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A TEST OF SEVERAL PARAMETRIC STATISTICAL MODELS FOR ESTIMATING SUCCESS RATE IN THE TREATMENT OF CARCINOMA CERVIX UTERI

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Summary.—The parametric statistical models discussed include all those which have previously been described in the literature (Boag, 1948—lognormal; Berkson and Gage, 1952—negative exponential; Haybittle, 1959—extrapolated actuarial) and the basic data used to test the models comprised some 3000 case histories of patients treated between 1945 and 1962. The histories were followed up during the period 1969–71 and thus provided adequate information to validate long-term survival fractions predicted using short-term follow-up data. The results with the log-normal model showed that for series of staged carcinoma cervix patients treated during a 5-year period, satisfactory estimates of long-term survival fractions could be predicted after a minimum waiting period of 3 years for stages I and II, and 2 years for stage III. The model should be used with a value assumed for the log-normal paramater S in the range S = 0·35 to S = 0·40. Although alternative models often gave adequate predictions, the lognormal proved to be the most consistent model. This model may therefore now be used with more confidence for prospective studies on carcinoma cervix series and can provide good estimates of long-term survival fractions several years earlier than would otherwise be possible.

ALTHOUGH the 5-year survival rate or, in more general terms, the m-year survival rate, determined from an m-year follow-up of all the surviving patients, is widely used as a criterion of success in cancer therapy, it is too crude and too long delayed a statistic to be a satisfactory way of comparing alternative treatments during the working life of a surgeon or radiotherapist. Even if this rate is assessed by the actuarial (*i.e.* life table) method, it still requires that a considerable proportion of all cases shall have survived the full m-year term. Statistical models which attempt to allow for the delayed mortality during the follow-up period have rarely been used, partly perhaps because when they were first put forward (Boag, 1949; Berkson and Gage, 1952) the tedious computation involved had to be done by hand. The digital computer has solved that problem for us and if the logical framework of a model can be shown to be valid, the evaluation of the various parameters is now easy. Such models do provide a way of bringing to bear a great deal of valuable past experience upon the assessment of new short-term results. Indeed, they often allow a useful prediction of longer term results to be made from the available short-term data. Moreover, the detailed classification they demand can be of help in assessing whether an improvement in m-year survival rate is due to long-term cures or merely to protracted survival with cancer. Confidence in any such model must, however, be built up by its successful use on actual follow-up data. This can be done retrospectively by using records of cases treated many years ago and followed up at intervals until death with or without cancer or long-term symptom-free survival had been

proved. However, detailed case histories are necessary and these are not readily available in sufficient numbers or over long enough periods—certainly not in a single cancer centre. The Regional Cancer Registries which provide data for the Office of Population Censuses and Surveys do, indeed, have data in bulk but not in sufficient detail for testing a parametric model, and since 1970 they are no longer required to record the disease stage (O.P.C.S., 1970). Also, there is no uniformity of data collection, storage and retrieval within the medical records departments of different hospitals. The only accurate method of obtaining the essential treatment and follow-up information is to consult the original hospital case records at a number of centres.

For the present study on a single site—carcinoma cervix uteri—material has had to be gathered from 6 large cancer centres, covering a 25-year period. We have used this material to test several possible statistical models which have been suggested, and some new ones.

These tests have been made in 2 stages—firstly, the actual survival time distribution for each group of patients examined has been compared, for each model, with the postulated analytical form, choosing the model parameters to give the best fit, and assessing the goodness of fit achieved by a χ^2 test. Secondly, accepting only the limited survival data which would have been available a few years (2, 3 or 4 years) after the end of the 5-year period under review, the models were used to predict the 7-year, 10-year or 15-year survival fractions as well as the proportion of long-term cures " C ". These predicted values were then compared with the observed 7-, 10-, or 15-year results, taking account of the standard errors of both predicted and observed results. The rationale of this " prediction " and " proof " test is illustrated in Fig. 1.

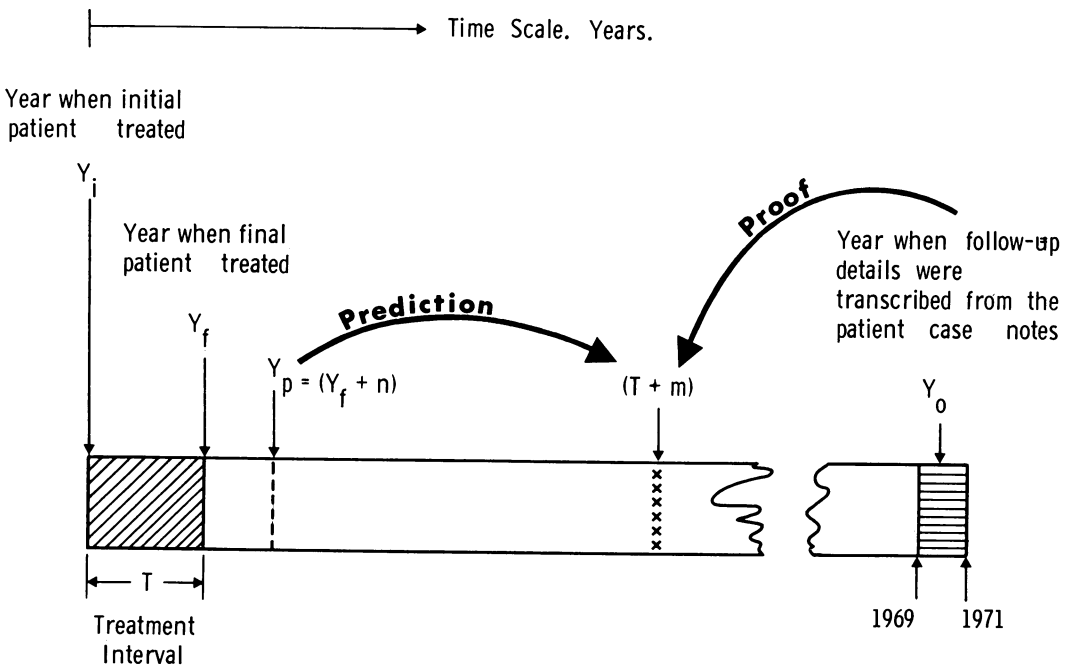

FIG. 1.—Validation of a statistical model.

MATERIALS AND METHODS

Patients

Two major factors which affect prognosis in cancer are the site of the disease and the stage it has reached before treatment. For this study we have therefore selected a single site and have separated cases into stage groups before analysis. Between 1969 and 1972 some 6000 case histories were examined of women treated between 1925 and 1962 at the hospitals listed in Table I.

TABLE I.—*Carcinoma Cervix Case Histories Available for Analysis*

Stage	Hospital	Treatment years
I–IV	Middlesex	1925–62
I–IV	Royal Marsden and Chelsea	1929–62
I–IV	University College	1941–62
I–IV	Hammersmith	1942–62
I	Christie, Manchester	1945–59
I	Oslo	1955–59

For those London hospitals included, all case records still available were reviewed and these data are therefore complete in the sense that no further data exist at these hospitals for carcinoma cervix treatments before 1962. It can be assumed that data before 1945 are fragmentary inasmuch as many of the early records have either been lost or destroyed. In view of this uncertainty, only post-1945 records have been used to test the various statistical models and the post-1945 era has been subdivided into three 5-year treatment periods—1945–49, 1950–54 and 1955–59. Since the records were examined in the period 1969–72 there was a minimum follow-up period of 20 years for the 1945–49 group, of 15 years for the 1950–54 group and of 10 years for the 1955–59 group.

The stage I groups from the 4 London hospitals were much smaller than the stage II or stage III groups, and therefore additional data for stage I was obtained from Manchester and from Oslo for the period 1945–59. Table II shows the grouping of cases available to test the validity of the different statistical models. For stages I–III there are data from at least 2 different single or grouped centres for each 5-year treatment period, except for stage III during the period 1945–49 where only a single group from the London hospitals was available.

TABLE II.—*Grouping by Stage, Hospital and Treatment Period*

Hospital	Treatment period	Stage	Total cases	Reference letter
CHUM	1945–49	I	138	A
CHUM	1950–54	I	179	B
CHUM	1955–59	I	265	C
Z	1945–49	I	101	D
Z	1950–54	I	127	E
Z	1955–59	I	292	F
N	1955–59	I	553	G
CHUM	1945–59	I	582	AA
Z	1945–59	I	520	BB
H	1945–49	II	68	H
C	1945–49	II	110	I
MU	1945–49	II	97	J
MU	1950–54	II	86	K
C	1950–54	II	144	L
H	1950–54	II	143	M
C	1955–59	II	117	N
MU	1955–59	II	123	O
H	1955–59	II	152	P
CHUM	1945–59	II	1040	CC
CHUM	1945–49	III	170	Q
CMU	1950–54	III	115	R
H	1950–54	III	90	S
MU	1955–59	III	77	T
H	1955–59	III	78	U
C	1955–59	III	78	V
CHUM	1945–59	III	608	DD
CHUM	1945–59	I+II+III	2230	EE

The stage IV group was also small and was gathered only from the London hospitals. Stage IV is not of any value for testing predictive models but we have tested its conformity with the survival time distribution of the unsuccessfully treated cases. The letters C, H, U, M, Z and N refer to the 6 hospital centres of Table I.

Methods

(a) *Construction of a statistical model.*—When a large group of patients is treated for cancer, a temporary remission is achieved in many cases and in some there is no return of the disease before the death of the patient from some other cause many years later. Although one cannot claim a *certain* " cure " in any individual case, in view of the residual risk of recurrence, it is surely not unduly optimistic to attempt to distinguish and estimate a " proportion cured " by appropriate statistical techniques applied to any large group of patients. Two kinds of model have been proposed and we shall

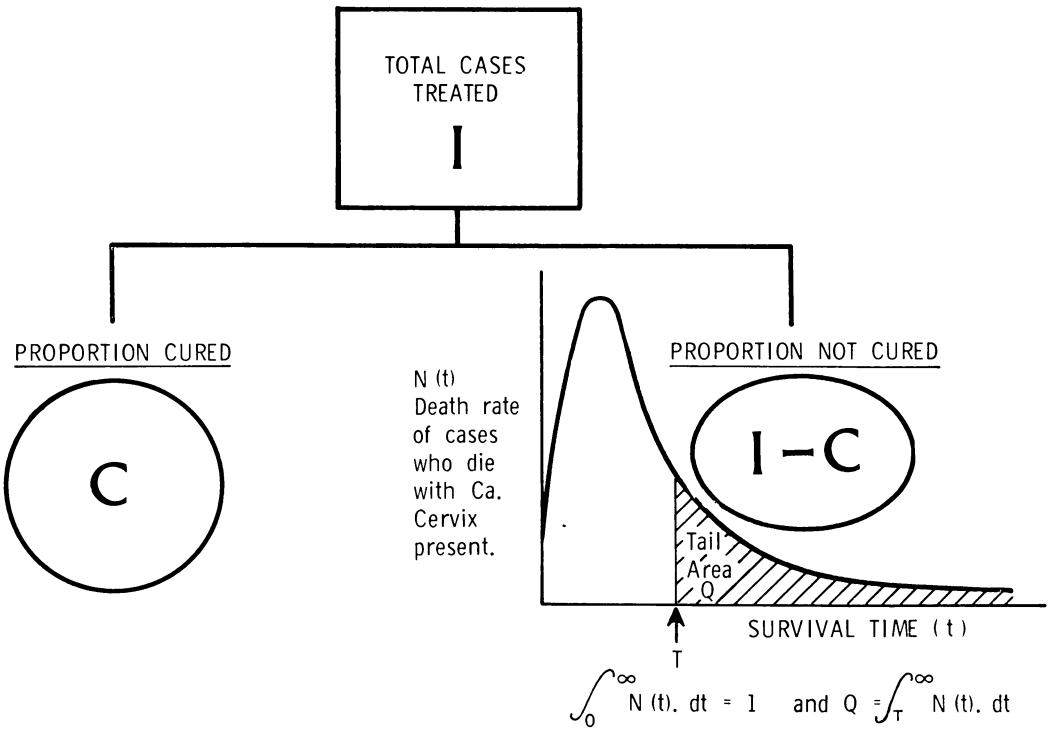

FIG. 2.—Statistical model, Type I.

test both kinds against the data on cervix cancer listed in earlier paragraphs.

The first kind of model explicitly recognizes the existence of a proportion cured, denoted by C, and assumes that only the complementary fraction (1/C) is at risk for a recurrence of cancer although, of course, all are at risk for other causes of death (Fig. 2). To complete a model of this kind, it is necessary to find an appropriate formula for the distribution of survival times which occur within this fraction (1/C). The general shape of the curve is skew, the mortality from persistent or recurrent cancer reaching a peak during the first one or 2 years after treatment and declining gradually thereafter. Several analytical forms for this curve have been proposed, among them the lognormal curve (equation 1), the negative exponential (equation 2) and the skew exponential (equation 3). The latter is a particular example of a family of skew curves with the general equation 4.

$$N(x) = \frac{1}{\sqrt{2\pi}} \exp\left(-\tfrac{1}{2}x^2\right) \qquad (1)$$

where $x = \dfrac{\log t - M}{S}$

$$N(t) = \alpha \,.\, \exp\left(-\alpha t\right) \qquad (2)$$

$$N(t) = \frac{\gamma^4}{12} \,.\, t \,.\, \exp\left(-\gamma \,.\, \sqrt{t}\right) \qquad (3)$$

$$N(t) = N_0 \,.\, t \,.\, \exp\left(-\gamma \,.\, t^\zeta\right) \qquad (4)$$

Table III lists the sources of these several proposals and the methods of analysis used.

The second type of model (Fig. 3), was first put forward by Haybittle (1959) and was called by him the "extrapolated actuarial" model. It postulates an analytical form for the gradually declining cancer mortality which affects the whole group of patients subsequent to treatment. Although the "cured" group was not explicitly postulated, it is implicit in this model also, since the declining mortality causes the whole group of patients to approach asymptotically a fixed fraction of its original size, which then survives from cancer indefinitely.

TABLE III.—*Parameters of the Various Models*

Model type	Model	Reference	Parameters	Method of determination of parameters
I	Lognormal	Boag (1949)	M (logtime) S C	Maximum likelihood
	Negative exponential	Berkson and Gage (1952), Haybittle (1959)	α (time)$^{-1}$ C	Least squares or maximum likelihood
	Skew exponential	Mould (1973)	γ (time)$^{-1/2}$ C	Maximum likelihood
II	Extrapolated actuarial	Haybittle (1959)	β (time)$^{-1}$ K C	Maximum likelihood for K and β C = exp (− K/β)
		Haybittle (1965)	β (time)$^{-1}$ C	Maximum likelihood
	Skewed extrapolated actuarial	The current paper	ε (time)$^{-1}$ C	Maximum likelihood

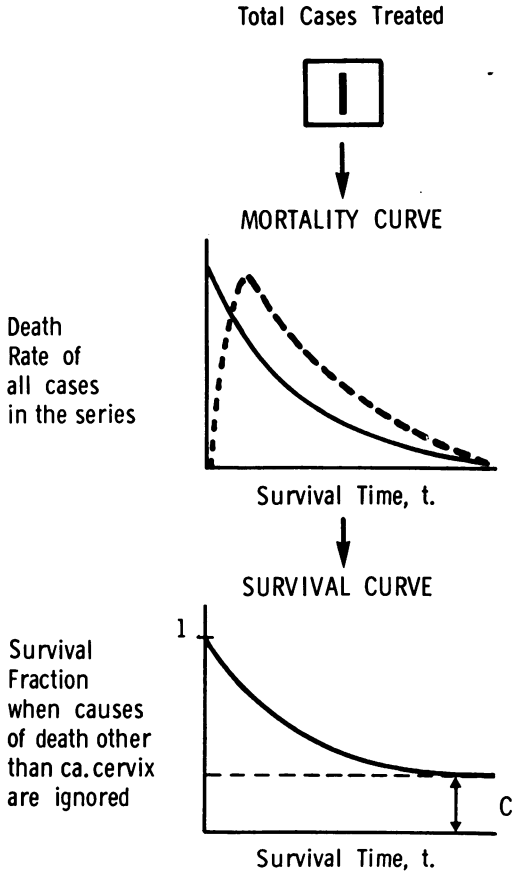

FIG. 3.—Statistical model, Type II.

If we put

$$-\mathrm{d}N = N \cdot \log\left(\frac{1}{\mathrm{C}}\right)\psi(t)\,\mathrm{d}t$$

where N is the number surviving to time t and $\psi(t)$ is any function satisfying the conditions

$$\int_0^\infty \psi(t)\,\mathrm{d}t = 1 \text{ and } \psi(t) \to 0$$

as $t \to \infty$ then we can deduce that

$$-\int_{N_0}^{N} \frac{\mathrm{d}N}{N_0} = \log\left[\frac{1}{\mathrm{C}}\right] \cdot \int_0^t \psi(t)\,\mathrm{d}t$$

that is

$$\log\left[\frac{N_0}{N}\right] = \log\left[\frac{1}{\mathrm{C}}\right] \cdot \Phi(t)$$

where Φ is the integral of ψ. Therefore as $t \to \infty$, $\Phi \to 1$ and so

$$\frac{N}{N_0} \to \mathrm{C}$$

and C measures the ultimate cure rate. Thus we may write

$$\frac{N}{N_0} = (\mathrm{C})^{+\Phi(t)}$$

where

$$\Phi(t) = \int_0^t \psi(t)\,\mathrm{d}t.$$

The function ψ can therefore be chosen with considerable freedom to provide a good fit to the observed or expected distribution of survival times. Ca deaths in any interval are then

$$N_1 - N_2 = N_0\{(\mathrm{C})^{+\Phi(t_1)} - (\mathrm{C})^{+\Phi(t_2)}\}$$

or, we may express the same relationship by saying that the probability that an individual patient in the treated group shall die of cancer in the interval (t_1, t_2) is $(N_1 - N_2)/N_0$, *i.e.* is

$$\{(\mathrm{C})^{+\Phi(t_1)} - (\mathrm{C})^{\Phi(t_2)}\}$$

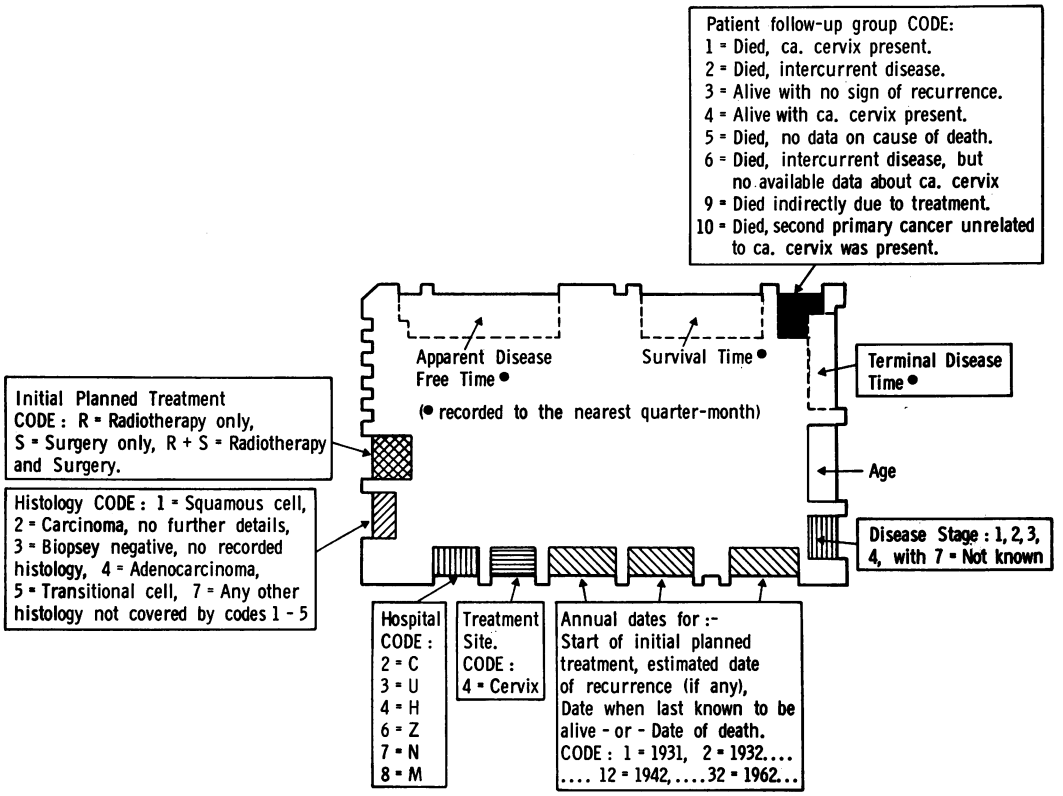

FIG. 4.—Parameter codes for the punched card system.

Various expressions have been tried for the function $\psi(t)$. Haybittle (1959, 1965) chose $\psi(t) = \beta \cdot \exp(-\beta t)$ and called this the "extrapolated actuarial" model. We shall test this model in various ways in later paragraphs using our carcinoma cervix data. This form for $\psi(t)$ implies that cancer mortality in the treated group will be a maximum at $t = 0$, that is, immediately after treatment, whereas all clinical experience indicates that mortality is low at $t = 0$ and rises to a peak which occurs at anything from a few months to a few years after treatment, depending on the site and stage of the disease. The various skew curves tried out in the Type I models to fit the distribution of survival times may be tested again as hypotheses for $\psi(t)$. In an attempt to find a simple single parameter representation for $\psi(t)$, we have tested the form $\psi(t) = \epsilon^2 t \exp(-\epsilon t)$, calling this the skewed extrapolated actuarial.

(b) *Data storage and retrieval.*—This survey was undertaken at a time when digital computers were readily available for calculation but much less available for data storage and retrieval—for these functions make quite different demands on the machine. The number of cases we had to examine was not too large—some 6000—to be dealt with manually on an edge-punched card system and we chose this for our data base, extracting all the relevant information for each patient onto a single 8 × 5 inch card of the design illustrated in Fig. 4 which shows the Formica template used to assist punching the data. All the information for each patient was thus in an immediately visible form, making checking easy, and the cards could be sorted quickly into their various groupings by means of the edge-punched holes and slots. Survival time data derived from these card sorting operations were punched onto paper tape as required and entered into the com-

puter in this form for the necessary statistical estimation procedures.

(c) *Estimation of the parameters of the statistical models being studied.*—In the first type of test referred to in the introduction, namely, testing the " goodness of fit " of a completed histogram of survival times with some postulated analytical distribution, the best values of a single parameter of the distribution could be estimated directly by a standard " least squares " method.

When 2 or 3 parameters have to be estimated simultaneously from the incomplete data of a treatment series—incomplete because further deaths with cancer will still be added to the histogram of survival times—more general estimation methods must be adopted and we have chosen the " method of maximum likelihood " (Lea, 1945; Fisher, 1922).

The logic of this method is to take as " best " values of the parameters those which would yield the highest chance of obtaining a sample of the type actually observed, when the calculation of probability is based on the chosen statistical model. The detailed algebra involved in applying maximum likelihood to the several models in Table III has been given elsewhere (Mould, 1973). The iterative computations involved in solving the equations have been carried out by writing programmes either in BASIC or in FORTRAN IV for each of the models.

Four mutually exclusive follow-up groups can be seen in the top right-hand area of Fig. 4 with codes numbered 1, 2, 3 and 4 respectively. Groups 5 and 6 occur when follow-up data in the patients' notes are incomplete: further supplementary information, if eventually available, may require the transfer of a patient from these groups to one of the Groups 1, 2, 3 or 4. If no additional information is forthcoming, a decision on this transfer must be taken on the basis of the last detailed follow-up report. The small Group 9 may be combined with Group 1 and the even smaller Group 10 combined with Group 2, of which it is a special case. Thus we can allocate all the cases to one or other of the first 4 mutually exclusive follow-up groups.

The lognormal model employs 3 independent parameters, whereas each of the other models uses only 2. This extra parameter makes the distribution curve more flexible and thus facilitates a good fit with the observations, but another consequence is that the standard errors of the parameter values increase so that the estimate of any one parameter—such as C —is less stable. A 2-parameter model is clearly simpler than a 3-parameter one and it is shown below that the parameter S in the lognormal can often be treated as a constant, thus converting this model also to a 2-parameter one. In the present survey of ca. cervix uteri, $S = 0{\cdot}40$ fits practically all our data.

(d) *Extrapolated survival fractions.*—The various models may be used simply as a framework for extrapolation instead of attaching absolute significance to the quantity, C, as " proportion cured ". Thus the " m-year survival fraction " may be calculated from the model (Fig. 2) as:

$$\text{S.F.}_{(m)} = \text{C} + (1 - \text{C})Q_{(m)}$$

even when the parameter estimates are based on survival data for less than m years. This is the " prediction " indicated in Fig. 1. The " proof " is then the actual survival fraction observed after m years follow-up when causes of death other than cancer are excluded, this fraction being evaluated by the actuarial method as described by Greenwood (1926), Merrell and Shulman (1955) and Cutler and Ederer (1958).

RESULTS

(a) *Testing the analytical form of the survival time distribution*

Agreement between the observed survival time distributions and the proposed analytical formulae was tested by grouping survival times into equal logarithmic intervals* and comparing observed with theoretical numbers in each interval by means of a χ-squared test for the 27 hospital series in Table II. The theoretical parameters were varied stepwise in the programme until a minimum χ-squared value was found and the computer then printed out this value together

* Basically the groups were 0–6, 6–9, 9–13·5, 13·5–20·25, 20·25–30·5, 30·5–45·5, 45·5–68·5, 68·5–102·5, 102·5–153·5, etc. but for small sample series these groups were sometimes combined in pairs.

TABLE IV.—*Goodness of Fit of Data to the Skew Exponentials*

Stage	No. of cancer deaths	Reference letter (see Table II)	P levels for different values of ζ Notation: ⊕ signifies $P>0\cdot05$, − signifies $P<0\cdot05$						
			$\zeta=1\cdot00$	$\zeta=0\cdot67$	$\zeta=0\cdot50$	$\zeta=0\cdot40$	$\zeta=0\cdot33$	$\zeta=0\cdot29$	$\zeta=0\cdot25$
I	55	A	−	−	−	−	−	⊕	⊕
I	61	B	⊕	⊕	⊕	⊕	⊕	⊕	−
I	86	C	−	⊕	⊕	⊕	⊕	⊕	−
I	38	D	⊕	⊕	⊕	−	−	−	−
I	37	E	−	⊕	⊕	⊕	⊕	⊕	⊕
I	94	F	⊕	⊕	⊕	⊕	⊕	−	−
I	157	G	−	−	⊕	−	−	−	−
I	202	AA	−	−	⊕	⊕	⊕	⊕	−
I	169	BB	⊕	⊕	⊕	−	−	−	−
I	No. of series for which a good fit to the data is obtained, $P>0\cdot05$		4	6	8	5	5	5	2
II	36	H	−	−	⊕	⊕	⊕	⊕	−
II	63	I	−	−	−	⊕	⊕	⊕	⊕
II	62	J	−	−	⊕	⊕	⊕	⊕	⊕
II	50	K	−	⊕	⊕	⊕	⊕	⊕	⊕
II	85	L	−	⊕	⊕	⊕	⊕	⊕	⊕
II	78	M	−	⊕	⊕	⊕	⊕	⊕	−
II	65	N	⊕	⊕	−	−	−	−	−
II	72	O	⊕	⊕	⊕	⊕	−	−	−
II	79	P	⊕	⊕	⊕	⊕	⊕	⊕	−
II	590	CC	−	−	−	−	−	−	−
II	No. of series for which a good fit to the data is obtained, $P>0\cdot05$		3	6	7	8	7	7	4
III	133	Q	−	−	−	−	−	−	−
III	96	R	−	−	−	⊕	⊕	⊕	⊕
III	65	S	−	⊕	⊕	⊕	⊕	⊕	−
III	54	T	⊕	⊕	⊕	−	−	−	−
III	59	U	−	⊕	⊕	⊕	−	−	−
III	66	V	−	⊕	⊕	⊕	⊕	⊕	⊕
III	473	DD	−	−	−	−	−	−	−
III	No. of series for which a good fit to the data is obtained, $P>0\cdot05$		1	4	4	4	3	3	2
I+II+III	1265	EE	−	−	−	−	−	−	−

In each case the symbol (⊕ or −) in the Table gives the result for a minimum chi-squared goodness of fit test, for the data on that horizontal level and the skew exponential distribution at the head of the vertical column.

with the corresponding values of the parameters—M and S for the lognormal, β for the negative exponential and γ for each member of the family of skew curves given by equation 4. We tried 7 members of this family with ζ defined by the formula:

$$\zeta = 2/(1 + r)$$

where r is integral and $1 \leqslant r \leqslant 7$. This restriction ensured that integration of equation 4 would lead to a complete gamma function and would therefore be easily evaluated.

When the skew exponential curves are tested against the data from the 4 London hospitals, Manchester and Oslo, the results are those shown in Table IV. The data in this table are for patients treated in the 5-year periods 1945–49, 1950–54, 1955–59 and followed up until 1969 so that the minimum follow-up period was 10 years, which gives some assurance that the tail of the distribution of recurrences is adequately represented. The ζ value which fits the largest proportion of the individual stage groups is $\zeta = 0{\cdot}5$. $\zeta = 0{\cdot}67$ and $\zeta = 0{\cdot}40$ also provide reasonable fits but curves $\zeta = 1$ and $\zeta = 0{\cdot}25$ provide poor fits to the

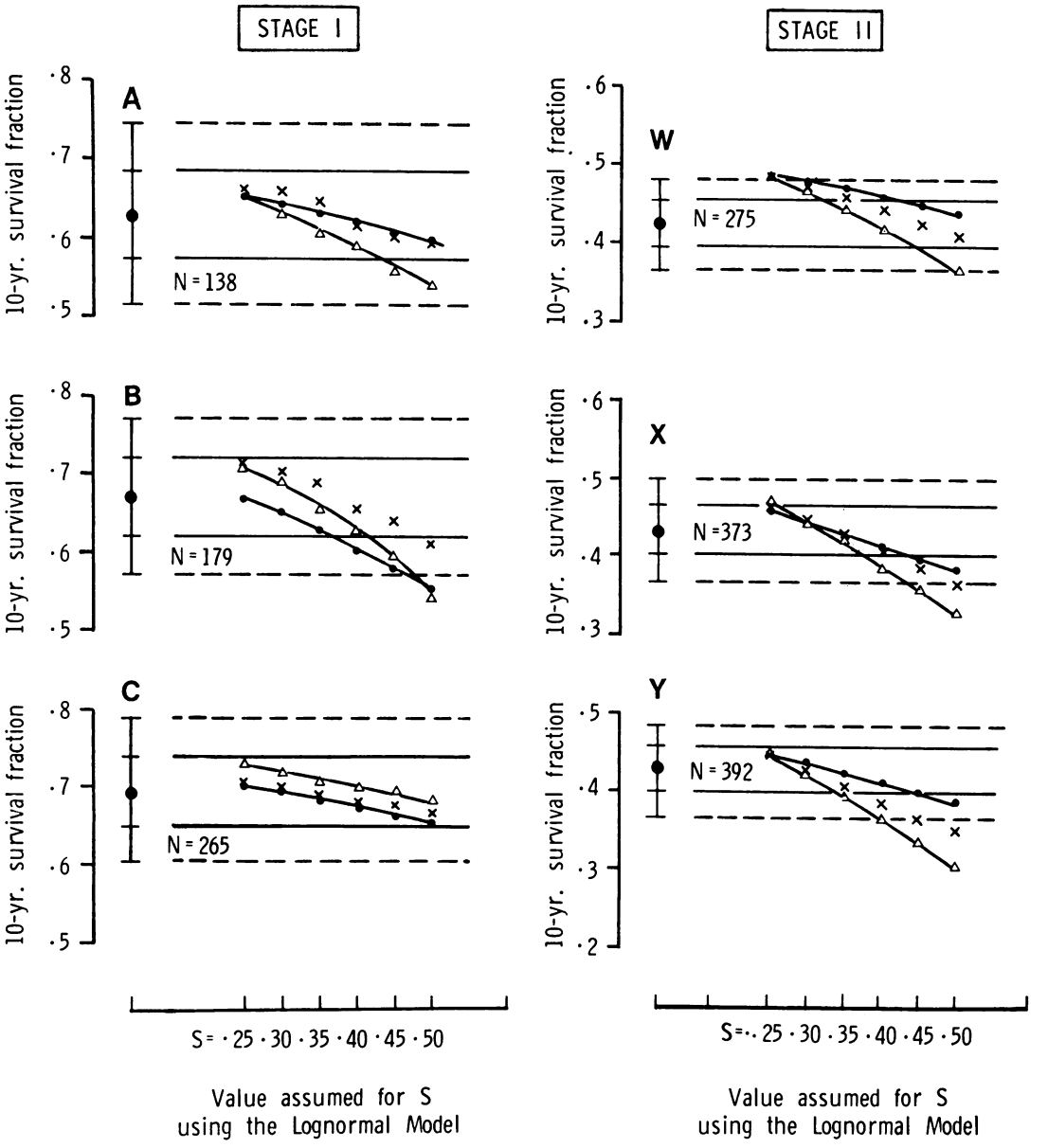

FIG. 5.—Comparison of observed and predicted 10-year survival fractions for stage I and stage II cervix carcinoma.

data. We have therefore concluded from Table IV that for carcinoma cervix, $\zeta = 0{\cdot}5$ is the best choice of exponent for the skew exponential model of the survival time distribution in follow-up Group 1 (see Fig. 4). We have noticed that if a skew exponential distribution is chosen, many published observational data including sites other than the cervix, are also best fitted by putting $\zeta = 0{\cdot}5$ (Boag, 1948, 1949; Wood and Boag, 1950; Smithers *et al.*, 1952; Haybittle, 1959; Ronnike, 1968; Sorensen, 1958).

It is noticeable that when all the complete London hospital series for 1945–59 are combined, the data are not fitted by any skew exponential curve, nor indeed by any lognormal or negative exponential curve either. For other sites also, if the data comprise a mixture of different stages, it is not usually possible to obtain a good fit to any of these distributions.

In Table V the lognormal and negative exponential curves are fitted to the same observational data, again using minimum χ^2 to fix the best values of the parameters. It is seen that the 2-parameter lognormal

TABLE V.—*Goodness of Fit of Data to the Lognormal and Simple Exponential Distributions*

Stage	No. of cancer deaths	Reference letter (see Table II)	*P* levels for different distributions. Notation: ⊕ signifies $P>0{\cdot}05$, − signifies $P<0{\cdot}05$. Lognormal	Negative exponential
I	55	A	−	−
I	61	B	⊕	⊕
I	86	C	⊕	⊕
I	38	D	⊕	−
I	37	E	⊕	⊕
I	94	F	⊕	⊕
I	157	G	⊕	−
I	202	AA	⊕	⊕
I	169	BB	⊕	−
I	No. of series for which a good fit to the data is obtained, $P>0{\cdot}05$		8	5
II	36	H	⊕	⊕
II	63	I	⊕	⊕
II	62	J	⊕	⊕
II	50	K	⊕	⊕
II	85	L	⊕	⊕
II	78	M	⊕	⊕
II	65	N	⊕	−
II	72	O	⊕	⊕
II	79	P	⊕	⊕
II	590	CC	⊕	−
II	No. of series for which a good fit to the data is obtained, $P>0{\cdot}05$		10	8
III	133	Q	⊕	−
III	96	R	⊕	−
III	65	S	⊕	⊕
III	54	T	⊕	−
III	59	U	⊕	−
III	66	V	⊕	⊕
III	473	DD	⊕	−
III	No. of series for which a good fit to the data is obtained, $P>0{\cdot}05$		7	2
I+II+III	1265	EE	−	−

In each case the symbol (⊕ or −) in the Table gives the result for a minimum chi-squared goodness of fit test, for the data on that horizontal level and the distribution (lognormal or simple exponential) at the head of the vertical column.

TABLE VI.—*Summary of the Results for the Minimum Chi-squared Goodness of Fit Tests*

Stage	No. of series for which a good fit to the data is obtained, $P>0\cdot05$, for different distributions: The general lognormal with M and S variable	Negative exp.	Skew exponentials $\zeta=1\cdot00$	$\zeta=0\cdot67$	$\zeta=0\cdot50$	$\zeta=0\cdot40$	$\zeta=0\cdot33$	$\zeta=0\cdot29$	$\zeta=0\cdot25$	Total number of series tested for a given stage
I	8	5	4	6	8	5	5	5	2	9
II	10	8	3	6	7	8	7	7	4	10
III	7	2	1	4	4	4	3	3	2	7
I+II+III	0	0	0	0	0	0	0	0	0	1
Totals	25	15	8	16	19	17	15	15	8	27

In each case the figure in the Table gives the number of series for which a good fit to the data was obtained, $P>0\cdot05$, for the stage on that horizontal level and the distribution at the head of the vertical column.

curve provides a good fit to all but one of the 26 samples of data grouped individually by stage while the negative exponential fits only 15 of them satisfactorily, Table VI.

When the lognormal is reduced to a single variable curve by fixing S equal to 0·40, it still provides an adequate fit for 20 of the 27 series of data. When S is fixed and equal to 0·35, the lognormal fits 12 series and when S is fixed and equal to 0·45, it fits 24 series. Moreover, when the model is used for prediction, as we shall see later, the predicted value changes little in the range S equals 0·30–0·40.

In testing the distribution of survival times given by " extrapolated actuarial " and similar models, one has to determine first the best values of the 2 parameters by fitting the model to the whole of the data and then, using these parameter values, to calculate the expected number of cancer deaths in each interval along the time scale for comparison with the numbers observed. This we have done for the original Haybittle model and for our modification of it but the results of a χ^2 test showed that the original Haybittle model provided an adequate fit for only 12/27 series and the skewed extrapolated actuarial model an adequate fit for only 9/27 series. Nevertheless, as will be seen later, both these type II models (Table III) give adequate predictions for long-term survival fractions for many carcinoma cervix series.

(b) *Estimation of the long-term survivors when a 10-year minimum follow-up interval is available*

With follow-up data available in 1969–71 the observation periods ranged from 10 years to 25 years and the actuarial method of calculating long-term survival should, and does, converge towards an estimate of " cure rate ". We have taken the value at 20 years subsequent to treatment as this asymptotic value, with which the estimates of " cure rate " based on each of the parametric models can be compared.

In addition to this comparison of " cure rates " our computer programme calculated for each of the 22 groups of cases in Table II, the expected survival fractions at times 5, 6, 7, 8, 9, 10 and 15 years after treatment using both the actuarial method and each of the 5 parametric models of Table III. A detailed listing of all these results (except the skewed extrapolated actuarial) is given by Mould (1973).

Table VII compares " cure rate " estimates for stages I, II and III carcinoma cervix based on each model with that from the actuarial calculation. The value of one standard error of the actuarial estimate is included in Table VII and it

TABLE VII.—*Estimates of the Fraction Cured " C ", Based on the Available Long-term Follow-up Information*

Stage	Total cases in series	Reference letter (see Table II)	20-year survival fraction calculated by the actuarial method (±1 s.e.)	Estimate of the fraction cured, " C ", using different models: Lognormal with an assumed value for S, S=0·30	S=0·35	S=0·40	Skew exp. with ζ=0·5	Negative exp.	Extrapolated actuarial	Skewed extrapolated actuarial
I	138	A	0·55 (0·05)	0·57	0·57	0·56	0·57	0·55	0·54	0·57
I	179	B	0·63 (0·04)	0·62	0·61	0·60	0·59	0·60	0·58	0·62
I	265	C	0·63 (0·04)	0·66	0·66	0·65	0·67	0·64	0·63	0·65
I	101	D	0·62 (0·05)	0·62	0·61	0·60	0·61	0·61	0·62	0·61
I	127	E	0·69 (0·04)	0·69	0·68	0·67	0·67	0·67	0·67	0·68
I	292	F	0·66 (0·03)	0·66	0·65	0·63	0·63	0·63	0·63	0·65
I	553	G	0·68 (0·03)	0·71	0·71	0·70	0·71	0·69	0·69	0·71
II	68	H	0·42 (0·07)	0·43	0·43	0·42	0·43	0·41	0·40	0·41
II	110	I	0·37 (0·05)	0·40	0·40	0·39	0·39	0·38	0·36	0·37
II	97	J	0·33 (0·05)	0·36	0·36	0·35	0·35	0·35	0·33	0·33
II	86	K	0·37 (0·06)	0·37	0·36	0·34	0·36	0·37	0·35	0·36
II	144	L	0·38 (0·04)	0·39	0·38	0·37	0·38	0·37	0·36	0·38
II	143	M	0·34 (0·06)	0·43	0·43	0·42	0·42	0·42	0·40	0·41
II	117	N	0·41 (0·06)	0·44	0·43	0·42	0·43	0·43	0·42	0·43
II	123	O	0·38 (0·05)	0·44	0·43	0·41	0·41	0·39	0·37	0·42
II	152	P	0·43 (0·04)	0·44	0·43	0·41	0·41	0·40	0·38	0·43
III	170	Q	0·18 (0·03)	0·20	0·20	0·20	0·20	0·20	0·21	0·17
III	115	R	0·13 (0·03)	0·14	0·14	0·14	0·14	0·14	0·13	0·12
III	90	S	0·25 (0·05)	0·25	0·24	0·24	0·24	0·25	0·24	0·21
III	77	T	0·28 (0·05)	0·27	0·27	0·27	0·27	0·29	0·29	0·27
III	78	U	0·22 (0·05)	0·20	0·20	0·19	0·20	0·22	0·22	0·19
III	78	V	0·13 (0·04)	0·14	0·14	0·14	0·14	0·14	0·13	0·13

In each case the figure in the table for the different models gives the estimate for " C " for the data series on that horizontal level and for the model at the head of the vertical column.

Value of " n "	Series for which patients have been followed up for at least " n " years
20 years	A, D, H, I, J, Q
15 years	B, E, K, L, M, R, S
10 years	C, F, G, N, O, P, T, U, V

can be seen that the " cure rate " estimates derived by the other methods nearly all lie within one standard error of this actuarial estimate. Thus, with long-term follow-up available it is clear that all these statistical models will give an acceptable estimate of C. The 3 parameter lognormal model requires for stability a larger number of cases than are available in these separate quinquennial groups, but the 2-parameter lognormal is satisfactory for any fixed value of S between 0·25 and 0·50 (only values for 0·3–0·4 are quoted in Tables). The standard errors in " C " were usually close to 0·05 for the values of C encountered and the small sample sizes of some 100–150 cases. The subdivision of the data into stage groups is highly desirable in any carefully planned clinical trial and 5 years is a reasonable period for a trial if clinical interest and continuity of plan are to be maintained. Any suggested modifications in treatment technique can then be applied without too long a delay. Standard errors of this magnitude must therefore be regarded as typical in most stratified clinical trials. To reduce the error by a factor of $\sqrt{2}$ would involve doubling the sample size and in this survey we have reviewed some 2000 case histories of carcinoma cervix from the 4 London centres alone. Clinical trials in cancer therapy are very

TABLE VIII.—*Estimates of Stage I and Stage II 10-year Survival Fractions and Stage III 7-year Survival Fractions, Based on the Available Long-term Follow-up Information*

Stage	Total cases in series	Reference letter (see Table II)	10-year survival fraction calculated by the actuarial method (±1 s.e.)	Estimate of the 10-year survival fraction, using different models: Lognormal with an assumed value for S, S=0·30	S=0·35	S=0·40	Skew exp. with ζ=0·5	Negative exp.	Extrapolated actuarial	Skewed extrapolated actuarial
I	138	A	0·63 (0·04)	0·58	0·59	0·60	0·64	0·61	0·61	0·61
I	179	B	0·67 (0·04)	0·65	0·66	0·66	0·67	0·69	0·69	0·66
I	265	C	0·69 (0·03)	0·67	0·67	0·67	0·67	0·68	0·68	0·66
I	101	D	0·62 (0·05)	0·63	0·63	0·64	0·63	0·64	0·65	0·62
I	127	E	0·72 (0·04)	0·70	0·71	0·71	0·72	0·73	0·73	0·71
I	292	F	0·68 (0·03)	0·68	0·67	0·68	0·68	0·69	0·69	0·67
I	553	G	0·74 (0·02)	0·72	0·72	0·72	0·72	0·73	0·73	0·72
II	68	H	0·47 (0·06)	0·44	0·43	0·43	0·43	0·43	0·43	0·41
II	110	I	0·44 (0·05)	0·41	0·41	0·42	0·42	0·43	0·43	0·40
II	97	J	0·40 (0·05)	0·37	0·37	0·38	0·38	0·40	0·40	0·36
II	86	K	0·43 (0·06)	0·38	0·39	0·39	0·40	0·43	0·43	0·39
II	144	L	0·41 (0·04)	0·39	0·39	0·40	0·40	0·40	0·41	0·38
II	143	M	0·46 (0·04)	0·44	0·44	0·45	0·45	0·45	0·46	0·43
II	117	N	0·45 (0·05)	0·44	0·44	0·44	0·44	0·44	0·44	0·43
II	123	O	0·42 (0·05)	0·45	0·44	0·44	0·44	0·41	0·42	0·43
II	152	P	0·43 (0·04)	0·45	0·44	0·44	0·44	0·44	0·45	0·43
			7-year survival fraction	Estimate of the 7-year survival fraction, using different models						
III	170	Q	0·24 (0·03)	0·20	0·21	0·22	0·22	0·22	0·23	0·18
III	115	R	0·18 (0·04)	0·15	0·15	0·16	0·16	0·17	0·18	0·13
III	90	S	0·30 (0·05)	0·25	0·26	0·27	0·27	0·28	0·28	0·23
III	77	T	0·28 (0·05)	0·28	0·28	0·28	0·28	0·26	0·30	0·27
III	78	U	0·22 (0·05)	0·21	0·21	0·21	0·21	0·23	0·24	0·20
III	78	V	0·16 (0·04)	0·15	0·15	0·15	0·15	0·15	0·16	0·13

In each case the figure in the table for the different models gives the estimate of the 10-year (or 7-year) survival fraction for the data series on that horizontal level and for the model at the head of the vertical column.

Value of "n"	Series for which patients have been followed up for at least "n" years
20 years	A, D, H, I, J, Q
15 years	B, E, K, L, M, R, S
10 years	C, F, G, N, O, P, T, U, V

seldom as comprehensive as that and it is evident that small treatment differences of the order of 5% will rarely be found to be significant.

Using a similar format to Table VII, a comparison of the observed 10-year survival fractions with those calculated from the parametric models for stage groups I and II, and of the 7-year survival fraction for stage group III, is given in Table VIII. For the lognormal, skew exponential ($\zeta = 0{\cdot}5$), negative exponential and extrapolated actuarial models, there is nearly always agreement between actuarial and parametric estimates to within one standard error of the actuarial estimate. The skewed extrapolated actuarial model gives consistently lower estimates for the survival fraction than those given by the other models. The low values given by the skewed extrapolated actuarial model for stages II and III are due to the fact that this distribution has a very broad peak. The 7-year survival fraction was chosen as the criterion for stage III as almost all cancer deaths among patients first seen in this stage will have occurred before 10 years

have elapsed, so that the 10-year survival fraction is virtually identical with the estimate of C. Close agreement was observed between the extrapolated actuarial and negative exponential. These 2 models, and the skew exponential model, gave predictions for 10-year and 7-year survival fractions which agreed fairly well with those given by the lognormal model, taking a fixed value of S in the range 0·30–0·45.

(c) *Estimation of the long-term survival fraction when only relatively short-term follow-up data are available*

The data already presented confirm that several of the statistical models examined can provide an accurate representation of the life experience of carcinoma cervix patient groups when long-term follow-up data are used to estimate the parameters of the model. It is therefore of great interest to determine with what accuracy the subsequent life experience can be predicted when only shorter term follow-up data are used, as would normally be the case in a planned clinical trial some 5–8 years from its commencement. To do this, the parameters of the statistical model to be tested were first estimated by the method of maximum likelihood from the incomplete follow-up data which would have been available in our series after only a limited follow-up period and these estimated parameters were used to calculate the expected 10-, 15- or 20-year survival fractions. These extrapolated survival fractions were then compared with the actual survival fraction calculated by the actuarial method from the long-term follow-up data on the same group of cases (see Fig. 1). The results for the several models, both type I and type II (Table III), are set out in Tables IX, X and XI, for disease stages I, II and III respectively. For stages I and II, the 10-year and 15-year survival fractions are shown but for stage III the 7-year and 10-year fractions were calculated instead. The format of Tables IX–XI is similar to that of Tables VII and VIII.

Tables VII and VIII give the results calculated from the long-term follow-up data and a single column of figures appears beneath the heading for each model. Tables IX–XI give results based on short-term follow-up information and the date at which the predictions were made is defined as " n years after the series closed " (see notation in Fig. 1). Hence for Tables IX and X (for carcinoma cervix stages I and II) there are 2 columns of figures beneath the heading for each model. They correspond to predictions made at 4 years or 3 years after the series closed (n = 4 and n = 3). In Table XI for stage III carcinoma cervix, the predictions were made at 2 years or 1 year after the series closed (n = 2 and n = 1).

Figures 5 and 6 show the results for treatment series A, B and C which are quoted in Table IX, and in addition results for the lognormal model with fixed values of S ranging from 0·25 to 0·50 and also for the same analysis carried out for n = 2 years. Series A, B and C represent the combined data for stage I of the 4 London teaching hospitals for the three 5-year treatment periods 1945–49, 1950–54 and 1955–59. A similar combination of data for stage II has been annotated W, X and Y, see Table XII.

DISCUSSION

Type I statistical models

The lognormal model.—The lognormal model with 3 floating parameters, M, S and C, requires for its stability a larger number of cases than are available in most of our quinquennial stage groups even when long-term follow-up is available. This was evident in the study of " information content " in the original publication (Boag, 1949) and has been confirmed in other practical examples (Wood and Boag, 1950; Smithers *et al.*, 1952; Mould, 1973). However, the lognormal model with M and C floating

TABLE IX.—*Predictions of Stage I 10-year and 15-year Survival Fractions, Based on the Available Short-term Follow-up Information (n = 4 years and n = 3 years)*

Stage	Total cases in series	Reference letter (see Table II)	10-year survival fraction calculated by the actuarial method (±1 s.e.)	Predicted 10-year survival fraction, using different models													
				Lognormal with an assumed value for S						Skew exp. with $\zeta = 0{\cdot}5$		Negative exp.		Extrapolated actuarial		Skewed extrapolated actuarial	
				S = 0·30		S = 0·35		S = 0·40									
				n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3
I	138	A	0·63 (0·04)	0·64	0·65	0·63	0·64	0·62	0·62	0·63	0·64	0·63	0·62	0·62	0·62*	0·62	0·61
I	179	B	0·67 (0·04)	0·65	0·70	0·63	0·68	0·60	0·66			0·69*	0·71*	0·69*	0·71*	0·59	0·67
I	265	C	0·69 (0·03)	0·69	0·69	0·68	0·68	0·68	0·67	0·69	0·69	0·70	0·68	0·70	0·68	0·67	0·65
I	101	D	0·62 (0·05)	0·65	0·63	0·64	0·62	0·63	0·60	0·64	0·61	0·64	0·59*	0·64*	0·58*	0·65	0·62
I	127	E	0·72 (0·04)	0·70	0·70	0·68	0·68	0·65	0·65			0·73*	0·65*	0·72*	0·64*	0·64	0·63
I	292	F	0·68 (0·03)	0·68	0·65	0·67	0·62	0·65	0·59			0·66	0·66	0·66*	0·65*	0·65	0·55
I	553	G	0·74 (0·02)	0·74	0·74	0·73	0·73	0·73	0·72	0·74	0·74	0·74	0·71	0·74	0·71	0·72	0·72
			15-year survival fraction	Estimate of the 15-year survival fraction, using different models													
I	138	A	0·58 (0·05)	0·64	0·65	0·63	0·63	0·61	0·61	0·63	0·64	0·61	0·64	0·60	0·59	0·61	0·61
I	179	B	0·63 (0·04)	0·63	0·70	0·59	0·66	0·54	0·63			0·64	0·67	0·63	0·66	0·52	0·65
I	265	C	0·63 (0·04)†	0·69	0·69	0·68	0·67	0·66	0·65	0·69	0·69	0·69	0·67	0·68	0·65	0·65	0·66
I	101	D	0·62 (0·05)	0·65	0·63	0·63	0·60	0·61	0·57	0·63	0·59	0·61	0·53	0·60	0·50	0·65	0·62
I	127	E	0·69 (0·04)	0·69	0·69	0·65	0·65	0·61	0·61			0·69	0·58	0·68	0·53	0·59	0·60
I	292	F	0·66 (0·03)†	0·67	0·63	0·65	0·59	0·62	0·53			0·61	0·60	0·59	0·58	0·62	0·48
I	553	G	0·71 (0·02)†	0·74	0·74	0·72	0·72	0·71	0·70	0·73	0·74	0·73	0·69	0·72	0·68	0·71	0·72

In each case the figure in the table for the different models and short-term availability of follow-up information (n = 4 years and n = 3 years) gives the estimate of the 10-year (or 15-year) survival fraction for the data series on that horizontal level and for the model and n-value at the head of the vertical column.

The symbol † adjacent to the 15-year actuarial rate for series C, F and G indicates that these series were treated in 1955–59 and therefore only a 10-year minimum follow-up is available for the actuarial calculation.

The symbol * adjacent to survival fractions for the negative exponential and extrapolated actuarial models indicates that the standard error in parameters α and β were greater than 50% of the parameter value.

The blank spaces for survival fractions for the skew exponential model indicate that the iterative procedure for solution for γ and C did not converge.

TABLE X.—*Predictions of Stage II 10-year and 15-year Survival Fractions, Based on the Available Short-term Follow-up Information ($n = 4$ years and $n = 3$ years)*

Stage	Total cases in series	Reference letter (see Table II)	10-year survival fraction calculated by the actuarial method (±1 s.e.)	Predicted 10-year survival fraction, using different models													
				Lognormal with an assumed value for S						Skew exp. with $\zeta = 0{\cdot}5$		Negative exp.		Extrapolated actuarial		Skewed extrapolated actuarial	
				S = 0·30		S = 0·35		S = 0·40									
				n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3	n = 4	n = 3
II	68	H	0·47 (0·06)	0·48	0·46	0·47	0·44	0·46	0·42	0·47	0·44	0·45	0·41	0·43	0·39*	0·48	0·45
II	110	I	0·44 (0·05)	0·50	0·49	0·49	0·48	0·48	0·46	0·49	0·47	0·49	0·51	0·48	0·50	0·47	0·45
II	97	J	0·40 (0·05)	0·47	0·48	0·46	0·45	0·45	0·44	0·44	0·44	0·44	0·48	0·43	0·47	0·44	0·42
II	86	K	0·43 (0·06)	0·43	0·47	0·41	0·45	0·39	0·43	0·36	0·41	0·47	0·47	0·46	0·46	0·36	0·41
II	144	L	0·41 (0·04)	0·43	0·41	0·41	0·39	0·40	0·36	0·39	0·34	0·44	0·45	0·43	0·43	0·40	0·36
II	143	M	0·46 (0·04)	0·47	0·48	0·46	0·46	0·44	0·44	0·43	0·43	0·48	0·46	0·47	0·44	0·43	0·45
II	117	N	0·45 (0·05)	0·44	0·44	0·44	0·42	0·43	0·41	0·43	0·41	0·44	0·42	0·44	0·40	0·45	0·44
II	123	O	0·42 (0·05)	0·43	0·41	0·42	0·39	0·41	0·37	0·40	0·36	0·41	0·39	0·40	0·37	0·41	0·38
II	152	P	0·43 (0·04)	0·44	0·43	0·42	0·40	0·40	0·37	0·37	0·29	0·45	0·45	0·44	0·43	0·39	0·37
			15-year survival fraction	Estimate of the 15-year survival fraction, using different models													
II	68	H	0·42 (0·07)	0·48	0·46	0·47	0·44	0·45	0·41	0·44	0·44	0·44	0·44	0·42	0·37	0·48	0·45
II	110	I	0·41 (0·05)	0·49	0·49	0·48	0·47	0·47	0·45	0·48	0·47	0·48	0·50	0·47	0·49	0·47	0·45
II	97	J	0·37 (0·05)	0·47	0·48	0·46	0·45	0·45	0·43	0·43	0·43	0·43	0·48	0·40	0·46	0·44	0·42
II	86	K	0·37 (0·06)	0·42	0·47	0·40	0·44	0·36	0·40	0·38	0·31	0·45	0·45	0·42	0·42	0·33	0·39
II	144	L	0·38 (0·04)	0·42	0·41	0·41	0·38	0·39	0·34	0·31	0·39	0·43	0·44	0·41	0·41	0·39	0·35
II	143	M	0·44 (0·04)	0·47	0·48	0·45	0·45	0·42	0·42	0·41	0·41	0·47	0·44	0·45	0·40	0·42	0·44
II	117	N	0·41 (0·06)†	0·44	0·44	0·43	0·42	0·42	0·40	0·42	0·41	0·44	0·41	0·43	0·38	0·45	0·44
II	123	O	0·38 (0·05)†	0·43	0·41	0·41	0·38	0·39	0·35	0·38	0·34	0·39	0·37	0·37	0·32	0·41	0·38
II	152	P	0·43 (0·04)†	0·43	0·42	0·40	0·38	0·37	0·34	0·32	0·21	0·42	0·42	0·40	0·39	0·37	0·35

In each case the figure in the Table for the different models and short-term availability of follow-up information (n = 4 years and n = 3 years) gives the estimate of the 10-year (or 15-year) survival fraction for the data series on that horizontal level and for the model and n-value at the head of the vertical column.

The symbol † adjacent to the 15-year actuarial rate for series N, O and P indicates that these series were treated in 1955–59 and therefore only a 10-year minimum follow-up is available for the actuarial calculation.

The symbol * adjacent to survival fractions for the extrapolated actuarial model indicates that the standard error in parameter β was greater than 50% of the parameter value.

TABLE XI.—*Predictions of Stage III 7-year and 10-year Survival Fractions, Based on the Available Short-term Follow-up Information (n = 2 years and n = 1 year)*

Stage	Total cases in series	Reference letter (see Table II)	7-year survival fraction calculated by the actuarial method (±1 s.e.)	Predicted 7-year survival fraction, using different models													
				Lognormal with an assumed value for S						Skew exp. with $\zeta=0\cdot5$		Negative exp.		Extrapolated actuarial		Skewed extrapolated actuarial	
				S=0·30		S=0·35		S=0·40									
				n=2	n=1	n=2	n=1	n=2	n=1	n=2	n=1	n=2	n=1	n=2	n=1	n=2	n=1
III	170	Q	0·24 (0·03)	0·24	0·18	0·21	0·15	0·19	0·12	0·18	0·08	0·20	0·17	0·18	0·14	0·20	0·14
III	90	S	0·30 (0·05)	0·29	0·27	0·27	0·24	0·26	0·21	0·26	0·21	0·28	0·30	0·26	0·28	0·27	0·23
III	114	R	0·18 (0·04)	0·25	0·29	0·24	0·27	0·23	0·26	0·23	0·28	0·29	0·27	0·27	0·24	0·23	0·27
III	78	V	0·16 (0·04)	0·19	0·17	0·19	0·17	0·18	0·16	0·18	0·17	0·18	0·19	0·16	0·17	0·19	0·17
III	78	U	0·22 (0·05)	0·22	0·20	0·21	0·18	0·19	0·17	0·19	0·16	0·23	0·19	0·21	0·17	0·19	0·18
III	76	T	0·28 (0·05)	0·32	0·29	0·31	0·27	0·29	0·25	0·30	0·25	0·33	0·29	0·32	0·25	0·32	0·29
			10-year survival fraction	Estimate of the 10-year survival fraction, using different models													
III	170	Q	0·22 (0·03)	0·24	0·18	0·20	0·14	0·17	0·09	0·16	0·04	0·18	0·15	0·14	0·10	0·20	0·14
III	90	S	0·28 (0·05)	0·29	0·26	0·27	0·23	0·24	0·20	0·25	0·20	0·27	0·29	0·23	0·25	0·26	0·23
III	114	R	0·16 (0·04)	0·25	0·29	0·22	0·27	0·20	0·25	0·23	0·28	0·29	0·27	0·29	0·27	0·23	0·27
III	78	V	0·16 (0·04)	0·19	0·18	0·18	0·17	0·17	0·15	0·18	0·16	0·17	0·19	0·14	0·16	0·19	0·17
III	78	U	0·22 (0·05)	0·21	0·20	0·20	0·18	0·18	0·16	0·18	0·15	0·22	0·18	0·19	0·14	0·19	0·18
III	76	T	0·28 (0·05)	0·32	0·29	0·30	0·26	0·28	0·23	0·29	0·24	0·33	0·28	0·31	0·23	0·32	0·29

In each case the figure in the Table for the different models and short-term availability of follow-up information (n=2 years and n=1 year) gives the estimate of the 7-year (or 10-year) survival fraction for the data series on that horizontal level and for the model and n-value at the head of the vertical column.

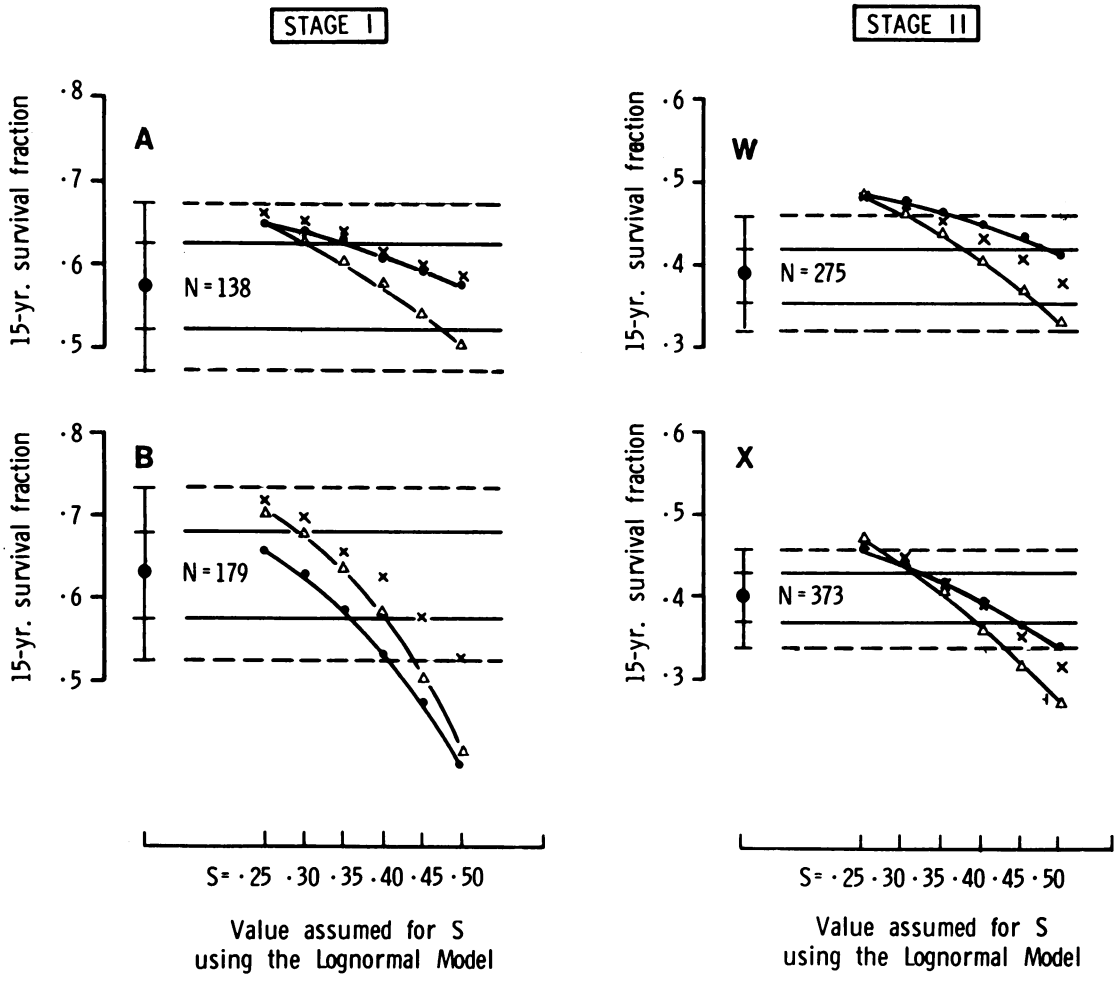

FIG. 6.—Comparison of observed and predicted 15-year survival fractions for stage I and stage II cervix carcinoma.

TABLE XII.—*Groupings by Stage, Hospital and Treatment Period for Fig. 5 and 6*

Hospital	Treatment period	Stage	Total cases	Reference letter
CHUM	1945–49	I	138	A
CHUM	1950–54	I	179	B
CHUM	1955–59	I	265	C
CHUM	1945–49	II	275	W
CHUM	1950–54	II	371	X
CHUM	1955–59	II	400	Y

but with S fixed at an appropriate value has been shown to give an excellent fit with survival time distributions both in the present series (Table V) and in numerous other series. To show how predictions vary with the value of S chosen, we have carried out predictive calculations for the 6 values from S = 0·25 to S = 0·50 in steps of 0·05. When

long-term follow-up data are used, the predicted 10-year survival fractions for the various values of S in this range do not usually differ by more than 0·03. With short-term follow-up data, however, extending over only 3 or 4 years subsequent to treatment, the long-term extrapolated survival fractions depend more strongly on the value of S adopted and in Tables VII–XI we have listed only the estimates based on the three central values S = 0·30, 0·35, 0·40. Figures 5 and 6 show the trends over the wider range of S.

For stage I carcinoma cervix, 10-year survival fraction, there is good agreement between actuarial calculation (" proof ", see Fig. 1) and lognormal prediction (" prediction ", see Fig. 1) for fixed values of S equal to 0·30, 0·35 or 0·40, and for both n = 4 years and n = 3 years short-term follow-up information (Table IX). The largest discrepancy occurs for series F, when n = 3 years and S = 0·40. For this series (Table IX) no results were obtained using the skew exponential model since the iterative procedure did not converge, while the standard errors of the parameters in all the other models were very large indeed. Evidently this series had a somewhat abnormal time distribution.

There is also a good general agreement between actuarial calculation and lognormal prediction of the 15-year survival fractions for stage I carcinoma cervix. Discrepancies occur again for series F, and also for series B with S = 0·40 and n = 4 years (but *not* for n = 3 years!). For series A, the predicted 15-year survival fractions are always higher than the actuarial value. This is due to the fact that, in this series, 7 patients died from carcinoma cervix 12–20 years subsequent to treatment and this frequency of later recurrences is unusual.

For stage II carcinoma cervix, 10-year and 15-year survival fractions, there is good agreement between actuarial calculation and lognormal prediction for S = 0·30, 0·35 and 0·40, and for n = 4 years and n = 3 years. The largest discrepancies occur when S = 0·40 and n = 3 years (Table X). Results for stages I and II carcinoma cervix have not been included for the shortest follow-up (n = 2 years) since good agreement could not be expected after only 2 years in these early stages where recurrence tends to be longer delayed.

For stage III carcinoma cervix, 7-year and 10-year survival fractions, there is reasonable agreement between actuarial calculation and lognormal prediction for n = 2 years (Table XI).

A summary of these conclusions is shown in Table XIII. The choice of S equal to 0·30 is not recommended because when testing the analytical form of the survival time distribution of patients known to have died with carcinoma cervix present, this particular value of S in the lognormal curve did not provide an adequate fit to most of the data under review (see Results, (a)). The lognormal curve with S = 0·40 provided a fit to more data than the S = 0·35 curve, but the data of Tables IX–XI indicate that either value is suitable for the purpose of predicting long-term survival fractions.

The skew exponential model.—Although

TABLE XIII.—*Summary of Conditions for the Use of the Lognormal Model to Predict Long-term Survival Fractions for Carcinoma Cervix*

Carcinoma cervix stage	Values which may be assumed for the lognormal parameter S	Minimum waiting period after a 5-year treatment series closes before use of the lognormal model (n years)	No. of cases in the series tested*
I	S=0·35–S=0·40	n=3	101–553
II	S=0·35–S=0·40	n=3	68–152
III	S=0·35–S=0·40	n=2	77–170

* See Table II.

a maximum likelihood solution was always found for the skew exponential model for stage 1 carcinoma cervix when long-term follow-up data were used, the equations did not always yield a solution when only short-term data were available. This failure of the iterative procedure to converge in 3 of 7 series when n = 4 and n = 3 years, indicates that this model is unsuitable for predictive estimates on stage I series. It is perhaps surprising that in those cases where a solution did exist good agreement was found between observation and prediction (Table IX).

For stage II carcinoma cervix, the results using the skew exponential model were inferior to those obtained with the lognormal model. This is particularly noticeable for short-term follow-up when n = 3 years. Of the 9 stage II series in Table X, only series P showed a large proportion of the cancer deaths occurring before the analysis time n = 4 years. Also, most of the remaining patients who would eventually die with cancer present were then already showing a recurrence. (This may reflect some differences in staging.) This high proportion of early cancer deaths has a more marked influence on the skew exponential model than on the other models, since the area under the " tail " of the skew exponential curve is larger than that of the similar curves in the other models. This explains the low survival fractions predicted for series *P* using this model.

For stage III carcinoma cervix, the skew exponential model is unsatisfactory for n = 1 year, but for n = 2 years the results are comparable with those obtained using the other type I statistical models (Table XI).

The negative exponential model.—For stage I carcinoma cervix, short-term follow-up when n = 3 years, the standard error in the negative exponential parameter α, was greater than $0{\cdot}5\alpha$ in 3 of the 7 series (Table IX). Thus although there is generally good agreement between actuarial calculation and prediction, the estimates are of little practical value and this model cannot be regarded as suitable for stage I series with sample sizes similar to those available for this study.

For stage II carcinoma cervix, there is better agreement when n = 4 years than when n = 3 years, and for n = 3 years the model is satisfactory for only some half of the series studied (Table X).

For stage III carcinoma cervix, the negative exponential model is unsatisfactory when n = 1 year, but when n = 2 years the results are comparable with those obtained using the other type I models (Table XI).

Type II statistical models

The extrapolated actuarial model.—The extrapolated actuarial model was introduced by Haybittle (1959) mainly for carcinoma breast data but has also been used by him for 2 series of carcinoma cervix patients obtained from follow-up information reported by Sorensen (1958) and by University College Hospital (1958). However, only estimates of C were derived and the efficiency of the model for predicting 10-year and 15-year survival fractions from short-term data was not discussed (Haybittle, 1960).

For stage I carcinoma cervix, it is seen from Table IX that the predicted values of the 10-year survival fractions using the type I negative exponential model and the type II extrapolated actuarial model are very similar. However, each of the model parameters α and β is often subject to a standard error of some 50% of its value, so these models are unsuitable for use with carcinoma cervix stage I series.

For stage II carcinoma cervix series, the extrapolated actuarial model does not always give good agreement with actuarial estimates of long-term survival rates (Table X).

For stage III carcinoma cervix, the model is unsatisfactory for n = 1 year, but for n = 2 years the results are comparable with those obtained using type I statistical models (Table XI).

The skewed extrapolated actuarial model.—Only one type II statistical model has previously been suggested, namely, the extrapolated actuarial model, and this model postulated an exponential mortality curve with maximum at time zero. A skew curve rising to a peak within the first year or two might be expected to represent the mortality curve with greater accuracy and the skewed extrapolated actuarial model was devised as a possible improvement. The form of this curve is

$$M(t) = (\log C)\epsilon^2 t\, e^{-\epsilon t}$$

but the peak proved to be too broad and generally too far from the origin to provide a good fit for the survival time distribution (Results, (a)) and its use in a predictive model is therefore somewhat artificial. For carcinoma cervix stages I and II the predicted values were found to be inferior to those derived from the ordinary extrapolated actuarial model, and for stage III they were similar to those of the other models tests (Tables IX, X and XI).

No doubt single-parameter skew curves could be found, possibly from the family given by Equation 4, which would provide a better fit but since the lognormal, with S fixed, has now been shown to be of rather wide application (see lognormal model, Discussion) there are little incentive to seek alternatives which are likely to be analytically much less convenient.

CONCLUSIONS

Parametric models seem to provide a useful alternative to the actuarial method of calculating survival percentages even when follow-up data are sufficiently extensive to allow the latter method to be used (Mould, 1976). They certainly extract more information from the clinical data than the crude m year survival figures which are still the common form of reporting treatment results in clinical journals. They offer the unique advantage that an early prediction of longer term results can be made, within calculable error limits.

Three parametric statistical models have previously been described, the lognormal (Boag, 1949), the negative exponential (Berkson and Gage, 1952) and the extrapolated actuarial (Haybittle, 1959). Each of these models makes a different assumption about the analytical form of the distribution of survival times of the unsuccessful cases.

In the present study, the validity of these several survival time distributions has been assessed, using the χ^2 test, with reference to 27 different series of carcinoma of the cervix patients, drawn from several hospitals. The patients had all been at risk for at least 10 years, having been treated during the period 1945–59 and followed up until 1969–71. Two further survival time distributions were introduced and tested—the skew exponential and the skewed extrapolated actuarial. A summary of the results of the tests for goodness of fit is given in Table VI. The lognormal and the skew exponential with $\zeta = 0{\cdot}5$ give the best fit to the observed data.

Previous tests of these parametric models have generally been limited to checking the goodness of fit of the survival time distribution with the proposed formula, but the extrapolated actuarial model has also been tested by comparing predicted long-term survival rates with the observed values for carcinoma of the breast (Haybittle, 1965).

In the present study, all 5 models referred to above have been tested as predictive models for carcinoma of the cervix with the results shown in Fig. 1, 5 and 6 and Tables IX, X and XI. When all these models are tested on stage I cases, the lognormal is consistently the most accurate in its prediction of longer term results; the other 4 models sometimes fail to give any satisfactory solution. For stage II cases, the lognormal is still the best model but the disparity between this and the other models is not so marked. For stage III cases, where the

number of long-term survivors is inevitably comparatively small, there are understandably no great differences between the predictions from the several models.

In summary, the lognormal model, with S fixed at an appropriate value (Table XIII), has been shown to be of wider validity than any of the other models tested and to give reliable extrapolated estimates of long-term survival rate for the separate stage groups in carcinoma of the cervix.

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