ALLOXURIC EXCRETION IN A CASE OF LEUCOPENIA.

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INTRODUCTORY.

It is now nearly half a century since it was first pointed out by H. Ranke[1] that the excretion of uric acid is increased in certain cases of leucocythæmia. Since then nearly fifty independent workers have repeated the investigations, and with few exceptions have corroborated Ranke's observation. Amongst those who obtained a contrary result may be mentioned Mosler[2] and Jacubasch,[3] but it must be remarked that in the cases investigated by these observers other factors presented themselves which might be held accountable for the absence of increase. Thus in Mosler's case there was very marked debility with a correspondingly low nitrogen excretion, whilst in Jacubasch's patient the existence of œdema and diarrhœa may account for the exceptional result.

In most of these observations, however, the method employed to estimate the uric acid was that of Heintz, which has since been shown to be far from correct. Since the introduction of the more exact methods of Hopkins, Salkowski and Ludwig the number of cases examined has not been great, and of these only a few are suitable for comparison with the physiological excretion, the composition of the diet having been left out of account in the majority of cases.

[1] Beobachtungen und Versuche über die Ausscheidung der Harnsäure beim Menschen. München, 1858.

[2] Virchow's *Archiv*, 1866, xxxvii, p. 45.

[3] Virchow's *Archiv*, 1868, xliii, p. 217.

Where both these sources of inaccuracy have been eliminated, the general result of the investigations has been to show that an increase in the number of leucocytes does not necessarily go hand in hand with a rise of endogenous alloxuric bodies in the urine, but that only in cases of spleno-medullary leucocythæmia is a distinct increase present.[4] On the other hand, the lymphatic form of the disease seems to show no increase, whilst leucocytoses, whether physiological[5] or produced by the administration of drugs,[6] are devoid of any constant effect. It would therefore seem that Horbaczewski's theory, which connects an increase of alloxur bodies with a corresponding leucocytosis, does not hold good for all forms of leucocytic increase.[7]

Investigations to decide the question of a parallelism between the number of leucocytes and the alloxuric excretion have usually been carried out on cases of leucocythæmia, whereas very few observations have been recorded in cases in which the number of leucocytes was diminished.

In the following case, where a distinct leucopenia was present, we estimated the amount of alloxuric nitrogen excreted in the urine each day during two periods of eight days each. In doing this consideration was taken of the valuable work of Burian and Schur,[8] who pointed out that, before any estimate could be formed of the amount of the bodies excreted, a careful regulation of the diet was necessary in order to be certain that endogenous purins only were excreted, for it is in them that any increase or decrease is of importance, since they alone arise from the metabolic processes in the tissues.

CLINICAL HISTORY.

Mrs. B., aged 37, a widow, was admitted to the London Hospital in the beginning of June, 1900, complaining of "general weakness." Her ill-

[4] Milroy and Malcolm, *Journal of Physiology*, 1898, xxiii, p. 235, and 1899, xxv, p. 109.

[5] Sivén, *Skandinav. Arch. f. Physiologie*, 1900, xi, p. 123, and Kühnau and Weiss, *Zeitschr. f. klin. Med.*, 1897, xxxii, p. 482.

[6] von Noorden and Zuntz, DuBois-Reymond's *Archiv*, *Physiol. Abth.*, 1894, p. 203.

[7] For details see Schreiber, Ueber die Harnsäure unter physiol. u. pathol. Bedingungen. Stuttgart, 1899.

[8] *Arch. f. d. gesammte Physiologie*, 1900, lxxx, p. 241.

ness had begun about twelve months before admission immediately after she left Gibraltar, where she had been living for about a year. Previous to this she had always enjoyed good health. There was no evidence of her having suffered from either syphilis or malaria. She was a poorly nourished, fair woman (weight 7 stones), pale and of somewhat yellowish complexion.

There was no jaundice, cyanosis nor dropsy. There were a few purpuric spots round the ankles, but no other evidence of hæmorrhage either in the skin or retina.

The spleen was enormously enlarged, extending down beyond the umbilicus into the right iliac fossa. The edge was rounded; the surface somewhat irregular and slightly tender. The liver was also enlarged, the lower border being three inches below the costal margin in the mammary line. Its surface was smooth and firm. There was no glandular enlargement and no ascites. No abnormality was detected in the thoracic organs, nervous system or urine.

The blood contained 4½ million red corpuscles, 65 per cent of hæmoglobin, and 1500 to 3000 white corpuscles. The lymphocytes and polynuclears were practically equal in number. No eosinophiles and no abnormal elements were seen in several stained films.

The temperature during her stay in the hospital was persistently irregular, usually running up to 103° F. or 104° F. in the evening. The pyrexia exhibited a tendency to occur in periods of 10 or 12 days, separated by 2 or 3 days of almost normal temperature. She had occasional bleedings from the nose and a tendency to diarrhœa, but ate well and maintained the same weight throughout.

At first the case was regarded as one of splenic anæmia and was treated on that assumption without improvement. The fact, however, that her illness had begun shortly after leaving Gibraltar aroused the suspicion that she might be suffering from Malta fever. The reaction of her serum to Micrococcus melitensis (Bruce) was accordingly tested by Dr. Bulloch. The serum was found to agglutinate the cocci in the proportion of one part of serum to 30 of culture, and in accordance with this the conclusion was arrived at that the case was one of Malta fever. The patient remained in hospital until the end of 1900 without exhibiting any marked change in her condition, though the leucocytes had increased to about 3000 per cubic millimetre under treatment with nuclein. From a clinical

point of view the case was remarkable as exhibiting an absence of the joint pains usually present in Malta fever and the presence of a much greater degree of splenic enlargement and of leucopenia than are usually found in that disease.

METHODS.

During both periods the patient was confined to bed, and was kept on a diet consisting of eggs, milk, bread and farinaceous foods, but containing no flesh nor other purin-yielding ingredients. The exact amount of food consumed was ascertained, and the urine was collected for each day. The fæces were neglected, since no appreciable amount of purins is lost with them.

The total nitrogen was estimated by Kjeldahl's method, and the nitrogen of the total alloxuric bodies by that of Camerer. Parallel estimations were made in each sample during the second, and in most of those of the first period.

RESULTS.

TABLE I.—1st Period.

Date.	N. of Food*.	Urine Amount.	Total N.	Alloxuric N.
July 2	16 grm.	812 cc.	9.630 grm.	0.1867 grm.
3	14	1315	6.996	0.1330
4	14.5	1475	8.152	0.1652
5	17	1350	11.1321	0.2295
7	16	1965	10.779	0.1224
8	16	1750	11.2000	0.1224
9	15	1940	14.550	0.2211
10	15	1965	12.3402	0.1670

* Calculated from König's tables.

During this experiment the patient received approximately about 15 grammes of nitrogen in the diet, but this amount varied somewhat and was accompanied by corresponding swings in the urinary nitrogen. It would seem as if a considerable nitrogen retention was taking place in the tissues, but the patient had several attacks of diarrhœa during the investigation, whereby some nitrogen may have been lost. The total alloxuric nitrogen averaged about .17 grm. in the 24 hours, but was on two occasions as high as .22 grm., and on another as low as .122 grm. Such variations in the endogenous alloxuric excretion have been denied by Burian and Schur to exist physiologically, but, as these observers point out, they may occur in disease. During the

period of examination, also, it is probable that, on several occasions, a certain amount of urine was lost with the fæces. The average, however—namely, .17 grm.—falls within the limits of the physiological excretion, this varying between .122 grm. and .20 grm.

TABLE II.—2D PERIOD.

Date.	N. of food.	Urine Amount.	Total N.	Alloxuric N.	Leucocytes.	S. P*.
Sept. 4	17.2 grm.	1140 cc.	13.23 grm.	0.2042 grm.	2184	1 : 1
5	18	1695	15.36	0.2084		
6	18	1560	12.036	0.2085	1560	3 : 2
7	18	1465	10.814	0.1871	....	
8	17.5	1205	10.567	.....	1872	2 : 3
9	18.5	1365	12.558	0.2064	3000	5 : 4
10	19	1100	13.530	0.2002		1 : 1
11	19	1570	14.750	0.2103		11 : 10

*S. signifies simple nucleated leucocytes; P. signifies polymorphonuclear leucocytes.

The investigation recorded in Table II was carried out about two months after the previous one, and during it the patient's general condition was much better, there being no diarrhœa. The urine was collected with greater care, and only on one occasion (namely, on Sept. 8) was there any admixture with fæces.

The diet was free from alloxur bodies and contained rather more nitrogen than on the previous occasion. The total alloxuric nitrogen showed only slight variations, its average being 0.20 gr. in the 24 hours. This is considerably more than during the previous period, which may be accounted for by the improved condition of the patient and the more careful investigation of the case. It still falls within the normal for alloxuric nitrogen however, although at the highest limit of this.

CONSIDERATION OF RESULTS.

The average number of leucocytes per cubic millimetre during the two periods was 2500, sometimes reaching as high as 3000 or falling to 1800. Regarding their nature, the most important point is the relative increase of lymphocytes, or, more correctly stated, the decrease in the total leucocytes affected the polymorphonuclear cells to a greater extent than the lymphocytes. This great diminution in the granular cells might conceivably be due to one of two causes:

1. To an increased destruction, the production remaining normal.

2. To a diminished production, the rate of destruction remaining normal.

If the former of these conditions were present, the amount of disintegration products of the leucocytes excreted by the urine—*i. e.*, of alloxuric bodies and of phosphorus—would be increased. If the latter obtains a diminution in these would be expected. In the case before us, however, the excretion falls within the normal, though at the highest limit of this; and if one considers that the patient weighed only 45 kg., and had probably a low endogenous factor, then it may be assumed that a slight increase was present, and therefore that the leucopenia was occasioned by active destruction of the polynuclears in the enlarged spleen, and that the red bone-marrow had not been able to make good the loss. It would seem as if in this regard the only difference between this case and one of spleno-medullary leucocythæmia was the bone-marrow activity. In leucocythæmia this organ is more active than normal, thus making good the increased destruction by the spleen and even overcompensating it, whereas in leucopenia it has not compensated for the splenic destruction.[9]

Another clue to the amount of leucolysis occurring in the body is, as Milroy and Malcolm [10] have pointed out, the amount of phosphorus excreted. In ascertaining this, however, the ingested phosphorus must be very carefully estimated, which fact introduces serious difficulties when we come to apply the method to patients. On four days following the second period we estimated the total phosphorus excreted with the following results:

TABLE III.

Date.	Urine Amount.	Total P_2O_5*.
Sept. 18	1100 cc.	2.266 grm.
19	1570	2.386
20	1220	2.170
21	1300	2.418

* Estimated by titration with uranium nitrate solution, using tincture of cochineal as indicator.

[9] In this connection, however, it should be pointed out that it is conceivable that both formative and destructive organs may act on a high or on a low level. In the former case the number of leucocytes might remain constant, but their life history be of short duration, and the alloxuric excretion consequently increased, whereas, in the latter case, where both organs were depressed in activity, and the life history of the leucocytes of long duration, a normal number of leucocytes would be accompanied by a diminished alloxuric excretion.

[10] *Journal of Physiology*, 1898, xxiii, p. 217, and ibid., 1899, xxv, p. 105.

The diet was similar to that during the previous examinations, and was of exactly the same amount each day, containing probably a little less phosphorus than an ordinary mixed diet. From this it would appear that, if anything, the excretion of phosphorus was slightly increased, pointing to an increased leucolysis.

A consideration of these different points renders it probable that the leucopenia in this case was due to an inability on the part of the red bone-marrow to make good an increased leucolysis in the spleen. The entire absence of any myelocytes or other abnormal blood-cells would seem to support this opinion.

SUMMARY.

1. In the case investigated, one of Malta fever, the leucocytes were reduced to between 1500 and 3000 per cubic millimetre.

2. Notwithstanding this, the alloxur bodies and the phosphoric acid in the urine, the patient being on an alloxur-free diet, showed no distinct diminution from the normal.

3. The suggestion is made that this result may be due to the leucopenia being brought about by an increased destruction of leucocytes in the spleen rather than to a diminished activity of the bone-marrow.