

MORPHOLOGICAL EXAMINATION OF THE BLOOD AND STERNAL MARROW OF NINE PATIENTS TREATED WITH THIOURACIL

By CARL J. GESSLER, M.D.

BECAUSE of the current interest in agranulocytosis following thiouracil administration it was determined to study the blood and bone marrow in a series of 9 patients under treatment with this drug for hyperthyroidism.

It is of interest that before treatment was instituted the total leukocyte count in 4 of the 9 cases was less than 4,000 per cu. mm., with a correspondingly low value of the absolute number of neutrophils (table 1). Two cases had hemoglobin values under 70 per cent, with a color index of less than 1.

EFFECTS OF THIOURACIL ON THE BLOOD

In 2 of the 9 cases treated with thiouracil the leukocyte count dropped below 3,000 per cu. mm. This does not mean that in our experience leukopenia developed in about 20 per cent of the cases, because actually a larger group of patients was treated with the drug and the only 2 cases which developed leukopenia are included in the smaller group of 9 patients whose bone marrow was examined. In a third case (no. 2) administration of thiouracil was discontinued because of the development of a severe urticaria; the absolute number of neutrophils fell from 2585 per cu. mm. at the time treatment was stopped to 1584 18 days later.

In 2 other cases (nos. 1, 9) "toxic" neutrophils were seen in the last blood smear, after fairly large amounts of the drug had been given. In case no. 1, 2 of 61 neutrophils showed a bluish cytoplasm, vacuoles, and coarse granules; in case 9 the only toxic change was a slightly coarse granulation of many neutrophils.

In case 2 a blood examination made 3 days before the onset of severe urticaria showed an increase of the eosinophils to 8 per cent. Such an increase might be considered as an indication that some form of allergic reaction was becoming manifest.

The slight hypochromic anemia in 2 of the cases mentioned above improved in both cases during the administration of thiouracil without any additional anti-anemic therapy.

EXAMINATION OF THE STERNAL MARROW AFTER ADMINISTRATION OF THIOURACIL

Puncture was readily performed in all cases except no. 6, a 39 year old acromegalic woman with hyperthyroidism (BMR + 48), which was probably of pituitary origin. The differential cell count was made according to the technic of Rohr.* By this method one does not simply count 500 nucleated cells but enough to obtain 500 cells of the granulocytic and lymphocytic series; the result is expressed in a percentage which permits a more exact comparison between the myelogram and the hemogram.

From the hospitals of Brussels, Belgium.

* Karl Rohr: Das Menschliche Knochenmark, Leipzig, 1940.

TABLE 1

Case no.	Before Thiouracil			Total amount of thiouracil given (grams)	After Thiouracil		
	Leuko-cytes	Neutrophils			Leuko-cytes	Neutrophils	
		%	Absol. number			%	Absol. number
1	7,600	32	2,432	32.6 in 66 days	7,100	61	4,331
2	3,100	61	1,891	16.4 in 17 days	4,700	55	2,585 (on 30—X)
					3,600	44	1,584 (on 17—XI)
3	8,500	62	5,270	34.3 in 56 days	8,100	79	6,399
4	3,900	60	2,340	36.4 in 68 days	4,800	53	2,544
5	3,900	35	1,365	47.4 in 76 days	2,500	35	875
6	6,700	63	4,221	42.6 in 56 days	3,800	66	2,508
7	3,500	40	1,400	31 in 31 days	2,500	49	1,225
8	4,800	59	2,832	26.1 in 50 days	5,600	63	3,528
9	7,100	57	4,047	61 in 99 days	8,300	64	5,312

TABLE 2.—Myelograms

Case no.....		1	2	3	4	5	6	7	8	9
Reticulum cells	macrophages	0	0	0	0	0	0	0.6	0	0
	plasmacytic	1.6	3	3	1.2	2.8	0.6	2.6	0	2.2
	lymphoid	0.4	5.2	3.4	0.8	0	0	1.8	2	0.8
Erythro-poiesis	Proerythroblasts	0.2	0.6	0.4	0.2	0.4	0.4	1.2	0	0.4
	Macroblasts									
	basophilic	2.6	2.2	1.6	1	0.8	0.6	1.6	1	2.4
	polychromatophilic	3.8	2.4	7.8	0.4	4.4	1.6	2.2	7	1.2
	Normoblasts									
	basophilic	1.2	1	1.4	2.4	1	0.8	1.4	0.7	0
Leuko- and lympho-poiesis	polychromatophilic	20.8	33.4	21.8	16.6	22.6	18.8	35	21.3	24.8
	orthochromatic	0	1.4	1	0.4	0.2	0.4	1.2	3.3	1.2
	Myeloblasts	0	2	0	2.2	0.6	0.8	3.2	1.7	0.8
	Premyelocytes	6.2	5.8	3.2	5	9	3.2	11.8	4.4	4.8
	Myelocytes									
	immature	11.8	10.8	9.4	12.4	16	10.6	13	7	11.8
	mature	16.2	6.8	14.8	10.8	5.4	14.2	6	6	7.6
	Metamyelocytes	9.4	6.4	12	6.6	7.8	18.8	4.4	7.7	7.2
	Neutrophils									
	nonfilament	27	40.2	27.6	37.2	41.6	39	36	38.3	35
filamented	16.8	9.2	24.6	10.4	8.8	8.8	8.4	18.3	18.4	
Eosinophil myelocytes	3	5.2	2.6	0	3.6	0	3	4.6	3.4	
Eosinophils	1.4	3	2.2	0	2.4	0.2	3.4	3	2.4	
Basophils	0.4	0.4	0.8	0	0	0.4	0	0	0	
Monocytes	0.2	0.4	0.8	1	0.2	0	0.2	0.6	1	
Lymphocytes	7.6	9.8	2	14.4	4.6	4	10.6	8.4	7.6	
Granulocyte-erythroblast ratio		3.2	2.2	2.9	4	3.2	4.2	2.1	2.7	3

The results of our study are given in table 2. In discussing these results, we shall consider the sum of the premyelocytes and immature myelocytes as a unit. In this group are included those cell forms between the myeloblast and mature myelocyte and on whose definition everyone is pretty well agreed. Most striking is the fact that the percentage of premyelocytes + immature myelocytes was found to be markedly increased in the 2 cases (nos. 5, 7) which had developed a leukopenia, as illustrated in the figure. These changes (decrease of the leukocytes and neutrophils in the blood with an increase of the premyelocytes and immature myelocytes in the marrow) are similar to, although less marked than, those seen in many cases of agranulocytosis (disappearance of the neutrophils from the blood and complete predominance of the premyelocytes in the marrow).

Besides the numerical changes there were also some morphological alterations in these 2 cases. In case 7 some of the premyelocytes were abnormally large; many of them had an irregularly shaped nucleus; the same irregularity was noted in a few myeloblasts.

In case 5 some of the premyelocytes had an irregularly shaped nucleus. In both cases one very large premyelocyte was seen with typical blue cytoplasm but a

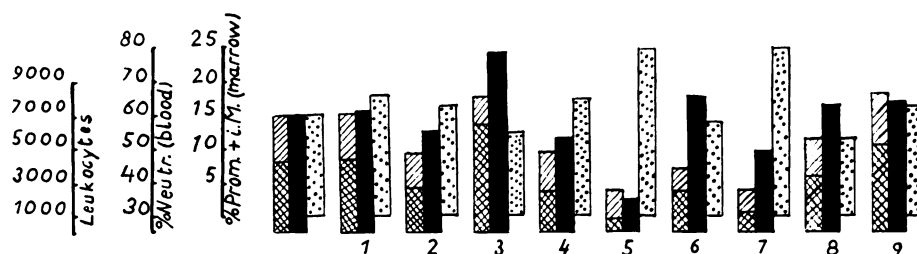


FIG. 1. BLOOD AND BONE MARROW FINDINGS—NORMAL AND THIOURACIL-TREATED CASES

Each group of three columns represents the findings in 1 patient (nos. 1-9), except the first one, which gives the average normal values. *First column*: total leukocyte count (hatched) and absolute number of neutrophils (criss-crossed). *Second column* (solid black): percentage of neutrophils in the blood. *Third column* (dotted): percentage of premyelocytes + immature myelocytes in the sternal marrow (here we have purposely given, in the first group, the *maximum* normal value, so that all values in excess must be considered abnormal). Note the striking contrast in cases 5 and 7 between the low values of the total leukocyte count and of the number of neutrophils and the increased number of premyelocytes and immature myelocytes.

large nucleus which had the shape of a curved rod and a fairly young structure; such cells are the result of an abnormal maturation with marked discrepancy between the aspect of the cytoplasm and nucleus. In case 2, which later developed a slight neutropenia, a few premyelocytes with irregular nucleus were also seen.

In the 2 patients who exhibited slight toxic changes of the neutrophils in the blood smear, examination of the bone marrow showed: (1) in case no. 1, 1 metamyelocyte with coarse granules and 1 immature myelocyte with vacuoles and coarse granules on a total of 500 cells of the leuko- and lymphopoiesis; (2) in case 9, a few neutrophils with slightly coarse granulation, it being impossible to say whether they belonged to the blood or to the marrow.

To complete the picture, we mention that a binucleated cell was seen in 2 cases: in no. 6, an immature myelocyte with 2 nuclei; in no. 9, a neutrophil with 2 rod-shaped nuclei with adult structure. This last cell might be a neutrophil myelocyte in which the mitotic division of the nucleus was not followed by a division of the whole cell and where the 2 nuclei continued their maturation, as shown by shape and structure, to the stage typical of adult staff cells.

The number of megakaryocytes was increased in cases no. 9 and, to a lesser extent, no. 5, which reaction can be seen in some forms of thrombopenia and panmyelopathy.

DISCUSSION

In the cases we have personally observed, we have failed to see the sudden development of severe agranulocytosis, which is largely an allergic manifestation. In 2 cases the leukocyte count dropped below the 3,000 mark; in these, the examination of the bone marrow showed evidence of impaired development* in the granulocyte series: increased percentage of premyelocytes and immature myelocytes, abnormally large premyelocytes, discrepancies in the maturation of nucleus and cytoplasm. It is conceivable that these changes, when allowed to develop further, might eventuate in a toxic agranulocytosis, which, contrary to the acute allergic variety, shows a definite relationship to the amount of toxic substance given.

Erythropoiesis did not suffer; a slight hypochromic anemia in 2 cases improved during treatment.

It should be emphasized that patients treated with thiouracil should have weekly leukocyte counts, together with careful examinations of blood smears with particular reference to the differential count of the white blood cells and to toxic changes in the granulocytes. In some cases, the number of neutrophils may be markedly decreased, although the total number of leukocytes remains within normal limits, and in others, the development of well-defined toxic changes in the neutrophils may be indicative of an impending serious disturbance.

* We purposely avoid the term "maturation," which has been too widely used without discriminating between the true maturation of a cell or group of cells and the ability for mitotic division. (See Rohr, pp. 107-08.)