the pressure was reduced from 100 mm. Hg. to 76 mm., and in 3½ minutes to 37 mm. It then commenced to rise, and 17 minutes after the administration of the drug stood at 71 mm.

Fig. 2.—Erythrol tetranitrate 0.05 g. per kilo. body-weight in 10 per cent. alcohol injected through catheter into stomach at 12.2'.

The effect of erythrol and mannitol nitrates is much less evident. No abrupt fall of pressure occurs, but there is also no subsequent return to normal; 23 minutes after the introduction of erythrol nitrate (Fig. 2) a fall of pressure from 85 mm. Hg. to 63 mm. occurred, and 30 minutes later the fall was further increased to 54 mm. The subsequent fall was trifling; 2 hours 48 minutes after the administration of the drug the pressure was 46 mm. Hg., and an hour later it stood

Fig. 3.—Mannitol hexanitrate 0.025 g. per kilo. body-weight in 33 per cent. alcohol injected into stomach at 10.48'.

at the same level. In the meantime the cannula had been changed from the left to the right carotid owing to a clot having formed in the former vessel. After mannitol nitrate a similar effect occurred (Fig. 3); 12 minutes after the introduction of the drug the blood pressure had fallen from 98 mm. Hg. to 84 mm. An hour later it had fallen to 60 mm. Subsequently a slight rise followed by a fall occurred; 4 hours 12 minutes after the commencement of the experiment the blood pressure still remained at 58 mm. Hg.

The effect of methyl nitrate upon the blood pressure is slight. After introducing 0.125 c.cm. of the substance (that is, about four times the quantity used in the case of the other,

liquid nitrates) dissolved in 5 c.cm. of water into the stomach (Fig. 4), the blood pressure fell from 96 mm. Hg. to 70 mm.

Fig. 4.—Methyl nitrate 0.052 c.cm. per kilo. body-weight, dissolved in water injected into the stomach at 11.47.30", in the course of a minute, but immediately commenced to rise again; 6 minutes 30 seconds from the commencement of

C.D. — Before Glycol Dinitrate

C.D. — 1 min after 100 gr.

A.C. — Before Nitroglycerine

C.D. — 2 m 10 s. after 100 gr.

A.C. — 1/2 min. after 100 gr.

C.D. — 3 mins. after 100 gr.

A.C. — 3 mins. after 100 gr.

C.D. — 6 mins after 100 gr.

A.C. — 5 mins after 100 gr.

C.D. — 10 mins after 100 gr.

A.C. — 10 mins after 100 gr.

C.D. — 16 mins after 100 gr.

A.C. — 1 hr. after 100 gr.

Fig. 6.—Glycol dinitrate. the experiment the pressure was 82 mm., and 11 minutes later was practically normal.

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A consideration, therefore, of the action of these drugs upon blood pressure leads us to the conclusion that the nitrates of erythrol and mannitol have a less marked but more prolonged action than those of glycerol and glycol, and that methyl nitrate has comparatively little action. These relations are again brought out in the accompanying pulse tracings. These have been selected from a number taken under varying conditions of health and disease, and they show in a graphic manner the fall of arterial tension and its relative duration; they are, in fact, a complement to the experiments which I have already described.

PULSE TRACINGS.

The tracing of methyl nitrate (Fig. 5) shows, perhaps, a more marked fall of arterial tension than we should expect from the previous experiments, but the dose is an excessive one, being 1,000 times that of the glycol and glycerol nitrates, and 10 times that of the solid nitrates. It is, however, essential for practical therapeutics that we should know the dose sufficient to produce a salutary effect, and hence the comparatively large dose given. The arterial tension was reduced in little more than a minute, continued to fall for 16 minutes, and then gradually returned to normal. Six hours after the administration of the drug the tension was still considerably below normal—a condition not reached until the following morning.

Glycol dinitrate in 100 grain doses, like nitro-glycerine, quickly reduces tension. The tracings (Fig. 6) were taken from a young woman suffering from anaemia. The normal tension of the pulse was somewhat low, but in less than a minute it was reduced still lower, and in 3 minutes was hyperdicrotic. The effect, however, was very transient, and in 16 minutes the pulse had almost reached its normal degree of tension. Fig. 7 shows the effect of a corresponding dose of nitro-glycerine. It is a little peculiar in that it exhibits a more transient effect than usual with nitro-glycerine, but otherwise it presents the same features as those obtained by other observers.

The pulse tracings of the solid nitrates show a marked difference. Thus during the time in which nitro-glycol and nitro-glycerine present their period of greatest activity these show little or no action. After the administration of 1 grain of erythrol tetranitrate (Fig. 8) no very marked effect is noticed until 50 minutes have passed; the tension then falls gradually for about 1 1/2 hour more, and afterwards as gradually returns. In the present case 5 hours 15 minutes after the administration the pulse tension had not yet reached its previous level. In the same dose mannitol hexanitrate produces a very similar effect (Fig. 9). The pressure in the arteries is scarcely affected until nearly an hour has passed, and it has not reached its former level even after 5 hours. But the relative effects of the various members of the "nitrite group" will perhaps be better understood by reference to a diagram (Fig. 10). This has been constructed from sphygmographic tracings controlled by perfusion and blood-pressure experiments, and although it does not pretend to minute accuracy, except as regards time relations, it will nevertheless serve the purpose I have in view. The time is stated in minutes and hours, and the fall of arterial tension is represented by a fall from the base line, which in its turn is supposed to represent the normal tension. It will be seen that erythrol tetranitrate and mannitol hexanitrate are quite inactive during the period of greatest activity of the other members of this series, but that their effect is markedly prolonged.

INSUSCEPTIBILITY.

In individual cases slight differences in the extent and duration of action of these bodies are noticed, and occasionally cases are met with comparatively insusceptible to their influence. Thus, in some cases of advanced heart disease where the artery presents a feeling of fullness, but yet remains easily compressible (virtual tension of Broadbent) vaso-dilators have often little effect. In these cases the arteries, like the heart, have lost their normal tone, are considerably dilated, and, though possessing a sense of fullness and, on superficial examination, of resistance, are yet arteries of low tension. Coupling with this fact the tendency to fibrous tissue formation in the various organs in this

Fig. 5.—Methyl nitrate

Fig. 8.—Erythrol tetranitrate.

Fig. 9.—Mannitol hexanitrate

Fig. 10.—Comparative action of certain nitrites and nitrates.

condition, we have some explanation of the comparative irresponsiveness of these cases.

In some cases of not far advanced Bright's disease in which the tension is very high, and is evidently due to causes existent in the blood, a comparatively large dose of nitro-glycerine or its allies is necessary to produce any marked reduction of tension. But, apart from such pathological conditions, we now and then come across individuals who can bear large doses of these drugs with impunity. Even in animals there seems to be considerable variation of susceptibility to the action of vessel-dilating drugs, and particularly of the organic nitrates. The reason is not always clear. Habitual use tends to diminish their action, but this is obviously not the explanation in many cases. With the solid nitrates the amount of food in the alimentary canal at the time of administration, as well as its reaction, will have an important influence in determining the amount of drug dissolved, and therefore absorbed. It may be that under the influence of the alkaline juices of the intestine these nitrates are converted into nitrites (for example, sodium nitrite), but I am rather inclined to believe that this change, if it occurs at all, takes place in the blood or in the cells which form the walls of the blood vessels. Hitherto, however, I know only of one case, a man suffering from dilated heart, the result of alcoholism, in which these drugs failed to have any distinct effect.

The action of organic nitrates upon other organs is of little practical importance. Upon the heart the direct effect of these compounds is very slight. Indirectly, owing to the diminished work consequent on dilatation of the blood vessels, increased rapidity and sometimes palpitation (especially after glycol and glycerol nitrates) are noticed. Certain nervous effects have been attributed to nitro-glycerine, but none have, as yet, followed the administration of the solid organic nitrates. The effect upon the urinary excretion is practically *nil*. These bodies, as far as they have been investigated, are not diuretic.

As ordinarily administered the organic nitrates possess no cumulative action. The continued use of nitro-glycerine produces a lessened susceptibility to its effects, but this has not yet been noticed after the administration of the erythrol and mannitol compounds.

Reviewing the action of these compounds upon the vascular system in regard to their practical application to the treatment of disease, I think we may, at the present at least, discard methyl nitrate as being the least likely to prove of clinical value. Glycol dintrate again is so similar in action to nitro-glycerine and, at the same time, so much more expensive, that it also is not likely to enter into our stock of remedies. The longer acting nitrates, however, may prove of value.

THERAPEUTIC INDICATIONS.

From the pharmacological action of these two nitrates, it would seem that the chief indication for their use is a condition in which the heart is labouring under increased work imposed upon it by contracted arteries. As life advances the hitherto elastic vessels become converted into more or less rigid tubes, the fibrous adventitia is thickened, and fibrous tissue replaces, to a greater or less extent, the muscular and elastic tissue of the middle coat. As a result, increased work is put upon the heart, and hypertrophy results. Sooner or later, however, central or peripheral degeneration occurs; either the heart fails from the increased strain put upon it on the one hand, or causes rupture of a vessel from excessive power on the other. In disease the normal evolution may be compressed into a much shorter space of time; thickened arteries and hypertrophied hearts may be found comparatively early in life; and the final results may be the same. If by any means we can dilate the vessels we diminish the work of the heart and the pressure upon each unit of area of the artery, and thus in both ways avert the tendency to death. Our difficulty hitherto has been, not so much to reduce arterial tension when desired as to keep the tension steadily below a certain level. Both nitro-glycerine and sodium nitrite have been used for this purpose, but their administration is attended with some inconvenience. As we have seen (Fig. 10) these drugs have comparatively little action after two hours, and it would therefore be necessary to give them at least every two hours to produce continuous low tension.

Even then there would be considerable variation in the arterial pressure. By the substances I have described the tension is not brought so low but the reduction is of longer duration and the pressure is less liable to fluctuation. They are also, as far as I am aware, free from poisonous properties, a quality readily explained by their slight solubility.

CARDIAC PAIN.

Under this name I include all forms of pain accompanying diseases of the heart or vessels. I adopt it in preference to angina pectoris, as the limits of this disease appear to vary with different authors; and while some would almost confine it to Heberden's classic form, others would extend it to cover the whole realm of cardiac pain. Is cardiac pain always accompanied by contraction of the arterial walls, and if so, is it the relation one of cause and effect? Since Dr. Lauder Brunton's discovery, the question has been asked many times, but there has been no unanimous answer. Some observers state that obvious increase of tension does not always accompany heart pain, and I agree with them; but, as Dr. Leech pointed out, the increase may be more relative than absolute. In a heart weakened by disease, a very slight increase of resistance may prove too much for the heart to overcome. This slight increase may be due to a general effect almost inappreciable in any one artery, or to an effect localised in one or more areas. Of greater significance is the fact that vaso-dilators do not always relieve angina-like pains, especially if these occur in cases of far advanced heart disease with a low tension pulse. In such cases morphine is of much greater value.

Can attacks of anginal pain be prevented by keeping arterial pressure below its normal level? Obviously this is the only way in which the solid organic nitrates can be of service. When an attack has come on, it is necessary to resort to more quickly acting drugs, and in cases of a sudden and severe nature inhalation of the fatty nitrites is advisable. For cases in which the pain is less severe and of longer duration the administration of nitro-glycerine or sodium nitrite is perhaps more beneficial. But if we can prevent the advent of these attacks, a great stride ahead will have been made. Much may be done by the exhibition of purgatives and attention to the general health, but in the majority of instances something more is needed. This something is I believe a vaso-dilator. Hitherto nitro-glycerine and sodium nitrite have been the drugs mainly used; but their evanescent and varying action render them unsuitable. Nevertheless, I have seen cases in which the continuous administration both of nitro-glycerine and sodium nitrite seemed to prevent the occurrence of anginal attacks, and other physicians have reported similar results. In many of these cases, however, attacks occasionally developed, and it is quite possible that longer acting remedies, such as erythrol nitrate, might have prevented them altogether.

CHRONIC BRIGHT'S DISEASE.

The most important change, and the one which affects us most closely, is the arterial thickening attending Bright's disease. This leads to hypertrophy of the heart, and both combined to a high tension pulse. Sooner or later, if the patient does not succumb to uræmia or some intercurrent disease, the increased vascular strain begins to tell either upon the heart or on the vessels, often on both. Either the symptoms of heart failure develop or attacks of apoplexy occur. Previous to such terminations headache, mental inaptitude, weariness, and similar symptoms are not uncommon, and sometimes these may be noticed, with a high tension pulse, where no other direct evidence of renal disease exists. In all such cases the longer acting vaso-dilators are often beneficial. I do not wish to convey the impression that I regard the thickened condition of the arteries as the primary cause of the high tension of Bright's disease. This, I believe, is due in the first instance to an impure condition of the blood, and the correct treatment under the circumstances is to rid the blood as far as possible of this impurity. Once, however, the fibroid and muscular thickening in the arteries is produced it becomes a danger in itself. It is a condition we cannot cure, and our treatment must therefore be symptomatic. By keeping down the arterial pressure in such conditions we may not only alleviate unpleasant symptoms, but

may also prevent the onset of such disastrous conditions as cerebral hæmorrhage. The fibroid thickening of the blood vessels does not annul the action of these nitrates, though it diminishes to some extent their power.

I do not anticipate any beneficial action from these drugs upon the kidney disease itself. They are not diuretic, at the same time they are not irritant to the kidney, and, given even in acute inflammatory conditions of these organs, are not likely to produce ill effects.

ANEURYSM.

In cases of aneurysm (I confine my remarks at present to those coming under the care of the physician) it is very necessary to keep the circulatory system as far as possible in a state of physiological rest. This is best accomplished by dilating the peripheral arteries, and for this purpose potassium iodide has for some time been the drug most in vogue. Without detracting in the least from the value of potassium iodide in this condition, it seems to me that the nitrates of erythrol or mannitol will accomplish this end better, and will give more satisfactory results in cases not of syphilitic origin. The pain which accompanies aneurysm is not often relieved by vaso-dilators, and, therefore, I do not anticipate any benefit from the drugs I have described. Usually the pain is a pressure effect which is only relieved by the administration of morphine.

RAYNAUD'S DISEASE.

Of other conditions connected with the contraction of blood vessels Raynaud's disease is one that has been successfully treated with nitro-glycerine. If vaso-dilators are of value in this condition, it seems to me that erythrol nitrate, as tending to keep up a more constant dilatation, would be of greater value.

DYSPNOEA.

With regard to respiratory conditions, I do not anticipate any beneficial effects from these bodies. In various forms of dyspnoea—uræmic, asthmatic, bronchitic—nitro-glycerine and the nitrites are sometimes of value, but they often fail to relieve. By their means sibilant rhonchi may be converted into sonorous, and sometimes may even disappear altogether, but I do not agree with Professor Fraser¹ as to the rapidity of this change. The change of pitch seems to occur *pari passu* with the fall of arterial tension, and in the majority of cases the effect is not marked. Where loud and numerous moist sounds are present even less effect is obtained. Seeing, then, that the action of these comparatively powerful vaso-dilators is not very distinct, we should not expect the less powerful drugs I have mentioned to exercise much influence. They may prove of prophylactic value in the dyspnoea occurring in Bright's disease, for example, but beyond that it would be useless to hazard conjectures. In chronic bronchitis and other conditions in which the dyspnoea is of cardiac origin, amelioration might be obtained from these compounds. In such cases the weak heart is unable to drive the blood with sufficient power along the arteries, stagnation therefore occurs in the veins, and the pulmonary system is often the first to suffer. Thus aëration is limited by the pulmonary lesions on the one hand and the cardiac on the other. By dilating the vessels, and thus relieving the heart, the circulation becomes more efficient and the blood is better aërated. But under such conditions, digitalis is usually of much greater benefit. Headache occurring in a case of chronic bronchitis, with full, rather tense pulse, disappeared after the administration of erythrol nitrate.

HEADACHE.

It is also very probable that anæmic headaches, occurring in patients with a high tension pulse, may be relieved by this drug, but my observations on this condition have been confined to those with a low tension pulse, and here the results have been somewhat conflicting.

NERVOUS DISEASES.

Although nitro-glycerine has been given in many nervous affections, I do not think much benefit will follow the use of erythrol or mannitol nitrates in these diseases. Migraine and neuralgia are oftentimes accompanied by reflex con-

traction of the blood vessels, and the use of vaso-dilators has sometimes proved curative. The solid organic nitrates, however, are much too slow in action to be of benefit, though it is possible they may prevent attacks of migraine if administered continuously.

The drugs might also be used by those who believe in the value of nitro-glycerine in epilepsy, but as I have rarely used this drug in this affection my experience on this point is limited. Other nervous diseases—epileptic vertigo, cerebral congestion, and tetanus—in which nitro-glycerine has been used, are not likely to yield to treatment with the nitrates under discussion.

In many other conditions nitro-glycerine is said to have proved of value. In various forms of poisoning (opium, coal gas, etc.), in vomiting from any cause (pregnancy, sea-sickness), in lenteric diarrhoea, in diabetes mellitus, in hysterical paralyses, and many other affections, nitro-glycerine is said to have proved curative or ameliorative. This is difficult to understand, and in most cases the results obtained were probably coincidences. I do not think that other organic nitrates will give beneficial results when administered in these or similar affections, and therefore I do not advise the use of the nitrates under consideration in such conditions.

DOSE AND ADMINISTRATION.

The dose of the solid organic nitrates may be taken as 1 grain; more may be given if it is thought necessary, but usually this amount will suffice. They may be taken in the form of pills or tablets, or in alcoholic solution. The last method I prefer. A solution of erythrol nitrate in the strength of 1 in 60 may be made and 1 drachm may be taken in an ounce of water every four or six hours. Mannitol nitrate is not quite so soluble, but a 1 per cent. alcoholic solution can be prepared, of which 1½ to 2 drachms may be taken in water. The solutions thus made are stable and free from irritating properties.

CONCLUSION.

In conclusion, the only condition in which I think these nitrates will be of benefit is one that I have already alluded to, namely, high arterial tension. Whenever we wish to keep down the blood pressure for a length of time, then I believe these nitrates will be of value. Such a result may be necessary for many reasons; a few I have attempted to indicate. It may be that the therapeutics of the drugs will widen with our increasing knowledge; it may be that the limits I have laid out for them will be much diminished; but whichever it be, I thought that a lecture devoted to the pharmacological action and therapeutic indications of a drug of which we stand so much in need would not be alien to the noble purpose which the foundress of this lecture had in view.

Although I know of no evil effects having followed the administration of these drugs, and though no such effects are anticipated, I ought to say that the research on these compounds is not yet complete.

CARBOLIC ACID POISONING.—In the course of an address to the Sheffield Chemists' Association last week, the President of the Pharmaceutical Society is reported to have said that the Council intends to make a renewed attempt to have carbolic acid placed on the poison schedule of the Pharmacy Act, together with a number of other articles. This is satisfactory intelligence, and so far as carbolic acid is concerned the daily occurrence of deaths caused by it either accidentally or in cases of suicide affords strong evidence of need for protective regulation of its sale. It seems unaccountable that a poison which occupies such a conspicuous position in the returns of the Registrar-General should have been allowed so long to be supplied indiscriminately in all kinds of shops to children as well as adults, and without any provision against accident. The fact that carbolic acid is useful as a disinfectant for sanitary purposes cannot be urged as a justification of this laxity, since there are various forms in which it would be equally serviceable for such purposes, and at the same time unlikely to be swallowed in the way that so frequently happens with carbolic acid in its natural condition.

¹ *International Journal of the Medical Sciences*, vol. xcv, p. 122.