Hematopoetic diseases

Bone-marrow and blood constitute an organic system, for which «cell therapy» is an excellent therapeutic method: *blood transfusions, transfusions of erythrocyte-concentrates, leukocytes, thrombocytes* belong to the standard treatments. In order to improve the tolerance and to reduce complications, the immunological criteria were refined in the course of the last decades. Another trend aimed at the differentiation i.e. attempts were made to substitute the lacking cellular ingredients of the blood by corresponding concentrates (e.g. erythrocyte-concentrates, thrombocyte-concentrates) without using also the «ballast substances» of the whole blood.

As blood and bone-marrow are not accessible to contact transplantations owing to their distribution over the whole body, implantations by injection (transfusion) have always been applied in these cases.

During the last 3 decades, impulses came chiefly from the radiation biology and from the therapy of systematized tumours.

Irradiation lesions

In thinking over the further perfection of the protective effects of *parabiosis* (BRECKER and CRONKITE, 1951), JACOBSON (1949–1952) protected various parts of the body during irradiation. When the spleen of a mouse was protected while its entire body was exposed to irradiation, the LD 50 increased from about 550 r to 1025 r. This protective effect was reached also by intraperitoneal injections of splenic tissue, and the spleen of new-born animals showed the greatest effect.

LORENZ (1951), relying on tests by REKERS (1948), maintained the idea that the protective effect was caused by a cellular mechanism. Mice treated with their whole bodies exposed to 900 r irradiation, got intraperitoneally or intravenously vital bone-marrow from long bones of untreated mice. The rate of survivors was 75%, the erythrocyte values did not decrease; islets of active hemopoetic tissue were found in the liver of the irradiated animals, and also in the Omentum maius after intraperitoneal injections. The protective effect was about equal with isologous and homologous tissues, and weaker with heterologous tissues.

The statistical significance for the survival of the donor cells in the recipient organism was established by extensive tests (FORD, 1956). Mice of the strain CBA (recipient) showed, three weeks after 950 r complete irradiation and transplantation of bone-marrow from mice of strain T 6, the chromosomal characteristics of T 6. When bone-marrow of rats was transmitted, is got a little touched. From this, the term *«irradiation chimera»* was derived. (The chimera is a fabulous being in Greek mythology, consisting of a goat's body, with a lion's head and a serpent's tail.)

The results certified repeatedly thereafter have proved that after the elimination of immunoresistance foreign cells can survive and function in the organism. The donor cells effect a «colonisation» and repopulation of the bone-marrow. If the recipient's immunity is not quite eliminated, mutual immunological reactions may come on. A variant with

the clinical symptoms of autoaggression is the *Runt-disease* (runt = dwarf cattle); this term is to express the stunted growth in connection with changes of the skin and mucosa, diarrhea and disturbed absorption.

Generally, the following alternatives are given:

1. Complete and lasting substitution of the recipient's bone-marrow by the donor's bone-marrow.
2. The implanted bone-marrow disappears gradually and is just as promptly substituted by the recipient's regenerating bone-marrow.
3. Hematopoetic tissue of the donor and recipient coexist so that an irradiation chimera originates. The formation of a chimera can proceed to such an extent that a kind of cells (e.g. granulocytes) originates from the donor, another one (e.g. erythrocytes) from the recipient.

After the practical use of fetal cells by Paul NIEHANS and others between 1931 and 1960, FEREBEE (1957, 1958) tried to avoid the immunological problems by using fetal tissues. UPHOFF (1958) tried to achieve this with undifferentiated lymphatic tissues.

The first case of application to man was the involuntary experiment by the nuclear research centre of VINCA (1958). An accident in the nuclear reactor affected 6 persons, 4 of them with a lethal dose of 700–1000 r, one with a supralethal dose between 1000 and 1200 r, and the 6th with a sublethal dose of 300–500 r. These persons were taken the next day by air to the hospital of the Curie-Foundation, Paris, and treated (JAMMET, MATHE, SALMON, 1959).

The clinical course showed 3 phases:

1. In the *initial shock phase*, which began 1 hour after the accident and persisted for the first day, there was a general alarm symptom with adynamia, vomiting, paraesthesia and profuse perspiration. The experimentator who had got a supralethal dose, suffered moreover from diarrhea.
2. A *latency period* followed and lasted 2–3 weeks. The general conditions were not too bad, but the affected persons showed loss of weight, general debilitation and disposition to profuse perspiration, sleeplessness and splitting headache. The disorders were seen also in the blood-count, skin and intestinal tract. The person who had got a supralethal dose suffered from attacks of fever on the 14th and 15th days.
3. The *crisis* lasted from the 4th to 7th week, with serious general collapses of health and diffuse drowsiness, decreasing diuresis, anorexia, very serious nausea, profuse perspiration. Only the person who had got a sublethal dose of 300–500 r did not show these symptoms. In that period, the patients had moreover marked conjunctivitis, dry and cracked skin as from the 20th day, and lost nearly all of their hair, including the beard as far as they were male. The patient who had got the supralethal dose died on the 32nd day, after invaginations, ileus and anuria.

The blood-count showed the following changes: Immediately after the irradiation, leukocytosis of 9000–11 000 leukocytes/mm^3 with lymphopenia developed. The various kinds of blood-cells decreased gradually during the latency period. Affected first were the lymphocytes. The myelogram showed a bone-marrow atrophy, which changed into a bone-aplasia at the beginning of the 7th week. Connected therewith were gingival bleedings, hemorrhages from the nasal mucosa, stomach and intestine. After

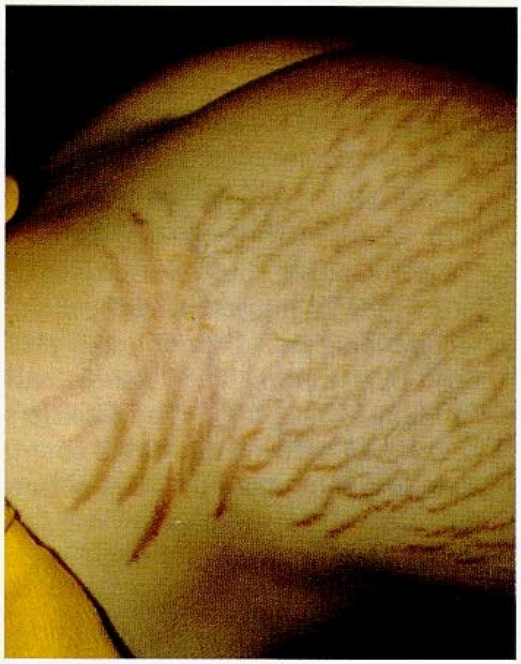
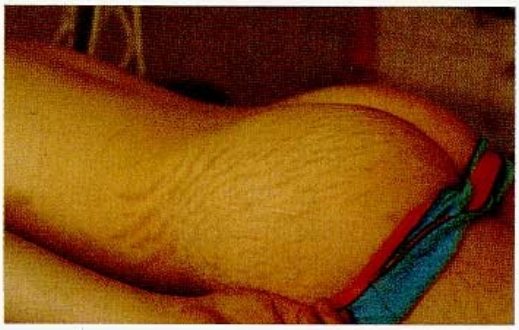


Fig. 308
Panmyelopathy; hypercorticism
The 12 8/12-year-old boy suffering from thrombocytopenia had been treated with 100 mg of urbason for 6 months. He developed more-over anemia, leukopenia, granulocytopenia and serious hypercorticism with Cushing's face and extensive striae.
When 60 mg of adrenal gland (male), 75 mg of spleen and 150 mg of liver-lyophilisate were implanted, the blood-count was as follows:
Hb 8.4 (52%), Ery 2.75, HbE 30.5, leukocytes 1700; segmented 24%, lymphocytes 69%, monocytes 7%.
The following day already, the granulocytes make 45%, on the second day 49%, and 68% on the 5th day. The changed numbers of the thrombocytes, leukocytes and erythrocytes seen in the following months appear from the diagram fig. 298 hereafter. Distinctive of the therapeutic outcome is the rapid response of the myeloic series, followed by the retarded reaction of the thrombocyte apparatus though weeks after the erythropoesia.
The hypercorticism decreases within a few weeks.



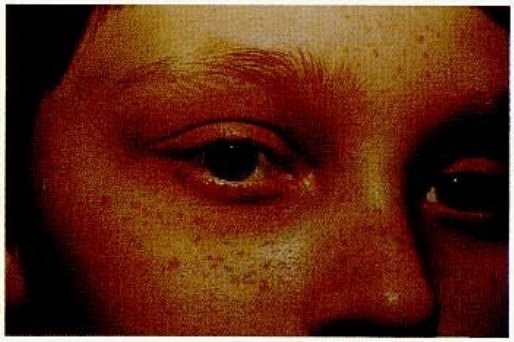
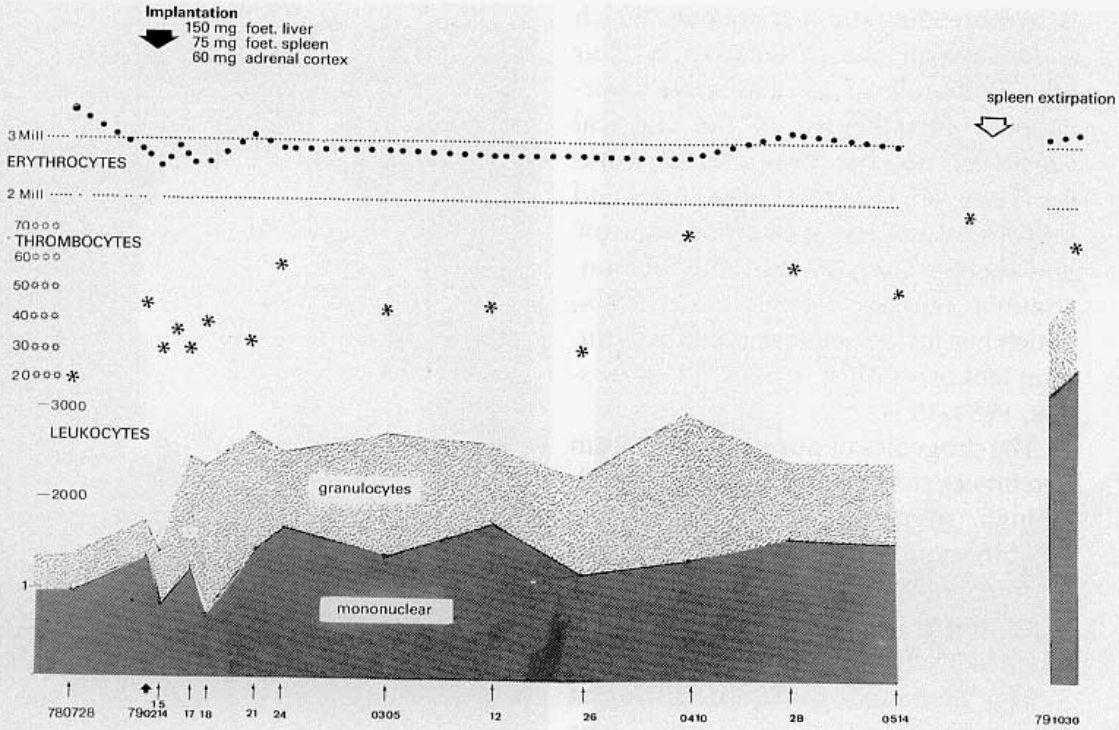


Fig. 309:
Pancytopathy of Fanconi-type with severe anemia and steady nose-bleedings since the 5th year of life. Till the age of 13 40 bloodtransfusions were necessary, when the hemoglobin dropped down to a level between 2.7–3.5 g%. Admission to the hospital with following values: hemoglobin 5.1 g%, erythrocytes 1600,000, white blood cells 2700; 19% granulocytes, 80% lymphocytes, 1% monocytes; sedimentation rate 56/100. The Panmyelocytopathy includes anemia, leukopenia, granulocytopenia and thrombocytopenia. 6 month after implantation of 75 mg fetal spleen-, 75 mg fet. bone marrow- and 150 mg fet. liver-lyophilisate no further bloodtransfusion was necessary.

Schwarz

bridging the critical phase with small blood-transfusions, first hematopoetic fetal tissue from the liver of a human fetus was implanted by injection. The number of cells was about $4{,}2 \times 10^9$ fetal liver cells. The effect was obviously small so that the next therapeutic measure was injections of adult bone-marrow cells from donors of similar blood-groups. The bone-marrow was taken from the sternum and injected intravenously. Transfused were 180–300 cm^3 of



(Fig. 308)

bone-marrow, the number of the cells came to about 8,5–14 × 10^9. After a short transfusion shock, the general conditions of the moribund patients improved. The sensorium came back, dynamics, appetite and increase in weight showed recoveries.

Under the special conditions of the elimination of immunity, implanted tissues of bone-marrow seem to take the functions in the recipient's organism till the own bone-marrow is active again. As the erythrocytes and the cells of the myeloic series as well as the thrombocytes recovered after the implantation of bone-marrow though they were not transfused direct, a general colonization can be presumed.

Implantation by injecting hematopoetic tissues in leukemia and systematisized blood-deseases

The second column of our knowledge of the effect of implantations by injecting hematopoetic tissues is constituted by the experience in the field of systematisized tumours and disorders of the apparatus of blood formation. The fundamental tests will be described in detail hereafter.

Effects and specific effects of various tissular lyophilisates on aberrations of the leukemic blood-count

Objects of trials for a possible therapeutic effect on cell suspensions on leukemic aberrations were AK-mice, which have been bred at the Dr. FURTH-laboratory, New York, since 1928. In question

is an inbreeding strain of animals, which shows a high rate of leukosis in their 6th–9th months of age. Extensive observations corresponded to the classical aspect described by other research workers (LEVEVRE, HOGREFFE, PEDERSEN and others); examinations of blood, marrow and tissues, however, can only demonstrate a marked «myeloic reaction», which has just a faint resemblance to human leukosis (W. SCHUSTER, H. SCHUSTER, 1954–1957).

The progenies of our strain bred from two braces sickened spontaneously with a high frequency (70–90%) in the 6th–8th months of age with this «myeloic reaction» and died within 4–8 weeks of a uniform aspect, which takes a course much like leukosis in children.

This hereditary disease occurring at the same age and in the same form can be outlined as follows:

Whilst these vital white mice thrive well in the beginning, their coat becomes dry and rough and turns yellowish, they shed hair in the course of the 5th or 6th months of age (fig. 311); 2–3 weeks later, the animals have no appetite, they become weary. Finally, the hair falls out entirely in the area of the snout and in the anal-genital region (fig. 312), thick infiltrates grow into the size of hazel-nuts, and colliquate, disintegrate, discharge pus, become incrusted. The tail shows knot-shaped thickenings, which ulcerate seldom.

In the blood count, the numbers of leukocytes increase by 2–5 times, the juvenile and segmentary granulocytes as well as immature myeloic forms augment whereas the lymphocytes (which make 60–80% of all white blood-cells in healthy white mice) decrease relatively or absolutely. These changes in the white blood-count proceed with a progressive anaemia, the blood grows thin, shows a lighter colour; bleedings can often hardly be stopped in the advanced stage. The condition of the animals worsens very rapidly, and they die of general cachexia within 4–8 weeks after the onset of the first symptoms. Autopsy reveals enlargements of liver, spleen and lymph-nodes in most cases. Liver and spleen are soft, fragile, show stained patterns and are difficult to separate from their physiological concrescences with neighbouring organs as they are easily injured. Histologically, attention is attracted by cell infiltrations and amyloid incorporations.

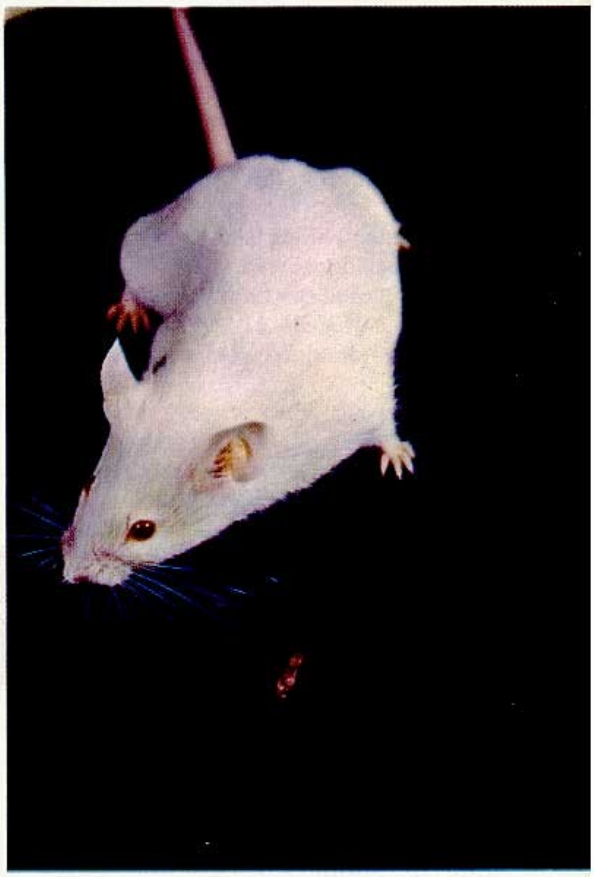


Fig. 310:
AK-mouse without manifestations of illness.

This hereditary aspect manifesting itself at a relatively constant age and accompanied by changes of the blood-count was used to examine the following questions:

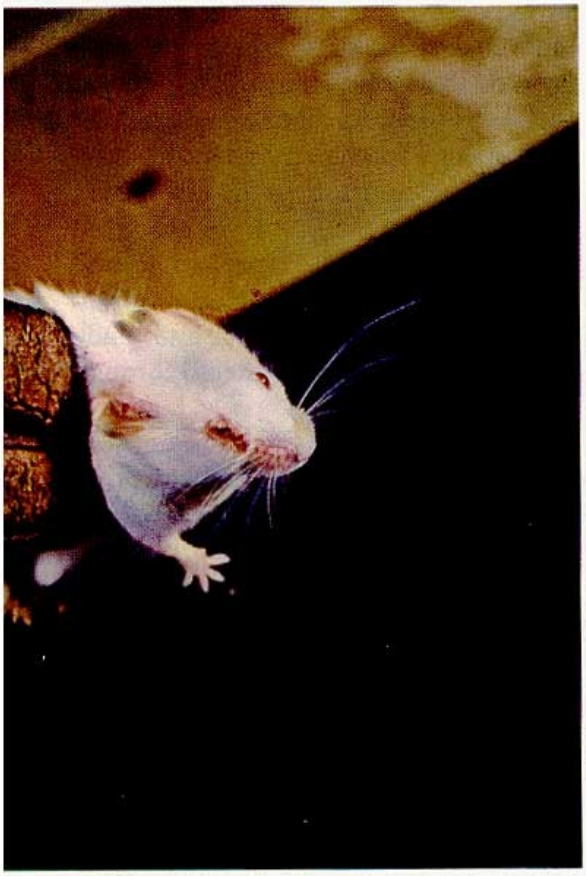


Fig. 311:
AK-mouse with beginning diagnostical symptoms. Shedding of hair and ulceration on snout, eyes and ear.

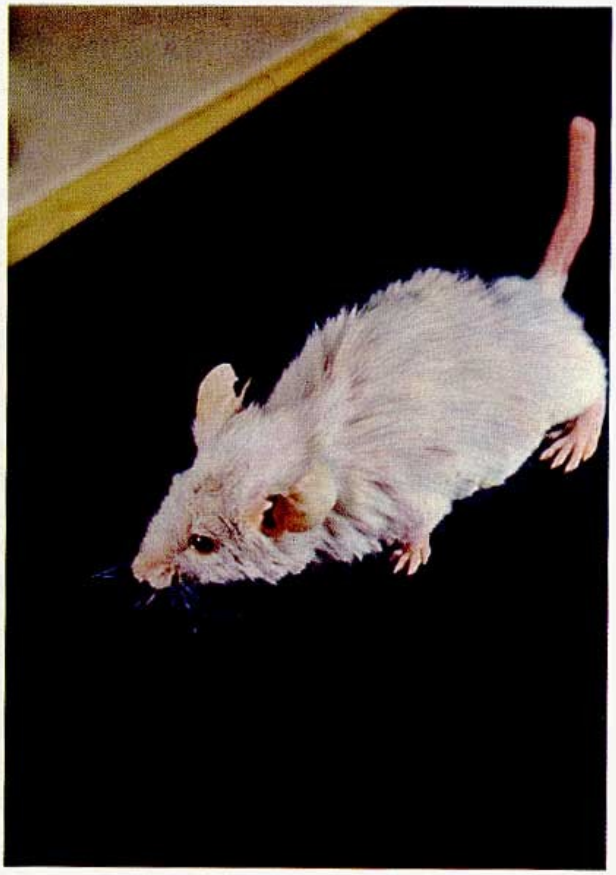


Fig. 312:
Florid pathological manifestations without leukaemoid changes of blood-count in a 7-month-old AK-mouse.

1. Can the progressive disturbances of the blood-count and general disorders be influenced by cellular suspensions?
2. If so, have the kinds of cells used equivalent effects?
3. Is the effect temporary or lasting?
4. What side-effects do occur after intraperitoneal administration of the cell suspensions?

These questions are examined in four test-groups.

In the *first group* consisting of seven test series on various cubes, heterogeneous dry-cell preparations of various mesenchymal organs (spleen, liver, bone-marrow, thymus) were used.

In the *second group* consisting of four test series, homogeneous, fresh fetal cell-suspensions (whole and organic suspensions) of a strain of healthy albino mices were studied.

The *third group* comprised four control series; in one of them, the effect of dry cells of bone-marrow on healthy mice was investigated, while in two more series some protein substances (sera) were used to find out whether the results observed constitute non-specific protein effects or not.

In a *fourth series* treated with dry brain cells, the question was whether also ectodermal tissues can influence the blood-count.

Another *test group* consisting of four test series was to clarify the question concerning the effect of cell suspensions of sick animals of the same strain.

The four test groups therefore comprise 19 test series. A total of 313 animals was tested, 250 of them AK-mice, 63 were healthy white mice. 63 AK-mice were used as controls in the test series, each comprised 4–20 animals according to the litters; mostly one litter was used, sometimes two.

First, however, 30 healthy mice had to be examined to know the numbers of leukocytes and the differential blood-count. It appeared that the results vary considerably according to how the blood is taken. The ends of the tails were cut off by scissors and the blood was taken from the stump. The results differed even if the tails, to promote the bleeding, were put into warm water before they were cut. Moreover, the numbers of cells were influenced by pressing and squeezing the stumps, which was probably accounted for by the tissue fluid. It was also worth mentioning that the readings of blood taken from the heart of a killed animal were by up to 100% lower than in the blood of its tail.

To obtain comparable results, it was necessary to apply always the same method. It appeared favourable to give the animals a slight etherization before their tails were cut. The resulting relaxation permitted to obtain blood without squeezing and pressing the stump. The numbers of leukocytes were counted in the Thomas' chamber, the blood-smears were uniformly stained after PAPPENHEIM. Blood-smears had to be prepared in preliminary tests also from considerable numbers of sick animals to coordinate the sometimes not easy classification of pathological cells in the test series. To prepare the suspension of dry cells, the cellular substance was dissolved in Ringer's solution; to prepare the suspensions of fetal cells, pregnant animals were killed immediately before the bearing, their abdominal cavities were opened and the embryos taken sterile from the uterus; then the embryos in toto or only certain organs were reduced to small pieces with scissors and ground into a pulp in a mortar. The pulp was diluted with Ringer's solution and made into a suspension, then filtered through sterile gauze.

All cellular suspensions and test substances (sera) were injected intraperitoneally. The quantity of suspension was 0,4–1,0 cm^3 uniformly within the series.

Blood examinations were performed before every injection in all test series, but were restricted to counting and differentiating the white blood cells. The first control followed three days after the injection. Further controls were performed not before long intervals (3–4 weeks) because too frequent takings even of small amounts of blood alone would have provoked considerable anaemia. The animals experimented upon were observed permanently and the times of survival were exactly recorded.

Results

Relying on the theoretical premises that gave occasion to the tests, namely the transmission of the biological potencies of fetal tissues to an insufficient system of blood-formation, we get the following results:

Mesenchymal tissues exert, at different degrees, a concrete, often deep, influence on the blood-count and on the disease of obviously ill AK-mice.

Within three days after the intraperitoneal injection, the numbers of leukocytes decrease to a maximum of more than 80% of the initial values. The differential blood-count is moved towards a normalization (fig. 317), the granulo-

cytes, juvenile and early forms of the myeloic series, are reduced by about 30–40 %, the lymphocytes augment relatively, often also absolutely. While the blood-count changes, the general conditions improve, the animals eat more, become more vital, their coats grow thicker and brighter, the formations of nodes

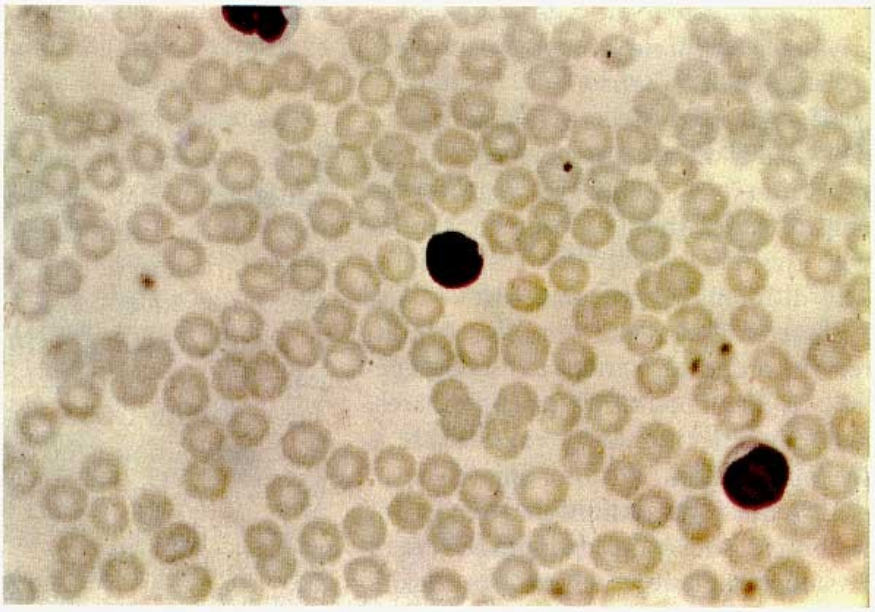


Fig. 313:
Blood smears of AK-mice without diagnostical symptoms. Small quantities of cells, chiefly lymphocytes.

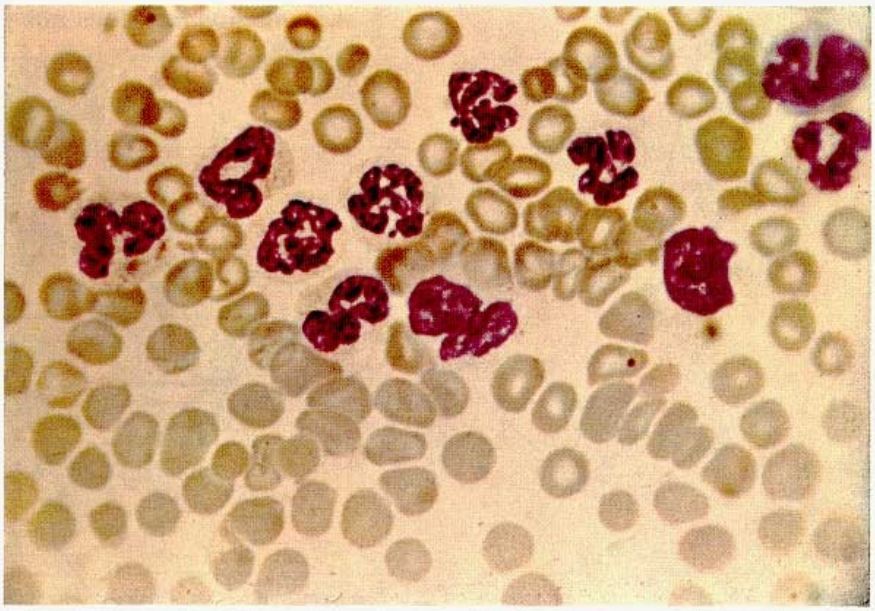


Fig. 314:
Blood-smears of AK-mice at the maximum of the leukaemoid blood-count aberrations. Considerable augmentation of cells. Atypical juvenile forms of the granulocytary series prevail. Scarce numbers of atypical monocytoids.

and ulcers are stopped or even decrease.

The average duration of life of animals treated with effective cell suspensions exceeds by about two months that of the untreated young or of the non-injected controls of the same litter. *Anaphylactic reactions were observed only after injections of sera.*

The different effects of the mesenchymal tissues on the numbers of cells appear from fig. 315. Fig. 316 compares the control series (brain substance, serum) with the effect of splenic suspensions. The different numbers of cases in the various series results from the use of litters, in order to guarantee the homogeneity of the material. Of special interest and theoretically hardly explainable is the observation that after injections of effective cell suspensions the numbers of cells were «normalized», irrespective of how high they were before. The considerably different results of injections of fetal «bone marrow» were explained later: the tissue was coarse osteoid splinters without any functioning bone-marrow.

Changes of the blood count and the influence on the general condition are passing phenomena, which persist 4–8 weeks after an injection, 6 weeks on an average. The effect is reproduceable though subsequent doses of cells seem to exert a less lasting influence on the general condition.

The basic idea that the biological potencies of fetal tissues could be transmitted to animals, turned out to be correct, but the result meant a disappointing restriction of the practical therapeutic consequences.

It appears that the affected organism utilizes temporarily the biological potencies of healthy tissues but after consuming them continues the specific course of its disease at least in tumorous processes.

Limited though the results respecting the initial questions were, yet they enlightened considerably the effect of injected cells:

1. The effect of injected cells as ascertained by our tests is caused by an *induction* but does not provide *lasting*

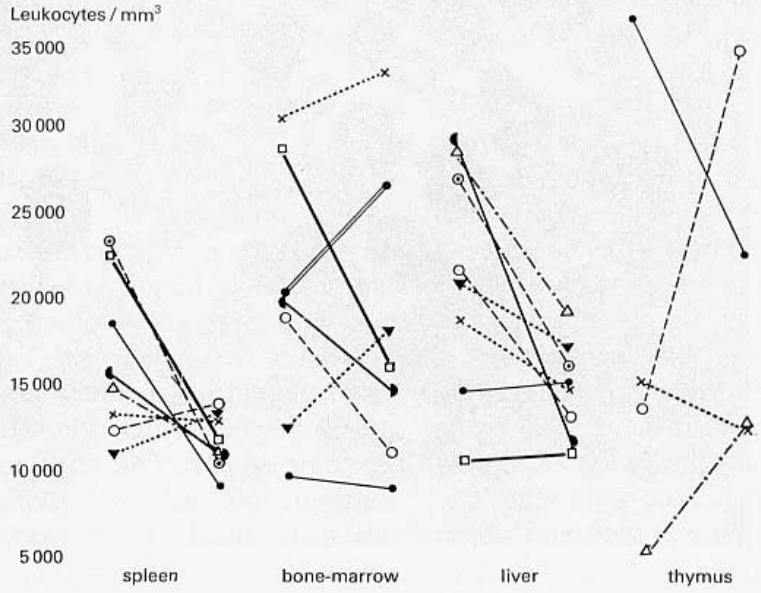


Fig. 315:
Different effects of various mesenchymal tissues on the cells of AK-mice of the same litter 3 days after intraperitoneal tissue-injection.

regeneration. Experiments on animals, therefore, have substantiated what clinical experience with the usual therapeutic fresh-cell methods (blood-transfusions, concentrates of leukocytes, transplantations of bone-marrow, implantations of hypophysis) foreshadowed.

2. The effect of injected cells is *specific*, does not rest upon a non-specific effect of protein. No effects are seen on cell-free protein carriers.
3. The effect of injected cells and tissues depends on germ-layer-dependant, and its extent is even *organ-specific.* Whereas the tested mesenchymal tissues provoked without exception the described changes of the blood-count, the latter were not seen after injections of ektodermal tissues. The effect of the mesenchymal tissues, however, is not equivalent. In our tests the changes of the blood-count were most distinct and constant after injections of spleen and liver, less constant after doses of bone-marrow and thymus.
4. The specific effect of the homogeneous and heterogeneous tissues cannot be obtained by homogeneous fetal general suspensions. In certain cases, the injections of particularisized feti of a healthy strain of mice, especially of the AK-strain, worsened the blood-findings.

These long-term tests

a) demonstrated the different specific effect of suspensions of heterologous and homologous tissues,
b) showed the temporary influence of leukaemia-like changes of the blood-count,
c) revealed no criteria for the antigenicity of heterologous fetal cells whereas homogeneous homologous tissues of adult animals provoked repeatedly shock symptoms.

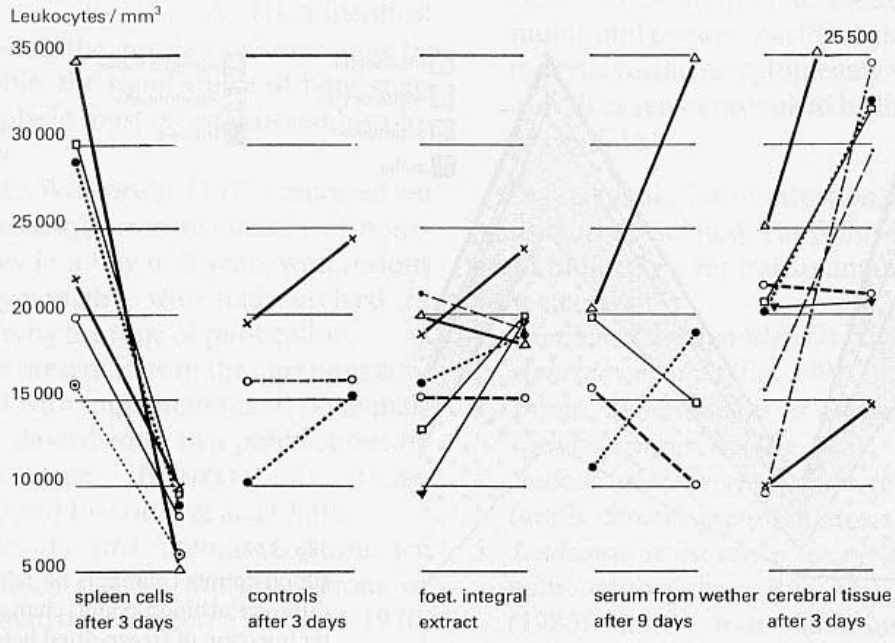


Fig. 316:
Controls of specific effects (e. g. splenic cells) with heterogenous sera and fet. integral extracts of healthy strains of mice as well as ectodermal tissues. Numbers of cells 3 days after injection.

Transplantations of bone-marrow

Relying on the ideas of Dessauer's «X-ray bath», several test series were conducted between 1950 and 1970 to study the experimental and clinical possibilities of this method. FEREBEE (1958) tried for leukemia to eliminate the immunological resistance by intense irradiation and to implant bone-marrow. FEREBEE was moreover the first to use human hematopoetic tissue of feti 16–28 weeks old. The use of xenogenous fetal cells of liver and bone-marrow was the subject of a first publication by NIEHANS (1952). SCOTT, MATHIAS and others (1961) obtained by intravenous injections of fetal hematopoetic cells different results in 14 cases of anemia. These intravenous injections of suspensions of fetal cells were tolerated without complication, also if they were repeated. Used was freshly taken and immediately transmitted tissue of liver, and a permanent remission was obtained in two cases of chronic pancytemia. The expectations set in implantations of bone-marrow after irradiation in treatments of human leukemia (THOMAS 1957, FEREBEE1958, KURNIK 1958, MATHE 1959) were not answered, though impressive temporary remissions were reached. WITTE (1961) took a similar way in acute leukemia by using first high doses of cytostatics and treating the resulting immuno-depression by subsequent transfusions of bone-marrow. According to his reports, 4 of 18 cases had a complete remission for up to 21 months, 4 cases of partial remission for 5–12 weeks. This experience corresponds to 4 cases of infantile leukosis treated by the author, which after intraperitoneal injection of fetal liver and spleen showed remissions for up to 2 months. FLEISCHHACKER and STACHER (1960) saw also in leukosis treated cytostatically with granulocytosis and thrombocytopenia complete remissions after transmitting bone-marrow of the same group.

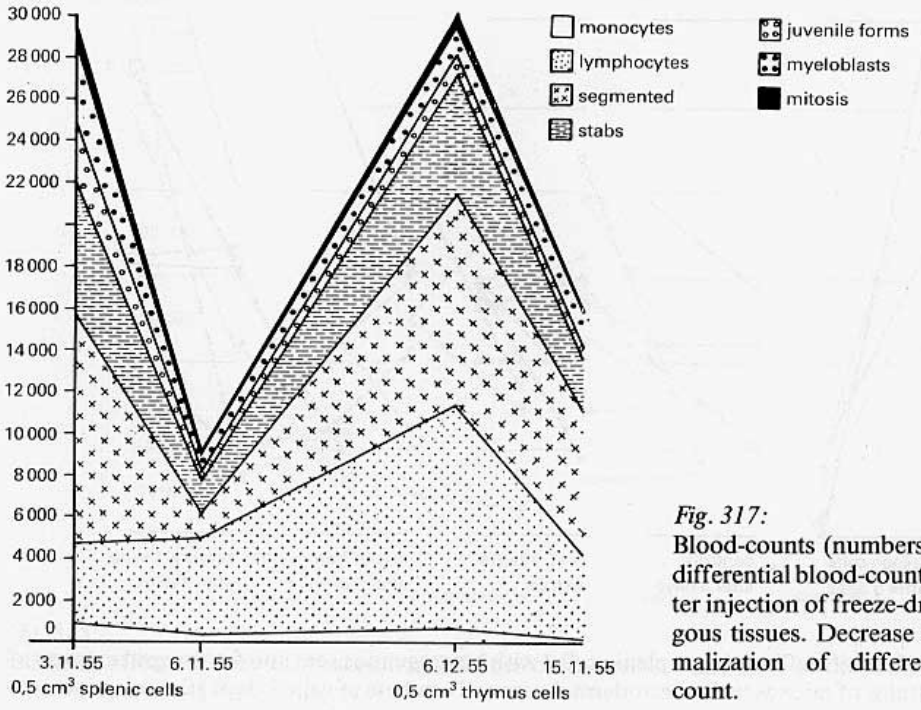


Fig. 317:
Blood-counts (numbers of cells and differential blood-count) changed after injection of freeze-dried heterologous tissues. Decrease of cells, normalization of differential blood-count.

Relying on observations of transplantations of marrow after reactor-accidents, encouraged by experiments on animals in the 1960s, 203 transplantations on man were conducted by 1977 according to a statement by H. J. KOLB, but only 3 had a positive outcome. The insufficient immunosuppressive preliminary treatment was regarded as an essential reason for the failure of the transplants. The following methods were recommended: preliminary treatment of the recipient with 1000 rd complete irradiation and cytostatic chemotherapy in leukemia, and with 200 mg per kg of cyclophosphamide in bone-marrow aplasia. To avoid the secondary disease: methotrexate (10 mg/m² day on the 1st, 3rd, 6th and 11th days, then weekly till the 102 nd day), cyclophosphamide; the secondary treatment proper i.e. the settlement between the cells of the donor and recipient, should be effected with antithymocyte serum (7 mg per kg of IgG every 2nd day for 20 days). In bone-marrow aplasia, the mortality comes in this series to 70–90%. A HLA-identical MLC-negative brother or sister must be available, the significance of bone-marrow aplasia must be established histologically.

G. F. WÜNDISCH (1977) reported on the successful transplantation of bone-marrow in a boy of 8 years with serious panmyelopathy, who had survived 22 months by the time of publication.

The present state of the questions connected with implantations of bone-marrow is described in two publications by NIETHAMMER, BIENZLE, KLEIHAUER (1977) and BHADURI et al. (1980).

After the first attempts to influence immunodefects by transplantations of bone-marrow between 1950 and 1970, this indication has meanwhile been extended to include aplastic anemia (panmyelopathia). Bone-marrow is taken from the crest of ilium of the anaesthetized donor by 100 and more aspirations, and treated with heparin to keep it from clotting. To dilute the bone-marrow it is filtered through sieves of various sizes, then the cell suspension is infused intravenously. Needed are about 1,5 times 10^8 nucleated cells per kg of body-weight of the recipient. In immunodefects this number is by 1–2 tenth powers lower than in aplastic anaemia. The risk of narcosis and a potential osteomyelitis are believed to be the only dangers to the donor. The risks to the recipient is microembolism, proceeding in part with dyspnoea, fever and chills. The main problems for the recipient are thought to be the following risks:

1. The toxicity of the high doses of cytostatics or irradiation during the conditioning.
2. Extreme predisposition to infection after the beginning of conditioning and in the first three months after the transplantation. The prevailing causes of death are interstitial pneumonia and pneumonia through Pneumocytis carinii on cytomegaly viruses as well as sepsis provoked by bacteria or candida.

Owing to this risk of infection, the patients must be isolated. The following is a list of indications for transplantations of bone-marrow:

1. *Combined immunodefects* (fig. 205);
2. *Aplastic anaemia* (fig. 309);
3. *Innate abnormalities of haemoglobin* with bad prognosis (fig. 318);
4. *Serious granulocyte defects* (e.g. infantile chronic granulomatosis);
5. *Leukemia* resistant to every therapy with cystostatics. BHADURI et al (1980) think transplantations of bone-marrow in serious aplastic anaemia the therapy of choice and

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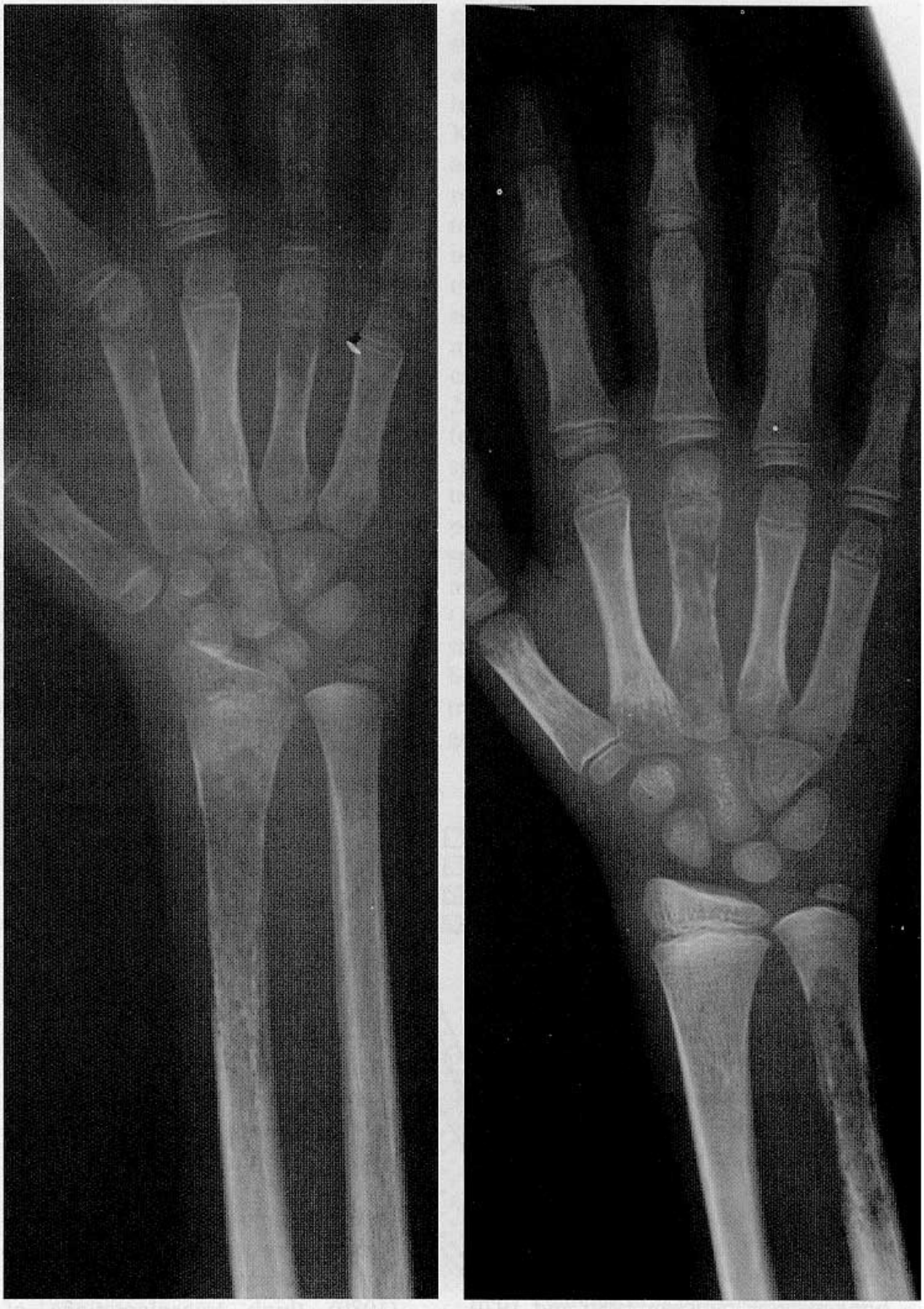
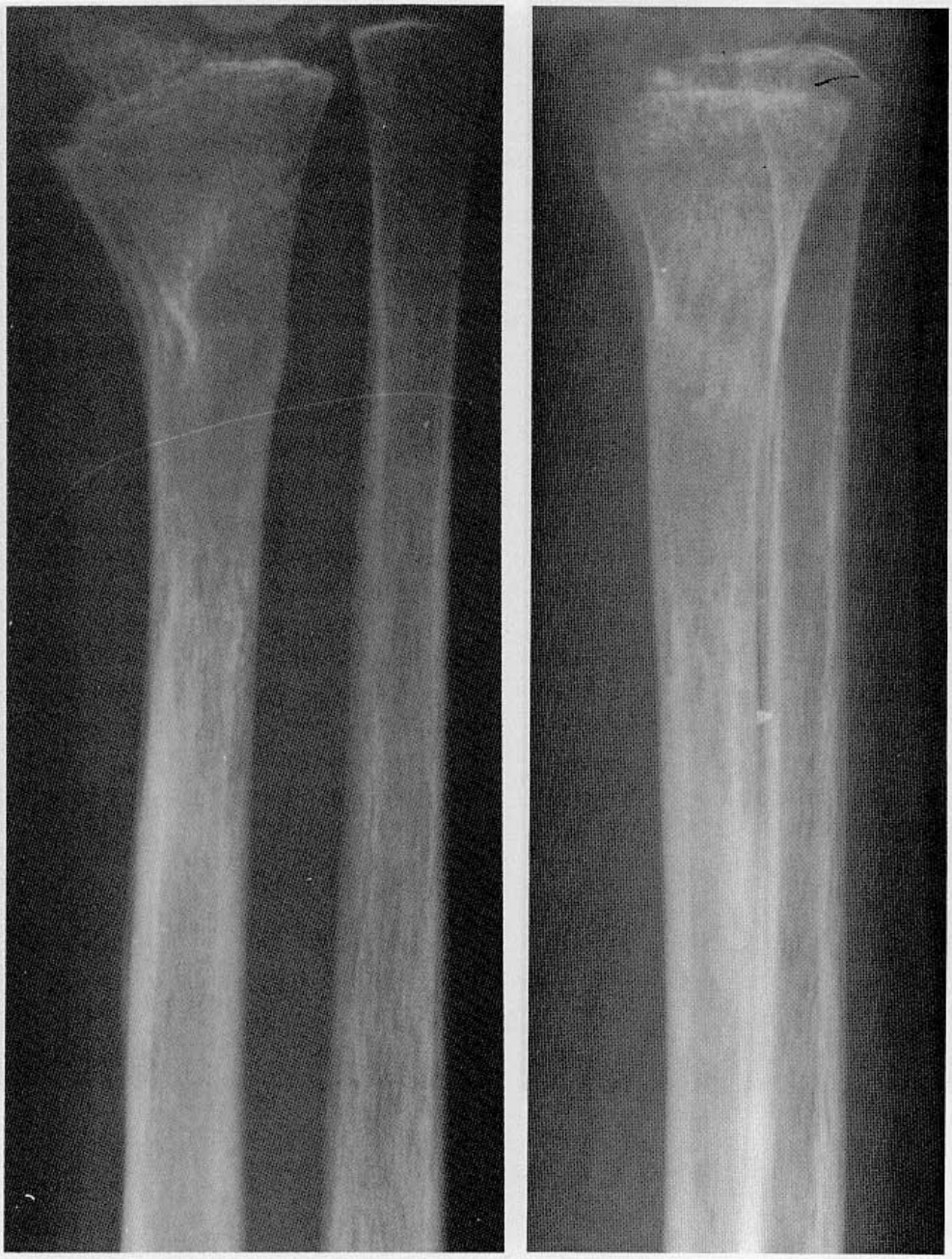


a b

Fig. 318:
Sickle-cell anaemia; generalized osteomyelitis



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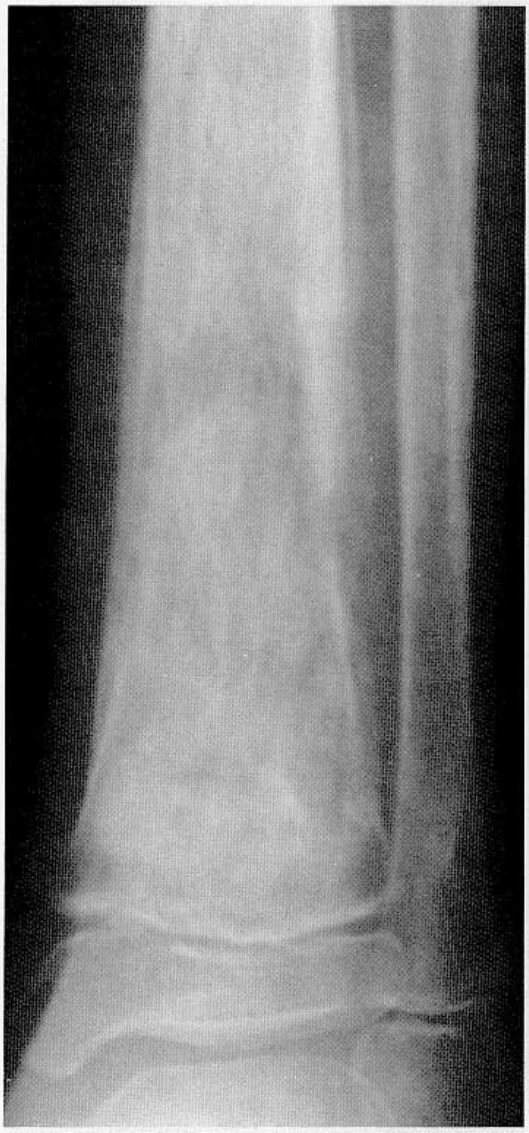
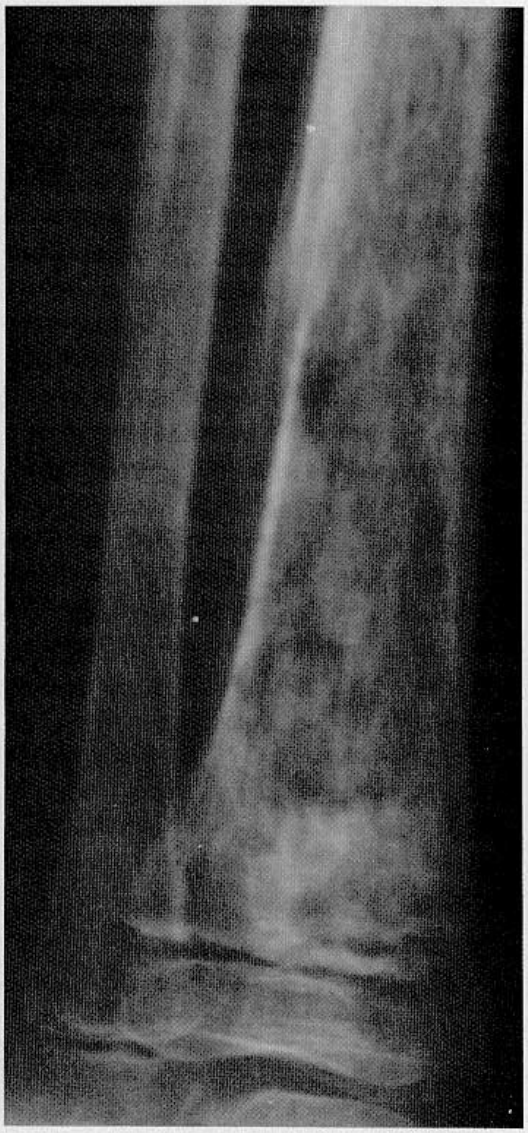
The 10-year-old Turkish boy had already been at several hospitals when he was admitted seriously ill in a cachectical condition; septic temperature, general icterus, many osteomyelitic fistulous wounds on all extremities. No normal adult haemoglobin.
HBS 89.5%, the rest for HbF and HB A_2.
HBS in father 29.8%, in mother 29.4%.
Serious anaemia: Hb 4.8 (29%), Ery 1.76 mill; reticulocytes 114%. The suppurative fistulae had been

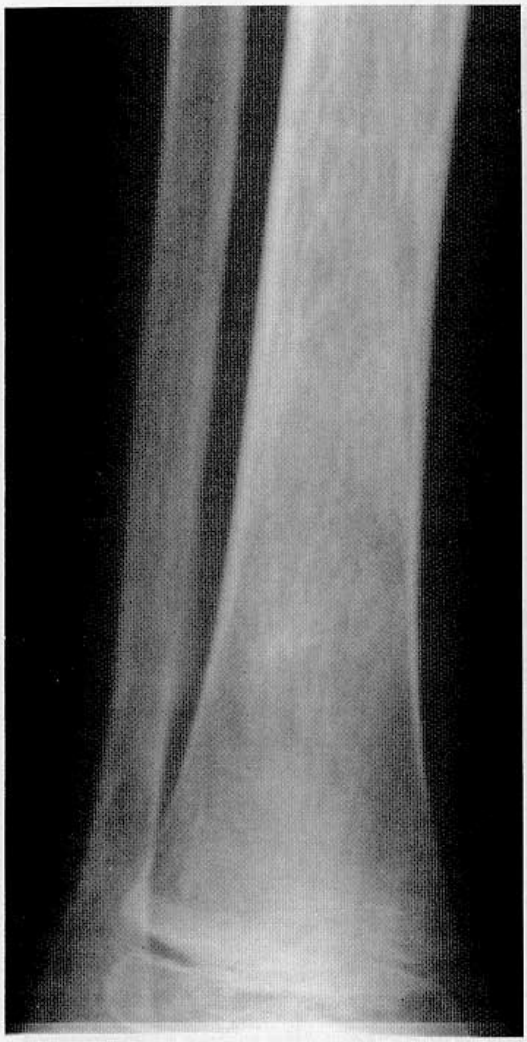


c

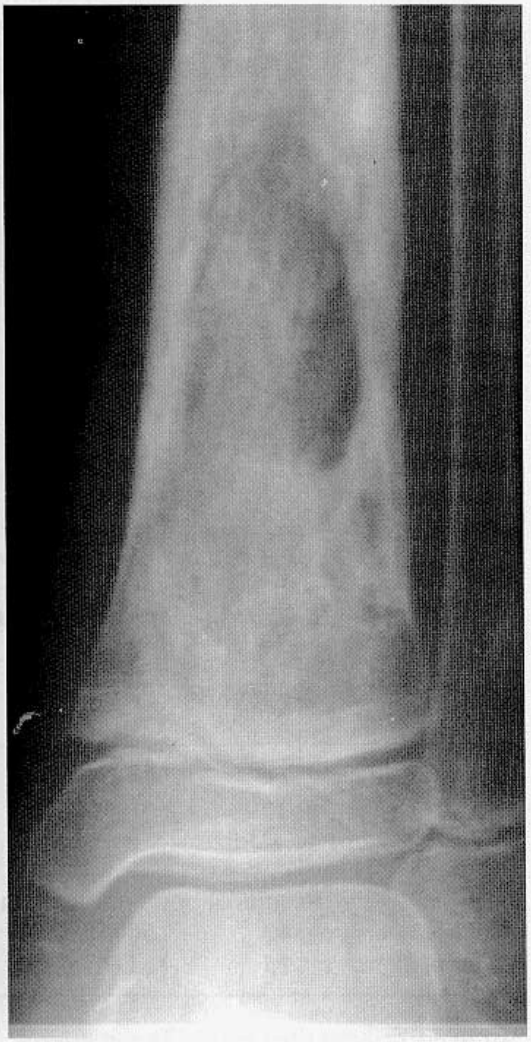


d

caused by extensive osteomyelitic focuses in the long hollow bones (a, b, c, d). Antiphlogistics, antibiotics and blood-transfusions had no influence on the septic temperatures. After two weeks of treatment as described, implantations of xenogenous tissues, fet. spleen (75 mg) and bone-marrow (100 mg). The fever declines within 3 days and the osteomyelitic focuses persisting for months heal gradually (a 1, b 1, c 1, d 1). Spleen and bone-marrow were implanted 3 × in all at intervalls of 4 weeks; additional treatment with vitamin-trace element-combinations.



c_1



d_1

Tab. 52: **Results of bone-marrow transplantation in panmyelopathia** (after BHADURI et al.)

centre	number of patients	number of survivors	death by discharge	GVHR	infection	other cause
Seattle	110	50	27	22	10	1
Internat. Aplast. An. Study Group	47	27	12	–	–	–
ACS/NIH Marrow Transplant Reg.	38	18	13	3	4	
UCLA	20	7				
Leiden	19	9	3	3	3	2
Baltimore	22	7	10	2	3	1
Paris	25	9	13	3	0	0

Tab. 53: **Results of bone-marrow transplantation in acute leukaemia**

centre	number of patients	number of survivors	death by discharge	GVHR	infection	other cause
Seattle	120	16	1	44	19 (34 recurrences)	6
UCLA	33	5	0	1	22 (3 recurrences)	2
Results of bone-marrow transplantation in the remission						
Seattle	42	50–60%				
Duarte	15	ca. 70%				

saw longer times of survival than in patients treated with «customary methods». Transplantations of bone-marrow, however, should not be considered as a last alternative because a sensitization of the body by many preceding blood transfusions must be avoided. According to this statement, the results of bone-marrow transplantation in acute leukemia are better if the transplantation is effected during the remissions. The results obtained so far in the transplantation centres of the world have been compilated by BHADURI et al. The figures and rates of survival in panmyelopathia and acute leukemia appear from Tab. 52, 53.

6. *Panmyelopathy* (fig. 308, 309).

The practical and clinical experience with the use of lyophilised xenogenous tissues are not extensive as only individual cases were published or reported verbally. Informative observations are represented in fig. 213, 308, 309, 318.