Cell Prolif. 1997, **30**, 341–349

Gompertzian growth curves in parathyroid tumours: further evidence for the set-point hypothesis

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(*Received* 17 *July* 1997; *accepted* 16 *October* 1997)

Abstract. *Background:* Clinical and cell kinetic data in parathyroid tumours show that their rate of growth slows down progressively and that tumour size approaches an asymptotic value. The Gompertz equation has been widely used in oncology to model growth retardation in malignant tumours; we describe its first aplication to a benign tumour. *Methods:* In 41 patients with radiation associated hyperparathyroidism, individual solutions were derived for the Gompertz equation: $N_t = \mathrm{Exp}[A/a(1-\mathrm{Exp}-at)]$, where A is the rate constant (years^{-1}) for initial exponential growth and a is the rate constant (years^{-1}) for exponential decline in A. Input data comprised three estimates of tumour age at surgery, 100%, 75% and 50% of the time since irradiation, cell number estimated from tumour weight, and current tumour growth rate, representing the difference between current cell birth rate, estimated from the prevalence of mitotic figures, and an assumed mean rate of cell loss of 5%. *Results:* With 100% tumour age, geometric mean values were 2.76 for A, 0.134 for a, and 0.87 g for the growth asymptote. As assumed tumour age decreased, the rate constants increased and the growth asymptotes declined from 22% to 9% greater than the geometric mean tumour weight. Depending on assumed tumour age, the rate constants were about 15–45 times smaller than in myeloma and in testicular tumours, and the growth asymptotes about 2500 and about 60 times smaller, respectively. A and a were highly correlated ($r^2 = 0.993$), with a slope of 20.9 and no significant intercept. Depending on assumed tumour age, the geometric mean time from the initial mutation to the first cell division ranged from 39 to 92 days, much longer than in malignant tumours. *Conclusions:* (1) The Gompertz modelling demonstrates that both the nonprogressive clinical course and the slow growth of parathyroid tumours can be accounted for by a single mutation. (2) The extremely low values for A and a, and consequent very long delay before the first cell division, support the notion that the initial mutation does not affect a growth regulatory gene, but increases growth indirectly via an increase in secretory set-point, the clone of mutant cells behaving as if they were in a hypocalcaemic environment until the plasma calcium rises to the new set-point. (3) The clinical characteristics of radiation-induced parathyroid tumours are modelled more closely if there is a substantial delay between time of irradiation and onset of tumour growth. (4) The rate constants A and a are highly correlated because the variability

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of tumour weight on a logarithmic scale is much lower than the variability of the rate constants.

In most parathyroid tumours, particularly those that are discovered in asymptomatic patients as a result of multichannel biochemical screening, both long term clinical observations (Rao *et al.* 1988) and cell kinetic data (Parfitt *et al.* 1991a) indicate that the rate of growth slows down progressively, and that tumour size approaches an asymptotic value. The rate of cell division is 10–20 times lower than in meningiomas (Parfitt, Braunstein & Katz 1993), so that very low cell turnover may be a specific characteristic of parathyroid tumours, rather than a non-specific characteristic of benign tumours in general. Parathyroid tumours, like other benign endocrine tumours, appear to be monoclonal, implying an origin from a single altered cell (Arnold 1994). Consequently, in most patients, the growth of a parathyroid tumour throughout its life span will conform to a sigmoid curve. Such a curve can be represented mathematically in several ways (Batschelet 1974). The one most frequently used in oncology to model growth retardation in malignant tumours is the Gompertz equation, developed by the 19th century English actuary, Benjamin Gompertz (Laird 1969, Norton 1988). The equation is characterized by two parameters, the initial specific rate of exponential growth and the rate of exponential fall in the initial growth rate (Table 1). Unlike the logistic function, which is symmetrical about the inflexion, the Gompertz function is asymmetrical about the inflexion, which is always 0.37 of the asymptotic value (Laird 1969). We have used this equation to model growth retardation in parathyroid tumours, its first application to a benign tumour.

MATERIALS AND METHODS

We applied the Gompertz equation to data from a previous study of radiation-associated parathyroid tumours, in which current cell birth rate was estimated from the prevalence of mitotic figures and an assumed duration of mitosis of 30 min (Parfitt *et al.* 1993). We made three different assumptions about the age of the tumour (Table 2a). First, that tumour age is given by the time between irradiation and surgery. This assumption is based on the ability of irradiation to rapidly induce DNA damage in single cells (Smith & Sykes 1992), the need for the damage to occur shortly before or during cell division in order to escape repair and become fixed as a mutation (Ames, Swirsky Gold & Willett 1995), and the clonal evolution theory of tumour development according to which each step, including the first, confers a selective growth advantage (Nowell 1976). According to this assumption, mean tumour age in this series was 39.2 years (SD = 12.1).

The second and third assumptions about tumour age are based on the notion that the initial effect of irradiation is to damage the DNA in some cells (in an unspecified manner) such that they acquire an increased susceptibility to subsequent mutation, rather than an

Table 1. Gompertz equation for tumour growth

N_t	=	$Exp[(A/a)(1-Exp-at)]$
A (y^{-1})	=	initial specific growth rate
a (y^{-1})	=	rate of exponential fall in A
t (y)	=	tumour age
Exp (A/a)	=	growth asymptote (N_α)

Equation written for origin from one cell. N_t=number of cells at time t; y=years.

Table 2. Input for solving equation and assumed rates of cell loss (%/year)

(a) Input for solving equation

t (years)	=	a—Irradiation to surgery
	=	b—Same * 0.75
	=	c—Same * 0.5
N_t	=	Weight (g) * 1.074×10^9
k ($year^{-1}$	=	Net growth = Birth rate − Loss rate (Estimated) (Assumed)

(b) Assumed rates of cell loss (%/year)

Birth rate (estimated)	<3.0	3.0–5.3	5.3–8.3	8.3–15.0	>15.0
n	4	9	15	9	4
Mean loss (assumed)	−1.0	−3.0	−5.0	−7.0	−9.0

immediate growth advantage (Kennedy & Little 1984, Little 1986). Based on direct measurements of the proportion of cycling cells in normal parathyroid glands obtained at autopsy, the geometric mean cell birth rate in normal parathyroid tissue is about 5% per year (Wang, Palnitkar & Parfitt 1997), corresponding to a mean cell age of about 10 years and a mean cell life span of about 20 years. Consequently, if the risk of initial damage was the same for all cells, the first growth promoting mutation would be delayed for a mean duration of about 10 years, modelled by a reduction in mean tumour age of 25% (29.4 years). If the risk of initial damage was borne only by dividing cells, the first mutation would be delayed for a mean duration of about 20 years, modelled by a reduction in mean tumour age of 50% (19.6 years).

Next, we assumed that the number of cells can be estimated from tumour weight (Table 2a). Tumour weight and other growth-related variables are most appropriately expressed on a logarithmic scale. After calculation of the mean of the log-transformed data, exponential retransformation gives the geometric mean in the original units. An analogous procedure gives the geometric (or multiplicative) SD, the number by which the geometric mean must be multiplied or divided to obtain ranges that correspond to addition or subtraction of the SD on an arithmetic scale (Batschelet 1974). The geometric mean tumour weight was 0.783 g and multiplicative SD 2.79. A commonly used approximation in oncology is that a tumour weighing 1 g contains 2^{30} (= 1.074×10^9) cells (Tannock 1989); this has been validated for parathyroid tumours by a comparison with tumour DNA content (Parfitt *et al.* 1991a). With this relationship, the corresponding geometric mean cell number was 0.841×10^9.

Finally, we assumed that the net tumour growth rate can be estimated from the current cell birth rate (Table 2a). The net growth of a tumour represents the balance between the addition of cells by mitosis, and the loss of cells by apoptosis (Kerr *et al.* 1987). As previously indicated, we assumed that the normal rate of cell loss was 5% per year; this estimate is more reliable than the previous indirect estimate of 3% per year (Parfitt 1994). In order to avoid negative rates of growth, we assumed that the rates of cell loss increased with the birth rate as shown in Table 2b, and that the mean for the entire group was 5%. The corresponding rates of net tumour growth are shown in Table 3. Using individual values for each of the three input variables, individual solutions for the two parameters of the equation were obtained using the built-in function MINERR of MATHCAD 5.0. MINERR is based on the iterative Levenberg–Marquardt method (Anonymous 1994) which forms the basis for all of the solve–block routines used in MATHCAD 5.0. The actual program used is available on request (DPF). The representative growth curves derived from the geometric means of the parameters A and *a* were constrained to pass through the points defined by the geometric

Table 3. Net rates of tumour growth

	Birth rate[a]	Growth rate[b]
Arithmetic means (SD)	7.47 (3.88)	2.47 (2.01)
Geometric mean (SD)[c]	6.51 (1.72)	1.77 (2.38)
Calculated range[d]	2.2–19.3	0.3–10.0
Actual range	1.7–15.7	0.3–7.7

Data expressed as %/year. [a]From Parfitt *et al.* 1993. [b]Calculated as in Table 2, assuming mean rate of cell loss is 5%/year. [c]Multiplicative. [d]Geometric mean $\times/\div$ multiplicative SD^2, corresponding to mean $\pm 2SD$ on an arithmetic scale.

mean tumour weight and the mean tumour age. This required only small changes in the fourth decimal place of the calculated values for a. The time from the initial mutation to the first cell division, equivalent to the initial doubling time, was calculated as $\log_e 2/A$ (Brunton & Wheldon 1978).

RESULTS

The data for the initial exponential growth rate (A) and the rate of exponential decline in the initial growth rate (a) in 41 patients with radiation-associated parathyroid tumours, according to the different assumptions for tumour age, are shown in Table 4. The approximate correspondence of the calculated and actual ranges indicates that, as expected, the data conform more closely to a log-normal than to a normal distribution. The rate constants increased as assumed tumour age decreased. For comparison, corresponding values obtained in 11 patients with myelomatosis, in whom tumour growth was estimated from the rate of immunoglobulin synthesis (Sullivan & Salmon 1972), and 10 patients with testicular tumours, in whom tumour growth was estimated from the size of lung metastases (Demicheli 1980), are included. In the parathyroid tumours, depending on the assumed tumour age, the initial

Table 4. Gompertzian growth in human tumours

	PT tumours[a] $n=41$	PT tumours[b]	PT tumours[c]	Multiple myeloma[d] $n=11$	Testicular tumours[e] $n=10$
A ($years^{-1}$)					
Geometric mean (SD)	2.76 (1.59)	3.94 (1.57)	6.46 (1.55)	126 (1.68)	112 (1.76)
Calculated range[f]	1.1–7.0	1.6–9.7	2.68–15.6	45–356	36–345
Actual range	1.18–11.78	1.74–16.3	2.99–25.8	43–274	44–411
a ($years^{-1}$)					
Geometric mean (SD)	0.134 (1.60)	0.191 (1.58)	0.314 (1.58)	4.41 (1.69)	4.52 (1.82)
Calculated range[f]	0.052–0.342	0.077–0.477	0.126–0.783	1.5–12.6	1.3–15.1
Actual range	0.051–0.549	0.077–0.762	0.134–1.20	1.5–9.5	1.7–19.2
Initial doubling time (d)					
Geometric mean	92	64	39	2	2.3
Actual range	21–215	16–145	70–85	0.92–5.9	0.62–5.8

[a]Assuming mean tumour age of 39.2 years (see Table 2a). [b]Assuming mean tumour age of 29.4 years. [c]Assuming mean tumour age of 19.6 years. [d]Sullivan & Salmon 1972. [e]Demicheli 1980. [f]Geometric mean $\times/\div$ multiplicative SD^2 corresponding to mean $\pm 2SD$ on an arithmetic scale.

Table 5. Growth asymptotes in human tumours

Method of calculation	PT tumours[a]	PT tumours[b]	PT tumours[c]	Multiple myeloma	Testicular tumours
Geometric mean (SD) of					
individual values	0.987 (3.13)	0.920 (2.99)	0.862 (2.89)	2216 (2.40)	59.2 (8.06)
Calculated range	0.101–9.7	0.103–8.2	0.103–7.2	885–17 764	0.9–3846
Actual range	0.091–17.6	0.091–12.6	0.092–9.0	254–6670	1.0–1743
Geometric means of A and *a*					
(Table 4)	0.874	0.844	0.819	2385	54

Data expressed in g. [a]Assumed tumour age of 39.2 years. [b]Assumed tumour age of 29.4 years. [c]Assumed tumour age of 19.6 years.

growth rate was about 20–45 times slower, and the rate of decline in the initial growth rate about 14–33 times slower than in myeloma. Corresponding ratios for testicular tumours were 17–40 and 14–34. The multiplicative SDs were quite similar among the three types of tumour, indicating similar proportional differences between the fastest and slowest growing tumours. The initial doubling time, equivalent to the time from the initial growth promoting mutation to the next cell division declined as assumed tumour age decreased, but remained much longer than in the other tumours (Table 4).

The asymptotic values for tumour weight, derived from the asymptotic values for number of cells (Exp(A/*a*)), are shown in Table 5, calculated in two different ways. For both methods of calculation, the mean asymptotic weight decreased as assumed tumour age decreased. Consequently, the actual weights at the time of surgery were progressively closer to the asymptotic values, and the proportion of cases that were at least 90% of the asymptotic value progressively increased (Table 6). The geometric means of the calculated asymptotic weights in parathyroid tumours were around 2500 times smaller than in myeloma, and about 65 times smaller than in testicular tumours (Table 5).

Representative growth curves for parathyroid tumours, based on the mean values of the parameters in Table 4, are shown in Figure 1. For mean tumour age of 100% of the interval between irradiation and surgery, such a representative tumour would weigh only about 4 mg after 10 years, and would take almost 17 years to reach 100 mg in weight, the smallest size likely to be clinically detectable. For 75% and 50% tumour ages, corresponding times after irradiation to reach 100 mg are 22 and 27 years. The curves also illustrate the difference between the growth asymptotes given in Table 5.

The relationship between the individual values for the two rate constants are shown in Figure 2. Regardless of the assumed tumour age, there was a remarkably high correlation between them, as previously found in myeloma (Sullivan & Salmon 1972), in testicular tumours (Demicheli 1980), and in several kinds of experimental tumour in small rodents

Table 6. Relationship between observed weight and asymptotic weight

Assumed tumour age	100%[a]	75%[b]	50%[a]
Weight as % asymptotic weight[b]	81.9 (17.8)	86.5 (13.8)	91.4 (9.1)
Range	30.5–99.9	45.3–99.9	63.8–99.9
Cases closer than 90% (%)	37	54	76

[a]Of time from irradiation to surgery. [b]Mean (SD).

(Brunton & Wheldon 1978), but the slope of the regression line was substantially lower in the parathyroid tumours, corresponding to the lower value for the mean growth asymptote (Table 5).

DISCUSSION

In previous applications of the Gompertz equation, to malignant tumours, only data from early stages of tumour growth were available, and the predicted asymptotic values for tumour size were never attained (Sullivan & Salmon 1972, Brunton & Wheldon 1978, Demicheli 1980, Norton 1988). Because of their benign nature and very slow growth, in parathyroid adenomas almost the entire course of Gompertzian growth can be modelled, the first time that this has been accomplished. The general forms of the calculated growth curves (Figure 1) resemble the hypothetical curves previously proposed (Parfitt *et al.* 1991a, Parfitt 1994), but differ in several major respects. Because of the extremely low values for the rate constants, both the minimum size for clinical detectability and the asymptotic value are attained more slowly than was expected; consequently, at the time of surgery, the tumours are further from the asymptotic value and are growing faster than was previously assumed. But the lower the assumed value for tumour age, the closer are they to their asymptotic value, and the more rapidly does predicted tumour growth beyond the time of surgery slow

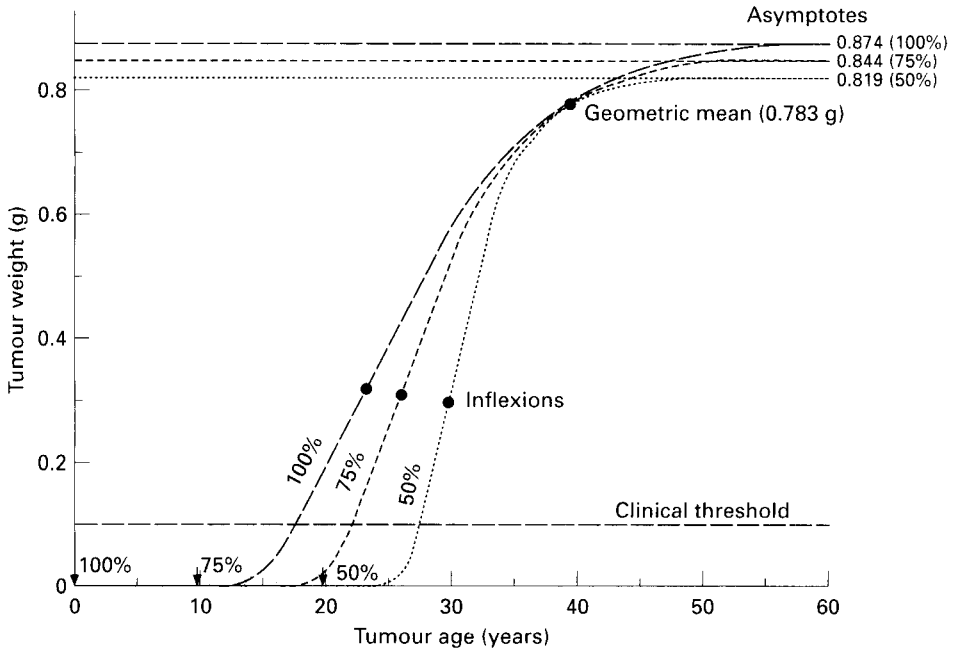

Figure 1. Representative growth curves for parathyroid tumours based on the mean values for A and *a* in Table 4, corresponding to three different assumptions concerning tumour age—100%, 75% and 50% of the time between irradiation and surgery; in each case, onset of tumour growth is indicated by a vertical arrow. The inflection is the point where the slope of the curve is at a maximum. The geometric mean is based on logarithmic transformation of the actual tumour weights. The shapes of the curves are independent of the relationship between the tumour weight and cell number, which affects only the values of the rate constants and other derived numerical values. The clinical threshold is the smallest weight of tumour likely to be detectable (0.1 g). Copyright A. M. Parfitt 1997; used with permission.

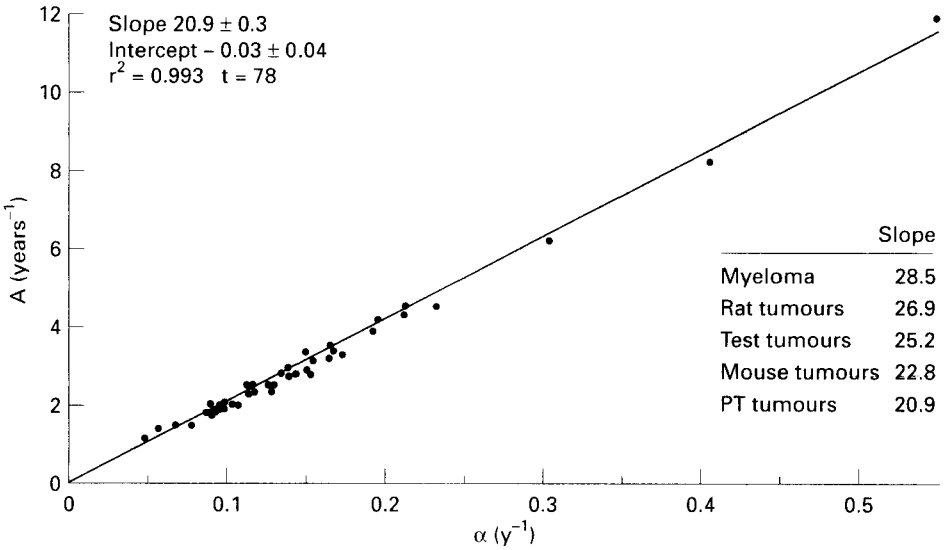

Figure 2. Relationship between individual values for the parameters of the Gompertzian growth curve in 41 radiation-associated parathyroid adenomas assuming 5% per year cell loss and tumour age 100% of the time between irradiation and surgery. The intercept is not significantly different from zero. The regression parameters were almost identical for tumour ages of 75% and 50%. Similar, very high correlations were found in myeloma (Sullivan & Salmon 1972), metastatic testicular tumours (Demicheli 1980), and in several experimental rodent tumours (Brunton & Wheldon 1968). Copyright A. M. Parfitt 1997; used with permission.

down, so that a delay in onset of tumour growth fits the clinical course more closely. Delayed onset also shortens the period of rapid growth, and so more fully explains the infrequency of significant disease progression at the time of diagnosis (Parfitt *et al.* 1991b). The clinical time scale is very much longer than the experimental, but the Gompertz modelling provides indirect support for the notion that a non-mutational event is the initial response to irradiation (Little 1986).

Although the exact form of the growth curve is uncertain, that growth slows with time is indisputable. Two aspects of growth must be distinguished. According to the Gompertz model, the specific cell growth rate, or fractional rate of cell birth, is maximal initially and declines progressively. Even with the longest tumour age and slowest initial growth rate, the magnitude of decline is greater than 97% (276% per year to 6.5% per year). In contrast, absolute tumour growth rate increases progressively to a maximum at the inflection and then declines. The calculated peak rates range from 47 mg/year with the longest mean age to 97 mg/year with the shortest, compared to 14 mg/year at the time of surgery. Growth retardation in malignant tumours is commonly attributed to failure of the blood supply to keep pace with demand, and consequent restraint on the rate of cell division (Sutherland 1986), but this seems highly unlikely for small highly vascular parathyroid tumours in which growth is already very slow. Another frequently proposed explanation for retarded tumour growth is increased cell loss (Laird 1969, Steel 1977). Necrosis was not found by routine histopathology in any of our cases, and apoptosis, an alternative and more common mode of cell death in tumours (Kerr *et al.* 1987), was not observed in a different series by examiners familiar with its microscopic appearances (Parfitt *et al.* 1991a). Apoptosis could not be detected in the rat parathyroid gland (Naveh-Many *et al.* 1995, Wang *et al.* 1996), and in the human parathyroid

gland has not yet been studied by current histological methods (Wijsman *et al.* 1993). Apoptosis seems a more likely explanation for growth retardation in tumours such as meningiomas that have a much higher rate of cell division (Parfitt *et al.* 1993), than in parathyroid tumours in which the rate of cell division is so low.

An alternative explanation for marked retardation of both cell division and tumour growth has previously been proposed, namely the set-point hypothesis (Parfitt *et al.* 1991a, Parfitt *et al.* 1993, Parfitt 1994). According to this hypothesis, the initial mutation affects growth not directly, but indirectly via an increase in the secretory set-point, which is the plasma calcium value that parathyroid cells recognize as normal and attempt to defend. Regardless of how such an increase was brought about, such a cell would perceive itself to be in a hypocalcaemic environment and would maximize its rate of hormone secretion, but to no avail. Because hypocalcaemia stimulates cell proliferation as well as hormone secretion in the parathyroid gland (Parfitt 1994), eventually the mutant cell will be driven to divide. The new clone will grow in response to *perceived* hypocalcaemia by *exactly* the same mechanisms as normal cells grow in response to *actual* hypocalcaemia, without the need for any disruption in the regulation of normal parathyroid cell division. Growth will continue very slowly until the new clone is large enough to raise the plasma calcium to the new set-point. The Gompertz modelling has provided additional support for this hypothesis in two respects. First is the unusually long time from the initial mutation to the first cell division, the geometric mean ranging from 40–100 days depending on the assumption made concerning tumour age. It seems unlikely that a cell with a primary mutation in a growth control gene would wait so long before dividing. Such duration seem more reasonable for a cell that will divide only as a last resort, as predicted by the set-point hypothesis. Second, the Gompertz modelling explains how both the growth characteristics and the clinical course of the majority of parathyroid tumours can be accounted for by a single mutation.

An invariable feature of Gompertz modelling is the very high correlation between the two rate constants A and a. When first noted, this relationship was attributed to species specific limits for maximum tumour weight in relation to body weight (Brunton & Wheldon 1978). This interpretation is inconsistent with numerous data on experimental tumours (Steel 1980), and is ruled out by our observations on parathyroid adenomas, in which the correlation is just as high as in malignant tumours but the largest tumours are less than 0.02% of body weight. The high correlation between A and a has been regarded as an artefact due to extrapolating growth data back to a single cell (Steel 1980) but this explanation is equally untenable (Brunton & Wheldon 1980). We propose what we believe is a more plausible alternative. When tumour weights are expressed on a logarithmic scale, their variability between subjects is much lower than the variability of the rate constants. For example, parathyroid adenomas are rarely less than 0.1 g or more than 10 g in weight (Table 5). This range corresponds to a range for A/a of 18.5–23, values which are only about 10% less than and 10% more than the regression slope of 20.9 (Figure 2). But there is more than a 10-fold range of values for both A and a (Table 4, Figure 2). Inspection of published graphs indicates that the same explanation applies to all previously recorded instances of a high correlation between the rate constants.

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