

obeyed in comparatively few instances, and yet the satisfactory progress of the cases was unimpaired. The patients, whenever possible, were detained in hospital until a complete result had been obtained, because the bulk of them, being illiterate and not ambitious to work more than was necessary, were apt to be content only with a degree of vision which would enable them to walk about readily alone. There were 40 operations on secondary capsules.

Two cases of detachment of the retina were operated on by posterior puncture with an entirely successful result.

With regard to tumours of the orbit, it was occasionally found difficult to obtain consent for their complete removal in those cases where the growth had not yet involved the globe; consequently they sometimes attained most unusual proportions before the necessary assent was expressed, and by then the operation was often no longer useful and sometimes was even impossible.

Harley-street, W.

THE PATHOGENY OF GOUT.¹

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IN this effort to elucidate one of the most obscure problems in medicine I begin by declaring that my position is that of the clinical investigator, and that much of my past study respecting gout has been directed to prove what are the exact manifestations of this malady as distinguished from other morbid states often confounded with it. As we shall find, the secret of its precise pathogeny has not yet been wrested from nature by the most skilful masters of chemistry or physiology, although some of our best conceptions of it have issued from these sources. The clinician has much to do in pursuing this inquiry.

In one of the best modern text-books on medicine, that of Professor Osler of Baltimore, it is declared that "the nature of gout is unknown." Is it too much to expect that after our deliberations to-day we shall be able to refute this opinion as well as that of M. Rendu who remarks: "Il est encore impossible de formuler une pathogénie définitive comme de donner une définition exacte et complète de la goutte"?

Without undue presumption I may venture to claim for my countrymen, and especially for the veteran Alfred Garrod, still enthusiastic in the pursuit of knowledge, a creditable share in the elucidation of this recondite subject. I may add that while my country has long been, and still is, a classical soil for gout, there is happily less of it in the acute form than there was a century ago.

In entering on a study of the question before us it appears to be the safest course to state the fundamental facts respecting gout upon which all observers are agreed. We recognise, therefore, in gouty persons a special diathetic habit or proclivity, more marked in some countries and races of men than in others—one which, like other diatheses, may be inherited and transmitted and may also gradually be acquired and modified. Next, we recognise a peculiar condition of the blood which is abnormal in respect of the presence of uric acid (urichæmia); and, lastly, we find in various localities of the body deposits of urate of soda. In any patient presenting truly gouty symptoms we expect to meet with at least the first and second of these conditions. In many cases, however, we can find no ante-mortem evidence of uratic deposit, nor, indeed, do we always find this post mortem. It is further certain that persons may be gouty in various degrees, presenting all varieties from the acute to the chronic forms, including the phases of irregular or incomplete gout.

The primary cause of gout doubtless lies in some constitutional defect of nutrition which permits the development sooner or later of its symptoms. With Noël Guenneau de Mussy I would say that this defect is the veritable disorder—"un trouble profond, primordial, qui a sa racine dans l'ensemble de la constitution et dans la race elle-même." It

is in this direction that we have to push our inquiry. The tissues and their intimate modes of nutrition differ in the gouty from those not similarly impressed.² What is the nature of this difference?

Many of the most thoughtful students of gout have long been impressed with the fact that gout as a morbid state is not expressed or fully explained by the mere aberrant relations of uric acid in the body. Urichæmia of one variety is certainly a factor in the case, but it is itself the result of an antecedent faulty nutritive metabolism ("le trouble primordial").

In recent years much labour has been expended in the effort to determine the site or sites of production of uric acid in the body but at the present moment the best physiological authorities are not agreed upon this matter. The true solution of this question in regard to gout is probably only to be found by a study of the metabolic processes in the human subject, inasmuch as the origin of uric acid may possibly differ in different animals, and it may conceivably own special and abnormal sources in the gouty subject. Herein lies one of the great difficulties of the problem. Time forbids me to enumerate the different views which are held regarding the sites of formation of uric acid. It will suffice to state that the latest researches point to the kidneys as the organs in which it is alone produced from a conjugation of urea and glycocine, and this view has the support of Garrod, Latham, and Luff, who also maintain that uric acid is never present in normal blood but is always excreted by the kidneys which produce it. Charcot and Murchison regarded the liver as the principal seat of uric acid formation, but the latest researches tend to show that in gouty conditions the liver does no more than supply by undue stimulation an excess of urea and glycocine as antecedents for conversion by the kidneys into uric acid. Garrod and Luff believe that the source of uric acid is the same in the gouty as in healthy persons, but regard the kidneys as inadequate in the former to excrete it. This inadequacy is probably one of the peculiarities of the tissues of the gouty individual. Ebstein presumes as part of the abnormality in these persons a wider field for uric acid production and believes that gouty subjects may form it in muscles and bone-marrow as well as in the kidneys. We wait for proof of these assertions from the eminent professor at this sitting. So far as we know, this renal inadequacy to excrete uric acid normally from time to time is not manifested by any alteration of tissue recognisable by the microscope. It is quite apart from any degree of interstitial nephritis which is apt to supervene in the later stages of gout.

Kolisch of Vienna will tell us to-day that some antecedents or allies of uric acid constitute the *materia peccans* of gout and that certain alloxur bases induce a form of renal degeneration which precedes the development of gout. I think, on the contrary, that the fact of urichæmia in gout is proved and I deny that any recognisable degree of renal degeneration exists in the majority of patients who suffer from regular gout, at all events in the early course of the disease.

So far, then, as gout depends on urichæmia we have to consider whether its manifestations are associated with (a) an over-production or (b) a diminished excretion of uric acid.

We know that over-production of this acid occurs in some other diseases without including any gouty symptoms, as, for example, in anæmia and leukæmia, and it has been proved that a diminished excretion of it is the rule in gout. Further, it is known that agents which diminish excretion of uric acid tend to induce gouty symptoms in predisposed persons. The latest researches indicate that consequent on renal inability to excrete the uric acid formed in those organs absorption of it into the blood takes place, with liability to gout. Other varieties of urichæmia appear to depend on the transformation of nuclein derived from leucocytes or on the production of uric acid in areas outside the kidneys, and these urichæmic states in no degree determine gout, renal function being adequate. I accept the teaching of Garrod, Roberts, and Luff respecting the condition of the blood in gouty urichæmia. Uric acid is present in the form of a soluble, but unstable, gelatinous quadriurate of sodium. This is non-toxic and gives no evidence of its presence in the system, but it is readily converted by sodium carbonate in the blood into the bi-urate which is a

¹ A paper read in the Section of Internal Pathology at the Thirteenth International Medical Congress, Paris, on August 6th, 1900. The conclusions were published in our issue of August 11th.

² Hence may we not affirm with Jaccoud, "Au fond, la goutte est toujours une maladie chronique"?

crystalline and noxious salt. The precipitation of insoluble bi-urate of sodium from the gelatinous quadriurate is apt to occur whenever the blood is surcharged with the latter, and this appears to be coincident with a specific gouty crisis and a localised attack. The crystals thus formed are irritating to any tissue in which they may be deposited.

The greater frequency of gout in persons who take little exercise and habitually consume strong food and liquors in excess of their physiological requirement is to be attributed partly, if not entirely, to the disordered hepatic metabolism thereby induced. Whether uric acid is formed in the liver and other tissues in persons of a gouty habit is, as we have seen, not yet determined. I am disposed to regard with favour the hypothesis of Ebstein that amongst the peculiarities of the gouty subject there may be a tendency to form uric acid in abnormal situations, and to agree further with him in the view that this peculiarity of tissue may be transmitted to the progeny in varying degree, sometimes, perhaps, in a latent condition, but yet capable of being roused into activity by habits of life provocative of gout.

We are here, however, in a region of conjecture, and the nearest point of certainty we can reach for the present is to regard this humoral part of the pathogeny of gout as dependent on a special mode of tissue metabolism inherent in the subject of it, implanted in varying degrees and capable of transmission. This view receives support from our knowledge of cases of what is termed "poor gout," in which we find that the disease is well marked although the patient leads the most prudent and abstemious life. The intimate metabolic fault is present and gouty developments occur without any direct provocation from without. The patient inherits the peculiar defect of his tissues, a degradation, as it were, from the normal condition, constituting, as suggested by Gull, a reversion to a lower animal type of metabolism, a peculiarity, possibly, as Sir William Roberts thought, of a vestigial nature. With Bouchard we may regard it as a "ralentissement diathésique de la nutrition." In the realm of pathology there are doubtless other tendencies and states which are developed and transmitted in like fashion.

The foregoing conceptions are supported by the doctrines applicable to other diathetic conditions. Up to this point, however, the theory laid down is founded on a basic tissue-defect, leading to a purely humoral pathogeny for gout.

This I regard as incomplete and inadequate to explain all the phenomena of gout. We have yet to discuss the relation of urichæmia to the different symptoms of the malady, and in particular the specific determination of urate of sodium to the joints, especially in the earlier stages and the classical form. In my opinion another element has to be considered which materially influences the character of the disease. This is the nervous element and to this we must now direct our attention. I am entirely in agreement with the doctrine of the Parisian school in respect of the arthritic diathesis.³ This was the original conception, I believe, of Féréol,⁴ adopted by Pidoux, G. de Mussy, Charcot, and others, and it is now accepted by some British authorities. The subjects of this basic habit of body are especially prone to suffer from rheumatic and gouty disorders. Under provocation, whether from the *materia peccans* of rheumatism or the urichæmia of gout, the specific manifestations of these states are mainly directed to the articular system. I take note at this point of nervous or neuro-trophic influence, and, encouraged by the analogy of other arthropathic conditions, venture to agree with those who predicate the existence of a nutrient centre for joints situated probably in the medulla oblongata. There are good reasons for the belief that derangement of this trophic centre induces marked changes in joints such as occur, for example, in rheumatoid arthritis or in locomotor ataxia. I believe, then, that the second factor in the pathogeny of gout is a disordered condition or neurosis of this centre whereby the manifestations of the urichæmia are specially determined to the articulations. I also believe that this peculiar neurosis influences the features of rheumatic fever, an infective disorder affecting persons of arthritic habit. In cases of ab-articular gout we have to deal with the chronic and irregular phases of the disease and are then in the presence of a gouty cachexia pervading the whole system. ("Totum corpus est podagra.") No careful clinical student of gout can fail to recognise the nervous element in the disorder. The onset of a paroxysm is often due to such influence. The condition of

urichæmia grows up, as it were, to saturation. A nerve storm is aroused by mental influences or arises either out of shock, depression, or excitement, and forthwith the crisis occurs and the attack is localised.⁵

Twenty years ago I ventured to submit the opinion that the peculiarities of the gouty habit were altogether the outcome of a central tropho-neurosis. My friend, the late Professor Ball of this school, in reviewing my theory reproached me with "seeking to localise at too limited a point the primordial lesions of a malady essentially general, one which is, and always will be, typical of one of the best diathetic conditions." I now confess that his criticism was just, and an extended study of the subject disposes me to limit the influence of the nervous system more particularly to the phenomena of paroxysms, metastases, and the determination of the sites of uratic deposit. I hold firmly to the idea that none of these occur casually or indiscriminately, but that local conditions of tissues are assigned, under neuro-trophic influences, for gouty manifestations. There must be some directing and determining force in the case. I cannot conceive of such a specific process occurring independently of nervous influence.

Let me remind you that this part of our inquiry is altogether outside the scope of experiment in chemical or physiological laboratories. The clinician has alone to find the key which will disclose this mystery.

I claim therefore for gout a dual pathogeny and speak of it as a neuro-humoral disease. This conception is not new. It was certainly adduced by Sydenham in the quaint terminology of the seventeenth century. Cullen of Edinburgh discarded the humoral side and exclusively developed the theory of the nervous origin of gout. By so doing he long prevented the study of the subject on profitable lines of inquiry. Garrod and the majority of modern investigators have, with rare skill and intuition, developed the humoral theory, and much, if not altogether, discarded the nervous element in the pathogeny of gout. For an adequate explanation of this malady we have to include both the hæmic and the neural elements which present themselves, and this was the doctrine of Laycock, taught 40 years ago in Edinburgh. Time forbids me to enter on multitudinous details of interest and importance in relation to the disease as a whole. I would add that we have to conceive of the gouty habit and tendency as originating and transmitted in varying degrees, as blended sometimes with, and modifying, other diathetic states. Yet it is always specific and ready to assert itself. Some persons are not, and cannot become, gouty, just as some are not, and cannot become, scrofulous.

I believe that the tendency to gout may be originated in persons not disposed to it by habits of life which are known to provoke it, together with excessive nervous exhaustion; and if these conditions fail to induce overt gout in certain individuals they may be potential to influence and modify the trophic processes in their progeny so as to induce gouty manifestations. Unless the descendants of such parents lead very different lives from those of their progenitors they are hardly likely to escape the worst effects of their inheritance, and even when such children lead lives of temperance and activity there may often appear in them the signs of irregular or incomplete gout.

Respecting uratic deposit as a permanent indication of past gout in any part I would express my belief that this is not always to be found. It is most likely to remain in non-vascular tissues, such as cartilage, but even from this and other textures I believe it may be removed in course of time, provided the patient ceases to suffer from repeated attacks. It is also certain that deposits may be formed in abundance without any painful paroxysms of gout. My experience further shows that paroxysms with a tendency to excessive deposits do not always have, as has been alleged, obviously damaged kidneys. There may be only slightly marked interstitial changes. The special features which entail incapacity and inadequacy in the tissues of the gouty subject are, as I have already stated in respect of the kidneys, incapable of detection by histological methods.⁶ We only recognise them by the symptoms they induce, and

³ I also accept the teaching of M. Bouchard respecting the different diatheses.

⁴ Some attribute this to Bazin.

⁵ "A slight excess of any kind, whether in diet or exercise, will excite the disease in those predisposed to it. When the train is laid an additional glass of claret may have acted as the match, but in all such cases the explosion would have equally taken place had instead of claret some other exciting cause fired it." (On Diet and Regimen, Dr. Paris. London: 1837.)

⁶ The same is the case in diabetes mellitus where no histological faults have as yet been discovered but in which a grave metabolic defect exists.

we know that the peculiar metabolism of such persons is morbidly sensitive to impregnation of the system by agents such as iron, lead, or alcohol.

To sum up my conceptions respecting the pathogeny of gout I will venture to affirm:—

That gout as a morbid condition depends on an inherent vice of nutrition, which is manifested by an imperfect metabolism in various organs or parts of the body, presumably in the kidneys and probably in the liver.

That this trophic disorder or inadequacy (“ralentissement de nutrition”) leads to the formation of uric acid, probably in excess, and to the periodic retention of it in the blood (gouty urichæmia).

That histology throws no light upon the intimate nature of this defect, which thus relates to cellular potentiality, possibly under neuro-trophic influence, and not, so far as we know, to structural alteration.

That this textural disability, or a tendency to it, may be primarily acquired and also transmitted as a fault, thereby inducing from time to time urichæmia with gouty manifestations in the descendants.

That in most instances, under conditions which provoke it, and in some cases independently of these, attacks of gout may grow up and come to a crisis. Such crises are attended by an alteration in the solubility of the uratic salt in the blood, whereby irritating crystals of biurate of sodium are produced and precipitated in various parts of the body.

That a paroxysm of gout, the sites of its occurrence, and its metastases are determined by nervous influences, probably dominated from a bulbar centre, and that the local attacks alight either in the joints or in textures which have been weakened or rendered vulnerable by impaired nutrition owing to past injury or over-use.

That this central neurosis is an essential and transmissible feature in the pathogeny of gout and pertains to the arthritic diathesis generally.

That the urichæmia of gout is peculiar and unlike that which is induced by other morbid conditions, but that the occurrence of urichæmia in the gouty is by itself inadequate to induce attacks of gout.

That uratic deposits in any part of the body may be removed in course of time but are apt to be permanent in the least vascular tissues.

That uratic deposits may occur to an enormous extent in gouty persons without the occurrence of any pain or paroxysms.

That the clinical features of gout indicate that both hæmic changes (due to inherent morbid tissue metabolism) and a neuro-trophic disturbance act as pathogenic factors, and that consequently gout is to be regarded as a neuro-humoral malady.

DIPHTHERIA IN THE HORSE.

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ON May 22nd, 1900, Dr. A. Mearns Fraser, the medical officer of health of Portsmouth, sent to this laboratory a culture of a bacillus which he had obtained from the nasal discharge of a pony and which had appeared to him to be identical with the bacillus of diphtheria. The history was as follows. A little girl having fallen ill of diphtheria Dr. Fraser, while seeking the source of the infection, found that a pony belonging to the child's father was ill with a purulent and slight sanguineous discharge from its nose. Subsequently the animal suffered from enlargement of the glands under the tongue and laryngeal obstruction, with difficulty of breathing and retraction of the abdominal wall, and a bacillus obtained from the nasal mucus having been pronounced morphologically indistinguishable from the diphtheria bacillus the animal was killed.

The bacillus which I isolated from the culture sent to me had the usual appearance and habit of growth of the bacillus diphtheriæ. It belonged to the short variety. It did not liquefy gelatin, it formed acid in media containing glucose, it clouded beef broth and subsequently cleared it, and, like many diphtheria bacilli freshly isolated from man, it formed only a scanty film on the surface. It was pathogenic to guinea-pigs, causing local hæmorrhagic œdema and

the general symptoms which are seen in these animals when they are inoculated with the bacillus diphtheriæ. It formed a powerful toxin, the filtrate from broth cultures causing a little œdema at the seat of inoculation, followed in about 10 days by falling out of the hair in the neighbourhood, widespread hæmorrhagic œdema and necrosis of the tissues immediately affected, or death, occurring sometimes within 24 hours, according to the quantity of poison injected. The effect of injecting large doses of living culture, or even 100 fatal doses of filtrate was completely neutralised by diphtheria antitoxin.

The following experiments were made.

TABLE I.—Living Broth Culture 24 Hours old.

Weight of guinea-pig in grammes.	Quantity of		Result.
	Culture in cubic centimetres.	Anti-toxin in cubic centimetres.	
290	0.1	0.0	œdematous swelling about the seat of inoculation. Death on the sixth day.
250	1.0	0.01 = 5.5 units.	Remained well.

TABLE II.—Filtrate of a Broth Culture Five Days old.

Weight of guinea-pig in grammes.	Quantity of		Result.
	Culture in cubic centimetres.	Anti-toxin in cubic centimetres.	
340	0.1	0	Small œdematous swelling. Recovered.
360	0.5	0	Small swelling following by loss of hair about the seat of inoculation. Recovered.
380	1.0	0	œdematous swelling. Necrosis. Recovered.
320	5.0	0.01 = 5.5 units	Remained well.

TABLE III.—Filtrate of a Broth Culture 11 Days old.

Weight of guinea-pig in grammes.	Quantity of		Result.
	Culture in cubic centimetres.	Anti-toxin in cubic centimetres.	
415	0.05	0	œdematous swelling. Death on the third day.
405	0.1	0	œdematous swelling. Death on the third day.
400	0.5	0	œdematous swelling. Death on the second day.
390	1.0	0	Death in 24 hours.
375	2.5	0	Death in 24 hours.
375	5.0	0.01 = 5.5 units.	Remained well.

It will be noticed that the filtrate which was used on June 6th was much less deadly than that which was used on June 26th. The reason, no doubt, is partly that that used on the last occasion was obtained from a culture which had been grown for 11 days, while that first used was obtained from one which had been grown for six days only. But there is also another reason: in the interval the culture had been daily re-sown on beef broth, and had thereby become accustomed to this medium and had come to form a denser pellicle on the surface of the liquid than before. Consequently it is probable that its power of producing toxin had considerably increased.

These experiments put it beyond doubt that the bacillus obtained by Dr. Fraser from the pony was a true diphtheria