of this epiphysis must be emphasised. Nothing will so certainly be followed by arrest of growth as roughly rubbing the fragments together, even if reduction is effected, and so destroying the delicate epiphysal disc of cartilage.

A very important question arises as to how far an operation is justifiable in a case where the diaphysis has remained partly or wholly displaced and the patient comes under care some weeks or months after the accident. What bad results have we to expect if nothing is done? First, arrest of growth, since the epiphysal disc almost certainly remains with the epiphysis. But the nearer the subject approaches adult age the less need we think of this; further, if by operation we replace the diaphysis it is by no means certain that we can prevent shortening occurring. Secondly, impaired movement at the shoulder-joint, especially in the direction of abduction and rotation. If these are much limited an operation is probably advisable, and still more so if there is evidence of pressure on the axillary vessels or the brachial plexus (both, however, rare). Thirdly, ankylosis of the shoulder. Much will depend on the peculiar circumstances of the case and the operative zeal of the surgeon, but the example of Bruns's two cases and of Smith's is very encouraging in the direction of operation. In one case (a recent compound one) the diaphysis was fixed in place of a steel needle (Helferich), with good result. If the diaphysis remains displaced to a considerable extent a very fair result may in many cases be expected (although shortening will probably occur—this is shown in the cases recorded by Puzey, Hamilton (two), and in one of my own. In all these, firm union occurred, and movements at the shoulder-joint were very good. Owing to ossification in the connecting bridge of periosteum, we have little cause to fear non-union between the diaphysis and epiphysis. However, in two cases (both occurring at birth) recorded by Bertrandi and Durocher, a false joint appears to have formed.

In recent cases, after reduction, care must be taken that the humerus be not rotated on its vertical axis, especially in the inward direction. The epiphysis tends, as already said, to be somewhat abducted, but not to be materially rotated. It is inadvisable to use a bulky axillary pad, and a neatly fitting poroplastic shoulder cap is one of the best forms of of retentive apparatus. Weight extension can but rarely be required.

REFERENCES.

¹ Time will not allow of an introduction dealing with the history and literature of the subject. It must suffice to say that during the last forty years no one has more contributed to our knowledge of injuries to the epiphyses than my father, and I should be pleased if the present work were regarded as in any way supplementary to his. Bruns, Vogt, and Bardenheuer, in Germany; Ollier, Manquat, and Salmon, in France; Bryant, Humphry, and Hamilton, amongst English writers, should be named among the chief authorities on the subject. ² Goyrand followed up three other cases; in neither did shortening result. ³ *Bulletins de la Soc. Anatomique*, 1888. ⁴ *Clinical Society*, November 10th, 1882. ⁵ Out of 207 cases of true dislocation, only two were in subjects under 20 years of age (Krönlein, Stimson). ⁶ Bruns, two cases; W. J. Smith, one case; operated on four weeks, five weeks, and two months after the accident. In all, reduction and a good result were obtained. ⁷ In Professor Humphry's case at six months; in two of Vogt's cases at birth; in Malgaigne's "at an early age."

MEDICAL STUDENTS IN GERMAN UNIVERSITIES.—According to Ascherson's *Universitäts-Kalender* just issued, the total number of students in the universities of the German empire in the current summer semester is 27,500. Of these, 8,575 are students of medicine, a falling off of 263 as compared with the corresponding semester last year.

PROFESSOR KUNDT, of Berlin, and Professor Kekulé, of Bonn, have been elected Knights of the Peace, or Civil, Class of the Prussian Ordre pour le Mérite. This distinction, which was valued even by that arch-enemy of shams, Thomas Carlyle, is reserved for men of the very first rank in science and literature.

MEDICAL EDITORS IN SPAIN.—The editors of the medical journals published in Madrid recently dined. The gentlemen taking part in this interesting Agapemone were Dr. Serret, of the *Siglo Médico*; Drs. Quintana and Aycart, of the *Revista de Sanidad Militar*; Dr. Ulecia, of the *Revista de Medicina y Cirugía*; Dr. Larra, of the *Revista de Terapeutica*; Dr. Navarro, of the *Boletín de Medicina Naval*; Dr. Pinilla, of the *Medicina Contemporanea*; Dr. Marin y Sancho, of *La Farmacia Española*; and Dr. Valledor, of the *Revista Dosimetrica*.

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 II.—(Concluded).

I PASS on to the pharmacology of the nitrate group before dealing with the therapeutics of the nitrites, because the organic nitrates, about which I shall have most to say, have in some respects a similar physiological action to the nitrites, and it will be convenient to deal with their therapeutic uses together. The similarity seems to arise from the fact that under certain conditions the NO_3 molecule of organic nitrates is reduced to NO_2 , and not from any likeness in the action of the two molecules. I do not propose to do more than indicate a few points of special interest in connection with the metallic nitrates.

I have already pointed out the very marked difference in toxic influence on skeletal muscle between the groups NO_2 and NO_3 , when combined with a metal of small physiological activity like sodium. I have shown that whilst nitrite of sodium is a powerful muscle poison, the nitrate tends to preserve muscle vitality. The striking contrast between the action of these two salts can only depend on the difference between the physiological properties of the group NO_2 and NO_3 . This difference can be traced in all the metallic compounds of the two groups.

The nitroxyl ONO gives evidence of its influence in every compound into which it enters. The nitrate group ONO_2 plays a neutral part, and does not seem to interfere with the physiological activity of the metals with which it combines.

I have already shown this with regard to the sodium salts, and have only to add that in dilute solutions of the nitrates of potassium, barium, calcium, and strontium, the physiological influence of these metals on the skeletal muscles is as well seen as in the corresponding chlorides.

Dilute solutions of nitrate of sodium are as little irritating to the mucous membranes and raw surfaces as they are to muscular tissue. It is commonly thought that the nitrates of potash and soda are irritants; as a fact, however, their solutions when dilute are not more irritating than a solution of sodium chloride of corresponding strength, and their presence in water up to a certain amount prevents the irritation of mucous membranes which water itself causes.

A solution containing under 2 per cent. of either chloride or nitrate coming into contact with the Schneiderian membrane, the conjunctiva, or raw surfaces gives very little discomfort, if, however, left long in contact with a raw surface it gives rise to severe pain and a stronger solution of either salt is at once painful.

By the stomach mucous membrane a 10 per cent. solution of sodium nitrate is well borne, but if more concentrated and in considerable quantity, it may cause great irritation like other strong saline solutions.

The organic nitrates to which I shall allude are glyceryl trinitrate, $\text{C}_3\text{H}_5(\text{ONO}_2)_3$ (nitro-glycerine); ethyl nitrate, $\text{C}_2\text{H}_5\text{ONO}_2$; propyl nitrate, $\text{C}_3\text{H}_7\text{ONO}_2$; isobutyl nitrate, $\text{C}_4\text{H}_9\text{ONO}_2$; isoamyl nitrate, $\text{C}_5\text{H}_{11}\text{ONO}_2$. In these organic nitrates two effects have to be considered: (1) the actions of the compounds themselves; (2) that resulting from the products of their decomposition.

Nitro-glycerine.—I shall speak of nitro-glycerine first because

of its great therapeutic importance. Professor Hay has shown that nitro-glycerine, in the presence of alkalies and their carbonates or of sodium phosphate, is decomposed, about two-thirds of the ONO_2 being reduced to ONO and uniting with the alkali to form a nitrite; the remaining third forms a nitrate with the alkali. It is even decomposed under some conditions by contact with water.

When nitro-glycerine is taken into the stomach it probably undergoes little or no change there, but is absorbed unaltered and quickly converted in part or altogether into sodium nitrite. Any part which is not thus destroyed is excreted by the kidneys, and when large doses are given to animals by the mouth nitro-glycerine has been recovered from the urine and the blood. After large medicinal doses in man it has been detected in the urine. On the skeletal muscles the vessels and the excised frog's heart dilute solutions of nitro-glycerine act exactly like solutions of sodium nitrite of similar strength. The gastrocnemius of a frog in normal saline containing one part in 1,000 of nitro-glycerine dies in 20 to 40 minutes, as it would do in the same strength of sodium nitrite, and it gives when contracted a similar muscle tracing. The dilatation of the vessels of the tortoise when weak solution of nitro-glycerine is perfused through them, is just as great as with sodium nitrite. Inasmuch as nitro-glycerine is decomposed to some extent in the experiments, nitrite being formed, it is impossible to say how far the effects are due to the nitro-glycerine itself.

When given internally the effects of nitro-glycerine are almost identical with those of sodium nitrite, but in a few points the action of the two substances differs somewhat. Nitro-glycerine tends to stimulate the spinal cord and medulla, and in the lower animals, especially the frog, may cause tetanic spasms. Sodium nitrite has no such effect.

In man the only difference observed, so far as regards the nervous system, between nitro-glycerine and sodium nitrite is that the former much more often causes headache, which, when induced, is at times of longer duration than that caused by sodium nitrite.

The throbbing headache felt immediately after nitro-glycerine may be due to the direct effect on the circulation of the nitrite into which the trinitrate of glycyl is converted. But it at times lasts many hours after the circulatory effects have apparently passed away, and it seems possible that the nitro-glycerine headache is not entirely due to the nitrite effect, but that the nitro-glycerine molecule, or it may be certain compounds, due to decomposition of the glycyl, take some part in its production. There can be little doubt that the tetanus produced in the lower animals is due to the nitro-glycerine molecule itself.

The difference between the effects produced in the circulation in man between sodium nitrite and nitro-glycerine though small are yet of some practical importance. From the table I have shown (BRITISH MEDICAL JOURNAL, July 1st, 1893, p. 6) it will be seen that the action of nitro-glycerine is more rapid than that of sodium nitrite or ethyl nitrite.

Not only is the action of nitro-glycerine distinctly evident earlier than that of the nitrites of sodium and ethyl, but the point of the lowest pulse tension is also earlier, as seen in the table which I have given. I have not, however, found the influence of a minim of nitro-glycerine usually quite as prolonged as the influence of 2 grains of nitrite of sodium, but there is no important difference. The minute amount of nitro-glycerine which will affect the pulse is very marvellous. One-sixteenth of a minim of liquor trinitrini will, in some, distinctly lower tension. The effect of small doses is more remarkable when we consider the very large doses which the circulation will bear without suffering injury. Dr. Murrell records that on one occasion he gave a patient 10 minims eight times daily, the only effect being to relieve anginal pain and cause some headache. I have only to add the explanation which Hay has given of the more powerful influence of nitro-glycerine than nitrite of sodium. The glycerine compound is absorbed into the blood and then forms a nitrite. The sodium nitrite undergoes decomposition by the acids of the stomach, and though the nitrous acid set free is in part absorbed, there is naturally considerable loss by escape of the acid vapour and by its decomposition.

The Fatty Nitrates.—The nitrates of ethyl, propyl, butyl, and amyl are all stable bodies very slightly soluble in water

and not disagreeable to smell or taste. The boiling point of the series increases with the molecular weight, nitrate of ethyl boiling at 190° and nitrate of isoamyl at 296° .

Unlike nitro-glycerine, the nitrates of ethyl, propyl, butyl and amyl do not readily decompose even when mixed with an alkaline fluid. When I added 0.2 c.c. of these nitrates to 10 c.c. of a 5 per cent. solution of sodium carbonate, and kept the mixture at 38°C . no trace of nitrate could be detected in 30 minutes. On leaving the mixture for several hours the tests indicated the presence of a trace of nitrite, but it was not till 6 days had elapsed that any considerable quantity of nitrite was present. On adding 2 per cent of ethyl nitrate to blood methæmoglobin does not immediately appear, but on keeping the mixture at 38°C . the characteristic band can be detected by the spectroscope in about 30 to 40 minutes. The nitrates of the higher members of the series isobutyl and amyl do not under similar conditions show the presence of methæmoglobin for many hours. I have several times dialysed the mixture of nitrates and blood in which methæmoglobin has been produced without detecting the presence of nitrites in the dialysate, though on keeping the compound for 24 to 36 hours at 38° a nitrite reaction is obtained from it: manifestly, however, the fatty nitrates do not readily yield nitrites as easily as nitro-glycerine does.

Although the nitrates seem to be decomposed into nitrites with some little difficulty outside the body, it seems probable that in the living body the change takes place more readily, since, as I shall show, an effect on the circulation somewhat like that caused by nitrites is produced by giving the nitrates, but this nitrite effect is less quickly produced and longer lasting than when nitro-glycerine is given.

When a muscle is exposed to a mixture of 1 of ethyl nitrate in 1,000 of normal saline solution the contractions diminish in height somewhat more rapidly than with normal saline, but vitality is well maintained and the muscle lives as long as in normal saline; 1 in 500 causes a somewhat rapid fall in the height of the muscular contractions, but a muscle will live in the solution over three hours.

Propyl nitrate diminishes the irritability of muscle more powerfully than ethyl nitrate, but the muscle will continue to live in a solution of 1 in 1,000 of normal saline, and give contractions at the end of 24 hours.

Isobutyl nitrate, of the strength of 1 in 1,000, greatly decreases the contractile power of muscle. At the end of about three hours it will only contract as a rule with strong stimulation.

Amyl nitrate is far more fatal than any of the other nitrates. If the muscle is immersed in 1 of 1,000 of amyl nitrate the contractions rapidly fall and the muscle dies in about an hour, contracture being often seen. The relative influence of nitrates as shown by their action on muscle bears out the well known fact that the toxicity of alcoholic radicles increases with their atomic weight.

The effect of the fatty nitrates on the vessel walls does not quite run parallel with their effect on skeletal muscles. Ethyl nitrate in the strength of 1 in 1,000 dilates the vessels, as shown in a perfusion experiment with a tortoise.

Ethyl nitrate increased the flow through the vessels of a tortoise by 50 per cent., but propyl nitrate in the same amount still more powerfully dilates the vessels, and if a solution of 1 in 5,000 be used extraordinary dilatation takes place. (Fig. 19.)

I shall point out when I come to speak of nitro substances that with them, too, the propyl compound seems to possess the strongest dilating power.

Isobutyl nitrate, in the strength of 1 in 1,000 of normal saline contracts the vessels. But in a strength of 1 in 5,000 to 1 in 10,000 it dilates them very distinctly.

Iso-amyl nitrate very markedly contracts the vessels in a strength of 1 in 1,000 of normal saline, the flow through them being very greatly decreased. Dilute solutions, even 1 in 10,000, do not dilate the vessels, but very weak solutions, 1 in 30,000, have a slight dilating effect.

It is interesting to notice the rise and fall of the dilating influence due apparently to the alcoholic radicles.

Nitrate of ethyl renders the action of the isolated frog's heart slightly quicker and weaker when in the strength of 1 in 1,000. The other nitrates have much the same effect as the ethyl compound, but are more toxic.

The chief interest in the action of the nitrates centres on the powerful and long-lasting influence they exert on the circulation in man. If 5m. of ethyl nitrate be taken internally the pulse tension falls in three or four minutes, but usually not

Fig. 19.—As in fig. 18, the figures at the base represent the number of minutes during which perfusion took place; those in the perpendicular line the number of c.c. passing through. The light squares show the flow when normal salt solution passed through the vessels; the dark squares when 1 in 1,000 of propyl nitrite was used.

ery considerably. It continues to fall, and reaches its lowest point in thirty to sixty minutes; sometimes it is very low for a longer time than this. The effects of ethyl nitrate on the pulse can often be distinctly seen four or five hours after a dose has been taken. (See Fig. 20A.)

As after nitrites, the pulse is somewhat quickened, but this effect is by no means marked. One minim has a distinct effect on the pulse. Propyl, isobutyl, and amyl nitrates all act in a similar manner, and as far as I have examined their action, they depress the tension for a longer time than the corresponding nitrites. Fig. 20B shows the effects of isobutyl nitrate on the man from whom the tracings after amyl nitrite and nitrate were taken.

Fig. 2

The inhalation of the nitrates very slightly lowers tension. The long-lasting action of the nitrates is doubtless due to the fact that, unlike nitro-glycerine, they are somewhat difficult of decomposition. I have found the nitrate of ethyl useful in various ailments for which nitrites are usually given. There is one drawback to its use. It seems to cause a headache more often than ethyl nitrite; this headache does not always come on immediately the drug is taken; it may

not appear for four or five hours. The other nitrates also tend to cause more headache than the corresponding nitrites.

NOTES ON MEDITERRANEAN OR MALTA FEVER.

I.—ITS BACTERIOLOGY.

BY SURGEON-CAPTAIN DAVID BRUCE, A.M.S.,

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In this paper I do not intend to enter into the clinical features or treatment of this fever, but to confine myself to the results of the bacteriological investigation of cases of the disease, which I hope will throw some light on its etiology, and help to establish the fact that here we have to do with no local variety of typhoid or malaria, but with a definite specific disease.

THE PRESENCE OF A DEFINITE MICRO-ORGANISM IN MALTA FEVER.

To detect the presence of micro-organisms in the bodies of those suffering from a given disease, two methods may be employed—either the microscopical examination of the blood during life and the tissues after death, or the planting of small quantities of blood or particles taken from the various organs in artificial nutrient media. In Malta fever the first method is not readily applicable, as the micro-organisms are not found in the blood,¹ and being very minute, are difficult to detect in coverglass preparations, or sections of the organs. On the other hand, the method of establishing their presence by means of artificial cultivations is easily carried out. These cultivations are most successful when made from the spleen.²

The test tubes containing the inoculated medium should be placed in an incubator at the temperature of the blood. This necessitates the use of a nutrient medium such as agar-agar, which remains solid at this temperature; and it is most essential that the medium should be as nearly neutral as possible, since any excess of alkalinity completely inhibits growth. The following is a list of the cases in which the presence of a definite micro-organism has been established by means of such cultivation experiments.

CASE I.—H. D., aged 24; duration of illness twelve days. Eight tubes of agar-agar nutrient jelly were inoculated from the spleen shortly after death, and remained at the ordinary temperature of the air (about 25° C. until the following day at 11 A.M. Six of the tubes were then placed in an incubator kept at 37° C., while two were left at the ordinary temperature of the room. Minute white colonies appeared on the surface of the agar-agar in the six tubes after a period of 84 hours, and in the two others at the end of 168 hours. (See chart.)

CASE II.—A. B., aged 24; duration of illness 15 days. As this case happened out of hospital I had no opportunity of making a *post-mortem* examination. I succeeded, however, in making inoculations into six tubes containing agar-agar in the following manner. Seven hours after death, having previously cleansed the skin over the region of the spleen by means of a strong solution of corrosive sublimate and absolute alcohol, I drew off a small portion of the splenic pulp by means of a sterilised trochar and cannula. Next morning five of these test tubes were placed in the incubator, and one left at the ordinary temperature of the air. No growth appeared in the tubes in the incubator until the end of 84 hours, when the same growth was observed. In the sixth tube, which had been left at the ordinary temperature, the colonies appeared at the end of 110 hours.

CASE III.—B. E., aged 23; duration of illness eight days. Six tubes of agar-agar were inoculated from the spleen and placed in the

¹ Surgeon-Captain Hughes informs me he has succeeded in one instance in cultivating the micrococci from blood taken from the heart of a monkey dead of the disease.

² This organ ought to be removed from the body as soon as possible after death, protected from contamination by being wrapped in a cloth saturated with a solution of corrosive sublimate (1 in 1,000), and taken to the room set apart as a laboratory. In transferring traces of the splenic pulp to tubes containing the nutrient material, certain precautions should be taken. Three extensive cuts, the second in a plane at right angles to the first, and the third at right angles to the second and parallel to the first, are made with three knives previously thoroughly sterilised by heat. A platinum needle heated to redness before each inoculation is then used to convey a small portion of the pulp from the depth of the third cut to the solid nutrient jelly.