

## Bone Marrow Hypoplasia in Anorexia Nervosa

F. Lampert<sup>1</sup> and B. Lau<sup>2</sup>

<sup>1</sup> Zentrum für Kinderheilkunde der Justus Liebig-Universität, Feulgenstraße 12,  
D-6300 Gießen und

<sup>2</sup> Universitäts-Kinderklinik München,  
Federal Republic of Germany

**Abstract.** Within a 2-year period, from March 1974 until May 1976 10 patients with anorexia nervosa were seen at the children's university hospitals of München (2 patients) and Gießen (8 patients). The patients were 10—16 years old, with one exception all girls, and had the typical cachexia, hypothermia, bradycardia, gray, hairy skin, and amenorrhea in those who had reached menarche.

The blood counts at diagnosis revealed a leukopenia (below 5000/mm<sup>3</sup>) in 6 patients and a thrombocytopenia (below 150000/mm<sup>3</sup>) in 4 patients. The bone marrow was examined in 7 patients and showed marked hypocellularity with only few megakaryocytes present and abundant vacuolated hyaline material. Bone marrow erythroblasts were decreased (below 20%) in 5 patients, although peripheral blood hemoglobin and hematocrit were normal or even elevated in all 10 patients. In 7 patients blood urea nitrogen was elevated above 30 mg%, the highest value being 145 mg%.

Blood and bone marrow alterations as well as the renal abnormalities disappeared within days to a few weeks after a regimen of strict fluid and caloric intake was initiated and a gain in body weight of up to 10 kg was achieved.

**Key words:** Anorexia nervosa - Bone marrow hypoplasia.

**Zusammenfassung.** In etwas über 2 Jahren, vom März 1974 bis Mai 1976, sahen wir an den Universitäts-Kinderkliniken von München (2 Patienten) und Gießen (8 Patienten) insgesamt 10 Patienten mit Pubertätsmagersucht. Die Patienten waren 10—16 Jahre alt, mit einer Ausnahme alle Mädchen, und zeigten die typische Magerkeit, Hypothermie, Bradycardie, graue, schuppige, haarige Haut und Amenorrhoe bei vorangegangener Menarche.

Bei Diagnose hatten 6 Patienten eine Leukozytopenie (unter 5000/mm<sup>3</sup>) und 4 eine Thrombozytopenie (unter 150000/mm<sup>3</sup>) im peripheren Blut. Das bei 7 Patienten untersuchte Knochenmark war zellarm mit nur wenig, ausreifungsgehemmten Megakaryozyten und wies fädig-gelatinöse, schwach rosa gefärbte, mit Vakuolen durchsetzte Massen auf. Die Erythroblasten im Knochenmark waren in 5 Fällen vermindert (unter 20%), obwohl die peripheren Hämoglobin- oder Hämatokritwerte bei allen 10 Patienten normal oder sogar erhöht waren.

Bei 7 Patienten waren die Serum-Harnstoffwerte erhöht (über 30 mg%); höchster Wert 145 mg%.

Die Blut- und Knochenmarkveränderungen sowie die erhöhten Harnstoffwerte verschwanden innerhalb von Tagen bis wenigen Wochen durch intensive Flüssigkeits- und Kalorienzufuhr mit entsprechendem Gewichtsanstieg.

## Introduction

Anorexia nervosa, primarily a psychogenic disease (Kanis et al., 1974), strikes by its severe secondary somatic abnormalities which, not too rarely, will lead to death.

Within a 2-year period we saw 10 patients with this self-imposed starvation of whom 7 also had marked bone marrow changes.

As thrombocytopenia and leukopenia in these severely emaciated patients posed quite a diagnostic puzzle in the beginning, we thought it worthwhile to call attention to these hematologic alterations in order to diagnose and treat anorexia nervosa more rapidly.

## Patients

A total of 10 patients—9 girls, 1 boy; 10—16 years old—were hospitalized from March 1974 to May 1976.

The following rules to attain the initial therapeutic goal, i.e., weight gain, (Silverman, 1974; Maxmen et al., 1974; Niederhoff et al., 1975) were applied to most of the patients:

1. Strict hospitalization—2—3 months.
2. Visit of parents—only once weekly or less.
3. Fluid intake—more than 1 l/day, the first 3 days i.v. or per nasogastric tube.
4. Caloric intake—standard diet of 2500 cal/day, supplemented by high caloric liquid (Biosorbin MCT 400 g = 200 cal) every 4 h (= 500—1000 additional cal/day) + Vitamin C, A (Stresscaps) + Acidol-Pepsin. Calories per kilogram body weight should be around 100.
5. Sedation, if necessary, by psychopharmacologic agents.
6. Daily measurements of body weight, pulse rate, temperature, blood pressure.
7. Firm, but friendly, guiding by nurse and doctor; no selection of food or clothing by the patient.
8. Psychiatric treatment of the patient—four times a week, and for the parents once a week by the same doctor. Later follow-up as outpatients up to 2 years after hospital discharge.

## Observations

The findings at diagnosis are summarized in Table 1:

*Physical.* A marked starvation was found in all patients. Body weight was found below the 3rd percentile in seven patients, and under the 10th percentile in three. The height of the patients was normal or even about average. Three girls who already had reached menarche were amenorrhoeic. Rectal temperatures were around or below 36° C with lowest value of 35° C. Bradycardia (with one exception) was

Table 1. Anorexia nervosa. Findings at diagnosis including blood and bone marrow. Children's University Hospitals of München (1974) and Gießen (1974—1976)

Patients	GW	CK	PH	CS	PD	AP	AP	CB	AK	IN
Age	10 <sup>3</sup> / <sub>12</sub>	13 <sup>11</sup> / <sub>12</sub>	12 <sup>8</sup> / <sub>12</sub>	10 <sup>4</sup> / <sub>12</sub>	14 <sup>2</sup> / <sub>12</sub>	14 <sup>10</sup> / <sub>12</sub>	16	11 <sup>8</sup> / <sub>12</sub>	11 <sup>7</sup> / <sub>12</sub>	11 <sup>1</sup> / <sub>12</sub>
Sex (f = female, m = male)	f.	f.	f.	f.	f.	m.	f.	f.	f.	f.
Secondary amenorrhoe	—	+	—	—	+	—	+	—	—	—
Skin hairy, rough, "dirty"	+	+	+	+	+	+	+	+	—	(+)
Weight (kg)	20.5	34.7	24.4	26.0	41.2	27.0	31.4	26.6	19.5	30.8
Temperature (° C)	36.0	36.4	36.2	35.8	35.0	35.6	35.8	36.6	36.2	36.1
Pulse rate (min)	46	56	40	52	64	68	40	60	56	48
Total protein (g%)	8.6	7.6	6.8	6.8	6.0	7.0	6.4	6.7	7.4	7.6
Blood urea nitrogen (mg%)	50	12	49	39	—	145	8	48	45	60
Sedimentation rate (mm: 1st/2nd h)	3/6	3/6	4/13	2/5	—	3/7	2/4	—	4/12	2/5
Hemoglobin (g%)	16.4	14.6	12.6	12.7	12.9	13.9	15.4	14.4	12.2	14.7
Thrombocytes (× 10 <sup>3</sup> /mm <sup>3</sup> )	105	244	—	144	158	55	165	100	244	171
Leukocytes (× 10 <sup>3</sup> /mm <sup>3</sup> )	3.5	7.6	6.6	4.5	2.0	6.4	4.6	4.6	6.7	4.6
<i>Bone marrow</i>										
Cellularity	↓			↓		↓	↓	(↓)	↓	↓, ↓
Hyaline material	+++			++		++	++	++	+	++
Megakaryocytes	↓			(↓)		(↓)	(↓)	↓	(↓)	↓
Erythrocytic (%)	6.0			13.0		9.0	20.5	14.0	21.0	6.5
Granulocytic (%)	43.0			52.5		63.0	56.0	65.0	55.0	56.5
Lymphocytic (%)	45.0			32.0		28.0	23.5	29.0	20.0	26.0

present in all patients with lowest values of 40/min and bradypnea (less than 16/min). Six patients had hypotension with systolic pressures below 90 mm Hg. The skin was altered in all patients except one, appearing "dirty," rough, and scaly, resembling fine sandpaper. The back of the trunk and the extremities were covered with fine, long hairs. Fingers, toes, hands, and feet were usually blue and cold.

Rise in temperature and pulse rate were good parameters to indicate the beginning of clinical remission.

*Laboratory.* No hypoproteinemia was present in any of the patients. Erythrocyte sedimentation rate was decreased and never exceeded 4 mm in the 1st h. Elevation of blood urea nitrogen, usually slightly above the upper limit of normal, but 145 mg% in one patient, was found in seven patients. Accordingly, creatinine, and potassium levels were at the upper limit of normal. Evaluation of the pituitary function in one girl (G. W.) showed low levels of plasma LH (1.3 mg/100 ml) and FSH (0.7 ng/100 ml).

*Blood.* A thrombocytopenia (normal range of thrombocytes in our laboratory = 150 000—300 000/mm<sup>3</sup>) was detected in four patients, with lowest level of 55 000/mm<sup>3</sup>, accompanied by generalized petechiae and ecchymosis in two patients. Bleeding time was prolonged, coagulation time normal, as were the plasma factors. Leukocytopenia occurred in six patients with lowest value of 2000/mm<sup>3</sup>, affecting granulocytes as well as lymphocytes. In only three patients were granulocytes relatively more decreased. Hemoglobin and hematocrit were high in half of the patients, reflecting probably varying degrees of dehydration. Activity of erythropoiesis, however, was very low, as demonstrated by very few or even no reticulocytes in the peripheral blood. The response of hematopoiesis to rehydration and forced high caloric intake is demonstrated in Figure 1.

*Bone Marrow.* Bone marrow aspirations from the posterior iliac crest were done in seven patients and yielded in most cases only a few drops of sticky, gelatinous material. Microscopically more or less hypocellularity was present with increase in fat particles.

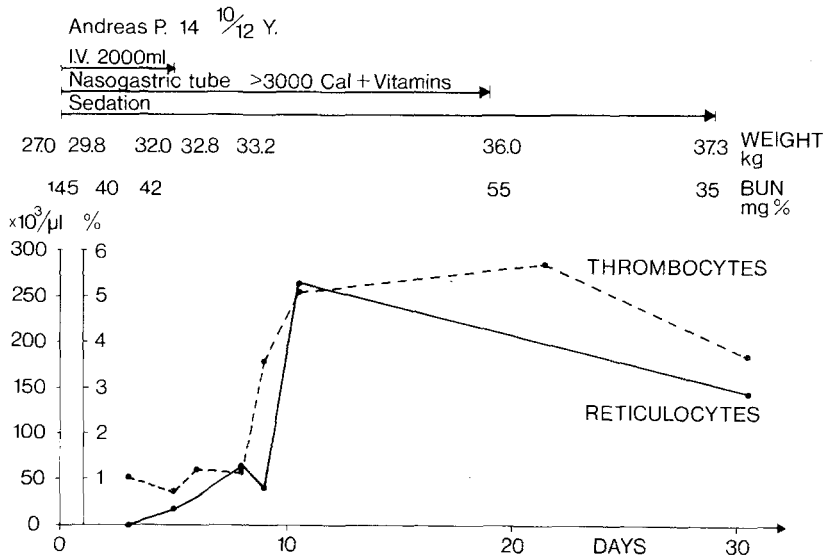
In most cases only a few immature megakaryocytes were present. Abundant grayish-pink homogenous material was seen throughout in Wright or Pappenheim stained bone marrow smears. It occurred in fibrous streaks (Fig. 2) or in large islands, in which cellular elements or vacuoles of different sizes were dispersed. There was only pale staining of this material in the periodic acid-Schiff reaction.

Differential counts revealed reduced erythroblasts (below 20% of all marrow cells) in five patients and a lymphocytosis (over 20%) in six patients.

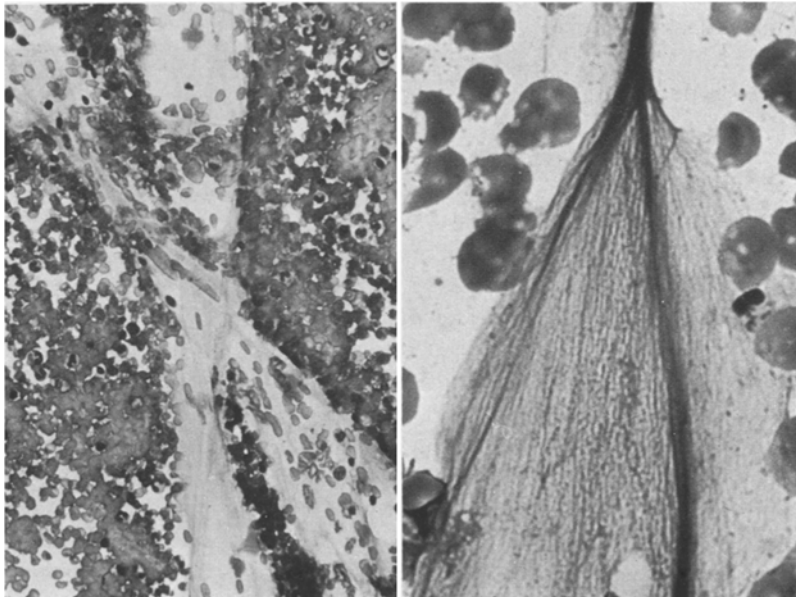
After successful restoration of body weight the mucous material disappeared and the differentials of bone marrow returned to almost normal: erythropoiesis from 6.0 to 24.0% (patient G. W.), from 13.0 to 18.5% (patient C. S.); lymphocytes from 45.0 to 20.0% (patient G. W.), from 32.0 to 28.0% (patient C. S.).

In one girl (G. W.) a biopsy was taken from the iliac crest and examined by the Abteilung für Knochenmarksdiagnostik (Prof. Dr. R. Burkhardt), 1. Medizinische Universitätsklinik München, and diagnosed as "areactive, edematous

### ANOREXIA NERVOSA



**Fig. 1.** Initial thrombocytopenia and reticulocytopenia together with increased blood urea nitrogen in a boy (A. P.) with severe anorexia nervosa which promptly disappeared after weight gain, induced by forced liquid and caloric intake



**Fig.2.** Initial bone marrow smear of a 16-year-old girl (A. P.) with anorexia nervosa: Note streaks of mucoid-fibrous material and paucity of nucleated cells

myelitis, moderate osteoporosis." There was a marked increase in fatty elements with striking diffuse interstitial edema containing only a few islands of granulopoiesis and erythropoiesis and only very few megakaryocytes. The marrow sinuses were hypoplastic with endothelial dissociation and extravascular erythrocytes. In a few instances hyaline alteration of capillaries and arterioles were seen.

### Discussion

Leucopenia and thrombocytopenia, due to deficient bone marrow function, were found in about half of our 10 patients. This means that patients with anorexia nervosa not only have a minimal metabolic rate and renal insufficiency, but also can bleed and are prone to infections. The function of granulocytes can also be altered as has been shown by Gotch et al. (1975), who found a reduced bacterial killing rate in three patients with anorexia nervosa which was reversible after the patients gained weight.

The frequency of our bone marrow findings are in accordance with Silverman (1974) who noted a hypoplasia of bone marrow in 12 of his 29 patients (= 41%) with anorexia nervosa. Leukopenia (below 5000/mm<sup>3</sup>), however, was found by him in only 7 patients (= 24%).

A histologic and histochemical study was performed by Pearson (1964) in three patients with severe anorexia nervosa and bone marrow hypoplasia. Besides the paucity of cellular elements he, too, observed an increase in mucoid material which he thought to be acid mucopolysaccharide ground substance. We think the presence of this patchy or streaky gelatinous material in the marrow smears can serve as a good diagnostic hint. This material could also be some kind of edematous fluid, as the bone marrow biopsy in our youngest girl (G. W.) revealed abundant diffuse interstitial edema. In contrast to Silverman (1974), who found peripheral edema in 6 of his 29 patients (= 20%), we could not detect edema anywhere at the periphery of our 10 patients.

The etiology for edema and for the bone marrow hypoplasia is unknown. There is no relation to hypoproteinemia as the total serum protein was well above 6 g% in all our patients. Protein deficiency, however, was thought to be the cause for blood disorders, mainly anemia, in victims of concentration camps with severe famine disease (Helweg-Larsen et al., 1952). There was also no lack of iron as the iron plasma levels (68, 84, 110, 111, 112 µg%) in our patients (when examined before treatment), were in the normal range. The humoral regulators of hemopoiesis also seem to be normal as has been shown by a normal hamatocrit-related response of erythropoietin excretion in one patient with anorexia nervosa (Kubaneck, 1975).

Thus, pathogenesis of bone marrow failure in anorexia nervosa remains obscure. The fact, however, is comforting, that all the severe somatic alterations disappear within 4 weeks, after normal body weight is restored by sufficient liquid and high caloric intake. As there is also a relation between body weight and the maturity of the luteinizing hormone pattern (Boyar et al., 1974)—i.e., menstruation in this puberty disease—a clinical management which is oriented toward weight gain will help these patients more rapidly toward body stability and, hopefully, also to lasting mental stability.

**References**

1. Boyar, R. M., Katz, J., Finkelstein, J. W., Kapen, D., Weiner, H., Weitzman, E. D., Hellman, L.: Anorexia nervosa: Immaturity of the 24-hour luteinizing hormone secretory pattern. *New Engl. J. Med.* **291**, 861—865 (1974)
2. Gotch, F. M., Spry, C. J. F., Mowat, A. G., Beeson, P. B., MacLennan, J. C. M.: Reversible granulocyte killing defect in anorexia nervosa. *Clin. exp. Immunol.* **21**, 244—249 (1975)
3. Helweg-Larsen, P., Hoffmeyer, H., Kieler, J., Thaysen, E. H., Thygesen, P., Wulff, M. H.: Famine disease in german concentration camps. Complications and sequels. *Acta med. scandinav.*, *Suppl.* **274**, 170—173 (1952)
4. Kanis, J. A., Brown, P., Fitzpatrick, K., Hibbert, D. J., Horn, F. B., Nairn, I. M., Shirling, D., Strong, J. A., Walton, H. J.: Anorexia nervosa: A clinical, psychiatric, and laboratory study. *Quart. J. Med.* **18**, 321—338 (1974)
5. Kubanek, B.: Aplastic anemia and erythropoietin excretion in anorexia nervosa. *Indo-German Symposium on Haematology, Hyderabad (India) 1975*
6. Maxmen, J. S., Silberfarb, P. M., Ferrell, R. B.: Anorexia nervosa. Practical initial management in a general hospital. *J. Amer. Med. Ass.* **229**, 801—803 (1974)
7. Niederhoff, H., Wiesler, B., Künzer, W.: Somatisch orientierte Behandlung der Anorexia nervosa. *Msch. Kinderheilk.* **123**, 343—344 (1975)
8. Pearson, H. A.: Marrow hypoplasia in anorexia nervosa. *J. Pediat.* **71**, 211—215 (1967)
9. Silverman, J. A.: Anorexia nervosa: Clinical observations in a successful treatment plan. *J. Pediat.* **84**, 68—73 (1974)

*Received May 11, 1976*