FROM THE DEPARTMENT OF RADIATION THERAPY, THE HOSPITAL FOR JOINT DISEASES AND MEDICIAL CENTER, NEW YORK, N.Y. 10035, U.S.A.

GROWTH RATE INVESTIGATION AND TUMOR LETHAL DOSE IN EWING'S SARCOMA

A. W. PEARLMAN

An estimate of a tumor's potential for malignant growth can be deduced from its duration, size and degree of histologic differentiation. These parameters yield, at most, an imprecise clinical index of tumor virulence. COLLINS et coll. (1956) published a more quantitative definition of the evolution and biologic behavior of malignant tumors. This was the first of a series of observations on tumor growth rate and indicated its clinical importance. Based on the serial observation of 46 individual pulmonary metastatic tumors in 15 patients with Ewing's sarcoma, a concept of tumor growth rate and doubling time was obtained. Based on the response of 71 individual tumors in 20 patients, to different doses of irradiation, the spectrum of tumor lethal dosage for this tumor was defined.

Experimental evidence that a tumor may exhibit a constant exponential growth rate during both its visible and invisible phase was presented by MOTTRAM (1935, 1936) who induced cutaneous epitheliomas in mice by local application of tar. Serial measurements of visible tumors were recorded graphically and the growth rate was found to be constant. Backward extrapolation, through the invisible growth period, coincided with the first application of the irritant suggesting that these tumors could have arisen from a single cell and that the growth

Submitted for publication 6 December 1971.

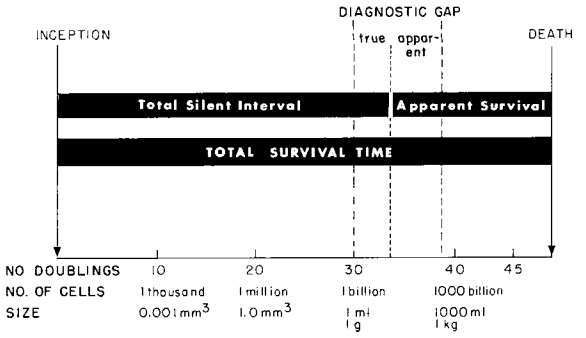

Fig. 1. Model of tumor growth of a hypothetical tumor illustrating the sequence of events when growth rate is exponential. The total survival time has been divided into preclinical (silent interval) and a clinical period from onset of symptoms to final status (apparent survival period). The preclinical period which may comprise as much as 75 per cent of the entire duration of the tumor, is the time required for a single cell 10 μ in diameter to attain a size of 1 cm diameter (approximately 30 tumor doublings). Increase in tumor size thereafter is quite rapid with each additional tumor volume doubling.

rate apparently constant in both the clinical and preclinical periods. This hypothesis of the development of a malignant tumor suggests that the tumor increases in volume in a geometric progression at a more or less constant rate throughout most if not all of its life. The rate of growth is expressed as the doubling time, the time required for a two-fold increase in volume (SPRATT & ACKERMAN 1961).

This simplistic concept of the evolution of malignant tumors has not gone unchallenged. SMITHERS (1968) has pointed out that there is no available experimental data on the growth rate of tumors of microscopic size and that the period of clinical observation from which many of the conclusions concerning tumor growth have been drawn, is after all only a small portion of the life of a tumor. Investigations of cell kinetics have demonstrated a discrepancy between the clinical doubling time and potential doubling time of tumors. The latter is calculated on the assumption that all mitosis produces two viable cells. These observed differences in growth rates may be explained by cell loss which occurs as a result of cell death, migration of cells outside the tumor or the inability of some daughter cells to reproduce (resting fraction) (BAGSHAWE 1968, FRINDEL et coll. 1968). GARLAND et coll. (1963) and GARLAND (1966) have stated that while exponential growth may not necessarily by present for the entire life of the tumor, it is reasonably well established that for moderate sized tumors (up to 2 cm in diameter) constant growth occurs over a significant part of a tumor's life. Even as a clinical approximation, the biomathematics of

exponential tumor growth helps clarify certain aspects of the behavior of human neoplastic disease and focuses attention on the long interval between the inception and the first visible manifestation of a tumor.

A model of exponential tumor growth is illustrated in figure 1 (COLLINS et coll. 1956, SCHWARZ 1961). The clinical diagnosis of carcinoma is only a single important event in the total course of the disease. It has been preceded by an invisible preclinical phase and will be followed by a variable though shorter interval during which unrestrained growth or unsuccessful treatment will terminate in death. The preclinical phase may occupy as much as three quarters of the entire life span of the tumor since it requires approximately 30 doublings in volume for a single cell, 10 μ in diameter, to reach a diameter of 1 cm, a size generally accepted as the smallest diagnosable tumor. Should growth continue at the same rate it would require relatively few additional doublings for the tumor to become huge so that by the 45th doubling, tumor size is incompatible with the life of the host. The clinical diagnosis is usually made some time after a tumor reaches diagnosable size. There is usually a diagnostic gap between the earliest diagnosable tumor and the onset of symptoms. This has been designated the true diagnostic gap. The presence of tumor is not clinically suggested during this interval and it is not likely that this gap can be shortened in the interest of earlier diagnosis. A second delay in diagnosis may occur between the onset of symptoms and the actual diagnosis and has been designated the apparent diagnostic gap. This diagnostic delay can be shortened. Taken together, the true and apparent diagnostic gaps usually occupy a relatively small portion of the life cycle of the tumor. Considering the long preclinical period of growth, clinical diagnosis is not an early event.

Material and Method. Fifteen patients fulfilled the following criteria: The diagnosis was histologically documented, all had measureable pulmonary metastases, and sequential films were available for analyses. The clinical course of each patient is illustrated in figure 2.

Doubling times were calculated according to a formula proposed by GERSTENBERG (quoted by PHILIPPE & LE GAL 1968) which assumes that carcinoma cells divide at approximately equal and constant intervals.

$$Dt = \frac{0.1\ (t - t_0)}{\log dt - \log d_0} \qquad (1)$$

where d_0 and d_t are two successive diameters of a cancerous nodule observed at an interval of t days. In this investigation only the first and last measured diameters were used to calculate the doubling time. Minor variations in growth rate were disregarded. Each patient had from one to six nodules. Multiple

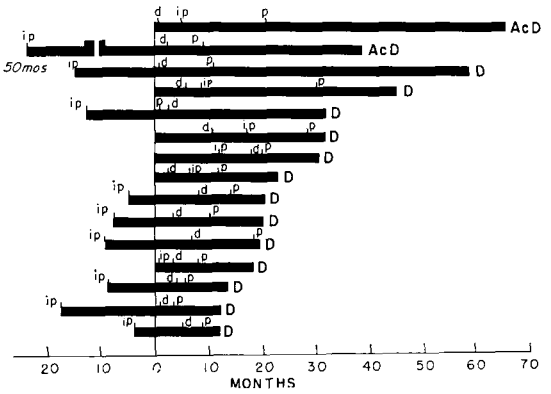

Fig. 2. Clinical course of the 15 patients in this series. Onset of symptoms (0) is the common starting point; first clinical evidence of pulmonary metastasis (p); first diagnosis (d) and final status, alive with disease (AcD) or dead (D). The growth rate of the first pulmonary metastasis was used to determine by backward extrapolation the probable time of inception of the first pulmonary metastasis (ip). In 9 patients inception of pulmonary metastasis preceded the onset of symptoms and in another patient preceded diagnosis. One patient (second from top) had an unusually long preclinical period estimated to be 50 months from the inception of pulmonary metastasis to the onset of symptoms. In the other patients, the short pre-clinical period reflected the rapid tumor growth.

diameters were recorded for each nodule and the results averaged. The same nodules were measured at different times and discrepancies adjusted by averaging the results.

There are difficulties inherent to the accurate mensuration of pulmonary nodules. Margins may blend into the surrounding lung parenchyma, ribs or mediastinum. As adjacent nodules grow, they tend to become confluent. Minor errors in measurement of large tumors are of little significance but assume some importance for small tumors.

The average diameter of each nodule was plotted on semilogarithmic graph paper. From the curves so constructed (Figs 6, 7, 8) it is possible to determine growth rate, the average growth slope and to observe the influence of various treatment modalities on tumor size.

Clinical course. The clinical course of the fifteen patients is illustrated in figure 2 with the 'onset of symptoms' as the common starting point. A number of significant events has been recorded chronologically: diagnosis, the first radiographic evidence of pulmonary metastasis, and the status at last observation, dead or alive with disease. The growth rate of the first pulmonary metastasis was calculated from measurements of tumor diameter on serial chest

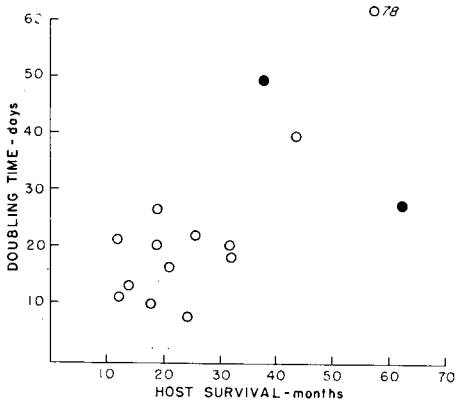

Fig. 3. Survival in months correlated with the tumor doubling time of the most rapidly growing pulmonary metastasis. Rapidly growing tumors (doubling time of 25 days or less) had a uniformly poor prognosis. No patient survived beyond 32 months. Three of the four longer survivors had doubling times of 40 days or longer (cf. Fig. 6). The number 78 refers to the doubling time in days of this patient's tumor. This patient survived 55 months. Open circles indicate patients dead, solid circles patients alive at the time the investigation was completed.

films, using formula 1. By backward extrapolation the probable time of inception of the first pulmonary metastasis was determined and recorded.

Two patients are alive, both with disease. The majority of patients are dead within 36 months of onset of symptoms. The apparent diagnostic gap for the primary tumor (time of onset of symptoms to time of diagnosis) is relatively short: 3 months or less in two-thirds of the patients, indicating a minimal delay in diagnosis and an aggressive clinical course. Diagnostic delays of this order of magnitude probably have little influence on the subsequent course of the disease.

The estimated time of inception of the first pulmonary metastasis preceded the symptoms in 9 patients and preceded the diagnosis in 10. There is a high probability that a patient with Ewing's sarcoma will develop pulmonary metastasis at some time in the course of the disease. In this selected group of patients, the extrapolated data indicate that microscopic metastatic pulmonary disease occurred before clinical manifestations in some two thirds of the patients. This aggressive biologic behavior precludes 'cure' for most patients, with available treatment methods.

The relationship between tumor growth rate and survival is shown in figure 3. Rapidly growing tumors (doubling time 25 days or less) were associated with a rapid clinical course. Eleven of 12 patients were dead within 36 months. Three of the 4 patients who survived for longer intervals (including two still alive at

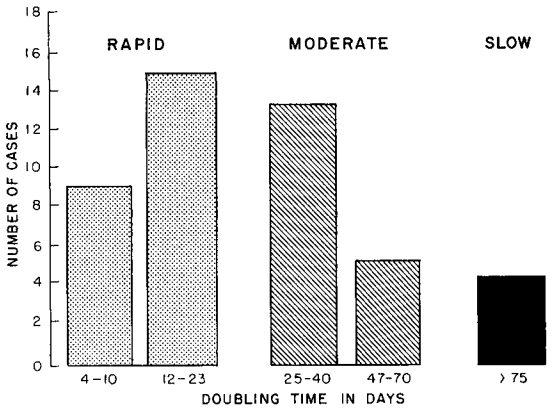

Fig. 4. Tumor doubling time of 46 individual tumors in 15 patients. Doubling times of 25 days or less are considered rapid, 26 to 75 days moderate and over 75 days slow. Over 50 per cent of tumors (24/46) were in rapid growth category. For convenience in analysis the rapid and moderate growth category have been further subdivided into two subgroups, respectively.

40 and 60 months) had slower growing tumors, as manifested by prolonged doubling times.

Doubling time of Ewing's sarcoma. The doubling time of 46 individual pulmonary tumors in 15 patients were calculated from serial measurements and recorded in figure 4. Tumors may be classified as rapidly growing (doubling time 25 days or less); moderate (25 to 75 days) and slow (greater than 75 days) (COLLINS et coll. 1956, BAGSHAWE 1968, PHILIPPE & LE GAL 1968). More than half the tumors fell into the rapid growth rate category and at least one-third had doubling times of 4 to 10 days, indicating extremely rapid growth. Only four tumors had doubling times in excess of 75 days (slow category). While the growth rate of different nodules in the same patient may vary, at least one rapidly growing tumor nodule was recorded for 11 patients. These observations of tumor growth rate are consistent with the known biologic aggressiveness of most Ewing's tumors.

Volume doubling times of 4 to 750 days have been recorded for various human tumors (COLLINS et coll. 1956, SCHWARZ 1961, SPRATT & ACKERMAN 1961, NATHAN et coll. 1962, GARLAND et coll. 1963, SPRATT et coll. 1963 a, b, SPRATT 1965, GARLAND 1966, BAGSHAWE 1968). GARLAND estimated that the average peripheral squamous cell carcinoma requires approximately 8 years to attain a diameter of 2 cm. PHILIPPE & LE GAL calculated the doubling times of mammary carcinoma, using patients with recurrent nodules in the operative scar, and

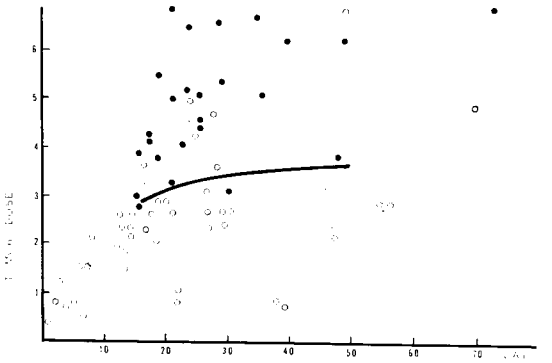

Fig. 5. Scatter diagram of 71 tumor dose points, culled from 20 patients. The solid circles are successful doses and the open circles failures (tumor dose in krad). A free hand iso-effect curve has been constructed. All doses below the curve were sublethal. Some failures are, however, observed at almost all dose levels. The curve delineates a minimal tumor lethal dose range and is not necessarily optimal for irradiation of Ewing's sarcoma.

found a bimodal distribution, one of quick growth, less than 25 days, and another of slow growth averaging 93 days. Generally, rapid tumor growth is not usual for human tumors but occurs often in skeletal and soft tissue sarcomas, lymphomas and some embryonal tumors. In one reported series, the mean doubling time of metastatic skeletal sarcomas, including Ewing's sarcoma was 32 days (SPRATT 1965). This compares with a mean doubling time of 30 days for this series.

Tumor dose. Seventy-one dose points culled from 20 patients have been assembled in a scatter diagram in figure 5. The solid circles represent doses that destroyed a primary or metastatic tumor. With few exceptions, minimal observation period was one year or longer. The successful dose points were obtained, for the most part, from the irradiation of the primary bone tumor. The open circles represent doses that were sublethal i.e., persistent or recurrent tumor after irradiation.

A free-hand iso-effect curve has been constructed through the smallest successful dose points and defines a dose range of approximately 3 000 rad in 10 days to 3 500 rad in 40 days. This is the minimal dose range for arrest of tumor growth for more than one year in this group of patients. All tumor doses below this zone failed but there were some failures at almost every dose level. Based on the distribution of successes and failures, there is an approximately 75 per cent probability of destroying a tumor with doses larger than indicated by the curve.

One clinical problem that arises in patients with Ewing's sarcoma is the

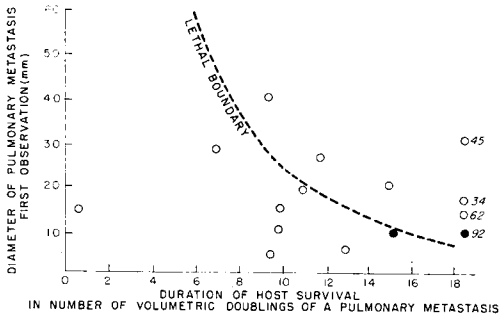

Fig. 6. The lethal boundary is the limit of survival of untreated patients measured in multiples of tumor volume doublings when the size of the pulmonary metastasis, at first observation, is known. There is a probality of only 0.05 that the untreated patient will survive beyond the lethal boundary based on the log normal distribution of growth rate of pulmonary metastasis. The life span of approximately one third of the patients, in this group, exceeded the lethal boundary. The patient who reached 92 volume doublings is now dead with disease. The other survivor, indicated by a solid circle, is still alive with disease and is now well beyond the lethal boundary. This would suggest that treatment benefited one in three patients. The figures adjacent to the circles on the right margin refer to the survival as measured in multiples of tumor doubling time. Open circles indicate patients dead, solid circles patient alive at the time the investigation was completed.

irradiation of pulmonary metastases. MARGOLIS & PHILLIPS (1969) irradiated the whole lung for pulmonary metastases and concluded that normal tissue tolerance ranged from 2 100 rad in 10 days to approximately 5 000 rad in 60 to 70 days. Two of their 7 patients with pulmonary metastases from Ewing's sarcoma achieved local control with relatively small doses (2 200 rad in 18 and 35 days, respectively.) The minimal lethal dose range of figure 5 for this series is greater than the whole lung tolerance, quoted above. No pulmonary nodules in our patients were destroyed with doses smaller than this lethal dose range. Irradiation of a segment of a lung with higher doses did achieve local control. It would appear unlikely that one could sterilize pulmonary metastases by whole lung irradiation and still remain within the tolerance of the normal tissues, in any but the most radiation sensitive Ewing's sarcomas.

Lethal boundary. The therapeutic efficiency of a treatment program may be evaluated by comparing the survival of treated patients with the maximum expected survival of untreated patients. The concept of a lethal boundary for untreated patients with pulmonary metastases was introduced by SPRATT et coll. (1963, 1964, 1965). It is a statistical correlation between measured rates of growth and duration of host survival. Maximum survival is recorded in multiples of tumor volume doublings when the size of the pulmonary metastases at the

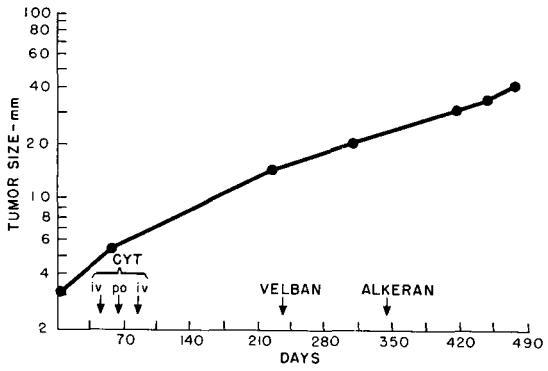

Fig. 7. Male, aged 5. Growth curve of a single pulmonary metastasis observed for 1 1/3 years. Backward extrapolation of the growth curve which is exponential (constant rate of growth) made it possible to recognize the earliest metastatic focus when its size was 3 mm. Cytoxan, velban and alkeran administered at different times did not appreciably affect growth rate. Survival for 38 months from onset of symptoms and 18 months from first diagnosable pulmonary metastasis; as measured in volume doublings not exceeding the lethal limit and no longer than might be expected in an untreated patient (probability 0.05).

first observation, is known. The mathematic analysis of the lethal boundary concept is based on the observation that the growth rate of pulmonary metastases for a variety of tumors and the survival of patients follows a log normal distribution. The probability is only 0.05, that a host with an untreated pulmonary metastasis would survive beyond the lethal boundary. Conversely, there is a 95 per cent chance that the host will die before reaching the lethal boundary. Since survival is measured in tumor volume doublings, the actual survival is the product of the number of doublings and the doubling time. Reference to the original publication is recommended for the details of this unusual analytic method.

The survival of the 15 patients in multiples of tumor volume doubling is plotted in figure 6 in relation to the lethal boundary. The two patients who remain alive are designated by solid circles. One-third of the patients survived beyond the lethal boundary. For the remaining 10 patients, survival was no longer than might be expected for untreated patients. Since therapeutic efficiency is measured in terms of tumor volume doublings rather than in actual survival time, the rate of growth of the tumor is not a factor in this analytic method, as it would be, if a stated time interval were chosen as the end point.

The enhanced survival of one in three patients with pulmonary metastases suggests that a positive and vigorous therapeutic approach that includes irradiation and chemotherapy is justified. That none of the patients survived free of disease is no argument for therapeutic nihilism.

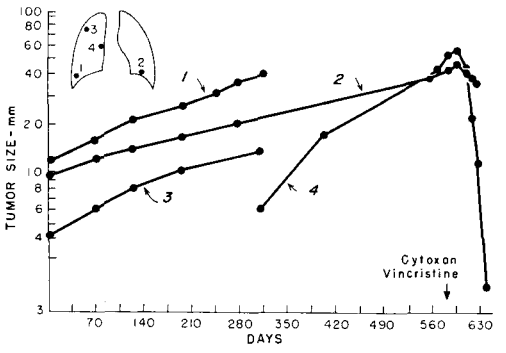

Fig. 8

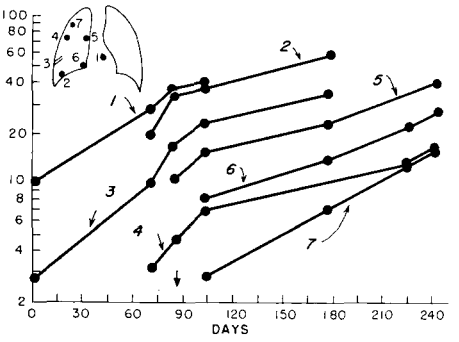

Fig. 9

Fig. 8. Female, aged 8. Growth curves of four pulmonary nodules. While there is considerable variation in growth rate of individual tumors (doubling times were 28, 62, 63, and 85 days, respectively) (individual nodules tend to grow at a constant rate for long periods. The response to chemotherapy with vincristine and cytoxan was a dramatic and rapid shrinkage of the pulmonary metastasis. The patient is alive and functioning well, 3 1/3 years after onset, on maintenance chemotherapy despite the presence of pulmonary metastasis. (In this figure and in Fig. 9 each pulmonary nodule observed has been graphed individually. The dots indicate a measurement of the diameter of the nodule on a serial chest film).

Fig. 9. Growth curves of multiple pulmonary tumors. The growth rate varied within a relatively small range (tumor doubling times 14, 20, 21, 23 and 34 days, respectively). Individual curves varied in growth rate but this was exponential for long periods.

The tumor growth curves for three representative patients, plotted semi-logarithmically, are illustrated in figures 7, 8 and 9. A straight line indicates a constant growth rate. There are variations in the growth rate of different nodules in the same patient for similar observation periods. There are also variations of growth rate of a single untreated nodule. These differences in growth rate tend to be small and are most evident for small tumors, less than 1 cm in diameter, where even small errors in measurement are disproportionately exaggerated. A more or less constant growth rate for long periods is usual.

The effect of chemotherapy on tumor size is illustrated in figure 7. In this patient, treatment with vincristine and cytoxan was immediately followed by rapid shrinkage of the pulmonary tumors. Another patient (Fig. 8) had no objective tumor response to a variety of chemotherapeutic agents. Both are alive with disease, for 3 and 5 years, respectively. No correlation could be established between the immediate tumor response and prognosis.

Modest variations in growth rate notwithstanding the clinical implications of the theory of constant exponential growth seem valid. Backward extrapolation to a time of inception of a tumor is a reasonable approximation in most instances,

and, if not mathematically exact, serves to emphasize the long preclinical phase during which the aggressive behavior of rapidly growing tumors may become manifest.

Discussion

The biomathematic approach to the behavior of malignant tumors, as outlined above has been applied in this investigation to analyze the clinical course of a group of patients with metastatic Ewing's sarcoma. Two observations may have applicability to malignant tumors generally. A specific growth rate is characteristic of an individual tumor. As suggested by COLLINS et coll., 'assigning a numerical value in the form of doubling time offers a more precise statement of rate of growth than descriptive phrases such as rapidly-growing or slowly-growing'. Secondly, the concept of origin from a single cell and subsequent exponential growth emphasizes the long preclinical period before diagnosis. Early diagnosis is not an early event in the total life of a tumor. This may explain the failure, at times, of early diagnosis to influence cure. Treatment failures are apt to be due to undectected metastases, already present, though not clinically evident when treatment is begun, especially in malignant bone tumors.

It is an accepted practice to report end results at stated times, usually 5 years or multiples thereof. As a measure of therapeutic efficiency for certain growths, this may be questioned. Long survivals in patients with slow-growing tumors may only reflect a long doubling time. It is suggested that comparisons of treatment results are more accurately reflected by recording survival in multiples of tumor doublings. Unfortunately this information is not available for most primary tumors either because they are inaccessible to direct measurement or serial observations are curtailed by early treatment.

The theory of exponential tumor growth has found clinical support in the concept of the 'period of risk'. This has led to an unique analysis of end results in certain childhood tumors. Children with Wilms' tumors who have survived symptom-free following treatment for a period, equal to their age at onset plus 9 months of gestation, have rarely had a recurrence (COLLINS et coll. 1956, KNOX & PILLERS 1958, POLLOCK et coll. 1960). Similar observations have been recorded in neuroblastoma (KNOX & PILLERS 1958, SUTOW 1958, BODIAN 1959, POLLOCK et coll. 1960), rhabdomyosarcoma (KNOX & PILLERS) and medulloblastoma (KIESEWETTER & MASON 1960). The 'period of risk' is based on the theory that viable tumor cells surviving after definitive therapy grow at more or less the same rate as the original tumor. A recurrent tumor should become clinically manifest within an interval no greater than the longest possible time that the original tumor was present.

The clinical course of our patients indicates that Ewing's sarcoma is a biologically aggressive tumor with a rapid growth rate and a propensity for early dissemination. This is supported by the preponderance of tumors with doubling times of less than 25 days, by the high probability of microscopic pulmonary metastases before the primary tumor attains a diagnosable size, and by the short clinical course after onset.

There is some evidence that an aggressive therapeutic approach which includes radiation and chemotherapy may prolong life. Based on survival as measured in tumor volume doublings, one in three patients with pulmonary metastasis, had a survival significantly longer than the expected survival of untreated patients.

Conclusions

The growth of tumors that lend themselves to serial measurements can be described in terms of doubling time, the time required for a twofold increase in volume. The doubling time characterizes the rate of growth which tends to be more or less constant during the period of observation for most tumors of moderate size.

The majority of pulmonary tumors in this series were rapidly growing (doubling time 25 days or less). Slow-growing tumors with a doubling time of 75 days or longer were unusual.

Ewing's sarcoma is an aggressive tumor. The great majority of patients are dead within 3 years of onset. There is a high probability that microscopic pulmonary metastases will occur during the preclinical period, before onset or diagnosis.

A suggested minimal tumor dosage, based on 71 tumor-lethal dose points, ranges from 3 000 rad in 10 days to 3 500 rad in 40 days. All doses below this range failed to destroy the tumor. Some failures occurred with higher doses.

Survival as measured in multiples of doubling time suggests that a significant prolongation of life in approximately one-third of patients follows an adequate treatment program.

Acknowledgement

I am most grateful to Dr Milton Friedman for reviewing and correcting the manuscript. His critical comments were most helpful.

Addendum

Since submitting this manuscript two additional patients with pulmonary metastasis were treated. Five pulmonary nodules in patient A had tumor doubling time of 4, 4.5, 7, 7, and 14 days, respectively. Two pulmonary nodules in patient B had doubling times of 14 and 19

days, respectively. In both patients backward extrapolation of the growth rate of the first pulmonary metastasis suggested the presence of microscopic implants in the lung before onset of symptoms (Fig. 2). The pulmonary nodules of patient A responded to irradiation, but not to chemotherapy with vincristine, cytoxan, or actinomycin D. Patient B's pulmonary metastases responded to both chemotherapy (one lung) and radiation plus chemotherapy (opposite lung). Patient A survived 1 year from onset. He survived 25 tumor volume doublings from the first appearance of pulmonary metastases. This exceeds his expected lethal boundary of 13 tumor doublings (see Fig. 6) and suggests prolongation of life as a result of therapy. Patient B is alive and well and to the present time has exceeded 25 tumor doubling times since onset of pulmonary metastasis.

SUMMARY

Ewing's sarcoma is a biologically aggressive tumor with a rapid growth rate (tumor volume doubling time) and a propensity for early dissemination. Investigation of growth rate of individual pulmonary nodules indicates an exponential (constant) growth rate for long periods. Backward extrapolation of the growth curve of the first pulmonary metastasis suggests that the earliest pulmonary implant occurred before onset of symptoms or diagnosis in two-thirds of the patients. A minimal tumor lethal dose range is proferred, below which dose levels no tumors were destroyed. This range is between 3 000 rad in 10 days and 3 500 rad in 40 days.

ZUSAMMENFASSUNG

Ewings Sarkom ist ein biologisch aggressiver Tumor mit einer raschen Zuwachsrate (Tumor-Verdopplungszeit) und einer Neigung zu frühzeitiger Streuung. Untersuchungen der Zuwachsrate individueller Knötchen in der Lunge deuten auf eine exponentielle (konstante) Zuwachsrate während langer Perioden. Rückwärtige Extrapolation der Zuwachskurve der ersten Lungenmetastase deutet darauf hin, dass bei 2/3 der Patienten das erste pulmonelle Implantat vor Einsetzten der Symptome oder vor der Diagnose aufgetreten war. Man kommt zu einem letalen Tumordosisbereich, unter dem keine Tumoren zerstört werden. Dieser Bereich liegt zwischen 3 000 rad in 10 Tagen und 3 500 rad in 40 Tagen.

RÉSUMÉ

Le sarcome d'Ewing est une tumeur biologiquement aggressive avec un taux de croissance rapide (temps de doublement du volume tumoral) et une propension à la dissémination précoce. L'étude du taux de croissance de nodules pulmonaires isolés indique un taux de croissance exponentielle (constant) au cours de longues périodes. L'extrapolation rétrograde de la courbe de croissance de la première métastase pulmonaire fait penser que la première greffe pulmonaire s'est produite avant le début des symptomes ou avant le diagnostic chez les deux tiers des malades. L'auteur propose une limite minimale de dose léthale pour la tumeur au dessous de laquelle aucune tumeur n'a été détruite. Cette limite est entre 3000 rad en 10 jours et 3 500 rad en 40 jours.

REFERENCES

BAGSHAWE K. D.: Tumor growth and anti-mitotic action. Brit. J. Cancer 22 (1968), 698.

BODIAN M.: Neuroblastoma. Pediat. Clin. N. Amer. 6 (1959), 449.

COLLINS V. P., LOEFFLER R. K. and TIVEY H.: Observations on growth rates of human tumors. Amer. J. Roentgenol. 76 (1956), 988.

FRINDEL E., MALAISE E. and TUBIANA M.: All proliferation kinetics in five human solid tumors. Cancer 22 (1968), 611.

GARLAND L. H.: The rate of growth and natural duration of primary bronchial cancer. Amer. J. Roentgenol. 96 (1966), 604.

— COULSON W. and WOLLIN E.: The rate of growth and apparent duration of untreated primary bronchial carcinoma. Cancer 16 (1963), 694.

KIESEWETTER W. B. and MASON E. J.: Malignant tumors in childhood. J. Amer. med. Ass. 172 (1960), 1117.

KNOX W. E. and PILLERS E. M. K.: Time of recurrence in cure of tumors of childhood. Lancet 1958: I, p. 188.

PHILIPPE E. and LE GAL Y.: Growth of seventy eight recurrent mammary cancers. Cancer 21 (1968), 461.

MARGOLIS L. W. and PHILLIPS T. L.: Whole lung irradiation for metastatic tumors. Radiology 93 (1969), 1173.

MOTTRAM J. C.: On origin of tar tumors in mice whether from single cells or many cells. J. Path. Bact. 40 (1935), 407.

— Further considerations of growth rates of tar warts in mice and their anti grafts. Amer. J. Cancer 28 (1936), 115.

NATHAN M. H., COLLINS V. P. and ADAMS R. A.: Differentiation of benign and malignant pulmonary nodules by growth rate. Radiology 79 (1962), 221.

POLLOCK W. F., HASTINGS N. and SNYDER W. H.: The Collins' 'period of risk' formula for malignant tumors in children with particular reference to Wilms' tumor and neuroblastoma. Pediat. Surg. 48 (1960), 606.

SCHWARZ M.: Biomathematical approach to clinical tumor growth. Cancer 14 (1961), 1271.

SMITHERS D. W.: Clinical assessment of growth-rate in human tumours. Clin. Radiol. 19 (1968), 113.

SPRATT JR J. S.: The rates of growth of skeletal sarcomas. Cancer 18 (1965), 14.

— and ACKERMAN L. V.: The growth of a colonic adenocarcinoma. Amer. Surg. 27 (1961), 23.

— and SPRATT T. L.: Rates of growth of pulmonary metastases and host survival. Ann. Surg. 59 (1964), 161.

— SPJUT H. J. and ROPER C. L. (a): The frequency distribution of the rates of growth and the estimated duration of primary pulmonary carcinomas. Cancer 16 (1963), 687.

— TER-POGOSSIAN M. and LONG R. T. L. (b): The detection and growth of intra thoracic neoplasms. Arch. Surg. 86 (1963), 283.

SUTOW W. W.: Prognosis in neuroblastoma of childhood. Amer. J. Dis. Child. 96 (1958), 299.