THE INFLUENCE OF X-RAYS ON THE NITROGENOUS METABOLISM AND ON THE BLOOD IN MYELOGENOUS LEUKAEMIA

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During the past two years the medical literature has contained many articles shewing the value of X-Ray therapy in the disease myelogenous leukaemia.

In November, 1905, Sir James Barr asked me to determine the nitrogenous excretion in such cases, and an investigation was made of the nitrogenous metabolism in a case then admitted.

The methods adopted were those originally introduced by Professor Vaughan Harley for the investigation of metabolic changes, and which I have had repeated opportunities of carrying out in his laboratories.

In brief, the observations were carried out thus :—After several days trial diets, the patient was put on a diet containing 25 grams of nitrogen per diem. Each day the diet was accurately weighed and measured by the nurses at the Royal Infirmary, for which trouble and the care they expended my thanks are due to them. At the commencement of the first day of the observation the patient took one drachm of charcoal. From this time the urine was accurately gathered for each day and the first faeces blackened by charcoal shewed the food taken at the commencement of the observation. Similarly at the end of the last day of the observation another one drachm of charcoal was given and the faeces then blackened shewed the food taken after the period of observation, and so were rejected, the faeces in the interim being weighed and estimated.

This method gives also the motor time of the intestine, and as the bowels in this case were opened twenty-four hours after the

charcoal was given, and each day at the same time it was justifiable to presume that the faeces contained the unused nitrogen of the previous day's food.

The total nitrogen in the faeces and urine was estimated by Kjeldhal's method, and the uric acid by the Folin-Hopkin's method. Blood films were examined each day and a leucocyte count made on alternate days.

The investigation was divided into two parts :—

- (1) To show the average nitrogenous excretion of the patient.
- (2) To show the effect of daily exposures to the X-Rays.

The first series of observations shewed the average intake of nitrogen over a period of five days to be 25·67 grams—the average excretion of nitrogen in the urine was 11·39 grams. The nitrogen in the faeces was not determined during these first observations. The average excretion of uric acid was ·4738 grams per diem, thus being within the normal limits. A normal excretion of uric acid was also recorded in two other cases in the Royal Infirmary—one under the care of Sir James Barr, and another under the care of Dr. Abram. This is interesting to note in connection with the statement found in the Text Books of Medicine that the excretion of uric acid in this disease is always increased.

In the second series of observations, during the period of treatment by X-Rays, the following results were obtained .—

	Nitrogenous Intake	Nitrogen in Urine	Nitrogen in Faeces	Total Nitrogen output
1st day	24·27	14·27	3·6	17·87
X-Ray treatment began on second day.				
2nd „	20·24	16·6	2·34	18·94
3rd „	21·13	19·18	1·6	20·78
4th „	13·28	13·25	1·67	14·92
5th „	16·01	16·98	·89	17·87
6th „	18·20	15·69	1·32	17·01

During the first series of observations the patient's weight remained constant. During the second series of observations the patient lost $1\frac{1}{4}$ lbs. in weight.

At 10 a.m. on the second day of the second series of observations an exposure to the X-Rays was given, lasting ten minutes ; the day, as far as the estimations were concerned, commencing at 6 a.m., so that for twenty hours of that day the metabolism was carried on under the influence of the exposure. Dr. Thurstan Holland (Radio-grapher to the Royal Infirmary) arranged that the exposures which were to be given on each successive day should be given under exactly the same conditions.

The table shows that the first day the nitrogenous intake exceeded the output by 6·4 grams. On the second (after the first exposure) the balance in this direction was only 1·30 grams, and on the third day it was reduced to 0·45 grams. On the fourth day the patient vomited his breakfast immediately after taking it, and when I saw him he was in bed feeling very ill, so it was considered inadvisable to take him to the X-Ray room, or to disturb him by taking blood films, or by making a leucocyte count. His nitrogen intake on this day (allowing for his vomiting his breakfast) was only 13·28 grams, whereas the output in his urine and faeces amounted to 14·92 grams, and the nitrogen balance had, therefore, gone to the other side, making a deficit of 1·64 grams which, therefore, had to come from his tissue proteids to make up the amount excreted. Similarly, on the fifth day, a deficit of 1·84 grams of nitrogen was noted. On the sixth day an attempt to return to the former condition before the treatment with X-Rays was noted, the nitrogenous intake again exceeding the output by 1·19 grams.

The uric acid excreted on each of the above days was as follows :—

1st day	2nd day	3rd day	4th day	5th day	6th day
·5100 grams	·6682 grams	·5610 grams	·9391 grams	1·022 grams	·9513 grams

showing a definite and well-marked increase ; which is especially well marked on the last three days.

It will thus be seen that the action of the X-Rays was to produce a marked increase in the nitrogenous excretion in the urine, and that on two days of the observation proteids were being utilized from the tissues.

The leucocyte counts on the second and fifth days of the first series of observations were 130,000 per *c.m.m.* and 140,000 per *c.m.m.* respectively.

On the first day of the second series of observations 100,000 per *c.m.m.*¹

On the day following his illness, viz., the fifth day of the second series, a count of 250,000 per *c.m.m.* was recorded, which surprising result caused me to do three successive counts, each with the same result.

On the last day the count recorded 135,000 per *c.m.m.*

This marked increase in the number of leucocytes occurring as it did with increase of nitrogenous excretion and of uric acid, led me to conclude that the synchronous constitutional disturbance had some relation to these changes.

I found on examining the records of other cases similarly treated in the Royal Infirmary that such an increase in the leucocytes within a few days of the commencement of exposure to X-Rays was quite a common event. Out of seven cases of which I have the full records it is noted on five occasions—all within eight days of the first exposure. Ambertin and Beanjard² have reported a rise after each sitting, the maximum rise being at the end of the first day; in two cases recently reported by Bruce,³ a similar variation was found in one case, in the other no count was recorded until twenty days after the commencement of the exposures.

The effect of X-Ray treatment on the temperature of these cases is difficult to determine owing to the complex variations usually found in the disease, but in some instances I find records of rises in temperature synchronous with the X-Ray exposures as in the case of the patient upon whom these observations were made.

When he first had X-Ray treatment in October, 1904, the evening temperatures for the first six days were

99·2° F., 99·6° F., 100° F., 100·2° F., 100·4° F., 100·6° F.
respectively.

1. The second series of observations commenced one day after the end of the first.

2. *La Presse Médicale*, Aug. 20, 1904, p. 533.

3. *Lancet*, Jan. 27, 1906, p. 211.

Then the temperature fell nearly to normal and remained so with occasional exacerbations until July, 1905, during which time he had been having X-Rays intermittently. In July, 1905, he had a severe illness with high temperatures reaching at times 103° F. Sir James Barr then diagnosed his condition as one of 'X Ray fever.' Two other patients in the infirmary have had similar illnesses.

Senn,¹ the originator of this treatment states that he had to suspend the exposures owing to patients having symptoms of intoxication accompanied by high temperatures.

Bryant and Crane² report that in their case after a few days exposure there was a severe constitutional reaction.

The blood films examined each day showed the following changes observed by Dr. R. J. M. Buchanan, which are here described by his permission :

'The films spread badly after exposure to X Rays, and a marked leucolysis is present. The nuclei of the cells are in many instances fragmented, and in others diffuent. The eosinophile myelocyte shews diffuence of granulation. The cells appear as "phantoms" and the so-called spread cells are increased in number.'

In addition to these changes I observed that before the action of X-Rays the leucocyte granules took in a basic stain—Methylene Blue—particularly well, but with the successive exposures this reaction became less and less marked. Dr. Buchanan kindly examined my films, stained others himself, and confirmed the observation. As the basic stain combines with granules of an acidific character the observation shows that the granules become less and less acid during the treatment, a fact interesting to observe in connection with the notable increase of uric acid in the urine.

The observations, I venture to think, show that the exposure to X-Rays of patients suffering from myelogenous leukaemia produces a disintegration of proteid material in the leucocytes, the products formed giving rise—in some cases at least—to grave constitutional disturbance.

1. *Medical Record*, August 22, 1903.

2. *Medical Record*, April 9, 1904.

That uric acid is the only body produced it is idle to suppose, but the uric acid increase may be taken as an indication of the amount of disintegration going on. Therefore, when X-Ray therapy is being used in this disease it may be suggested that it is advisable to allow the patient sufficient time between each exposure to excrete the toxic products formed, and as indication of this time daily estimation of the uric acid excreted would be of value, and give the physician a guide as to the safe dose of X-Rays to be used.

Gramegua and Quodrone report that exposure of normal rabbits to the X-Rays produced changes in the leucocytes and an increased (though not regular) excretion of uric acid and phosphates. It is, therefore, possible that patients undergoing X-Ray therapy for any reason have these changes produced, and if so the above conclusions might possibly lead to a more rational use of X-Rays as far as their therapeutic dose is concerned.

I have to thank Sir James Barr for providing me with the apparatus for the above research, and also for his kindness and help during its conduction. I have also to thank Dr. Bradshaw and Dr. Abram for the use of the records of their cases in the infirmary.