THE CROONIAN LECTURES ON THE CHEMISTRY AND THERAPEUTICS OF URIC ACID GRAVEL AND GOUT.

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LECTURE IV.—CHEMISTRY OF URATIC PRECIPITATION (CONTINUED): BEARING OF THE INVESTIGATION ON THE THERAPEUTICS OF GOUT.

Topography of Uratic Deposits.—The topographical distribution of uratic deposits through the various organs and tissues of the body exhibits certain well-marked characteristics; these deposits are found almost exclusively in structures belonging to the connective tissue class—in cartilages, ligaments, tendons, and other fibrous structures, and in the cutaneous and subcutaneous connective tissues. On the other hand, uratic deposits are conspicuously absent from the muscular tissue, and from the substance of the brain, liver, spleen, and lungs. The tissues which are liable to uratic precipitations are, however, not equally so in the different parts of the body. The cartilages, ligaments, and tendons in and about the joints, which are bathed with synovia, are much more obnoxious to these deposits than are cartilages and fibrous structures situated at a distance from joints, and which are not bathed with synovial fluid. It is further to be noted that uratic deposits favour the more superficial and cooler parts of the body, especially the upper and lower extremities, and are more rare in the deeper and warmer interior parts of the trunk. It may be inferred from these particulars that the influences which co-operate to determine the site of uratic precipitations are of several and quite different kinds. I do not propose to discuss this subject comprehensively, but to refer only to two points which seem capable of a chemical or physical elucidation. These are the influence of the proportion of sodium salts in the several organs and tissues, and the influence of synovia.

(a) *Influence of the Proportion of Sodium Salts.*—We have seen that the dominant factors in uratic precipitation, as studied in the laboratory, are the proportion of urates and the proportion of sodium salts contained in the medium.¹ The highest tendency to precipitation is reached when there is a concurrence of these two factors in maximum intensity. A medium may be rich in urates, but if it be at the same time poor in sodium salts, its tendency to precipitation is very feeble, and *vice versa*. This fact has a direct bearing on the topography of uratic deposits. For supposing the system of a gouty man, on the eve of an outbreak, to be throughout equally impregnated with urates, it is obvious from the experimental evidence before adduced that uratic precipitation would take place earliest, and most copiously, in those parts which were richest in sodium salts; and take place latest, or not at all, in those parts which were poorest in sodium salts. Let us now examine the distribution of sodium salts in the body, and seek to ascertain if there be any correspondence between the liability to uratic deposits in the several tissues and organs and the proportion of sodium salts contained in them. In the subjoined table I have arranged the results of analyses on this point. The materials available for comparison are not so full and precise as could be desired, but their general significance is, I think, quite unmistakable. In order to render the comparison more complete and instructive, I have included in the table not only the results with respect to the solid organs and tissues, but also those with respect to blood serum, lymph and synovia.

An inspection of the table shows that the tissues which are liable to uratic deposits are very much richer in sodium salts than the tissues and organs which are not thus liable. The remarkable immunity from uratic deposits enjoyed by the muscular tissue, by the brain, liver, and spleen may be in-

ferred to be due, for the greater part at least, to their poverty in sodium salts.

TABLE XVIII.—*Showing the Percentage of Sodium Salts in the several Fluids, Tissues, and Organs of the Body.*²

Blood serum ...	...	...	0.70 per cent.
Lymph ...	...	...	0.70 "
Synovia ...	...	...	0.80 "
Cartilage ...	...	...	0.90 "
Fibrous tissue ...	...	...	0.70 "
Blood corpuscles ...	...	...	0.20 "
Brain ...	...	...	0.20 "
Muscle ...	...	...	0.08 "
Spleen ...	...	...	0.04 "
Liver ...	...	...	0.02 "

Turning to Table XIII, we see that the solvent power of a medium for sodium biurate increases in correspondence with its lessening proportion of sodium salts. Brain has only about one-fourth the percentage of these salts as compared with cartilage and fibrous tissue, and muscle only one-tenth. This difference signifies (roughly) that brain has four times more power, and muscle ten times more power, of dissolving sodium biurate than cartilage and fibrous tissue, and therefore, respectively, four and ten times more power of resisting its precipitation in their substance. It might probably be truthfully said on this ground that brain, muscle, liver, and spleen could not become the sites of uratic deposits until the connective tissues had been in this respect exhausted. It is true that the immune tissues and organs have a quicker circulation than cartilages and tendons, and this doubtless contributes importantly to the difference; but it scarcely fully accounts for it, otherwise we should expect that the skin, which is abundantly supplied with blood vessels, would share this immunity. The prepotency of the cartilages and fibrous tissues to induce uratic precipitation must obviously operate in a conservative direction, and serve to protect the more vital organs of the gouty from similar precipitations where they would produce more deadly effects.

(b) *Influence of Synovia.*—The connection between synovia and gouty deposits is evidently very close and special. Synovial fluid has itself been repeatedly found heavily laden with crystals of sodium biurate. In the great majority of the less severe cases of gout the deposits are exclusively confined to those cartilages, ligaments, and tendons which are in actual contact with synovial sacs or synovial sheaths. With regard to the articular cartilages, it may, I think, be demonstrated that the uratic precipitation actually takes place from the synovial fluid, and is not self-originating in the cartilaginous substance. Vertical sections of gouty cartilages are very convincing on this point. If such sections are examined under the microscope, it is seen that the deposit hugs the synovial surface of the cartilage, and that it becomes progressively sparser and sparser towards the deeper layers, the central and deepest parts being usually quite free from deposit.

This mode of distribution, moreover, implies that the process of deposition, so far as concerns the cartilage, is a purely passive one, and in no wise active and vital in its initiation. We may suppose that the urate dissolved in the synovia penetrates by liquid diffusion into the superficial layer of the underlying cartilage, and that when the critical moment arrives precipitation takes place simultaneously in the synovia and in the cartilage. On this view the after-consequences are entirely secondary, and are due to the reaction of the tissue against the presence of a foreign body lodged in its substance. It may interest you to know that this process can be artificially imitated in the laboratory, and that a counterfeit gouty joint can be produced in the articulations of a dead animal. I here show you samples of such counterfeits. They were prepared in the following manner: Tarsal bones of a pig were suspended in wide-mouthed phials charged with a saturated solution of sodium biurate made in hot water and then cooled. The phials were chloroformed, corked, and placed in the warm chamber or at the temperature of the room. Reprecipitation of the biurate takes place in two or three days. If the bones are now examined, the articulating

¹ The proportion of calcium and magnesium salts is always too small to have any appreciable influence on the occurrence of uratic precipitation.

² The figures in this table are to be taken as approximate numbers. Most of them are deduced from analyses cited in *Gangue's Physiological Chemistry*. The figures for synovia and fibrous tissue are deduced from the author's own analyses of the synovial fluid and tendons of the ox, the amounts being reckoned as chlorides. A more recent analysis of human lymph by Munk and Rosenstein (*Maly's Jahresbericht*, Bd. xx, p. 40) gives the sodium salts as 0.80 per cent.

ends are found to be encrusted with a chalky matter, which cannot be wiped off with a towel nor removed with a nail-brush. They present an exquisite imitation of the plastered appearance of a gouty cartilage. If vertical sections of such cartilages—previously hardened in absolute alcohol—are made, and examined with the microscope, the deposit is seen to be situated in the substance of the tissue, close beneath the synovial surface of the cartilage, and to be composed of a dense felt of fine needles of biurate. The deeper layers of the cartilage are not affected. It may be inferred that the deposits which occur in the ligamentous and tendinous structures of gouty joints are produced in the same way as those found in the cartilages, and that the precipitation takes place—chiefly, at least—from the synovial fluid bathing them, and that they are not due to primary morbid changes in the structures.

Two questions may now be asked: first, Why does gouty precipitation take place preferentially in synovia rather than in its cognates, the serum of blood and lymph? and secondly, Why do the joints differ so much from each other in their liability to attack? I will discuss the two questions together, as the arguments often dovetail into each other. It may be that there is, as Sir A. Garrod suggests, some special attraction in the joints for uric acid. But there are undoubtedly other factors which come into play. Synovia is a comparatively motionless fluid, while serum and lymph are in ceaseless motion; and as a still pool crystallises into ice sooner than a running brook, so likewise—supposing serum, lymph, and synovia to be equally impregnated with urates and sodium salts—the tranquillity prevailing within the synovial cysts would give to synovia a priority in uratic precipitation over the restless blood serum and lymph. Then, as regards the varying liability of the different joints to gouty attacks, it may be pointed out that the synovial pouches and sheaths are shut sacs standing apart from each other, and isolated from the general panmixia of the circulation. It might consequently be expected—indeed, it is an observed fact—that the synovial fluid in different joints should present differences in the relative proportion of their constituents. Some are certainly more concentrated than others, and we can easily believe that they are not quite identical in their degree of impregnation with urates and with sodium salts. In this way the several joints might come to vary considerably in their liability to uratic precipitation.

Frerich has contributed some interesting particulars on synovia in animals.³ His observations indicate that synovia varies both in quantity and quality under different modes of life. He found that stall-fed horses and oxen, leading an idle existence, had twice as much synovia in their joints as similar animals roving in the meadows or doing work. Moreover, the composition of the fluid varied in the two cases. In the idle animals the synovia was more watery and contained less albuminoid matters, but—and this is significant—a larger proportion of mineral salts, which consist almost entirely of sodium salts. We might conjecture from this fact that if horses and oxen were liable to uratic precipitations, the idle stall-fed animals would be more subject to such deposits than the same animals leading a more active life. Perhaps we may discern herein one reason why men who lead a sedentary life are more subject to gouty deposits than men who take active exercise.

Interpretation of the Appearances Found at the Necropsy of Gouty Subjects—Re-solution of Gouty Deposits.—Before leaving the subject of the topographical distribution of gouty deposits I should like to say a word on the need of caution in interpreting the appearances, both positive and negative, observed at the necropsy of gouty subjects. The incidents of the gouty diathesis, especially in the early periods, pursue a markedly interrupted course. Long intervals of months or years often elapse between the arthritic outbreaks. During these intervals the blood of the gouty recovers its purity more or less completely, and approximates in its content of uric acid to the blood of a healthy person. The solvent relation of the bodily fluids to the material of uratic deposits is simply a question of saturation and subsaturation. If the lymph or synovia at a certain spot become saturated, or rather supersaturated, with sodium biurate precipitation of that substance will inevitably take place into the contiguous fibrous tissues.

And if, after such an event, the lymph or synovia recover its purity and become approximately free from biurate, as in due course usually comes about, a process of slow re-solution will of necessity set in. For, as has been before demonstrated, sodium biurate, although very sparingly soluble, is by no means insoluble in these media. The rate and amount of re-solution of uratic deposits must necessarily vary greatly in different cases, according to the degree of subsaturation attained by the bodily fluids, the massiveness and penetrability of the deposits, and the length of the time during which the favourable conditions endure.

If regard be had to the often long survivorship of gouty persons, and the interrupted course of the arthritic incidents, it seems highly probable in the lapse of a long life that deposition and re-solution of uratic matter may take place once and again in a gouty joint. There are undoubted instances, of which Sir Dyce Duckworth⁴ records one observed by himself, where no uratic concretions have been found after death in joints which had at some previous period undergone typical gouty attacks. The presumption in such a case is not that deposits never existed, but that they had been redissolved in the intervals of amendment. Uratic concretions in the pinna of the ear have sometimes been actually observed to come and go, and come again. There is no reason why the same thing should not occur within the joints, and such vanished concretions might leave behind them permanent changes in the cartilages and bony structures as tell-tale evidence of their former presence. On the other hand, the discovery after death of uratic deposits in a joint is not always to be regarded as a certain proof that the joint had passed through an inflammatory gouty attack. The observations of Moxon and Fagge seem to warrant this conclusion, and they reasonably suggest that when the precipitation of the urates takes place slowly and by degrees there may be no accompanying inflammatory outbreak to mark the event.⁵

The experimental evidence before adduced indicates that when lymph or synovia is impregnated with sodium biurate to or above 1 part in 6,000 the medium is supersaturated, and precipitation either actually occurs or is impending. On the other hand, when these fluids contain less biurate than 1 part in 10,000 the medium is under-saturated, and there resides in it a certain power of redissolving uratic deposits; and of course the nearer the medium is to freedom from urates the higher rises this solvent power. It may further be inferred that the solvent action will be most effective in the case of deposits situated in textures, like fibrous tissues, which have a comparatively free lymph flow, and, conversely, that it will be least effective in textures, like the cartilages, which have a sluggish lymph flow. This is probably the reason, or chief reason, why the cartilages figure more prominently than the fibrous structures in the morbid anatomy of old gouty joints. Probably both tissues were originally infiltrated with biurate crystals in equal degrees, but the fibrous structures afford greater facilities for their re-solution in the periods of amendment than the cartilages, and hence the greater persistence of the deposits in the latter tissues.

The Mode in which Uric Acid Produces its Injurious Effects.—A problem of great interest in regard to the elucidation of gouty manifestations is the mode or modes in which uric acid produces its injurious effects. The main question is, whether these effects are exclusively due to the mechanical damage consequent on its precipitation as sodium biurate in the tissues, or whether, in addition, uric acid circulating in the blood in a state of solution is capable of acting as a true poison.

With regard to the incidents of regular gout, the mechanical theory seems to offer a natural and complete explanation. The crystalline urates precipitated in the cartilaginous and fibrous structures of the joints necessarily act as foreign bodies; they excite irritation, clog the lymph channels, exercise pressure on the tissue elements and impede their nutritive operations. These effects sufficiently account for the inflammation, pain, and swelling which ensue, and explain the remoter degenerative changes which follow after. Nor need we look beyond physical conditions to account for the diversity witnessed in the local manifestations. It is easy to understand that depositions occurring within the tense unyield-

³ R. Wagner's *Handwörterbuch d. Physiol.*, Bd. III, Pt. 1, p. 463.

⁴ *Treatise on Gout*, by Sir Dyce Duckworth, p. 68.

⁵ Fagge and Pye-Smith's *Handbook of Medicine*, p. 674.

ing structures of the joints would produce widely different results from similar depositions in the loose subcutaneous tissue or in the rim of the ear. It is equally easy to understand that the suddenness or slowness of the precipitation, its copiousness or scantiness, would necessarily cause great variation in the intensity and character of the local disturbance. So easy and natural is this explanation that we might even predicate, from our general knowledge of pathological cause and effect, that if similar depositions of crystals of carbonate of lime, or of any other inert substance, were to take place in the same localities, there would follow very much the same train of morbid sequences as are witnessed in connection with uratic precipitations.

It is in the explanation of the phenomena of irregular gout that the mechanical theory of the action of uric acid seems inadequate; and it is to meet this lack that the theory of a poisonous action has been set up and is invoked. The visceral disturbances and manifold neuroses which trouble the gouty have not yet been anatomically traced to uratic precipitation; and there seemed no other way of explaining their occurrence, if they were to be linked with uric acid at all, except by assuming that uric acid was possessed of toxic properties. The acceptance of this view appears to me on several grounds to be extremely difficult. There is first the complete absence of direct experimental proof. Animals have been made to ingest large quantities of uric acid with their food, and urates in solution have been freely injected into their veins without eliciting any signs of poisoning. In the next place, the idea that uric acid is poisonous seems opposed to broad biological analogies. Uric acid is the physiological homologue of urea; each of these bodies constitutes in its separate domain the final term of nitrogenous metabolism. Now, it cannot be said, without an abuse of terms, that urea is a poisonous substance,⁶ and it would be strange if its homologue, uric acid, differed from it in so important a particular as the possession of toxic properties.

The theory appears not less improbable when examined from a nearer point of view. The system of the gouty man is at times surcharged with uric acid. On the eve of an outbreak, the fluids of his body, in parts at least, must be impregnated with biurates to saturation, for, of course, no precipitation can occur until this point is reached. Yet, with fluids saturated with urates, such persons often betray not the slightest sign of poisoning, and enjoy complete immunity from symptoms of every kind until overtaken, unwarned, by the sudden precipitation which provokes the arthritic attack.

Again, the manifestations of irregular gout are so extremely diverse in seat and character, that it is hard to believe that they can be produced by one and the same toxic agent. Sometimes they implicate the stomach, sometimes the liver or heart or lungs, and oftenest of all the nervous system. This diversity is, however, easily explicable on the supposition that the disturbances are caused, not by uric acid in a state of solution acting as a poison, but are really due to actual precipitation of crystals of biurate into the connective and fibrous structures of the implicated organs, or into the fibrous sheaths of the nerves which control their functions.

Observations at the bedside and in the dead room lead to the inference that uratic precipitation is very variable in its mode of incidence. In certain conditions the crystals would seem to descend in sudden and copious showers, which provoke a sharp inflammatory reaction, as in the regular arthritic seizures. In other conditions the crystals would seem to fall in gentle sprinklings sufficient perhaps to excite irritation if the implicated tissue be a sensitive one, but not enough to cause downright inflammation. The peculiar pricking pains in the joints, which some gouty persons invariably experience after partaking of certain wines, are highly suggestive of the occurrence of these slighter precipitations. Now if these slighter precipitations, instead of falling on the joints, fell upon the membranes of the

brain or upon the fibrous sheaths of the nerve roots, this would, I submit, afford an adequate explanation of the phenomena of irregular gout. Of course, it may be objected that no such slight precipitations have actually been found. But have they been looked for? Has the microscope been used in the investigation? In prosecuting such a search it would have to be borne in mind that the precipitations would be apt to be fugitive, and that negative results would have to be interpreted with caution. For it is obvious, in the case supposed, that when the stress of saturation of the fluids with urates was relaxed, and the blood again recovered its power of dissolving these compounds, these slight deposits would be speedily removed by re-solution, and not a trace of them might remain at the necropsy.

We scarcely realise how imminent a slight, but widespread, precipitation of the crystalline biurate must not infrequently be in the gouty system. It was shown in the last lecture that when the serum of the blood is impregnated with sodium biurate to the extent of 1 part in 6,000, supersaturation is attained, and precipitation is then, of course, imminent. It was also pointed out that Sir A. Garrod had proved by quantitative analysis that the blood serum of the gouty man is sometimes actually impregnated with uric acid to this extent. These two facts taken together indicate that the explanation here suggested of the phenomena of irregular gout stands on a strong basis of *a priori* probability, and thus dispenses with the necessity of assuming that uric acid and its compounds are endowed with poisonous qualities.

This mode of viewing the subject enables us to bring the diverse morbid effects of uric acid into uniform line. Uric acid and its compound are deleterious simply because of their sparing solubility in the bodily media. It may be said that the final cause of uric acid gravel is the sparing solubility of free uric acid in urine, and, in like manner, it may be said that the final cause of gouty precipitations is the sparing solubility of sodium biurate in blood serum, lymph, and synovia.

BEARINGS OF THE INVESTIGATION ON THE THERAPEUTICS OF GOUT.

In dealing with the therapeutics of gout, I shall confine myself to those points which have a chemical bearing, and which can be brought into touch with the results of the foregoing investigation. According to the views developed in these lectures, the mischief done by uric acid in gout is contingent on its precipitation as crystalline biurate in the tissues or in the fluids of the body. Within this limited scope the study of the treatment of gout resolves itself into a study of the means we possess of controlling the factors which promote or hinder this precipitation. These means may be divided into those which belong to the domain of diet and regimen, and those which consist in the administration of medicinal substances.

(A) Diet and Regimen.

Restricting the Production of Uric Acid.—It has been shown that one of the main factors in determining uratic precipitation is the percentage of urates in the medium. Other things being equal, the larger the proportion of urates present the earlier and more abundant is the deposition of the crystalline biurate. Our power of controlling this factor lies almost entirely in the direction of regulating the diet. Numerous experiments have been made on the effect of diverse kinds of food on the production and excretion of uric acid. The chief point of therapeutical interest that has been clearly made out is this, that the ingestion of large quantities of proteid matter is attended with an increased production of uric acid, and *vice versa*. It does not appear clear that proteid substances derived from the animal kingdom differ in this respect from those derived from the vegetable kingdom. But inasmuch as the commonly used articles of food of animal origin, such as butcher's meat, poultry, game, fish, eggs and cheese are richer in proteid stuff than the commonly used articles of vegetable origin, such as bread, oatmeal, rice, potatoes and garden products, it is true that a vegetable diet is less productive of uric acid than an animal diet. The most trustworthy experiments indicate that fat, starch, and sugar have not the least direct influence on the production of uric acid; but as the free consumption of these articles naturally

⁶ The word poisonous is here used with its ordinary meaning. Almost any substance which could be got into solution in the blood in very large quantities would produce deleterious effects, even common salt. Urea can be taken into the stomach in drachm doses without harm; and Dr. Rose Bradford, who has paid particular attention to this point, informs me that the human body contains habitually in the normal state some 30 to 45 grains of urea, and may contain very much larger quantities than this without provoking any signs of poisoning.

operates to restrict the intake of nitrogenous food, their use has indirectly the effect of diminishing the average production of uric acid. There may be, and indeed undoubtedly are, other differences between animal and vegetable articles of food, and between one article and another of the same class, which are highly important. They differ considerably among themselves in their digestibility, and in their stimulating qualities, but in regard to the point under review, namely their direct influence on the production of uric acid, articles of diet must, as far as our present knowledge goes, be classified according to the percentage of albuminoid matters contained in them. As a rough guide in the choice of food for the gouty, the subjoined table may prove useful.

TABLE XIX.—Showing the Average Percentage of Albuminoid Matters contained in diverse Articles of Food.

Animal Food.	Albuminoid Matters.
Butcher's meat	19 per cent.
Fowl	20 "
Game	22 "
Fish	17 "
Egg	13 "
Milk	4 "
Cheese	30 "
Vegetable Food.	
Bread	8 "
Oatmeal	12 "
Rice	6 "
Green peas	6 "
Potatoes	2 "
Carrots and turnips	1 to 2 "
Green vegetables and salads	1 to 2 "
Fresh fruit (excluding nuts)	0.5 to 1 "

In choosing a diet for persons who are disposed to uratic precipitations, regard must, of course, be had to the whole condition, and especially to peculiarities of the individual. Nowhere, perhaps, is it more necessary than in gout to consider the man as well as the ailment, and very often more the man than the ailment; but the general rule in reference to the point under notice is, I think, pretty clear. Gouty people should be advised to partake cautiously of butcher's meat, fowl, game, and cheese, and to partake as freely as their digestion will permit of bread, rice, garden vegetables, salads, and fruit. The advantage to be gained from an adjustment of the dietary on these lines may be inconsiderable or even inappreciable in cases of inveterate gout, but it may be of critical moment in the slighter cases. A diminution of 1 or 2 grains per day in the amount of uric acid thrown into the circulation may make all the difference between the occurrence or non-occurrence of an arthritic attack.

The use of alcoholic beverages, as constituting an important feature in our dietetic habits, may here claim a word of comment. The most reliable researches indicate that these beverages, in their legitimate use, exercise no appreciable influence either way on the quantity of uric acid produced in the body. It was, moreover, found in my laboratory experiments that the addition to the medium of small quantities—such as might conceivably reach the circulation—of spirits, wines, or malt liquors, had not the slightest effect on the solubility of sodium biurate, nor any influence in accelerating or retarding the precipitation of the biurate in blood serum impregnated with uric acid. The special and highly-important part played by certain classes of alcoholic beverages in fostering a proclivity to uratic depositions, is evidently of a very subtle and complex character, and has apparently no direct reference to the chemical problems discussed in these lectures.

The Use of Culinary Salt.—It was shown in the preceding lecture that the solubility of sodium biurate was conspicuously influenced by the proportion of sodium salts in the medium. I observed, moreover, in my experiments on the maturation of blood serum impregnated with uric acid, that the addition to the medium of small quantities of sodium chloride (0.1 per cent., or even less), always appreciably hastened the precipitation of the crystalline biurate. It has also been shown that the topographical distribution of uratic deposits through the body bears a close and striking relation to the percentage of sodium salts contained in the several organs and tissues. Indeed, it might apparently be said with truth that if we possessed the power of regulating the dosage of sodium salts in the fluids and tissues, we should be able effectively to control the occurrence of uratic depositions. Our power in this respect is, however, limited. Sodium salts belong to the physiological constants of the blood, and their

proportion therein can only be modified within a comparatively narrow range. These remarks apply especially to the most abundant of them—the sodium chloride. It has been found in experiments on animals that when common salt is given in excess with the food, or injected into the veins, the surplus is for the most part quickly removed by the kidneys, and there is only a small and transient increase of its percentage in the blood. And, conversely, when animals are fed with food abnormally poor in salt there is only a slight falling off in its proportion in the blood, while it almost disappears from the urine. The blood clings with great tenacity to its proper percentage of sodium chloride, and the experimental evidence indicates that in case of a threatened salt famine within the economy the blood has the faculty of supplying its necessities by extracting salt from the less vital fluids and tissues, and contrariwise, in case of a glut of salt in the blood, the overplus is temporarily passed over into the serous cavities until such time as the kidneys have succeeded in restoring the normal equilibrium.⁷ All this leads to the inference that by lessening the intake of salt with the food we should abate its proportion in the blood only to a slight degree, but should diminish its proportion in the synovial fluids and fibrous tissues considerably. Acting on these ideas, I have been in the habit for some years past of directing gouty patients to restrict, as far as practicable, the use of common salt with their meals.

(B) Administration of Medicinal Substances.

In forecasting the possible effects of medicinal substances given internally in the treatment of gout it is well to realise fully the actual conditions of the problem. These are widely different from those presented to us in urinary gravel. In the latter case the daily dose is designed to form an addition to a comparatively small bulk of fluid, namely, to the 40 or 50 ounces which constitute the diurnal discharge of urine. In the case of gout we are seeking to make an impression on a much larger bulk of fluid, namely, on the totality of the blood, lymph, and synovia—a quantity in a man of average weight certainly not less than 20 lbs. Consequently the effect of our dose must be proportionately less. Moreover the urine is a dead excretion, it takes and keeps what is cast into it and has no power of self-purification. The blood, on the other hand, is a living stream with high powers of self-adjustment to a normal standard. A practicable dose of an alkaline carbonate enables us to alter the urine radically, to change its reaction from acid to alkaline, and thereby to exercise a decisive therapeutical effect in uric acid gravel. But the same dose only produces a feeble and transient effect on the mass of the blood and lymph, the blood passes on the surplus alkali with all speed through the kidneys into the urine, and quickly reattains its proper physiological standard of alkalinescence.

The medicinal agents which have been chiefly employed in the treatment of gout, with a view of controlling the tendency to uratic precipitation are the carbonates and phosphates of potash and soda, the carbonate of lithia, piperazine, and the waters of mineral springs—and it is to these alone that I propose to call attention.

Alkalies.—Alkaline substances are largely employed in the treatment of gout, both as pharmaceutical preparations and as components of mineral springs. It is believed that the alkaline carbonates and phosphates administered internally by increasing the alkalinescence of the blood enhance its solvent power on the material of gouty deposits, and thereby delay or prevent their formation. The experimental evidence laid before you entirely destroys this hypothesis. It has been conclusively proved that alkalinescence, as such, has no influence whatever on the solubility of sodium biurate. It has, moreover, been shown that the addition of an alkaline carbonate to blood serum impregnated with uric acid produces no appreciable effect on the process of maturation and the advent of precipitation of the crystalline biurate in the medium. The use of alkalies in gout has been advocated on another ground. It is held, in a vague sort of way, that there is an undue prevalence of acid in the gouty system, and that the blood is less alkaline than it should be. In some quarters it is even believed that this is the primary vice of the gouty state, and that there exists a so-called "acid dyscrasia" which

Lavage du Sang, by Dastre and Loye, *Archives de Physiologie*, 1888, p. 93.

dominates the whole condition. I have been at some pains to ascertain what foundation there is for this belief; I have found very little of any kind, and none that is really valid. In the numerous examinations of the blood in gouty subjects made by Sir Alfred Garrod, the serum was invariably found to be alkaline, never acid nor even neutral. But he remarks that there is often (not always) a marked alteration in the degree of its alkalinity, and that in cases of chronic gout the serum sometimes shows a near approach to neutrality. It is, however, obvious that observations on the alkalinity of the blood have no validity in regard to the point under consideration unless they are made on cases of gout pure and simple. Gout is often complicated, not only with pyrexia, but with serious secondary lesions in the kidneys and joints which lead to a profound cachexia. These secondary lesions bring with them blood changes of their own, which are only remotely connected with the primary disorder, and have no bearing on the etiology of uratic precipitation. In the last few years some exact quantitative measurements have been made of the alkalinity of the blood both in health and in disease.⁸ These researches indicate that a diminished alkalinescence of the blood is a common pathological deviation, and that it occurs in a variety of conditions which have no special relation to gout, namely, in pyrexia, in diabetes, carcinoma, acute rheumatism, anæmia, leukæmia, and apparently in every kind of general cachexia. These facts and considerations suffice to show that in the present state of our knowledge the belief in an acid dyscrasia in gout rests on a pure assumption.

Carbonate of Lithia and Piperazine.—These two substances have been introduced into the treatment of gout expressly on chemical grounds. Solutions of these substances possess a high solvent power on free uric acid, and it has been inferred from this fact that their administration internally might exercise a favouring influence on the solubility of sodium biurate in the bodily fluids, and thereby tend to prevent the formation of uratic depositions. This inference does not, however, appear to be justified. I found experimentally that the addition of carbonate of lithia or piperazine in the proportion of 0.1 per cent. and 0.2 per cent. to blood serum or synovia had not the slightest effect in enhancing the solvent power of these media on sodium biurate, nor the slightest effect in retarding its precipitation from serum and synovia artificially impregnated with uric acid. If these bodies have any beneficial action in gout, it is I think certainly not due, as has been supposed, to their solvent action on the material of gouty concretions.

Mineral Springs.—The bearing of the inquiry on the use of mineral waters is, I think, of important practical interest. A considerable number of the springs to which gouty patients resort are strongly impregnated with the salts of soda. Now it has been conclusively shown that all the salts of soda act adversely on the solubility of sodium biurate and hasten its precipitation, and it may be inferred that the introduction of these salts into the circulation must tend to favour the occurrence of uratic depositions in the body. It is not therefore surprising to learn that, not infrequently, the first effect of these waters on a gouty patient is either to provoke a downright attack of gout or to aggravate the symptoms under which he was suffering. This event is now recognised by the physicians practising at these spas as a thing to be looked for, and experience has taught them the necessity of caution in regard to the quantity of the waters to be taken by new comers. They comfort themselves and their patients, however, in the belief that this preliminary storm is a necessary prelude to the calm amendment which is to follow. There is no doubt some foundation for this idea. It is no fiction that a gouty man, tormented with symptoms of irregular gout, is relieved by a regular arthritic attack. I presume that this arises from the complete, or approximately complete precipitation of the urates floating in his blood and lymph into the structures of the joints. The urates are thereby as effectually removed from the vital fluids as if they were eliminated by the kidneys. But it must I think be allowed that this is a rough mode of cure, and that it brings with it serious pains and perils of its own. My impression is that gouty persons should either entirely avoid springs which owe their activity

to sodium salts, or should use them very sparingly. It is difficult to believe that they can do any direct good, and easy to believe that they can do direct harm. If they do any good at all it must be indirectly, by acting on the liver and the intestinal tract; and we possess other means of effecting this purpose without inducing any collateral risk.

There are, however, other springs of high and growing repute in the treatment of gout which are not open to these objections. These springs contain no soda, or only traces, and the sum of their mineral constituents does not exceed that which is often present in ordinary potable waters; they contain for their chief component a little carbonate or sulphate of lime, and it is very doubtful whether the whole of this is absorbed into the blood; most of it probably passes out inertly with the fæces. In fact, springs of this class may practically be considered as equivalent to ordinary drinking water, except that several of them have the advantage of being thermal. Among springs of this kind may be mentioned, in our own country, the waters of Buxton, Bath, and Strathpeffer; in Germany the waters of Gastein, Wildbad, Pfeffers, and the Sauerling spring at Carlsbad; in France the waters of Aix-les-Bains, Contrexéville, Vittel, and Barèges. Now there can be no reasonable doubt that the efficacy of these springs has nothing to do with their scanty mineral ingredients, but depends on their watery constituent. They are drunk freely, and on an empty stomach. Their action would be to dilute the blood temporarily, and lower its percentage of urates and sodium salts. This effect would tend to retard or prevent uratic precipitation, and thus give the defective kidneys additional time to overtake their arrears in the task of eliminating uric acid.

It may be asked whether the drinking of water at home would not answer as well as resorting to a mineral spring. The inference, from my experiments, is that, other things being equal, the beneficial results would be the same; but the "other things" never are equal. It would scarcely be practicable for a man going about his usual business to drink eight or ten tumblers of water on an empty stomach every day for two or three weeks. At a watering-place the visitor has nothing to do except to attend to his "cure." Moreover, in getting away from home, he leaves behind him the worries of his daily life, and experiences the advantage of change of air and scene, with a salutary modification of diet, and he has abundant leisure for outdoor exercise. All these collateral influences help to raise the general level of health, and quicken the action of the secretory cells. I do not think, therefore, that we can forego the advantages of the time-honoured practice of a visit to a mineral spring. At the same time, a word may be said in favour of a more systematic use of water in the every-day life of the gouty. I have observed that some gouty persons are very sparing in their use of diluents; such persons should be encouraged to be habitually more liberal in this respect. In a few cases it might even be possible to imitate with plain water the regular two or three weeks' course at the spa, and to repeat this course twice or thrice a year as a prophylactic measure.

I may observe that in scarcely any complaint is there more need of caution in judging the effects of remedies than in gout. The incidents of the gouty diathesis exhibit a waviness—a flux and reflux—which is highly characteristic. There is a natural tendency for the periods of aggravation to be followed by periods of amendment, and it requires a good deal of sobriety of mind to avoid being made the dupes of our own preconceptions.

I believe that the most promising road to an improved therapeutics of gout lies through a fuller and more accurate knowledge of the chemistry of uric acid and the urates, and a more penetrating study of the reactions of these compounds with the fluids and tissues of the body. This is a large and difficult field of inquiry, and demands the co-operation of many labourers. That is my apology for the fragmentary character of the present contribution. I shall, however, be quite satisfied if what I have done prove an incentive and a help to other workers in the same field.

MEDICAL MAGISTRATE.—Dr. John E. Jones, of Bryn-y Ffynon, Dolgelly, has, on the recommendation of W. R. M. Wynne, Esq., the Lord Lieutenant, been placed on the commission of the peace for the county of Merioneth.

⁸ See Peiper in *Virchow's Archiv.* 1889, and a paper by Rumpf in *Centralblatt f. klin. Med.*, 1891.