The Radiobiology of Human Cells and Tissues

The Radiobiology of Human Cells and Tissues

Proceedings of the 15th L. H. Gray Conference

held at

The University of Kent,
Canterbury, U.K.

11–15 April 1989

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Preface

The 15th L. H. Gray Conference was held at the University of Kent at Canterbury, U.K., from 11 to 15 April 1989. There were 130 participants from 15 different countries. This was perhaps the first international meeting that specifically focused on the radiobiology of *human* cells and tissues. The intention was to review data on radiation effects at four levels: subcellular, cellular, tissue (i.e. xenograft) and clinical. Data on tumour and normal-tissue cells were included.

This is a topic in which there is increasing scientific interest. Over the past few years the techniques of xenografting and human–tumour cell cloning have led to a growing tendency to prefer human rather than mouse tumour systems for experimental tumour therapy. There is a rapidly expanding literature on the cellular and molecular characterisation of human genetic disorders that are associated with radiosensitivity. Some newer approaches to the improvement of radiotherapy *require* data on human tumour cells, for instance the attempts to predict clinical response in individual patients on the basis of laboratory data or to calculate the therapeutic effectiveness of targeted radioisotopes.

The meeting consisted of a mixture of invited review papers and shorter proffered contributions. All the manuscripts were refereed according to the usual procedures of the Journal. One half day was devoted to a Symposium on the Molecular Basis of Radiation Sensitivity. A highlight of the meeting that does not appear in the published proceedings was the Conference Lecture by Professor Dirk Bootsma on 'The Molecular Biology of DNA Repair'.

This was a successful meeting that was enjoyed even by the organisers.

G. Gordon Steel
July 1989

The L. H. Gray Memorial Trust

This 15th L. H. Gray Conference was organised under the auspices of the L. H. Gray Memorial Trust, founded in 1967 by the British Institute of Radiology, the Association for Radiation Research and the Hospital Physicists' Association (now the IPSM). The purpose of the Trust is to commemorate the work of the late L. H. Gray, to further, for the benefit of the public, the knowledge and understanding of all apsects and all applications of radiation and kindred sciences, and to promote research and exchange of knowledge concerning such sciences by the organisation of conferences.

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The picture has changed in the 1980s†

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Substantial developments have been made during the 1980s in the radiobiology of human tumours, in particular in studies of the radiosensitivity of human tumour cells. It is now clear that tumour cells differ considerably in radiosensitivity, to an extent that by itself is capable of explaining the clinical response of tumours to radiotherapy. There also is evidence that the radiosensitivity of human tumour cell lines to low radiation doses correlates with clinical experience. Irradiation at low dose rate amplifies the differences between cell lines. In conjunction with mathematical modelling, a study of the dose-rate effect also allows a distinction to be drawn between repairable and non-repairable damage. The differences seen between cell lines at low acute doses or low dose rates are associated with the non-repairable component. The most radiosensitive cell lines have a steep component of non-repairable damage and they give the impression of being recovery-deficient; this may, however, be incorrect for when evaluated at constant dose levels recovery is found to *increase* with increasing radiosensitivity. This leads to the view that recovery from radiation damage may reflect the amount of recoverable damage inflicted rather than the 'capacity' of the cells to recover.

1. Introduction

Prior to 1980 most studies of the radiobiology of tumours were done on mice. These employed a range of transplanted (or occasionally spontaneous) murine tumours, and cell lines derived from them. A question often discussed was which type of mouse tumour provides the best model for human cancer: no satisfactory answer is possible. Berry (1974) summarized early cell survival data on murine tumour cell lines, including lymphomas, sarcomas and carcinomas, and concluded that there were no significant differences. Some human tumour cell lines were studied *in vitro* during the 1970s, notably the HeLa line derived from a cacinoma of the cervix, also the experiments on melanoma cells by Barranco *et al.* (1971), and others. The Sixth L. H. Gray Conference (Alper 1975) emphasized the mechanistic and clinical importance of the initial slope of the cell survival curve, but there were few hints at that time of an actual correlation with clinical response. V. D. Courtenay developed an improved method for cloning human tumour cells *in vitro* and this led to the first cell survival curve for human tumour cells irradiated *in vivo* as a xenograft (Courtenay *et al.* 1978). Weichselbaum *et al.* (see review, Weichselbaum, 1980) compared the *in vitro* radiosensitivity of a range of human tumours of differing radiocurability and found no difference.

This paper describes changes that have occurred largely during the 1980s. They will mostly be illustrated with results from this laboratory but it is not thereby claimed that our work has been pre-eminent.

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2. The initial slope of the cell survival curve

An important development was the survey performed by Fertil and Malaise (1981) of the *in vitro* radiosensitivity of human tumour cells and their demonstration that the response *at low doses* correlated with the clinical response characteristics of the various tumour types. This study included 26 non-HeLa cell lines, and as a measure of radiosensitivity Fertil and Malaise used the surviving fraction at 2 Gy (which we may call SF_2); it is convenient that 2 Gy is also a typical dose per fraction in clinical radiotherapy. It has become customary to describe SF_2 as a measure of the initial slope of the cell survival curve. This is based on the linear-quadratic model (see below) in which the initial slope is given by α, and on the fact that for most mammalian cell lines the survival at 2 Gy is close to this slope.

We ourselves were so surprised at the correlation found by Fertil and Malaise that we repeated the survey of the published literature, extending it to include 51 non-HeLa cell lines, and employing a somewhat more cautious ranking of clinical responsiveness to radiotherapy (Deacon *et al.* 1984). The results confirmed the conclusions of Fertil and Malaise: SF_2 values range widely, but they average about 0·5 for the least responsive tumours and about 0·15 for the most responsive. We showed that the discrimination between different cell lines was best at around 2 Gy and argued that since the effect of N fractions of 2 Gy is roughly $(SF_2)^N$, the difference between 0·5 and 0·15 is by itself capable of explaining success and failure in clinical radiotherapy.

Figure 1 shows the results of a more recent update of this review (Steel 1988).

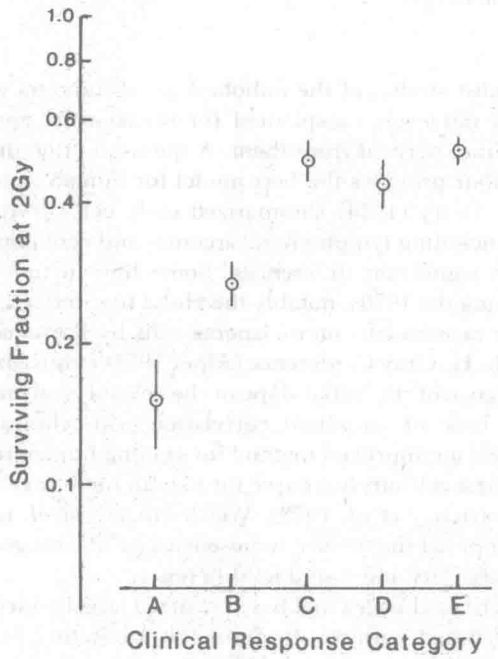

Figure 1. The surviving fraction at 2 Gy for 76 human tumour cell lines. Clinical radioresponsiveness is classified among groups A–E, A the most responsive and E the least (from Steel 1988).

The clinical response categories are as described by Deacon *et al.* (1984), A being the most locally curable by radiotherapy and E the least. The number of cell lines is now increased to 76 and the results are plotted as the mean and standard error for each category. This does not indicate the overall spread in the data, which is very broad, but it does show that amongst categories C, D, and E there is no difference, whilst categories A and B have significantly lower survival at 2 Gy and thus a steeper initial slope.

The possible clinical impact of such differences is indicated in figure 2. It is a very bold assumption that SF_2 values obtained on oxic cells irradiated *in vitro* might apply *in vivo*, mainly because of the modifying effects of hypoxia and intercellular contact. Nevertheless, if we make this assumption, and also assume that SF_2 is constant through a clinical course of 2 Gy fractions, we get the straight lines shown in figure 2. The vertical scale is the number of clonogenic cells per tumour (assumed initially to be 10^9) and the horizontal scale is dose, given in 2 Gy fractions. Changing SF_2 only from 0·2 to 0·6 produces the fan of lines shown. The number of clonogenic cells that might survive 60 Gy ranges from 220 to below 10^{-6}, and the dose to reduce survival to one cell ranges from 26 to 80 Gy. In view of the fact that this calculation ignores the modifying processes mentioned above, it is remarkable that this range of tumour cure doses corresponds to clinical experience with radiotherapy of sensitive and resistant diseases. This suggests that SF_2 could be an important and very sensitive determinant of the overall effect of a course of fractionated radiotherapy (Barendsen, 1980).

3. Time–dose relationships: the emergence of the linear-quadratic model

The linear-quadratic equation for cell killing has been actively discussed for many years (Kellerer and Rossi 1972, Chadwick and Leenhouts, 1973). Although

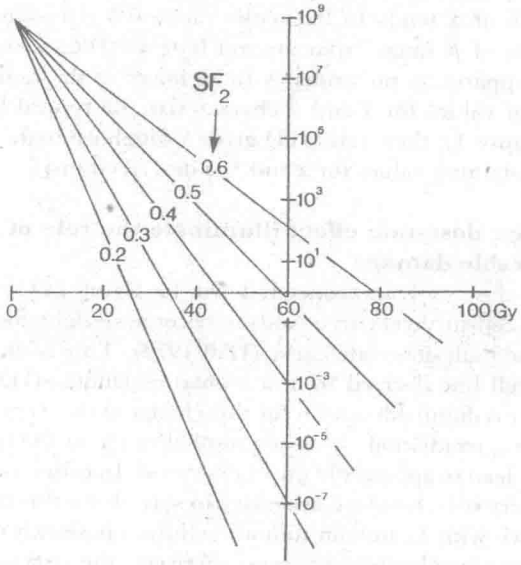

Figure 2. The effect of multiple 2 Gy fractions in reducing cell survival within a tumour that initially contains 10^9 clonogenic cells. Lines are calculated for various values of SF_2.

attempts have been made to describe a mechanistic basis for this relationship, most people now regard it as a simple, continuously bending survival equation that well simulates much experimental data and thus is empirically useful:

$$\text{Surviving fraction} = \exp(-\alpha D - \beta D^2) \quad (1)$$

An important stimulus for change in radiobiological thinking was the paper by Thames *et al.* (1982) that first drew attention to systematic differences among the normal tissues of experimental animals in the steepness of 'reciprocal-dose plots' for fractionated radiotherapy. The analysis was in terms of the linear-quadratic equation, and it was found that the ratio of α to β was generally lower in late-responding than in early-responding normal tissues. Although it is still not clear whether values for α/β obtained in this way do correspond to the properties of the target cells, this implied that survival curves for the late-responding tissues were more 'curvy' in the low-dose region. The therapeutic implication was that if tumour cells have a high α/β ratio there will be a tendency to spare late normal-tissue reactions by the use of a reduced dose per fraction. This has led to much experimental interest in the α/β ratio (Fowler 1984, Williams *et al.* 1985) and to clinical attempts to evaluate hyperfractionation (i.e. multiple small fractions per day).

It is now widely realized that the linear-quadratic equation successfully fits most cell survival data for human tumour cell lines, and authors are increasingly making the switch from quoting radiosensitivity in terms of n and D_0 to α and β. Unfortunately, the values that are obtained by fitting acute cell survival data alone are not very precise: rather similar curves can be produced by trading off an increase in α with a decrease in β. Some values from our own work on human tumour cell lines are given in table 1 (see Steel and Peacock 1989). It can be seen that with the exception of the highly radiosensitive cell lines (neuroblastomas and WX67), the value of α tends to lie in the range 0·2–0·6 with a mean of about $0{\cdot}35\,\text{Gy}^{-1}$. Values of β range from around 0·02 to 0·06, with a mean of about $0{\cdot}032\,\text{Gy}^{-2}$ and apparently no tendency to be lower in the radiosensitive tumour lines. These mean values for α and β characterize the typical human tumour (of groups C–E in figure 1); their ratio (11) gives a rough estimate of the α/β ratio. A new method of obtaining values for α and β is described in § 7.

4. Studies of the dose-rate effect illuminate the role of recoverable and non-recoverable damage

As radiation dose rate is reduced down to about 2 cGy/min cell survival increases and the cell survival curve tends to become straight and to extrapolate the initial slope of the high dose-rate curve (Hall 1972). This is illustrated in figure 3 with data for a cell line derived from a human melanoma (HX118, Kelland and Steel 1986). The predominant reason for this change is recovery of cellular damage taking place during irradiation. At dose rates below about 1 cGy/min cell proliferation will usually lead to apparently greater survival. In order to derive information on cellular recovery it is therefore necessary to stay above this limit.

Our experience with 12 human tumour cell lines is shown in figure 4. At high dose rate there is considerable difference between the survival curves, and the values at 2 Gy are consistent with those shown in figure 1. The most sensitive cell lines produce high-dose-rate curves that are close to exponential. At the lower dose rate of around 2 cGy/min most of the curves have become straight and they have

Table 1. Linear-quadratic parameters† of a group of human tumour cell lines.

					Surviving fraction at 2 Gy†		
		α	β	α/β	α effect	β effect	SF_2
HX34	Melanoma	0·32	0·030	11	0·53	0·89	0·47
HX118	Melanoma	0·36	0·032	11	0·49	0·88	0·43
HX32K	Pancreas	0·42	0·060	7	0·43	0·79	0·34
HX58	Pancreas	0·66	0·021	31	0·27	0·92	0·25
HX99	Breast	0·20	0·052	4	0·67	0·81	0·54
HX156	Cervix	0·16	0·037	6	0.72	0·86	0·62
WX67	Bladder	1·18	0·008	150	0·095	0·97	0·09
HX144	Lung AdCa.	0·44	0·009	49	0·42	0·96	0·40
HX148	Lung AdCa.	0·32	0·017	19	0·53	0·93	0·49
HX147	Lung LC	0·056	0·048	1·2	0·89	0·82	0·74
HC12	Lung SC	0·43	0·019	23	0·42	0·93	0·39
HX149	Lung SC	0·63	0·024	26	0·28	0·91	0·26
RT112	Bladder	0·10	0·029	3	0·82	0·89	0·73
GCT27	Teratoma	0·37	0·044	8	0·48	0·84	0·40
HX138	Neurobl.	1·08	0·005	180	0·12	0·98	0·11
HX142	Neurobl.	0·84	0·081	10	0·19	0·72	0·13
HX143	Neurobl.	1·16	0·03	27	0·10	0·89	0·08
Mean		0·51	0·032		0·44	0·88	0·38
Standard error		0·36	0·020		0·24	0·07	0·21

†α and β values obtained from the acute cell survival curve.
‡α effect × β effect = SF_2.
From Steel and Peacock (1989).

fanned out. The right-hand panel in figure 4 very graphically illustrates the range of radiosensitivity among human tumour cell lines: in terms of the dose required to give a survival of 0·01 they differ by a factor of approximately 7. It can be seen from figure 3 that the low-dose-rate curves (1–2 cGy/min) roughly extrapolate the initial slope of the high dose-rate survival curves. Thus the family of low dose-rate curves in figure 4 approximately indicate the expected effects on oxic tumour cells of fractionated radiotherapy with low dose per fraction. The notion mentioned in § 1 that tumour cell lines do not differ much in radiosensitivity is thus dramatically refuted.

4.1. *Dynamic models of cell killing*

The value of dose-rate studies of this type is greatly increased by mathematical modelling. Most cell survival equations are static in that they do not handle dose rate or treatment duration. A further important development in the 1980s has been the description of dynamic cell survival equations. The following are two that we have used extensively.

4.2. *The lethal–potentially lethal (LPL) model (Curtis 1986)*

This mechanistic model envisages that radiation induces two types of lesion: lethal lesions that are non-repairable, and potentially-lethal lesions whose fate depends upon competing processes of repair and fixation. Fixation is envisaged as binary interaction between sublesions leading to lethality. It is this assumption that

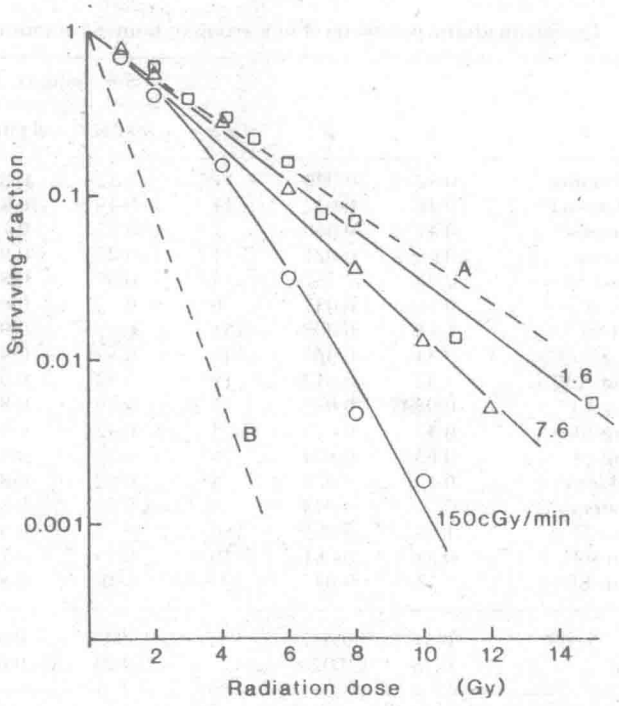

Figure 3. Cell-survival curves for a human melanoma cell line (HX118) irradiated at 150, 7·6, or 1·6 cGy/min. The data are fitted by the LPL model from which we derive the survival curve where repair is complete (curve A) or totally absent (curve B). From Steel *et al.* (1987).

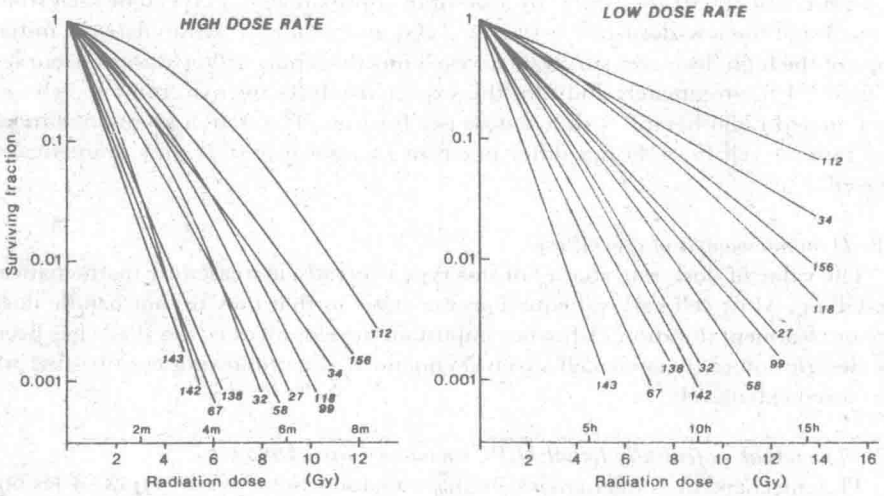

Figure 4. Cell-survival curves for 12 human tumour cell lines irradiated at high dose rate (approx. 150 cGy/min) or low dose rate (approx. 1·6 cGy/min). From Steel *et al.* (1987).

generates the bending component in cell survival, and in the low-dose approximation this component is quadratic. In contrast, the lethal lesions are single-hit events that generate a linear component of cell killing. The LPL model provides a unifying view of radiation damage repair, simulating the shoulder on the cell survival curve, low dose-rate recovery, and delayed-plating recovery.

The data in figure 3 are all simultaneously fitted with the LPL model. The derived line A indicates the component of non-repairable damage. Line B is also derived from the fit and it indicates the survival that would be expected if no repair occurred (i.e. if every lesion is lethal). The 150 cGy/min curve is higher than line B due to 'unstoppable repair' of potentially lethal lesions. For acute doses of 2 Gy or less, this repair is almost complete.

4.3. *The incomplete repair (IR) model (Thames 1985)*

This is an empirical model based on the assumption that cell survival at high dose rate is linear-quadratic and that the dose-equivalent of effect decays exponentially with time. This leads to

$$S = \exp(-\alpha D - \beta \cdot g \cdot D^2) \tag{2}$$

where

$$g = 2[\mu t - 1 + \exp(-\mu t)]/(\mu t)^2$$

(where S is survival after an exposure time t at dose rate D/t; μ is the time constant for recovery, i.e. ln(2)/half-time). Note that the time-dependent function influences only the D^2 term in the linear-quadratic equation. For very short exposure times $g \rightarrow 1$ and the curve is given by the linear-quadratic equation. As the duration of exposure increases, $g \rightarrow 0$ and survival approaches that given by the linear term in the equation.

4.4 *Comparison of models*

These two models have very similar properties and in the low-dose range they are equivalent (Thames 1985). The LPL model has the advantage of being based on mechanistic concepts, but so far as we know this has not so far allowed useful deductions to be made about the reason why one cell line is more sensitive than another. The LPL model has five parameters (compared with three for the IR model) and in our experience it is difficult to obtain sufficient data to locate these reliably.

Both models envisage that radiation cell killing is described by two components, one linear and the other bending. The linear component is determined in the IR model by the parameter α; in the LPL model this is the component of direct infliction of lethal lesions. In both cases the linear component is conceived as being non-recoverable during continuous or fractionated radiation exposure. The bending component is determined by β in the IR model, and in the LPL it depends on the frequency of induction of potentially lethal lesions, on the rate constants for repair and fixation, and on the time available for repair. This assumption that there are two underlying components is also a feature of other (static) models of cell killing. A linear term must be added to the multitarget model in order to simulate a finite initial slope (Bender and Gooch 1962). The Q-repair model of Alper (1979) also requires a linear component of non-repairable damage for the same reason.

5. Importance of the linear component of radiation cell killing

It has long been appreciated that cellular response at low radiation doses is dominated by the linear component. What has perhaps not widely been realized is the extent to which differences in response to fractionated radiotherapy could be attributed to differences in the steepness of this component; the therapeutic and mechanistic implications of this have also not been widely discussed.

In a recent publication (Steel and Peacock 1989) we calculated for the human tumour cell lines studied in this laboratory the relative contributions of the linear and bending components of cell killing to the surviving fraction observed at low radiation doses. The values for α and β were obtained only from acute survival curves and are therefore subject to considerable uncertainty. The contributions at 2 Gy are listed in table 1, and in figure 5 they are shown graphically at four dose levels. The linear-quadratic model is assumed, and it must be emphasized that we do not know that it applies perfectly at these low dose levels. These tumour cell lines cover the full range of clinical radiocurability, and yet it can be seen that at 2 Gy almost all the dispersion in sensitivity is due to differences in the steepness of the α-component. The β-effects are small. Following the type of calculation used in figure 2 the effect of fractionated radiotherapy with 2 Gy doses will be related to a power function of the 2 Gy survival; this will magnify the differences between the α- and β-contributions, and the latter will then be even less significant. At 1 Gy (figure 5) this conclusion is even more true. At higher doses the β-effect increases with the square of the dose and it then becomes important. But this line of reasoning leads to the conclusion that for doses per fraction below about 2 Gy the nature of differences in radiosensitivity between these tumour types is to be sought in the linear, not the quadratic (recoverable) component.

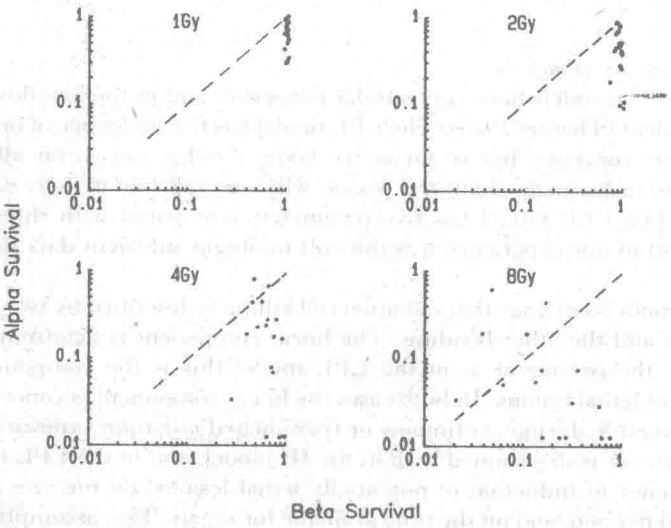

Figure 5. Relationship between the surviving fraction due to the α-component and that due to the β-component, calculated at four dose levels for 17 human tumour cell lines. The dashed lines indicate equal values. At 4 Gy and 8 Gy the points at the bottom of the diagram indicate a survival of 0·01 or less. From Steel and Peacock (1989).