RESEARCHES ON GOUT.

BY

WILLIAM BUDD, M.D.,

PHYSICIAN TO THE BRISTOL ROYAL INFIRMARY.

Received May 10th.—Read May 22d, 1855.

IN the month of October, 1852, an elderly man died in the Bristol Royal Infirmary who had long suffered severely from gout; and through the kindness of one of my colleagues, whose patient he was, I was enabled to obtain an examination of some of the diseased joints. The parts which came into my possession were taken from the knees and elbows. The cartilages covering the ends of the bones composing these joints presented fine specimens of the characteristic gouty deposit, and the bursæ which overlie the patella and olecranon, were also full of it.

Since then, I have obtained incrustated joints from seven other gouty subjects. In one case they were taken from the body of a man, and in another from that of a *woman* recently dead; in the five others from preparations in museums.

The series which has thus come into my hands has comprised specimens of diseased cartilage from the knees, elbows, wrists, ankles, and from nearly all the smaller joints of the hands and feet, besides several bursæ connected with these various structures.

All these specimens have been subjected to careful microscopic and other examination.

The results thus obtained constitute the first part of the

following researches. The second is devoted to the blood and some other fluids of persons suffering from acute gout.

The bursal deposits may be very briefly disposed of. The result of my examination of these may be best stated by saying that it almost entirely accords with that obtained by other observers. The great bulk of the foreign matter in all the specimens I have examined consisted of urate of soda, associated in various proportions with calcareous salts. The amount of the latter was sometimes considerable. Much more minute in quantity, but constantly present, were some organic compounds, which I pass by at present, but of which an account will be given in another page.

The diseased cartilage must be more minutely dealt with.

When a cartilage, which has become the seat of gouty deposit, is closely examined, it is at once perceived that the foreign matter is not laid down on the free surface of the cartilage, as one might have at first sight supposed, and as the descriptions of many writers would seem to imply, but is in the strictest sense interstitial.

The general distribution of the deposit in the diseased structure is in many points worthy of remark.

In well-marked specimens it extends over the greater part of the surface of the cartilage in a continuous layer.

Two very important circumstances are to be observed of this layer. The *first* is that *it penetrates to a comparatively small depth into the substance of the cartilage*—occupying, generally, not more than a fourth or a sixth of its thickness; the *second*, that, as a general rule, *it either stops short of the borders of the cartilage, or is more or less irregular in outline, or broken in continuity, as it approaches these*. One of the recent specimens exhibited a fact of still greater interest.

It is well known that, in the case of the larger cartilages (such as those of the knee-joint, for example,) immediately under the synovial membrane, and at the point where this membrane becomes attached to the border of the cartilage,

there is a rich network of blood-vessels. From this network a series of straight vessels arise which pass to a certain distance over the free surface of the cartilage, forming loops which often present considerable dilatations.

In the specimen referred to, whether from recent inflammation or some other cause, they were more developed than common, and being distended with blood were very conspicuous.

Now the fact to which I wish to draw attention is, that wherever these vessels extended the gouty matter was either very scanty or altogether absent. A margin of free cartilage surrounded them on all sides, so that the deposit seemed, so to speak, to recede before the blood-vessel.

Although these facts may seem, at first sight, to be of slight importance, there is reason to believe that they hold a relation of fundamental interest to the pathology of the disease before us.

If the superficial continuous layer just described be removed by a thin section, the substance of the cartilage beneath is seen to be speckled over by a number of minute dots of the same white material. In their form, size, and general appearance, these dots bear a certain resemblance to the minute nodules of *oolite*, which have earned for that geological formation the name it bears. Exactly similar dots are often more or less thickly sprinkled over the space which lies between the continuous layer and the borders of the cartilage. *Whether we pass, therefore, from the centre of the cartilage towards its border, or penetrate from its surface to the layers beneath, we meet with the same general fact; namely, a minor degree of impregnation by the foreign matter.*

When a series of sufficiently thin sections of cartilage thus affected are examined under the microscope many facts of remarkable interest are at once disclosed.

The first thing that strikes the attention is the beautifully crystalline character of the deposit. On further examination, however, the foreign matter is found to take two distinct forms. In some situations it is granular or

amorphous, in others, as already mentioned, perfectly crystalline.

Figures 1, 2, and 3, present good examples of these opposite types.

Figure 1 exhibits, in addition, a fact of some importance. The specimen from which the drawing was taken was obtained by a slightly oblique section, and the continuous curved outline represents the free surface of the cartilage. When examined by the naked eye, the gouty matter in this specimen looked exactly as if it were deposited *on* this free surface, and *externally* to it. But so far from this being the case it will be seen, by reference to the figure, that it was separated from the surface by an overlying lamina of considerable thickness. This lamina, which appears to be fibrous in its structure, and which, I presume, must be styled the perichondrium, was, in the greater part of its extent, entirely free from any impregnation by the foreign matter. I have observed the same fact in many other instances, and it is well shown in many of my mounted specimens.

Of the two forms of deposit the crystalline is by far the more general, and I need scarcely add that it far surpasses the amorphous in point of interest for the pathologist.

Although the crystalline groups of which it is made up exhibit some varieties, they may nearly all be referred to one leading type. Its form is that of a central opaque mass, from which radiate, in all directions, crystalline needles of great delicacy and beauty.

Figures 2, 3, 4, give a better idea of the character of these deposits than could be conveyed by any description. From an inspection of these figures it will be seen that the chief variation to be remarked in them has relation to size.

In regard to this point the range is wide. From the larger masses visible to the naked eye, there is an unbroken series of deposits, whose centre is a single microscopic granule of extreme minuteness.

Beside these leading types, there are now and then met with, crystals in grass-like tufts, and, in a few specimens,

others, which, in general appearance and mode of ramification, closely imitate some of the simpler *algæ*.

Foliaceous crystalline scales are numerous in some examples.

I have also met with a single crystal of the thorn-apple variety (Urate of Ammonia), and once with a group of well-defined rhombic prisms, radiating from a common centre.

Two questions have now to be considered regarding the peculiar matter which is deposited in these interesting forms in the living tissue.

1st. What is the chemical constitution of this matter? and 2d, What relation does it hold to the living elements in which it is imbedded?

The exact relation of the gouty matter to the structural elements of the cartilage is, for many reasons, difficult to make out. One principal difficulty arises out of the great opacity of the deposit. The result of this is that wherever the deposit occurs in mass, the elements of the tissue with which it is united are entirely hidden from view. Other circumstances might be mentioned, if need were, which tend still further to perplex the observer. In studying a sufficiently extended series of specimens, it gradually becomes evident, however, that a relation of some sort subsists between the deposit and the proper cartilage-corpuscle or cell: or, to be more explicit, that, (in many instances, at least,) the cartilage-cell is the focus of each individual deposit—the original centre, within and around which the crystallization occurs.

It would occupy much space to detail at length the evidence on which this statement is founded. It is gathered, partly, from the form, size, and grouping of individual deposits; partly from appearances disclosed by the help of reagents, and partly from the occurrence of groups of crystals in a very early stage, in which the relation between the cell and the crystalline matter is plain to the eye. The nature and value of the evidence to be drawn from the first and last of these three sources can only be fully appreciated by an examination of actual specimens.

It is important to add that this relation between the

foreign matter and the cell is far from being universal, and that even where it does exist it is transient only.

In the growth of each individual deposit it is evident, in fact, that the needles radiating from it soon come to radiate, not to this or that individual cell, *but to the whole central mass*. So that whatever dynamic relation (if any) may once have existed between the cell and the foreign matter, is soon superseded by the common physical influences in action around it.

The facts bearing on the chemical constitution of the deposit are simple and clear, and may be stated in few words.

By appropriate methods it may be readily ascertained that this deposit is almost entirely made up of a single substance—the *urate of soda*.

In one point, the deposit in cartilage offers a very great contrast to the deposits which occur in *bursæ*. In these last, as I have already remarked, there is always a considerable admixture of calcareous salts; or, to speak more precisely, of carbonate and phosphate of lime. In some specimens these substances even outweigh the urates with which they are associated.

In the cartilage, both these salts are almost entirely absent; the mere traces of them which do exist being altogether insignificant when compared with the urate of soda which constitutes the bulk of the foreign matter.

This fact is important because it not only entirely confirms the view that the calcareous salts are only incidental constituents of the deposit, but because it indicates, not obscurely, what is their real origin.

Their absence in the non-vascular cartilage, and their presence in the concretions of the comparatively vascular *bursæ*, point clearly enough—as Dr. Garrod had, on other grounds, already surmised—to inflammatory effusion as their real source. They are not related to gout as *gout*, but to gout as *inflammation*.

Certain other organic compounds which were mentioned as occurring in minute quantity in the bursal concretions are again met with in the incrustated cartilage.

For reasons which will appear in the sequel, what little I have to communicate respecting them will be best deferred to the latter part of this paper.

Reserving for some other occasion the inferences to which the preceding observations lead, as to the first origin and subsequent growth of this singular deposition of crystalline matter in the substance of a living tissue, I pass to the second series of researches; those which relate to the blood and other fluids of persons suffering from acute gout.

These researches were undertaken with a specific object.

There are many and conclusive grounds for believing that in attacks of acute gout, beside the gouty matter which is deposited in the cartilage and other structures in the forms already described, there is another portion which *disappears* in consequence of its reduction in the more vascular parts of the inflamed joint into more elementary compounds, by the agencies at work in the seat of the local paroxysm.

These grounds are partly pathological, partly chemical. To develop them fully would occupy much space. Of the pathological grounds it will be enough, at present, to say that they are founded chiefly on considerations which tend to show—1st. That the cartilage, although the principal, and, in many cases, the exclusive seat of the gouty *deposit*, is not the principal and still less the exclusive seat of the gouty *action*; and—2d. That, in many cases, at least, while the fit of gout is plainly, as far as the system is concerned, a depurative process, the amount of depuration effected in individual fits is not represented by the amount of gouty matter actually deposited on the joint.

The chemical grounds are based, principally, on the well-known and cardinal discovery by which Liebig and Wöhler showed that when uric acid, (the principal ingredient of the gouty matter,) is acted upon by peroxide of lead it is converted into urea and other compounds, and on the more recent researches by Frerichs and Wöhler, which render it probable that this substance undergoes a similar change, even in its passage through the living organism.

The view that in attacks of gouty inflammation the mor-

bid matter is disposed of in the twofold manner here indicated—partly, that is, by way of deposit, and partly by way of resolution into other compounds, by the oxidizing agency of the inflammatory act—is in striking conformity with all the leading facts in the morbid anatomy of the disease.

Among these may be mentioned, especially, the well-known preference of the gouty deposit for the non-vascular structures of joints; and, next to these, for all those structures in which, whether from organization or disease, the circulation of arterial blood is hindered or inactive.

Some of the principal facts detailed in the preceding pages appear to give a special sanction to the same view. I refer especially to those which relate to the distribution of the foreign matter within the cartilage itself. In all cases the bulk of the deposit occurs in the superficial layer of the cartilage, and in its central portions; that is to say in those points which are most removed from the sphere and influence of arterial blood, and of the inflammatory changes to which it ministers.

Of especial value in the same sense is the particular case spoken of in a former page, in which around every blood-vessel or group of blood-vessels which could be traced into the thickly incrustated cartilage, there existed a free marginal space in which no atom of deposit existed. The following inquiries were the direct offspring of these considerations.

Assuming it to be the fact that in acute gout a portion of the morbid matter is resolved into other compounds in the way here suggested, it seemed probable that under appropriate conditions we might be able to detect the products of its decomposition in the blood of the patient.

Whatever their result may be supposed to indicate, it was with the express object of determining this point that the following experiments were made.

Of the known products of the metamorphosis of uric acid, urea was the one sought for, as being, on many grounds, the most likely to lead to appreciable results.

The method followed for its detection was that in ordinary

use. An alcoholic extract obtained in the usual way from the blood or serum of the gouty patient was treated by nitric acid, and the result subjected to microscopic, and, where necessary, to other examination.

In every case but one the specimen to be examined was rendered slightly acid, prior to evaporation, by the addition of a small quantity of acetic acid, as recommended by Lehmann—a precaution which I believe to be absolutely necessary, in the majority of cases, to prevent the examination from being entirely nugatory.

In all cases the examination of the morbid product was begun within an hour of its removal from the body, and in most, it was completed without any pause in the necessary operations.

CASE I.—On the 5th of April, 1853, three ounces of serum were obtained by means of blisters applied to the knees of a man who was suffering at the time from acute gout in these and several other joints.

On adding a drop of nitric acid to a small portion of the alcoholic extract of this serum on a slip of glass, crystallization began at the moment and at the point of contact, and diffused itself with the diffusion of the acid until nearly the whole became a crystalline mass.

On examining the specimen under the microscope, the crystals composing it were found to consist chiefly of rhombic and hexagonal plates thickly grouped together, and a few obtuse octohedra. In form and general arrangement these crystals presented the well-known characteristics of nitrate of urea. On drying the specimen there were observed, on the borders of the field, and beyond the limits of the action of the acid, numerous rods of urea; some tapering and conical, others with bevelled ends, and all of quite characteristic forms.

The remainder of the alcoholic extract, on being treated with nitric acid, became immediately an almost solid mass.

The patient's urine was transparent, of pale amber colour, and of specific gravity 1.016. It contained no trace of

albumen; no casts of the uriniferous tubes; no mucus corpuscles or other evidence of renal obstruction, old or recent. The exact quantity passed in the twenty-four hours was not ascertained, but was estimated to be quite equal to the average.

It is worthy of mention, that in this case the morbid product exhaled, pending its evaporation, a strong *urinous* smell;—a phenomenon I have met with in other cases where the blood has been charged with similar ingredients.

CASE II.—One fluid ounce of blood obtained by leeches applied to the hand of a man who was suffering from gout in that and other parts, was treated in the same way as the serum in the last case, and with the same result. On the addition of nitric acid the alcoholic extract instantly became a solid mass of nitrate of urea.

Some serum procured two days afterwards, by means of a blister to the gouty hand, was also found to be largely impregnated with urea.

This man's urine was of a bright amber colour, transparent, and of specific gravity 1.023. It contained no trace of albumen, fibrinous casts, or other indications of renal disease, old or recent.

Since making these analyses I have met with nine other cases in which I have detected urea in the blood, or serum, or both, of persons suffering from acute gout, there being at the same time no albumen in the urine, or any other indication of renal disease or obstruction. The quantity of blood subjected to examination varied from three fluid ounces to six fluid drachms. The exact amount of urea obtained was not determined, but, in the smallest portion of blood examined it existed in quantity sufficient to admit of its ready identification by microscopic and other characters.

In seven of the nine cases, the specific gravity of the urine ranged from 1.022 to 1.024. The quantity secreted in the twenty-four hours being very nearly, if not quite, equal to the average. In all the local inflammation ran high, and

in the greater number several joints were at the same time severely affected.

I have now to add that uric acid and its derivatives are not the only compounds which are met with in abnormal amount in the blood and other parts in gout; but that, in some cases, at least, if not in all, these compounds are associated with another group.

In the month of October, 1853, I made an analysis of two fluid ounces of blood taken from a man—Coleman by name—who was at the time the subject of severe and acute gout.

After having satisfied myself of the presence of urea in it, the great bulk of the alcoholic extract was treated by nitric acid in excess. A copious precipitate of nitrate of urea at once occurred, followed by a gradual crystallization of slower growth, which took place on the surface and around the edges of the liquid.

On examining the product afterwards, under the microscope, there were found, beside the nitrate of urea, great numbers of prisms of a pale yellow colour, very regularly formed, and of considerable size and length.

Figure 5 gives a tolerably accurate representation of them.

Beside the forms there delineated, there were numerous groups of rhombic prisms ranged round a common centre in the form of rosettes. In these rosettes, which in general appearance strikingly reminded one of certain species of *echini*, there were usually one or two crystals greatly exceeding the others in length.

All these crystals dissolved readily in alcohol, as also, but more sparingly in boiling ether; sparingly in cold, but readily in hot water.

I may add, that I have met with a compound possessing the same general characters in several other specimens of blood from persons suffering under acute gout; although in none did it exist in so large a quantity as in the case now related. I have also extracted a precisely similar substance from several specimens of gouty cartilage, from which,

although its quantity is minute, it may be very readily obtained in a separate state.

Under the blowpipe this substance burns without residue, exhaling copious white fumes, and a strong odour of cumarin.

From these characters I presume it consists of hippuric acid. In confirmation of this opinion, I may state, that on heating the substance obtained from diseased cartilage over a spirit lamp, a sublimate was obtained which possessed the general characters of benzoic acid. It consisted of very minute needles, rapidly soluble in liquor ammoniæ, and also in ether, to which it communicated an acid reaction.

On comparing this sublimate, side by side, under the microscope, with a sublimate obtained from benzoic acid, itself, no difference could be observed between them.

Two other important observations were made in Coleman's case. The urine, on the day after his admission to hospital, was of a bright amber, transparent, of specific gravity 1.022, and of strong acid reaction. On being allowed to stand, it deposited a light cloud, which scarcely troubled the transparency of the liquid, and which closely resembled the cloud which attends the precipitation of oxalate of lime.

Examined under the microscope, this deposit was found to be made up of extremely minute, bugle-shaped crystals, in some places uniformly scattered over the field, in others closely aggregated into clustered groups. Along with these, there were, also, a few extremely minute octohedra, and a few very delicate rhombic plates.

All these crystals were readily soluble in hot alcohol and in ether. On being exposed to a gentle heat they sublimed without apparent change.

On examining, under the microscope, some mounted specimens of the crystalline mass, formed by the addition of nitric acid to the alcoholic extract of gouty blood-serum, myriads of minute bugle-shaped crystals were seen, so perfectly identical in form and mode of grouping with those which have just been described that it was impossible to resist the impression that they were the same compound.

These crystals, also, were soluble in alcohol, ether, and

boiling water ; and on being exposed to a gentle heat, they sublimed without apparent change. Exactly similar crystals, I may add, abound in many other specimens in my possession prepared from gouty blood-serum.

These properties point to benzoic acid—a compound whose presence is rendered readily intelligible by assuming that of hippuric acid in the same situations.

Whatever its nature, the same compound often makes its appearance in the urine, in certain phases of gout, as a single and distinct precipitate.

I have also obtained a substance possessing identically the same characters from gouty cartilage, where it may often be recognised by the microscope as a distinct element of the gouty deposit.

Although these observations are as yet very incomplete, they render it probable that hippuric acid is a frequent, if not an essential ingredient of the gouty matter. They seem to show, also, that the proportion in which this compound exists is subject to wide variation.

Fig. 3.

Urate of Soda in Cartilage. Deposit in an early stage.
From specimen mounted in Canada Balsam.

Fig. 4.

Cartilage with Gouty Deposit. Vertical Section.
specimen mounted in Canada Balsam. Deposit crystalline.

Fig 2

Urate of Soda in Cartilage.

Fig 1

Oblique section of cartilage containing Gouty Deposit.
Deposit amorphous.

Crystals formed on the addition of Nitric Acid to the Alcoholic Extract of the blood of a man suffering from Acute Gout; Supposed to be Hippuric Acid.