times BMR will still leave substantial energy available for physical activity, and it has therefore been argued that the FAO/WHO/UNU value may be too high.

The average energy intake in early pregnancy for all our subjects amounted to 8·95 MJ/day. Since energy intake before pregnancy and in early pregnancy did not differ, the mean pre-pregnant energy intake for all women can be taken as this value, which is quite similar to the estimated daily energy expenditure rate. Because the predicted pre-pregnant BMR was 5·9 MJ/day, in our non-pregnant women some 3·1 MJ/day were left for the two other major components of energy expenditure—physical activity and the metabolic response to food. The metabolic response to food (dietary-induced thermogenesis) is assumed to be 10% of the daily energy intake (0·9 MJ/day for this study). The remaining 2·2 MJ/day was probably used for physical activity. Our findings make it necessary completely to rethink assumptions made in the past on energy balance in pregnancy.

The energy cost of pregnancy in our women calculated as the energy deposited as new tissues plus the associated increase in basal metabolism amounted to 286 MJ, only 11% lower than the theoretical estimate of 323 MJ.[9] The present FAO/WHO/UNU Expert Consultation,[7] suggests that all 335 MJ of the extra energy cost of pregnancy should be supplied by the diet, and therefore advises an average addition to daily intake of 1200 kJ. If healthy women reduce their activity, the Expert Consultation considers an additional intake of 840 kJ/day reasonable. We observed only a very small non-significant increase in energy intake of 80 kJ/day in our women. If they had actually increased their energy intake by 840–1200 kJ/day, because of the study design and the number of subjects, we would have had a greater than 95% chance of observing such an increase. The absence of an appreciable increase in energy intake in pregnancy means that the energy balance of our pregnant women shows a gap 940 kJ/day in comparison with pre-pregnant energy balances. Part of this gap might be explained by behavioural adaptions in physical activity. The average daily energy expenditure during pregnancy in our women was 1·500 times BMR, whereas that 1 yr post partum was 1·525 times BMR. The energy savings from this difference in activity pattern will probably not exceed 170 kJ/day. Energy saving by a reduction in work pace is mainly limited to late pregnancy and to weight-bearing activities.[10,11] Therefore, it seems reasonable to assume that for our women the energy savings from behavioural adaptions in physical activity will not exceed the value of 355 kJ/day proposed by FAO/WHO/UNU.[7] Thus, our women showed an unexplained discrepancy in their pregnancy energy balance of at least 585 kJ/day.

We postulate that physiological and metabolic adaptions will result in a lowering of energy expenditure in pregnancy by a reduction in dietary-induced thermogenesis and/or an increase in work efficiency. Seitchik[12] suggests that work efficiency might be increased in pregnancy, but it seems very unlikely that this mechanism could explain the whole deficit. No studies on dietary-induced thermogenesis in pregnancy have so far been published, but in lactating women dietary-induced thermogenesis seems to be reduced.[13] This question is of great scientific and public health importance and warrants further research.

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References at foot of next column.

Hospital Practice

CRITERIA FOR SEVERE APLASTIC ANAEMIA

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Summary To study the validity of currently accepted international criteria for severe aplastic anaemia, 213 consecutive cases of bone marrow aplasia from a single institution were analysed. The distribution percentiles of peripheral blood values and multivariate analysis showed that the current reticulocyte count limit of 1% (corrected for haematocrit) is inadequate as an indicator of severe disease and should be substantially lowered. Since the choice of treatment in aplastic anaemia may depend on the prognosis current criteria for severe aplastic anaemia should be modified.

INTRODUCTION

APLASTIC anaemia has a variable course. The biphasic shape of the survival curve[1] suggests that there are at least two subgroups, one more severe than the other. Some complex attempts have been made to separate severe cases.[1-3] Simpler prognostic criteria,[4] which are considered as standard international criteria for severe aplastic anaemia, are usually adopted in clinical trials.[4-8] These criteria are: (1) marrow of less than 25% normal cellularity or a marrow of less than 50% normal cellularity with less than 30% haemopoietic cells; and (2) two or three abnormal peripheral blood values (granulocytes below $0{\cdot}5 \times 10^9$/l, platelets below 20×10^9/l, or anaemia with reticulocytes corrected for

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haematocrit less than 1%). These criteria do not seem to have been developed from an analysis of a series of patients.

An accurate prognostic classification of patients with aplastic anaemia will permit not only comparison between different series but also selection of adequate therapy for individual patients. When a donor is available, it may be difficult to decide between bone-marrow transplantation (BMT) and immunomodulatory treatment (IM). This decision needs to be taken quickly because delay increases the likelihood of treatment failure.[7-9] One criterion is age; in younger patients BMT yields better results than IM while in older patients, the reverse seems true.[10] An additional criterion might be the severity of aplastic anaemia. BMT could be reserved for severe aplasias with no residual haematopoiesis and a low probability of autologous haematopoietic reconstitution. IM, a less risky procedure, has been used in non-severe aplastic anaemia[8] and the probability of a response to IM seems to be greater the more residual haematopoiesis there is.[7,11,12]

We have evaluated current prognostic criteria in a series of patients with aplastic anaemia.

PATIENTS AND METHODS

116 male and 97 female patients (mean age 37·8, SD 21·1) from one institution were included in the study. Aplastic anaemia (idiopathic in 119 cases, secondary in 94) was diagnosed on currently accepted criteria.[1] 134 patients were treated with androgens, 40 patients underwent BMT, and 39 received IM.

To study whether the current haematological cut-off points were adequate we analysed, besides % reticulocytes (corrected for haematocrit) and granulocyte and platelet counts, mean corpuscular volume (MCV) and monocyte count, both shown to be of prognostic value.[3,12] Statistical techniques used were: multivariate principal-component analysis (not presented in detail here); survival analysis (restricted to patients treated with androgens or IM [ie, treatments depending on haematopoietic self-restoration]) by the actuarial method of Kaplan and Meier;[13] and the Mantel-Cox test.[14]

RESULTS

All five peripheral blood indices at diagnosis were significantly correlated with one another (r ranging from 0·15 to 0·60). Table I shows the distribution, in percentiles, for these peripheral blood values. We chose percentiles 42·5, 66, and 90 because these in turn yielded the three main cut-offs currently used. Thus the cut-off of 1% for reticulocytes encompassed an unwieldy 90% of patients. Percentile 42·5 is a more reasonable proportion. The percentile corresponds to $0{\cdot}5 \times 10^9/l$ granulocytes and $10 \times 10^9/l$ platelets, but to only 0·14% for corrected reticulocytes (table I).

TABLE I—DISTRIBUTION PERCENTILES OF PROGNOSTIC VARIABLES

Percentile	Reticulocytes (% corrected for haematocrit)	Granulocytes ($\times 10^9/l$)	Platelets ($\times 10^9/l$)	MCV (fl)	Monocytes ($\times 10^9/l$)
42·5	0 14	0 50*	10·0	90	0·06
66	0 36	0·95	20·0*	97	0·14
90	1·00*	2·10	46·0	109	0·25

*Limits of current criteria for severe aplastic anaemia.

TABLE II—PRINCIPAL COMPONENT ANALYSIS*

Group	Reticulocytes (% corrected for haematocrit)	Granulocytes ($\times 10^9/l$)	Platelets ($\times 10^9/l$)	MCV (fl)	Monocytes ($\times 10^9/l$)
1 (N = 105)	0·14	0·31	13·6	89·1	0·04
2 (N = 84)	0 53	1·17	29·7	96 4	0·15
3 (N = 24)	1 23	3·25	127·3	102·9	0·35
Total (N = 213)	0 42	0·98	32·8	93·5	0·12

*Mean values of prognostic variables.

Principal component analysis yielded three groups of patients (table II): group 1 (49% of total) probably includes most cases of severe aplastic anaemia. Fig 1 shows the survival curves of patients classified according to current criteria. Cases with only one peripheral blood criterion (or none) clearly had a much better chance of survival than those meeting two to three criteria. A subset of patients with much better survival can be isolated from the group with two or three criteria (fig 2): this subgroup was the one with less than 1% corrected reticulocytes and less than $20 \times 10^9/l$ platelets.

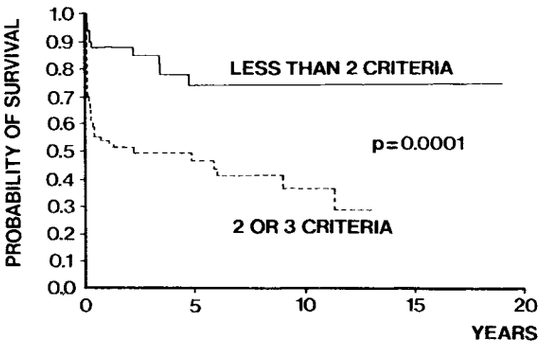

Fig 1—Survival curves of patients classified according to current criteria of severe aplastic anaemia.

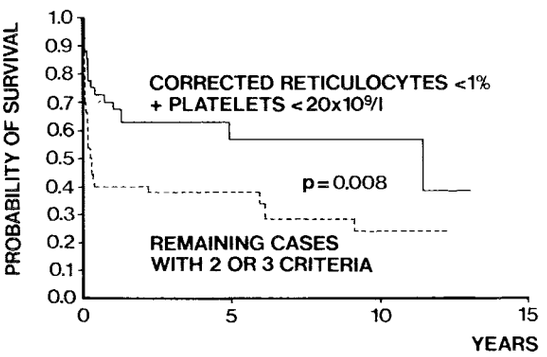

Fig 2—Subgroups of patients with two or three criteria of severe aplastic anaemia.

DISCUSSION

It is generally agreed that the more severe the bone marrow failure the more pronounced the peripheral blood cytopenia. This is why low cell counts have been included in every attempt to devise prognostic criteria for aplastic anaemia. It is not surprising to find that the different peripheral blood values are significantly correlated, and it might have been expected therefore that different levels of cytopenia reflecting different degrees of marrow failure would be similarly distributed. However, the distributions we found (table I) show that the cut-offs for the three current peripheral blood criteria for severe aplastic anaemia

correspond to percentiles that are wide apart. Most patients had less than 1% corrected reticulocytes irrespective of the degree of their aplasia. If we accept that about 40% of patients with aplastic anaemia have the severe form, the recommended cut-off points based on our series (percentile 42·5) would be $0·5 \times 10^9$/l granulocytes, 10×10^9/l platelets, and 0·14% reticulocytes. The lack of discriminant capacity of a reticulocyte cut-off point of 1% was further demonstrated by our survival studies.

Although in some studies[8] the degree of aplasia, as estimated by peripheral blood counts or haematopoietic cellularity in bone marrow, was not correlated with the response to IM, some data suggest that a response is more likely the more residual haematopoiesis there is.[7,11,12] Torok-Storb et al[12] identified, by flow microfluoriometry, a population of small cells phenotypically associated with the erythroid lineage which was strongly correlated with the response to IM. In their series responders and non-responders differed significantly in respect of corrected reticulocytes (mean 1·26 [SD 1·19]% *vs* 0·46 [0·36]%; $p < 0·01$) and cases without detectable monocytes (0/22 *vs* 11/28; $p < 0·001$). These findings suggest a greater marrow reserve in responders. Similarly in a series of 24 patients treated with antilymphocyte globulin we found (unpublished) that the response was significantly associated with two pretreatment variables that probably reflect a greater marrow reserve—namely, higher monocyte count and higher MCV.

Pending larger multicentre analyses, it seems reasonable to maintain the current criteria for severe aplastic anaemia, except that the reticulocyte level (corrected for haematocrit) should be substantially lowered, to 0·25% at least.

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Anniversary

WHAT SHOULD BE DONE ABOUT SMALLPOX VIRUS?

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THAT landmark in medical history, the last endemic case of smallpox, will have its tenth anniversary this week. The occasion will not be loudly celebrated; nevertheless, the world has remained free of smallpox and the success of the eradication campaign seems fully established. The only known sources of variola virus are now the archival stocks held in two maximum-containment laboratories. Do these stocks of virus serve any function sufficiently worthwhile to justify their retention?

No scientist is working with viable variola virus or is likely to be allowed so to do. Although the variola stocks, technically, are safe enough, they present some political drawbacks. Many people, justifiably suspicious of official reassurances, will continue to believe that these viruses are a physical, infectious hazard. This is especially true in Britain, where past laboratory accidents are well remembered.

Would the destruction of these laboratory stocks be the end of all viable variola virus? There is concern about the possible survival of the virus in burial grounds or in mummified corpses of smallpox victims. The epidemiological evidence is that fomites have only exceptionally given rise to smallpox outbreaks and then only after short intervals. However, some investigations of virus survival in smallpox scabs indicate that they might be infective for several years. To extrapolate from these studies to the real risk under natural conditions is difficult, but danger from this source seems to be negligible. Although it would be prudent to take common-sense precautions if the remains of victims should have to be disturbed, there is no reason to think them a serious threat of the return of smallpox—borne out by the failure to demonstrate infectious virus in some mummified specimens, despite morphological evidence of recognisable virus particles. Smallpox could not anyway become established again as an endemic disease in civilised societies. Our understanding of the epidemiology and mode of spread of the variola virus is sufficient for any unforseen outbreak to be eliminated within the first few interhuman transmissions.

After the eradication of smallpox it was agreed that the virus should be retained by a few high-containment laboratories (i) to clarify the status of a few viruses that seemed to be variola but which had been isolated from non-human specimens; and (ii) to determine how closely variola virus was related genetically to various animal pox viruses. Monkeypox virus in particular had been suggested as a possible immediate ancestor of variola. Virus genetics experiments were initially done with live variola virus. Such experiments are no longer necessary because the genetic material of variola virus has, since 1981, been maintained in a series of bacterial plasmids. In this form the virus is not a hazard and the genetic studies may safely be continued by comparison of the structure and sequence of DNA molecules.

At the end of 1977, when all natural transmission of smallpox had ceased, there were still many laboratories that