Papers and Originals

Bone Marrow Graft in Man after Conditioning by Antilymphocytic Serum*

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Summary: Allogeneic bone marrow grafts carried out after previous administration of antilymphocytic serum alone were attempted in 16 patients. Of these, six had acute myeloblastic leukaemia, four acute lymphoblastic leukaemia, and one a blast cell crisis in polycythaemia vera. Ten of these patients were in an overt phase of the disease and resistant to chemotherapy, while nine had complete agranulocytosis. In five of these patients erythrocyte and leucocyte antigenic markers demonstrated the establishment of the graft. One patient had thalassaemia major, and four others had aplasia of the bone marrow, in one case due to chloramphenicol poisoning and in another to virus hepatitis. The grafts were successful in the last two patients and transformed their clinical condition.

No signs of early acute secondary disease were noted in any of the patients, either when the donor had been given antilymphocytic serum or when he was untreated. The grafts had no adoptive immunotherapeutic effect on the acute leukaemia. These observations have clearly shown that antilymphocytic serum has an immunosuppressive effect in man when it is used alone.

Introduction

The successful use of allogeneic bone marrow grafts in the treatment of accidentally irradiated persons (Mathé *et al.*, 1959a) led us to believe that total body irradiation would be a good method of suppressing immunological reactions before leukaemic patients were treated with allogeneic bone marrow grafts. Since 1959 we have given 24 patients with acute leukaemia allogeneic marrow grafts after total body irradiation. In 17 cases the grafts were successful, but in only five could the acute secondary disease be controlled (Mathé *et al.*, 1959b, 1960, 1963a, 1969b). Secondary disease can be prevented or cured in animals by giving methotrexate (Uphoff, 1958; Mathé *et al.*, 1962a; Thomas *et al.*, 1963; Muller-Berat *et al.*, 1966) or cyclophosphamide (Mathé *et al.*, 1962b; Muller-Berat *et al.*, 1966), by incubating the donor cells at 37°C. before transfusion (Mathé *et al.*, 1963b), or by giving antilymphocyte serum (van Bekkum *et al.*, 1970). In man, however, none of these methods has been really efficient (Mathé *et al.*, 1969b; Thomas, personal communication). The two components in secondary disease are a proliferation of lymphocytes, which infiltrate many tissues—especially the skin and liver—and an immunological deficiency syndrome with loss of immunological memory (Mathé *et al.*, 1961).

Though, in mice, the immunological insufficiency is the direct result of the graft-versus-host reaction, its intensity is increased by irradiation of the host, and a correlation exists between this intensity and the dose of irradiation (Mathé and Pouillart, 1970). The degree of lymphoid aplasia induced by irradiation of the host may be an important factor and possibly provides more favourable conditions for the proliferation of the donor lymphocytes. Santos *et al.* (1970), using cyclophosphamide to condition the patient before grafting, obtained a similar incidence of successes and secondary disease reactions as we had after giving total body irradiation. Alternatively, antilymphocytic serum may be given, as it does not cause the severe acute lymphoid aplasia which is induced by total body irradiation or cyclophosphamide given in high doses. In congenitally anaemic mice (Seller and Polani, 1969), or mice rendered pancytopenic with dimethylmyleran—a cytostatic drug that is not immunosuppressive (Floersheim and Ruszkiewicz, 1970)—antilymphocytic serum has also been used as an immunological conditioning agent. A preliminary trial of antilymphocytic serum in man for marrow allografts was biologically successful (Mathé *et al.*, 1968). The present paper reports the results of a clinical trial of antilymphocytic serum alone as a conditioning agent for patients receiving marrow allografts.

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Patients and Methods

In this trial 20 patients were studied, but in only 16 could the results be taken into account. In four a graft was attempted at a very advanced stage of the disease, and as death occurred within three days of the graft the clinical and biological effects of the grafts could not be assessed. Of the 16 patients, six had acute myeloblastic leukaemia, four acute lymphoblastic leukaemia, one blast cell transformation in polycythaemia vera, one thalassaemia, and four bone marrow aplasia (see Table).

In the four cases of non-leukaemic total marrow aplasia that were treated no aetiological factor could be found in two; one was probably due to chloramphenicol poisoning and the other a possible result of virus hepatitis.

Antilymphocytic Serum

Immunoglobulins were prepared from horses immunized against human lymphocytes. The lymphocytes were obtained from the blood of healthy volunteers by means of the I.B.M. continuous flow cell separator (Schwarzenberg *et al.*, 1968); of these, 5 to 20 $\times$ 10^9 were isolated during a four-hour session, the contamination with granulocytes varying from 0 to 8%. Though the number of lymphocytes removed was greater than the total number of circulating lymphocytes, in no instance did lymphopenia occur in the donor. The horses were immunized by eight weekly subcutaneous injections given into various sites. The first three injections each contained 5 $\times$ 10^9 lymphocytes, the next three 10 $\times$ 10^9, the seventh 15 $\times$ 10^9, and the final injection 30 $\times$ 10^9. The serum was prepared at the end of the ninth week.

Preparation of the Immunoglobulins.—The serum was decanted from the blood after storage for 24 hours at 4°C. and absorbed three times with human red cells for two hours

at 4°C. The globulins were precipitated with ammonium sulphate, fractionated by chromatography on diethylaminoethanol cellulose, and the IgG globulins were isolated (Choay *et al.*, 1970). The IgG fraction was filtered through a 0·2μ diameter Millipore filter.

In-vitro Tests of the Antilymphocytic Globulin.—The absence of cold anti-erythrocyte agglutinins was confirmed. The titre of the cytotoxic activity against human lymphocytes was estimated (Amiel, 1969) and found usually to be about 1/4,000. The test of the inhibition of rosette formation by sheep red cells on human lymphocytes (Bach, J F, *et. al,* 1968) was also carried out, titres of the order of 1/16,000 being recorded After these tests the sera were adjusted to have a cytotoxicity of 1/1,000 in vitro.

Conditioning Regimen

The patients were given the horse antihuman antilymphocytic serum intramuscularly or intravenously in daily doses of 20 ml. for adults and 10 ml. for children. The treatment was stopped 12 hours before the transfusion of allogeneic marrow. The duration of the treatment varied from 4 to 12 days according to the patient's general condition and the urgency for the graft, which is known to have an immediate, beneficial, and symptomatic effect. No other immunosuppressive therapy was given during this period, in particular no antimitotics or corticosteroids. All cytostatic therapy was withdrawn 15 days before the marrow transfusion.

In 11 cases in this series, both the donor and the recipient were treated with antilymphocytic serum before the marrow graft was carried out, whereas the donors for five patients were untreated (see Table). The marrow was aspirated from the donor under neurolepto-analgesia and was immediately injected intravenously as has been described previously (Mathé *et al.*, 1959a). The number of nucleated cells received by each patient varied from 7·8 to 28·7 × 10^9 (see Table). After transfusion the patients were treated symptomatically but given no further immunosuppressive therapy; they were nursed in pathogen-free rooms (Schneider *et al.*, 1969), antibiotics were given only when an infection had been identified or was probable, and platelet transfusions were used to control haemorrhage. The proliferation of the transfused allogeneic marrow cells was determined by means of erythrocyte or leucocyte antigenic markers, or both (see Table).

Results and Comments

The grafts failed to take in 9 out of the 16 patients in this series, the antigenic markers indicating the rapid fall and disappearance of the injected red cells. During the first week after the marrow transfusion these patients showed favourable symptomatic effects (Schwarzenberg *et al.*, 1966). In seven patients a functioning graft was established and a haematological chimaera produced. The maximum percentage of circulating cells carrying the antigenic markers and the functional survival of the graft are summarized in the Table. These quantitative assessments were based essentially on a study of erythrocyte antigens. Leucocyte markers were mainly used to see whether lymphocytes were produced by the allogeneic marrow graft, but not quantitatively.

Acute Leukaemia

Clinical Condition

Eleven marrow allografts were attempted in patients with acute leukaemia. Six patients had acute myeloblastic leukaemia, of whom five were in an overt phase of the disease and resistant to all forms of therapy and five had complete marrow aplasia in which allogeneic leucocyte transfusions had produced either no improvement or only a slight and ephemeral benefit. Four patients had acute lymphoblastic leukaemia, which was in an overt phase and resistant to all forms of therapy including leucocyte transfusion, and three of these had complete marrow aplasia. One patient with polycythaemia vera was in a blast-cell crisis with complete marrow failure.

An allograft was established in 5 of the 11 patients; in three of the six patients with acute myeloblastic leukaemia it was successful. These three patients all had aplasia of the bone marrow, one of them being in remission at the time the graft was attempted (Fig. 1). Allografts were successful in two out of the four patients with acute lymphoblastic leukaemia, one of whom was in an overt phase but without complete aplasia.

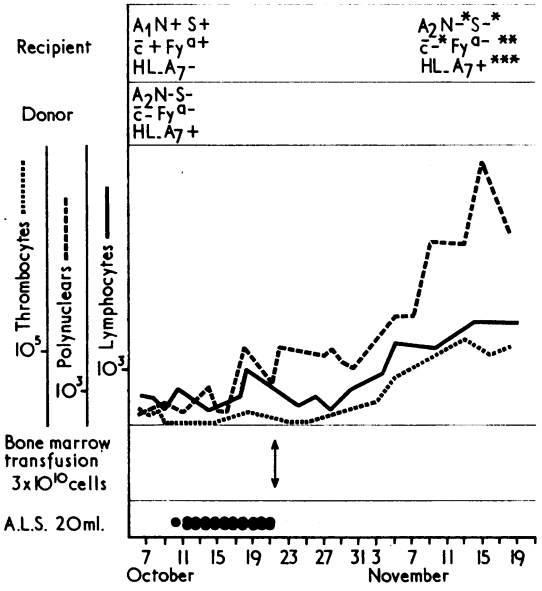

FIG. 1.—Allogeneic bone marrow graft after antilymphocytic serum in a patient with acute myeloblastic leukaemia, in a latent phase of the disease, and an aplastic marrow (Case 1). * 50% on 19 November and 80% on 22 December. ** Not quantified (indirect Coombs test). *** Not quantified.

Histocompatibility

Under this regimen of preparation optimal histocompatibility did not appear to be necessary for a graft to be established. In the case of the five successful grafts perfect compatibility did not exist. In no case was there a possible host-versus-graft reaction for the ABO groups, but in two patients (Cases 1 and 8) there were incompatibilities in the HL-A system that might have caused a host-versus-graft reaction. The donor HL-A genotypes could not have been identical in any of these patients. In one graft that took (Case 4) the HL-A phenotypes were identical, but the genotypes could not reasonably be expected to be so; as the donor was the patient's half-brother, they could have only one identical haplotype. An apparently good histocompatibility does not seem to be the only condition required for a successful graft. Despite study of the phenotypes of the patient, the sibs, and the parents, we were unable to determine the identity of the HL-A genotypes of the patient and the sib donor. In Cases 5 and 10 (see Table), where there were identical phenotypes between the donor and recipient for both the ABO and the HL-A systems, the graft failed (see Table).

Aplasia

In none of the five successful grafts in this series were we able to show that the recipient's erythrocytes had been totally

Details of Cases

Case No.	Age in Years	Diagnosis	Phase	Bone Marrow Appearance	Granulopenia (<1,000/cu. mm. When Grafted)	Donor	No. of Nucleated Cells (× 10^9)	Histocompatibility				Erythrocytic Antigenic Markers		Maximum % Donor Cells	Duration of Graft (Months)	Outcome
								ABO System		HL-A System						
								Recipient	Donor	Recipient	Donor	Recipient	Donor			
*1	42	Acute myeloblastic leukaemia	Latent	Aplastic	+	Brother	28·7	A_1	A_2	HL−A7−	HL−A7+	A_1 N+S+c+ Fy^a+Le a+b−	A_2 N−S−c− Fy^a−Le a−b+	80	2	Died of infection (without leukaemia but with functioning graft)
*2	14	Acute myeloblastic leukaemia	Overt	Aplastic	+	Brother	20·8	0	0	Identical phenotypes		N+S+ Le a+b−	N−S− Le a−b+			Died of leukaemia
*3	8	Acute myeloblastic leukaemia	Overt	Aplastic	+	Father	22·4	0	0	HL−A2− HL−A3+ HL−A7+	HL−A2+ HL−A3− HL−A7−	E−	E+			Died of leukaemia
*4	30	Acute myeloblastic leukaemia	Overt	Non-aplastic	+	Half-brother	8·5	0	0	Identical phenotypes		M+K−	M−K+	80	6	Died of leukaemia (with functioning graft)
†5	19	Acute myeloblastic leukaemia	Overt	Aplastic	−	Sister	11·6	A_1B	A_1B	Identical phenotypes		D+C+	D−C−			Visible phase of leukaemia
†6	49	Acute myeloblastic leukaemia	Overt	Aplastic	+	Brother	10	A_1	0	HL−A3+	HL−A3−	A_1M+	OM−	50	>3	Visible phase of leukaemia
*7	7	Acute lymphoblastic leukaemia	Overt	Aplastic	+	Sister	26·7	A_1	A_2	HL−A1+	HL−A1−	A_1P+	A_2P−	70	2	Died of leukaemia (with functioning graft)
*8	6	Acute lymphoblastic leukaemia	Overt	Non-aplastic	−	Mother	13·4	A_1	0	HL−A3−	HL−A3+	A_1P+	OP−	50	2	Died of leukaemia (with functioning graft)
*9	17	Acute lymphoblastic leukaemia	Overt	Aplastic	+	Father	21	A_1	A_1	?		S+E−	S−E+			Died of leukaemia
†10	11	Acute lymphoblastic leukaemia	Overt	Aplastic	+	Brother	8·2	0	0	Identical phenotypes		K−	K+			Died of leukaemia
*11	62	Blastic crisis of polycythaemia vera	Overt	Aplastic	+	Son	7·8	0	0	?		E−	E+			Died of leukaemia
*12	13	Idiopathic bone marrow aplasia		Aplastic	+	Brother	19·1	A_1	A_1	Identical phenotypes		c+	c−			Died of bone marrow aplasia
*13	10	Idiopathic bone marrow aplasia		Aplastic	+	Brother	11·2	0	0	Identical phenotypes		D+C+E+	D−C−E−			Died of bone marrow aplasia
†14	39	Bone marrow aplasia (chloramphenicol)		Aplastic	+	Daughter	20·3	A_1	A_1	HL−A1−	HI−A1+	M+	M−	50	>4	Apparently normal
†15	8	Bone marrow aplasia (hepatitis)		Aplastic	+	Sister	8·3	A_1	A_1	Identical phenotypes		N+P+E+K− Fy^a+Le a−b−	N−P−E−K+ Fy^a−Le a+b−	60	>3	Great clinical improvement
*16	8	Thalassaemia		Hyperplastic	−	Father	15·8	0	0	HL−A2−	HL−A2+	P−	P+			Condition unchanged

*Recipient and donor conditioned by antilymphocytic serum before allogeneic bone marrow graft. †Recipient only conditioned by antilymphocytic serum before allogeneic bone marrow graft.

replaced by erythrocytes produced by the graft, though this has been observed in a patient given a marrow allograft after total body irradiation (Mathé *et al.*, 1963a). The maximum percentage of donor red cells in these five patients varied from 50 to 80. Nevertheless, total bone marrow aplasia is not a necessary condition for a graft to be established in a patient with acute leukaemia. In only one of five successful grafts did the leukaemic patient have complete aplasia without any detectable blasts in the marrow; the other four patients still had abnormal numbers of blasts present in the marrow when the grafts were attempted. Furthermore, agranulocytosis was not an absolute requirement; in one of the successful grafts (Case 8) there were more than 1,000 W.B.C./cu. mm. in the blood at the time of grafting.

Chemotherapy

A study of the drugs and their doses used before the patients were grafted showed no noticeable differences between the groups with failed grafts and those with successful ones. A different drug had been used for the final course of chemotherapy in each of the patients in whom grafts were established, and this course finished at least 15 days before grafting. Hence the success of the graft does not depend on the prolonged immunosuppressive effects of corticosteroid or cytostatic therapy. Tests of cell-mediated hypersensitivity reactions (B.C.G. test) have shown that such an immunosuppressive effect does not persist after chemotherapy or corticosteroids have been stopped (Schneider, 1970). The fact that the graft was successful showed that tolerance persisted after treatment with antilymphocytic serum had been stopped. In four patients the effects of the grafts persisted, with some fluctuation, until their deaths; three of them died of leukaemia and one of a bacterial infection, their grafts surviving from two to six months (see Table).

Thalassaemia

A marrow graft was attempted in an 8-year-old child with homozygous thalassaemia whose marrow was hyperplastic (Case 16). The child's father was the donor, but the graft was a failure. This treatment was well tolerated, however, and in no way was the child's condition made worse as a result of the trial.

Total Bone Marrow Aplasia

Of the four patients with total marrow aplasia, an aetiological cause could not be detected in two (Cases 12 and 13), whereas in one (Case 14) the aplasia probably resulted from chloramphenicol poisoning and in the other (Case 15) it was secondary to virus hepatitis. In Cases 12 and 13 the grafts failed, despite favourably matched histocompatibility, though the identity of the HL-A genotypes was not confirmed. In these two cases the donors had been treated with antilymphocytic serum for a week before the patients were grafted. In the two others (Cases 14 (Fig. 2) and 15) the success of the marrow allograft was confirmed. The myeloid restoration (erythrocytes, polymorphonuclear leucocytes, and platelets) was not complete immediately, but it was sufficient to cause a spectacular change in the recipients' clinical condition. These patients had been critically ill before the graft; leucocyte transfusions given without previous immunosuppressive therapy had been of no benefit. After the grafts all signs of infection, fever, and haemorrhage had disappeared. In Case 14 the marrow was not completely compatible as it had been taken from the patient's daughter (see Table), whereas in Case 15 there was complete phenotype compatibility. In these cases

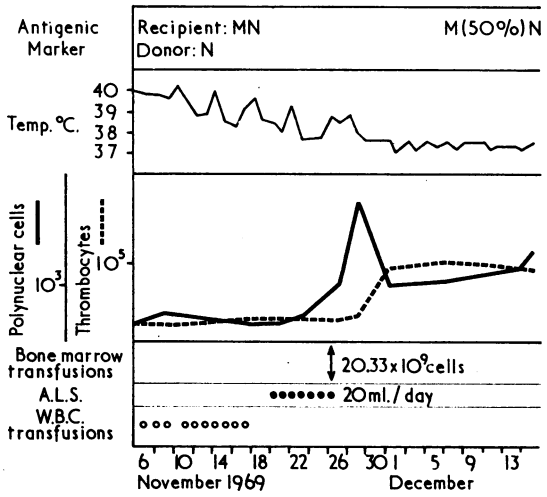

FIG. 2.—Allogeneic bone marrow graft after antilymphocytic serum in a patient with bone marrow aplasia after chloramphenicol poisoning. The previous white cells transfusions had no good effect (Case 14).

only the patients had been treated with antilymphocytic serum, while the donors were left untreated. These patients had not received cytostatic drugs and all corticosteroid therapy was withdrawn before giving antilymphocytic serum.

Graft-versus-Host Reaction

The patients in this series did not have either acute or subacute forms of secondary disease (Mathé *et al.*, 1965b). In particular, the cutaneous and gastrointestinal signs typical of the secondary disease that follows a marrow allograft after total body irradiation (Mathé *et al.*, 1960, 1965b) or after high doses of cyclophosphamide (Santos *et al.*, 1970) were absent. These signs have also followed the transfusion of large numbers of leucocytes from normal or chronic myeloid leukaemic donors in aplastic patients who had not been given immunosuppressive drugs (Schwarzenberg *et al.*, 1967).

The secondary disease was equally absent when the recipient alone had been given antilymphocytic serum (Cases 6, 14 and 15) as when both donor and recipient had been treated with antilymphocytic serum (Cases 1, 4, 7, and 8). It is not certain whether these patients developed chronic secondary disease. One patient (Case 1) died of a *Pseudomonas pyocyanea* cerebral abscess two months after grafting (Mathé *et al.*, 1968); he had had a perineal fistula infected with *Ps. pyocyanea* before the graft which later gave rise to metastatic abscesses in the joints and the brain despite an apparently complete haematological restoration. Such a development clearly suggests an underlying immune insufficiency that could have been the result of chronic secondary disease (Mathé *et al.*, 1965a, 1965b).

In those patients with septicaemia resistant to antibiotics and to white cell transfusions, but with no other signs of immune insufficiency, all signs of infection disappeared immediately after a bone marrow graft. So far no signs of a secondary immune insufficiency which would indicate a graft-versus-host reaction have developed in these patients.

Antitumour Effect: Adoptive Immunotherapy

No unequivocal antileukaemic effect was observed from the graft. Case 1 was in remission at the time of grafting and remained so until he died two months later. In four other patients who were in the overt phase of the disease no remission occurred. In Case 4 (Fig. 3) a remission occurred

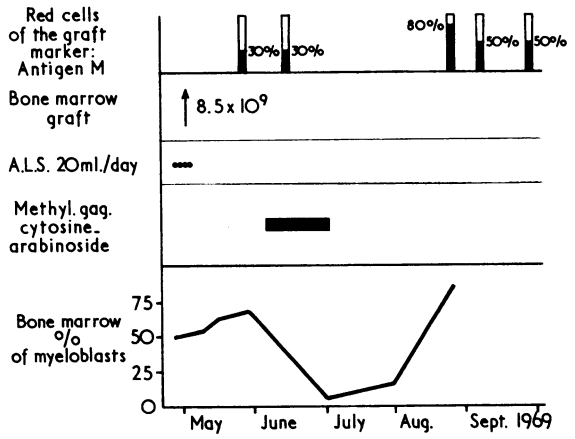

FIG. 3.—Allogeneic bone marrow graft after antilymphocytic serum in a patient with acute myeloblastic leukaemia in an overt phase of the patient. The graft was succesful but without any antileukaemic effect (Case 4).

after the graft; in this instance a new form of chemotherapy had been used which did not destroy the graft, and the leukaemia has since relapsed without causing the graft to be rejected. The production of erythrocytes by the graft was at its maximum at the time of the relapse.

Discussion

Before these trials were carried out there was no direct evidence to prove that antilymphocytic serum was effective as an immunosuppressive agent in man. In all previous trials of organ transplantation the patients were given antilymphocytic serum in combination with another immunosuppressive agent, azathioprine or prednisone (Kuss *et al.*, 1969; Carpenter *et al.*, 1970). In our trial antilymphocytic serum was given alone. Hence these grafts provide the only evidence available at the present time of antilymphocytic serum being a powerful immunosuppressive agent in man for tissue transplantation. The patients in our study had previously received various drugs, but none had received any cytostatic drugs, including steroids, in the two weeks preceding the graft, nor after the graft.

Since the start of the experimental and clinical trials (Mathé and Bernard, 1959; Mathé *et al.*, 1959b, 1960) on bone marrow transplantation after total body irradiation, we have wondered if bone marrow aplasia was necessary for the graft to proliferate, since irradiation (Mathé *et al.*, 1959b) and cyclophosphamide (Santos and Owens, 1968)—the two means used for preparing the hosts in experimental and clinical trials—both cause bone marrow aplasia as well as immunosuppression. Hence it seemed that myeloid aplasia was necessary for a successful graft. But grafts have been established in patients suffering from congenital immunodeficiency syndromes and who have lymphoid but not myeloid aplasia (Meuwissen and Good, 1970). This raises the question whether myeloid or lymphoid aplasia, or both, is a necessary condition for the success of the graft.

The trial described here does not give a definite answer to this question. In one patient the peripheral aplasia was incomplete, but in all cases, despite the presence of blastic cells in the bone marrow, the marrow tissue was severely depopulated. Moreover, animals successfully treated with allogeneic bone marrow grafts were either congenitally anaemic (Seller and Polani, 1969) or made pancytopenic by dimethyl-myleran (Floersheim and Ruszkiewicz, 1970). Hence possibly bone marrow depression is not necessary for allogeneic bone marrow grafts but is an enhancing factor.

The complication of secondary disease has usually been an obstacle in bone marrow transplantation in leukaemic patients when only total body irradiation was used for immunological conditioning (Mathé *et al.*, 1965b). In other trials in which irradiation was replaced by high doses of cyclophosphamide similarly severe secondary disease complicated the transplantation (Santos *et al.*, 1970). Another reason for using antilymphocytic serum was the difference in the manifestation of secondary disease when marrow allografts were given after total body irradiation and cyclophosphamide compared with those following such grafts in congenitally immunogically deficient patients (Bach, F. H., *et al.*, 1968; Gatti *et al.*, 1968; Koning *et al.*, 1969; Ammann *et al.*, 1970). The features of the secondary disease that complicate a marrow allograft after total body irradiation are lymphoid proliferation and infiltration of the skin and liver—probably due to the graft—and lymphoid insufficiency, which develops in patients whose immune responses were normal before irradiation. On the other hand, the only feature of the secondary disease which occurs in patients with congenital immunodeficiency diseases is lymphoid infiltration. These patients do not develop immunological insufficiency, but in fact those who were immunodeficient can be partially immunologically restored by the graft.

For these reasons total body irradiation at a lethal dose or cyclophosphamide at high doses might promote a very intensive proliferation of the graft lymphocytes, and thus be responsible for the severity of the secondary disease. If immunological insufficiency occurring during secondary disease is directly due to graft-versus-host reaction, its intensity is well correlated with the dose of irradiation administered to the host (Mathé and Pouillart, 1970).

Thus conditioning the recipient by antilymphocytic serum only before the graft does prevent the early and severe manifestations of secondary disease. It seems, however, that there is no need to condition the donor to obtain this effect, either in man or in monkeys (van Bekkum *et al.*, 1970). Nevertheless, it is more difficult to discover whether these haematological chimaeras will cause the late immunological insufficiency which is the main feature of chronic secondary disease. One patient (Case 1) died as a result of uncontrollable *Ps. pyocyanea* infection despite the good restoration of functioning myeloid tissue, but the non-leukaemic haematological chimaeras caused no signs of immunological deficiency.

In 1959 the use of marrow allografts after total body irradiation as a treatment for acute leukaemia (Mathé *et al.*, 1959b) was based on two concepts, derived from studies in animals: firstly, that lymphocytes produced by the graft were able to react against the leukaemic cells remaining after irradiation and to destroy them, and, secondly, that chemotherapy was inefficient at that time, since many patients with acute lymphoblastic leukaemias were resistant to chemotherapy, and active immunotherapy was not available. More chemotherapeutic compounds are now available for treating acute lymphoblastic leukaemia, and active immunotherapy keeps the patients in remission without relapse (Mathé *et al.*, 1969a) in cases of residual disease with a very small number of tumour cells (Amiel, 1967; Mathé, 1968). For this reason patients with acute lymphoblastic leukaemia will only rarely show indications for bone marrow grafting.

Acute myeloblastic leukaemia and acute blastic crisis of chronic myeloid leukaemia, on the other hand, are rarely sensitive to chemotherapy, and the remissions, when obtained, are very short. These diseases seem to affect not only the complete myeloid series but also the erythroblastic, megakaryocytic, and possibly monocytic precursors. It therefore seems quite logical to suppress the diseased bone marrow and to graft a normal one. It had been hoped that total body irradiation or the intensive administration of cyclophosphamide would act in this way, but this cannot be expected from antilymphocytic serum given alone. In the future an "operational" protocol to combine a subacute or chronic destruction of the myeloid tissue by irradiation or chemotherapy followed

by antilymphocytic serum administration may be required. In secondary and idiopathic marrow aplasias, our two successes—even though the myeloid restoration was incomplete—show that allogeneic bone marrow grafting after conditioning of the recipient by antilymphocytic serum is possible. For this reason non-malignant bone marrow aplasias are very good practical indications for this treatment. Marrow grafts have had a striking effect on infections or haemorrhagic syndromes which have been uncontrollable even after leucocyte transfusions without previous conditioning of the recipient. In these two successful cases the donor had not received antilymphocytic serum before grafting the marrow.

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Limitations of Radiology in the Differentiation of Diverticulitis and Diverticulosis of the Colon

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Summary: While barium enema is the most useful investigation in the primary diagnosis of diverticular disease of the colon, this paper presents further evidence that the terms "diverticulosis" and "diverticulitis" are unsatisfactory and shows that a radiological classification on the traditional criteria is not accurate in determining whether or not inflammation is associated with colonic diverticula.

Introduction

In 1914 Abbe published a paper entitled "A case of sigmoid diverticulitis simulating malignancy, demonstrated by radiology, operation and specimen." This appears to be the first account of the value of radiology in which "bismuth injection" was used to demonstrate colonic diverticula. Spriggs and Marxer (1927) stressed the importance of radiology in establishing a diagnosis and in assessing the stage of the disease. They recognized three interdependent conditions—the prediverticular state, diverticulosis, and diverticulitis. These distinctions, while widely used, have never been clearly defined and have been the subject of debate ever since. Thus, for example, the so-called prediverticular state has been represented as either diverticula in the early stages (Lockhart-Mummery and Hodgson, 1931; Edwards, 1939) or as evidence of diverticulitis (George and Leonard, 1919; Todd, 1955; Zunino, 1961).

Though initially the distinction between diverticulosis and diverticulitis was made, it is evident that confusion persists. The difficulty of distinguishing clinically and radiologically between diverticulosis and diverticulitis has been recognized and the term "diverticular disease" introduced as an acceptable compromise (Morson, 1963), but the older terms are still widely used in clinical, radiological, and pathological practice. Traditionally, the term "diverticulosis" describes the colon with multiple diverticula but with little evidence of narrowing or deformity of the lumen. Diverticulitis is said to be characterized by narrowing of the lumen, distortion and deformity of the haustral pattern, and an irregular contour.

The present study was undertaken to assess the accuracy of radiology in determining whether or not inflammation is present in association with colonic diverticula.

Patients Studied and Methods

A comparative study was made of the radiological and clinical features of 461 patients diagnosed and treated for diverticular disease of the colon at the Royal Victoria Hospital,

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