THE GOULSTONIAN LECTURES ON THE CHEMISTRY AND PATHOLOGY OF GOUT.

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ABSTRACT OF LECTURE III.

CAUSES AFFECTING THE DEPOSITION OF SODIUM BIURATE.

Deposition Encouraged by Concentration of Medium and Proportions of Sodium Salt Present.—Sir William Roberts found that sodium biurate is very sparingly soluble in blood serum. At blood heat the amount dissolved is about 1 part in 10,000 (about one-tenth of its solubility in water).

This lessened solubility is entirely due to the saline constituents of the plasma, and in particular the sodium salts; thus if a medium be rich in urates but poor in sodium salts, there will be but little tendency to precipitation, and *vice versa*. Now structures belonging to the connective tissue class are rich in sodium salts, while muscle, brain, liver, and spleen are poor in them, whence the greater liability to uratic deposition in the former. Sir William Roberts further considers that uratic precipitation takes place from the synovial fluid, and does not originate in the cartilage.

He considers (as opposed to Ebstein's view) that the process of deposition on the cartilage is a purely passive and physical one, and that the synovial fluid, charged with its dissolved urates, penetrates by liquid diffusion into the superficial layers of the cartilage, and that, when the critical moment arrives, precipitation takes place simultaneously in the synovia and in the cartilage.

As regards the varying liability of different joints to gouty attacks, Sir William Roberts considers that it is, at all events in part, dependent upon a greater concentration of the synovia on some joints, and on a varying proportion of sodium salts and possibly of sodium biurate.

Deposition Encouraged by Sluggish Movement of Medium.—It is highly probable that the very sluggish movement of fluids on the cartilaginous and fibrous tissues favours the deposition of urates from the medium in which they are dissolved. An interesting case has been recorded by Charcot,¹ who observed, in a hemiplegic woman of 40, that most of the articular cartilages on the right paralysed side were infiltrated with urates, whereas those of the non-paralysed side showed no such deposits.

Sir William Roberts attributes the greater frequency with which uratic deposits are found in cartilages than in fibrous tissues to the greater sluggishness in the lymph flow in the former. That gouty precipitation occurs in synovia rather than in blood or lymph he attributes to the sluggish movements of the joint fluid.

Deposition Encouraged by Nervous Influences.—It is possible, given the condition in which there is a fair amount of sodium quadriurate or biurate circulating in the blood, the amount not being quite up to saturation point, that nervous influences may accelerate deposition of the sodium biurate. It appears to me that a possible explanation of this result is that nervous influence affects the kidneys and depresses their excretory power for uric acid, which is consequently absorbed into the general circulation, and rapidly raises the quantity of urate in the blood to the point of over-saturation.

Deposition Encouraged by Abnormal Constituents of the Blood.—As previously stated, in cases of chronic lead poisoning there is a deficient excretion of uric acid in the urine and an accumulation of it in the blood. As to the natural way in which the lead favours or hastens the deposition of sodium biurate, and so produces gout, there are different opinions. Sir William Roberts² considers that gout and plumbism have one tendency or vice in common—namely, the tendency to uratosis. He considers it is more accurate, instead of speaking of ordinary gout and saturnine gout, to speak of gouty uratosis and saturnine uratosis. It appears to me that gout and plumbism have more in common than this tendency to uratosis, in that they both have the same tendency to cause the presence of an excess of urates in the blood.

I am of opinion that the influence of lead in producing gout depends solely on the extent to which the kidney parenchyma is damaged. With much damage done to the kidney cells, whose function it is to excrete uric acid, absorption of quadriurates into the blood occurs; the subsequent development of an attack of gout entirely depends on the amount of absorbed quadriurate.

Deposition Encouraged by Injury to Joints or by Interference with their Nutrition.—A slight injury to a joint, which in a healthy person would speedily pass off, in a gouty person renders the part susceptible to the deposition of sodium biurate by the sodium quadriurate circulating in the blood. This susceptibility is probably in some way connected with an impairment of the nutrition of the affected tissues.

As regards the relation between gout and rheumatism, points which have been the seat of acute rheumatism are especially predisposed in gouty subjects to become the seat of uratic deposits.

Dr. Latham³ considers that the uric acid circulating in the blood may exert a toxic influence on those parts of the spinal cord regulating the nutrition of the joints, and so lead to uratic deposition in them. Ebstein's views and the objections to them have already been referred to.

Klemperer⁴ believes that some unknown substances in gout lead to inflammatory and necrotic processes in various tissues; these necrotic areas then attract the uric acid from the blood, the chemical affinity of the necrotic parts for uric acid being so great that the blood cannot redissolve it. Von Noorden thinks the unknown substance which starts the inflammatory and necrotic processes is a ferment.

Deposition encouraged by Diminished Alkalinity of the Blood.—The view held amongst others by Mordhorst and Haig that diminished alkalinity of the blood causes uratic deposition, and that increased alkalinity of the blood causing re-solution of the uratic deposits is in my opinion erroneous and untenable for the two following reasons: (1) The view is apparently based on the deposit being uric acid, whereas it is sodium biurate, the solution of which, as Sir William Roberts has shown, is not increased by increased alkalinity of the blood; (2) from a series of experiments that I have conducted and which will be subsequently described, it appears that a diminution of the alkalinity of a medium does not affect the deposition of sodium biurate from that medium.

Reasons for the Special Selection of the Great Toe and Ear as Seats of Gouty Deposits.—These are mainly in the former case (1) the great liability to injury; in 14 out of 17 cases of non-gouty patients over 30 years of age and in all those over 50 examined by Garrod there was evidence of ulceration of the cartilages of one or both metatarso-phalangeal joints; (2) the remoteness of the joints from the centre of the circulation; and (3) their poor vascularity. In the helix of the ear, coldness and a sluggish circulation are quite sufficient to explain the selection.

Cause of the Inflammation which accompanies the Gouty Paroxysm.—I consider that the inflammatory part of the gouty attack is secondary to the deposition of sodium biurate crystals, but it must be granted that such deposition should occur fairly copiously and suddenly in order to start the inflammatory process. Undoubtedly urates may deposit slowly and quietly in joints without the development of any acute attack, or for some time antecedent to the development of an acute attack. The observations of Moxon and Fagge support the conclusion that the discovery after death of uratic deposits in a joint is not always to be regarded as a certain proof that the joint has passed through an inflammatory gouty attack.

CERTAIN CONDITIONS AND FACTORS AFFECTING THE SOLUBILITY AND THE PRECIPITATION OF SODIUM QUADRIURATE AND SODIUM BIURATE.

Diminution of the Alkalinity of the Blood.—A view to which I have previously referred, which is commonly held as to the influence of diet and certain beverages in accelerating an attack of gout, is that such substances reduce the alkalinity of the blood and so hasten the precipitation of sodium biurate. As I believe this view to be erroneous, I will ask your attention to a consideration of my reasons for holding this opinion. In the first place Klemperer's⁵ careful experiments show that in gout the alkalinity of the blood is but

little, if at all, diminished, while its diminution is a common pathological condition in diseases that are in no way associated with uratic precipitation, such as acute rheumatism, leukaemia, diabetes, carcinoma, and pyrexia. In the second place I have been unable to meet with any experimental proof that a diminution in the alkalinity of blood, containing uric acid in solution, either facilitates the deposition of sodium biurate from it, or diminishes its solvent power for sodium biurate as for uric acid. I therefore considered it advisable to experimentally investigate these different points, and for that purpose the following series of experiments were undertaken.

I. *Experiments showing to what extent the rate of Formation and Precipitation of Sodium Biurate is affected by Diminishing, by the addition of Acids, the Alkalinity of Blood Serum charged with Uric Acid.*—Seven bottles, each containing 40 c.cm. of blood serum, were raised to 1,000° F., and then charged with uric acid to the extent of 1 in 1,000°. As soon as the uric acid was dissolved, varying quantities of hydrochloric acid were added to the contents of three of the bottles, and of tartaric acid to another three, so as to partially reduce the alkalinity of the serum; the contents of the seventh bottle were left unaltered. The bottles were kept in a warm chamber at 100° F., and the commencement of the precipitation of sodium biurate crystals was then looked for by examining some of the contents of the bottles under the microscope every few minutes.

Table showing the Results of Experiments made with Blood Serum charged with Uric Acid and the Effect which the Diminution of the Alkalinity of the Serum, by the addition of Hydrochloric Acid, has on the Precipitation of Sodium Biurate.

Solution.	Commencement of Precipitation.
Blood serum containing 1 in 1,000 uric acid	Crystals of sodium biurate first appeared in 6-7 hours.
The same one-fourth neutralised by hydrochloric acid	"
The same one-half neutralised by hydrochloric acid	"
The same three-fourths neutralised by hydrochloric acid	Some crystals of uric acid appeared in 5 minutes. Crystals of sodium biurate first appeared in 12 hours.

It will be seen from the results of these experiments that the effect of diminishing the alkalinity of blood serum as far as one-half has no influence whatever in hastening the conversion of the sodium quadriurate into biurate, or, in other words, does not influence the deposition of sodium biurate from the serum. When the alkalinity is reduced by three-fourths, by the addition of hydrochloric acid, some crystals of uric acid were almost immediately precipitated, but when this precipitation of uric acid had ceased, then the deposition of sodium biurate did not begin till twelve hours had elapsed. This delayed deposition was due to the precipitate of the uric acid leaving the quadriurate solution weaker than before.

In the corresponding series of experiments with tartaric acid no difference in the time of appearance of biurate crystals was produced even by the reduction of the alkalinity of the blood serum by three-fourths. By estimating the acidity of some 1847 port I found that to reduce the alkalinity of a man's blood to that extent would require the instantaneous introduction of the acid contained in two bottles. The view, therefore, that a diminution of the alkalinity of the blood promotes an attack of gout by favouring the deposition of sodium urate, is, in my opinion, untenable.

II. *Experiments to show the Solvency of Uric Acid in Blood Serum, the Alkalinity of which has been Reduced by the Addition of an Acid.*—The experiments were carried out in the following manner. Seven bottles, containing 25 c.c. each of blood serum, were taken; three of them were treated

Table showing the Solubility of Uric Acid at 100° F. in unaltered Blood Serum, and in Blood Serum the Alkalinity of which is proportionately reduced by the addition of Hydrochloric Acid.

Solvent.	Uric Acid Dissolved	
	With Hydrochloric Acid.	With Tartaric Acid.
Unaltered serum	2.03 per 1,000	2.03 per 1,000
Serum one-fourth neutralised ...	1.48 "	2.01 "
" one-half " ...	1.00 "	2.01 "
" three-fourths " ...	0.45 "	2.02 "

respectively with different quantities of hydrochloric acid, so as to reduce the alkalinity of the serum in one case by one-fourth, in the second case by one-half, and in the third case by three-fourths; three others were similarly treated with tartaric acid; the contents of the remaining bottle were left untouched. The bottles were placed in the warm chamber till their contents were at 100° F., and then an excess (60 to 70 mg.) of uric acid was added to each. They were kept in the warm chamber for two hours, during which time they were frequently agitated; the contents of the bottles were then filtered from undissolved uric acid, and the dissolved uric acid in each filtrate was estimated. The preceding table shows the results.

The diminished solvency of the HCl-treated serum for uric acid is due to the conversion of some of its NaHCO_3 into NaCl , whereby less sodium remained available for the formation of the quadriurate. It appears, however, that in the case of the tartaric acid the uric acid is able to displace it from its combination with sodium, and use the latter as readily as if it had been in the form of the bicarbonate.

Since the acidity of wines is due to organic acids (mainly tartaric, malic, and succinic acids), it would seem very doubtful, judging from the results of these experiments, whether, even if any alteration in the alkalinity of the blood were produced by the drinking of acid wines, the solubility of uric acid in such blood could be affected in the slightest degree.

III. *Experiments to show the Solubility of Sodium Biurate in Blood Serum, the Alkalinity of which has been Reduced by the Addition of an Acid.*—The experiments were carried out in a similar manner to those just described, except that an excess of sodium biurate was substituted for the uric acid,

Table showing the Solubility of Sodium Biurate at 100° F. in Unaltered Blood Serum, the Alkalinity of which is Proportionately Reduced by the Addition of Hydrochloric and Tartaric Acids.

Solvent.	Sodium Biurate Dissolved	
	With Hydrochloric Acid.	With Tartaric Acid.
Unaltered serum	0.05 per 1,000	0.05 per 1,000
Serum one-fourth neutralised ...	0.05 "	0.08 "
" one-half " ...	0.07 "	0.08 "
" three-fourths " ...	0.10 "	0.12 "

These experiments show that the diminution of the alkalinity of blood serum by the addition of mineral or organic acids slightly increases its solvent power for sodium biurate.

I think that the view that uric acid is deposited in the liver, spleen, joints, and fibrous tissues owing to diminished alkalinity of the blood should be abandoned. It is based on an error, namely, that the deposit is uric acid, whereas it is sodium biurate. The results of the experiments that I have just described indicate that diminution of the alkalinity of the medium does not promote the deposition of sodium biurate. The other view that increased alkalinity of the blood dissolves and sweeps out the accumulations of uric acid from the various organs and tissues should also, in my opinion, be abandoned, as it is based on the same error. Nor is there any rational chemical evidence in support of Dr. Haig's view that small doses of calomel clear uric acid out of the blood and retain it in the body.

Influence of Certain Articles of Diet on the Precipitation of Sodium Biurate.—It is well known that the excessive consumption of rich nitrogenous food, combined with excesses in wine and malt liquors, both induce and excite gout. The subjects of gout are generally people who live well and consume a large amount of animal food. Dr. Budd, speaking from a long and extensive professional connection with a large rural district, states that he never knew an instance of gout occurring among agricultural labourers. The generally accepted view that a highly nitrogenous animal diet necessarily produces an excessive amount of uric acid is disproved by the experiments of Bleibtreu and of Hirschfeld previously referred to. I believe that as regards the production of uric acid from proteid matter it is of little importance whether the proteid is of animal or vegetable origin. As no researches have, so far as I can ascertain, been made with a view of determining the influence of the saline constituents of animal and vegetable food respectively upon the solubility of sodium

biurate, I have undertaken the following series of experiments.

Experiments showing the Influence of the Mineral Constituents of Meat, Milk, and Vegetables respectively on the Solubility of Sodium Biurate at 100° F.—A series of experiments were undertaken operating upon the ash respectively of lean beef, milk, and mixed vegetables (potatoes, spinach, and French beans).

The experiments were carried out in the manner devised by Sir William Roberts in determining the influence of various therapeutical salts on the solubility of potassium biurate. Bottles, each containing 100 c.cm. of distilled water were raised in the warm chamber to a temperature of 100° F., an excess of sodium biurate added, together with the salts under consideration; the whole was digested for five hours at this temperature, after which the amount of sodium biurate in the solution was estimated. The results are shown in the following table:

Solvent.	Sodium Biurate Dissolved.		
	Meat.	Milk.	Vegetable.
	Per 1,000.	Per 1,000.	Per 1,000.
Pure water ...	1.10	1.10	1.10
Water containing 1.0 per cent of ash ...	0.93	0.62	2.15
" " 0.50 " " ...	0.76	0.58	1.70
" " 0.20 " " ...	0.56	0.49	1.35
" " 0.10 " " ...	0.32	0.44	1.15
" " 0.05 " " ...	0.15	0.72	1.10
" " 0.02 " " ...	0.11	0.90	1.10
" " 0.01 " " ...	0.85	0.94	1.10

It is thus seen that the mineral constituents of meat in all proportions between 1.0 and 0.01 per cent. diminish the solvency of sodium biurate, and that the effects are most marked between 0.1 and 0.02 per cent., proportions which may certainly be present in the blood after eating a few ounces of meat. The ash of milk also diminishes the amount of sodium biurate dissolved, the diminution being most marked in the presence of 0.1 per cent. It is unlikely that the consumption of milk plays any part in the production or maturation of an attack of gout, since to introduce 0.1 per cent. of the mineral constituents of milk into the blood of a man of average weight would require the immediate consumption of 22 ounces of milk, an amount which is unlikely except in the case of a patient on exclusively milk diet. The mineral constituents of vegetables, on the other hand, in quantities of 0.1 per cent. and upwards, very appreciably increase the solvency of sodium biurate; it may hence be inferred that vegetable food, if taken in sufficient quantity, would delay the advent of an attack of gout.

I next endeavoured to ascertain whether the mineral constituents of milk, meat, and vegetables possessed any inhibitory powers over the decomposition of sodium quadriurate, and, if so, what were their comparative powers.

In connection with this investigation, some very remarkable results were obtained. The method I employed was that originally used by Sir William Roberts. Some pure sodium quadriurate was prepared by the method described by him. A very small quantity was placed on a glass slide and stirred up with a drop of water. A cover slip was applied, and the result watched under the microscope. The time was noted at which crystals of uric acid began to make their appearance. Fresh quantities of quadriurate were then treated in a similar manner, with 0.1 per cent. solutions of the mineral constituents of milk, meat, and vegetable ash respectively, and the different times at which crystals of uric acid commenced to form were noted. These were compared with the time required by distilled water to start the decomposition, which was taken as the standard of comparison. It was found that when the quadriurate was treated with distilled water, crystals of uric acid commenced to form at the end of half a minute, when treated with a 0.1 per cent. solution of milk ash in distilled water at the end of half a minute, with a 0.1 per cent. solution of meat (lean beef) ash at the end of one minute, and with a 0.1 solution of mixed vegetables (potato, spinach, and beans) ash at the end of two hours. In other words, the inhibitory power of a 0.1 per cent. solution of milk ash on the decomposition of sodium quadriurate is the same as that of distilled water; that of a 0.1 per cent. solution of meat ash is twice as great; while that of a 0.1 per cent. solution of vegetable ash is no less than 240 times as great. The inhibitory power of

blood serum is much greater than that of water, decomposition only occurring in that medium after several hours; it seems, therefore, probable that the addition of a small quantity of the mineral constituents of vegetables would delay the decomposition of the sodium quadriurate in the blood for a very considerable time.

I propose to follow up this line further, and to endeavour to ascertain which of the mineral constituents of vegetables especially possess this inhibitory power.

The net results of these experiments and of those previously described indicate that the mineral constituents of meat only delay for a brief period the decomposition of the quadriurate, and, when it is once decomposed, they hasten the precipitation of the biurate. On the other hand, the results indicate that the mineral constituents of vegetables delay for a remarkably long period the decomposition of the quadriurate, and then subsequently retard the precipitation of the biuret by increasing its solvency.

I do not wish to attribute the different effects of animal and vegetable diets on gouty subjects to the saline constituents alone; but it is, I think, to the different mineral constituents of animal and vegetable foods, and to the different effects they have on the quadriurates and biurates, that we must look for at least a partial explanation—perhaps a main one—of the known facts that an excessive diet of the one tends to produce gout and of the other tends to retard it.

Influence of Alcoholic Drinks on the Gouty Process.—It is well known that alcoholic drinks which have been subjected to fermentation but not to distillation, injuriously affect the gouty process. Those which have been distilled differ from these in containing little or no acid, and the harmful results of indulgence in wines have been attributed to their acidity. But if we arrange the various wines and beers in the order of their acidity as given by Bence-Jones and of their gout-inducing qualities as ascertained by Garrod, we find that the two do not coincide. Garrod hence concludes that the acidity can have but little to do with the causation of gout by fermented liquors, and this accords with the experiments I have already detailed, showing that a diminution of the alkalinity of the blood neither hastens the conversion of sodium quadriurate into biurate, nor promotes the deposition of the biurate, and so cannot be a determining cause of an attack of gout. My own experiments show also that the alcohol itself, in far larger quantities than could ever be present in the blood, has no effect either on the conversion of the quadriurate or the deposition of the biurate, and I have also confirmed Dr. George Harley's opinion as to the innocuousness of sugar in this respect. I have further extracted the volatile constituents of various parts and found them entirely without action upon the chemical changes referred to. I can therefore at present offer no final explanation of the *modus operandi* of such wines as hasten an attack of gout, but I incline to the opinion that the influence of wines on the development of gout is due, in great part, to the effect they have on the metabolism of the liver and the consequent increased amount of glycocine that passes on to the kidneys. At the same time it must be remembered that those accustomed to drink wine are also liable to indulge in other luxuries of the table, which greatly favour the development of gout.

CONCLUSIONS.

The main points and conclusions arrived at in these Lectures are as follows:

1. Uric acid is not normally present in the blood of man and other mammals, nor in the blood of birds.
2. Uric acid is normally produced only in the kidneys.
3. Uric acid is normally formed from urea, probably by conjugation of that substance with glycocine in the kidneys.
4. Uric acid is present in the blood in gout as the soluble sodium quadriurate. In its soluble form it is not a toxic agent. It deposits from the blood as sodium biurate, which acts passively and physically as a foreign body in the tissues or organs in which it is deposited.
5. The presence of uric acid in the blood in gout is due to its deficient excretion by the kidneys, and to the subsequent absorption of the non-excreted portion into the blood from those organs.

6. Gout is probably always preceded by some affection of the kidneys, functional or organic, which interferes with the proper excretion of uric acid. The probable seat of the kidney affection giving rise to gout is in the epithelium of the convoluted tubes.

7. In certain blood diseases and disorders accompanied by leucocytosis uric acid is formed within the system from nuclein. Under such circumstances it passes at once into the blood and is rapidly eliminated by the kidneys.

8. The solubility of uric acid in the blood is not affected by a diminished alkalinity of the blood produced by the addition of organic acids.

9. The deposition of sodium biurate is not accelerated by a diminution of the alkalinity of the blood.

10. An increased alkalinity of the blood does not increase the solubility of deposits of sodium biurate.

11. The saline constituents of vegetables exercise a remarkable inhibitory power over the decomposition of sodium quadriurate.

12. The solubility of sodium biurate in the blood is increased by the presence of the saline constituents of vegetables.

13. The solubility of sodium biurate in the blood is diminished by the presence of the saline constituents of meat.

14. The gout-inducing properties of certain wines are not due to their acidity. Probably they owe their gout-inducing action to the effect they exercise on the metabolism of the liver.

REFERENCES.

¹ *Maladies des Vieillards et les Maladies Chroniques*, 1874. ² *Med. Soc. Trans.*, vol. xiv, p. 88. ³ Croonian Lectures, BRITISH MEDICAL JOURNAL, i, 18:6. ⁴ *Deut. med. Woch.*, 1895, xxi, p. 655. ⁵ *Loc. cit.*

A CASE OF ANGINA PECTORIS TREATED BY ERYTHROL TETRANITRATE, WITH MARKED BENEFIT.

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E. G., aged 75, a medical man, twelve months ago began to suffer from angina pectoris. As no organic lesion was discovered the affection was declared to be neurotic, and treatment with digitalis, strophanthus, quinine, strychnine (hypodermically and by the mouth), cactina, arsenic, etc., successively, was tried without avail. The patient grew feeble, and the seizures became more frequent. The symptoms were pain in the sternum, elbows, and fingers; quick, painful, jerky respiration followed, unless the attack was cut short by nitroglycerine or inhalation of nitrite of amyl, by absolute agony, and an indistinguishable pulse. A fiftieth of a grain of nitroglycerine had always to be taken to enable him to dress, undress, creep out into the sunshine, etc., and seven or eight such doses were required in the twenty-four hours. The attacks were induced not only by slight physical exertion but also by mental effort (such as the writing of a letter), and they would even occur during perfect rest or during sleep. In the intervals of the attacks the pulse was 70, soft, and easily compressible. After taking a tabloid of nitroglycerine ($\frac{1}{10}$ gr.) the usual effects—throbbing at the temples, a fuller radial pulse, etc.—were felt, followed in two to three minutes by entire cessation of the pain, and return of normal breathing.

Erythrol tetranitrate (1-grain doses) was now suggested. Without my knowledge Dr. G. undertook some observations on himself, and very kindly afterwards sent me the following account: "Before taking the tetranitrate of erythrol at stated intervals I thought it would be instructive to ascertain by experiment the length of time the agent would afford immunity from the seizures of angina. It was taken, therefore, only when attacks were imminent, as known by pain supervening in the sternum, elbows, and fingers, before the breathing had become distressed or the point of agony approached. In this latter emergency nothing short of the inhalation of nitrite of amyl or the rapid mastication of nitroglycerine tabloids will lower arterial tension and afford relief. It would seem in my case that, notwithstanding the previously long-continued use of trinitrine, this tension was

more quickly lowered and longer relieved than is shown in your diagram (Fig. 10) in the Bradshaw Lecture.¹ Certainly in ten minutes I felt that the progress of the attack was arrested, and, as the figures below show, the interval of ease was more prolonged. The following table introduces the last three or four days' use of nitroglycerine by way of contrast. The system appeared to have become so insensitive to its action that $\frac{1}{15}$ gr. three times a day was now practically inert.

NITROGLYCERINE.

(In doses of $\frac{1}{15}$ gr. unless otherwise indicated; only taken on the approach of, or during, a seizure.)

February 28th, at 6, 8, 12, 3 ($\frac{1}{15}$ gr.), 7 ($\frac{1}{15}$ gr.), 10 ($\frac{1}{15}$ gr.)

March 1st, at 6, 8, 11 ($\frac{1}{15}$ gr.), 12, 4, 7, 9, 11.

" 2nd, at 3, 6, 8, 11, 1, 3, 5, 7, 9, 11.

" 3rd, at 1 ($\frac{1}{15}$ gr.), 8 (here erythrol tetranitrate arrived).

ERYTHROL TETRANITRATE.

(One grain was taken at each dose except where otherwise noted).

	Taken at	Repeated at	Interval.
March 3rd (cont.)	10 A.M.	7 P.M.	9 hours.
" 4th	6 A.M.	1 P.M. and 9 P.M.	—
" 5th	7 A.M. ($\frac{1}{2}$ gr.)	12 P.M. ($\frac{1}{2}$ gr.), 4 P.M. ($\frac{1}{2}$ gr.), 8 P.M.	—
" 6th	7 A.M.	6 P.M.	11 hours.
" 7th	6 A.M.	6 P.M.	12 hours.
" 8th	6 A.M.	1 P.M.	7 hours.

"Life being now rendered infinitely more tolerable and the potency of the remedy abundantly demonstrated, I determined upon taking it steadily, at about eight hours' interval, as a prophylactic. For three days there was immunity from attacks, although some weariness and oppression at the chest were wont to steal on after the lapse of six or seven hours from taking the tablets. I am now taking them four times in the twenty-four hours, and am sanguine enough to hope to keep the foe at bay altogether."

This case needs little comment. Dr. G. is right in stating that the pulse tension is more quickly lowered than is shown in the diagram to which he refers. The initial fall depends on the mode of administration. If the drug is given in spirit and water (1 grain in 1 drachm of alcohol and 7 drachms of water) the tension begins to fall in from two to three minutes; if given in a pill and swallowed the time is from twenty to forty minutes; if taken in tablet form and masticated the time lies somewhere between the two. The best form of administration is undoubtedly the tablet form. The alcoholic solution which I originally recommended sometimes irritates the stomach on account of the amount of alcohol it contains, and unless a rapid action is required it is better to give the drug in the solid form. Erythrol tetranitrate, however, was not introduced to replace amyl nitrite and nitroglycerine in cutting short attacks which have developed, but only to replace them in preventing the onset of the attacks. That it is capable of doing this much better than nitroglycerine, the best drug we had hitherto had for this purpose, I think the preceding case conclusively proves.

REFERENCE.

¹ BRITISH MEDICAL JOURNAL, November 16th, 1895, p. 1217.

THE DIRECTION OF ROTATION IN CEREBELLAR AFFECTIONS.

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In a paper on the Value of Experimental Evidence in the Diagnosis of Diseases of the Cerebellum, published in the BRITISH MEDICAL JOURNAL of May 18th, 1895, when discussing rotation as a symptom of cerebellar disease I stated that animals deprived of one lateral lobe of the cerebellum rotated away from the side of the lesion. I then went on to explain how a human subject with disease of one lateral lobe of the cerebellum would be expected to rotate in order to be in agreement with the experimental results which I had obtained.

The JOURNAL of the following week contained a letter from Dr. Bruce Ferguson, in which he expressed the opinion that I had fallen into an error of expression; and he gave his reasons for considering that the direction of the rotation which I had described was towards and not away from the side of the lesion. As it was impossible to reply to his criticisms in the space at my disposal for a letter, I promised to write a paper dealing more fully with the question than I