BELLE Newsletter Vol 6, No. 1, September 1997

A Theory for Growth Hormesis

A.R.D. Stebbing, Ph.D.
Plymouth Marine Laboratory, Prospect Place, The Hoe, Plymouth, Devon, PL1 3DH, UK
Phone: 44-17-52-633-161 Fax: 44-17-52-633-101 E-mail: JLC@wpo.nerc.ac.uk

FIRST ENCOUNTER WITH HORMESIS

It is over 30 years since I first became interested in hormesis, prompted by the need to understand some unexpected results. I was trying to develop a laborator y bioassay sensitive enough to provide a direct measure of seawater quality; some experimental measure was needed of the combined effects of the numerous low levels of contaminants in polluted coastal waters. To achieve sensitivity with precision the best option was to use a clone of the marine hydroid *Laomedea flexuosa* . The index of sub-lethal effect was the inhibition of asexual growth of the hydroid colonies. The first phase was to carry out some concentration-response experiments using low levels of metals to establish the sensitivity of the hydroids and to find what replication was necessar y to obtain adequate precision. The range of concentrations used in these early experiments extended well below those that typically cause toxic effects in other species. The first examples of the stimulation of growth at these low levels were dismissed as aberrant and attributed to experimental error, but with improved precision, it became clear that the stimulator y effects were real. They were as significant as they were reproducible with enhancements in growth spanning more than an order of magnitude of copper concentrations (Figure 1), following a pattern now known as the beta curve.

These early experiments to develop the techniques tested copper as a growth inhibitor and the stimulatory effects prompted the idea that perhaps the concentrations which enhanced growth were satisfying a deficiency in the sea water, or in the diet of the hydroids (*Artemia salina* nauplii), but these possibilities were soon eliminated when similar, if less marked effects were observed in response to other metals. Most of the later experiments were designed to look at the effects of metals such as cadmium and mercury, which unlike copper are not also micro-nutrients (Stebbing, 1976, 1981b). Experiments to determine the effect of reduced salinity or the toxicity of fresh water resulted in the same phenomenon, supporting the idea that hor mesis was a response to some effect all these agents had in common, rather than the result of any specific property of the agents themselves.

Examples of hormesis gathered from the literature show that hormesis has a long and inter esting history. The concentration-response curves for quite a wide range of toxic agents followed a typical pattern, termed the betacurve (Townsend & Luckey, 1960). The occurrence of such curves in toxicological experiments was discovered independently and named on several occasions. Over a century ago Schultz's experiments (1888) showed that many chemical agents had the effect of stimulating the growth and respiration of yeast. The phenomenon became known

as the Arndt-Schultz Law and was widely referred to in the pharmacological literature for over 30 years and became one of the scientific principles on which homeopathy is based. However, the potency of homeopathic medicines is believed to increase with their dilution over many orders of magnitude, rather than restricted to a narrow range of concentrations like hormesis. Hueppe (1896) at about that time made similar obser vations on bacteria, apparently unaware of Schultz's experiments. His generalization became known as Hueppe's Rule. Long before them both, the German alchemist and physician Theophrastus Bombastus von Hohenheim ((1493-1541), who coined for himself the name *Paracelsus*, had recognized with respect to the medical use of small amounts of toxic chemicals that their efficacy depended principally on the dose. Such ideas are perhaps more easily accepted nowadays, when it is in the experience of most to use the stimulatory effects of alcohol, caffeine or nicotine, all of which are toxic at high concentrations. Much later Southam and Ehrlich (1943) studied the effect of a natural antibiotic in cedar wood that inhibits the growth of wood-decaying fungi. They found that subinhibitory concentrations of the antibiotic had the reverse effect and stimulated fungal growth. The term "hor mesis" was coined to describe it; which we still use today. Some of the observations have an interesting origin. In the later stages of World War II, when supplies of penicillin were in such short supply, work of Miller et al. (1945) explained why reducing the dose to make short supplies of the new drug go further sometimes had the reverse of the desired effect. At low doses penicillin actually stimulated the growth of *Staphylococcus* . In other examples closer to my own field, experiments with oyster lar vae showed that low levels of many pesticides actually stimulated growth in the same way (Davis & Hidu, 1969). The greatest authority in the field of hormesis is Dr Thomas Luckey, whose early work was on the use of antibiotics as dietar y supplements to stimulate growth in poultr y (Luckey, 1956).

Hormesis has had an unusual history, in that while the phenomenon was discovered over a century ago and redis-covered more than once since, it has not really gained general acceptance. Hayes (1975) emphasized that the acceptance of hormesis as a generally occurring phenomenon should not depend on understanding its cause(s). Nevertheless, the implication is that the Arndt-Schultz Law (and Hueppe's Rule) fell into dis-use because there was no explanation to account for it. It is possible that the use of the Ar ndt-Schultz Law to provide scientific underpin-ning for homeopathic medicine may have discouraged investigators. It may also be because the context in which examples are found is one in which hormesis is as unwanted as it is unexpected. For these kinds of reasons investigation of hormesis lost momentum, publication was sometimes discouraged, or papers directed to obscure journals, and there is good evidence that the occurrence of hormesis in toxicological experiments is far more common than is indicated in the literature (Calabrese, pers comm). The examples included in my review (Stebbing,

1982) and the many more that have been accumulated since, show that hormesis may be found in all the major taxa as a consequence of exposure to ever y class of chemical, from metals and pesticides to antibiotics. A recent review of the toxicological literature shows that of 4000 potentially relevant papers, chemical hormesis was found in approximately 350 (Calabrese & Baldwin, 1997, in press) instances.

The examples gathered from the literature reviewed, corroborated by others since, led me to conclude that: 1. Hormesis is not a specific ef fect of the agent that induces it, since it can be induced by such a wide variety of agents, of different kinds.

2. The ubiquity of hormesis following a similar patter n (beta curve) in many taxa, suggests a common explanation.

3. The hypothesis tested therefore was that hormesis is a consequence of an adaptive response common to biological systems to the inhibitory effect that the different agents have in common at higher concentrations.

A METHOD OF GROWTH ANALYSIS REVEALING EVIDENCE OF CONTROL

These interesting findings led over the next 15 years to a study of the dynamics of growth and how it is controlled in a variety of biological systems (mainly microalgae, prot ozoa, yeast, hydrozoa) and a range of toxic agents. In each case experiments and t he subsequent analysis of growth data were designed to reveal the behavior of the underlying cont rol mechanism responsible for regulating growth processes.

All self-regulating processes operate through some kind of feedback mechanisms and a hypothetical rate-sensitive control mechanism is shown schematically, indicating the flow of information (Figure 2) through such systems. They have certain properties which determine their behavior and suggest how it should be investigated. Here, in the sim - plest case, the actual growth rate is compared to some required rate; the difference between them constitutes an error which the control mechanism works to minimize by adjusting the metabolic processes that determine growth. Errors are not minimized instantaneously, because various factors in the feedback loop contribute to a delay

between error detection and the response to counter it. Consequently processes regulated in this way tend to fluctuate char- acteristically when disturbed, typically oscillating with decreasing amplitude until equilibrium is restored. Since the hypothesis that hormesis is a consequence of such behavior and the novelty of the approach depends critically on the experimental design and method of analyzing growth data, the essential features will be summarized:

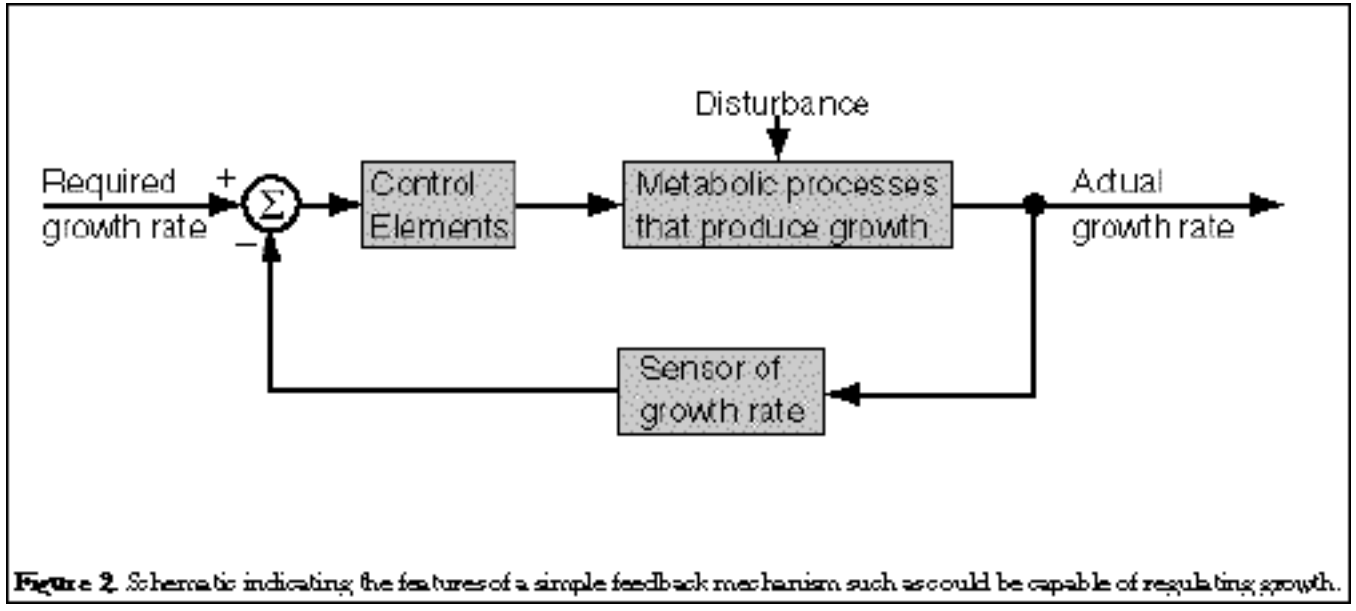


Figure 2. Schematic indicating the features of a simple feedback mechanism such as could be capable of regulating growth.

1. Growth as a process. Biologists interested in growth have been most concerned with increase in biomass over time and with the description of growth cur ves characteristic of different systems. Growth control has been perceived as homeostasis, or the regulation of state, rather than as a process controlled by its rate, which is correctly termed homeorhesis (Waddington, 1977). Interpretation of growth as defined by its changing rate under different circumstances is central to the approach adopted. The experimental systems chosen here, whether hydroid colonies or cell suspensions, do not have any innate limitation to their size, so the regulation of rate is not overlain by control of state. It is important to recognize that biosynthesis is a rate-controlled process, typically controlled by end-product inhibition. The use of cumulative gr owth curves (Figure 3a) to seek evidence of control is uninformative and analogous to using the odometer instead of the speedometer when checking to see if the speed limit is being exceeded. It is therefore important to consider growth rates (GR = dN/dt), where N is a measure of biomass that is

estimated in numbers at inter vals in time. However, GR increases with size because the products of growth also grow (Figure 3b), so changes in rate, which might pr ovide evidence of control, are most likely to be detected if growth rate is considered independently of the organism's size. It is more appropriate therefore to consider growth as the rate of change in biomass as a function of biomass (Figure 3c); that is the specific gr owth rate (SGR= ((1/N).(dN/dt)). This has long been considered physiologically the most appropriate measure of growth and is more likely to reveal the behavior of underlying control mechanisms.

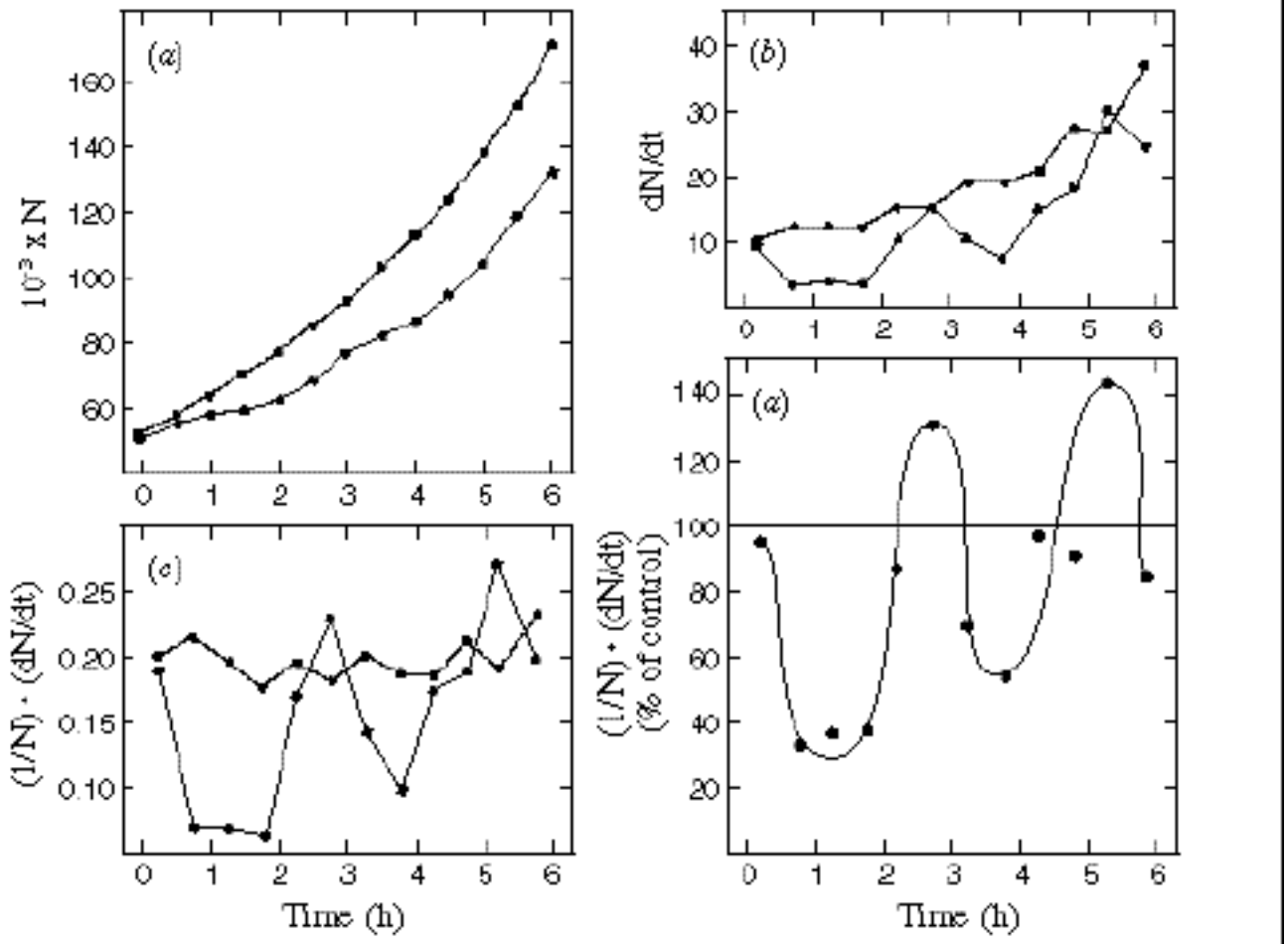


Figure 3. The results of an experiment in which cultures of a marine yeast (*Rhodotorula rubra*) were exposed to 3 mg/l^{-1}. The data of the experimental culture are indicated by the solid line, while those for the control culture by a broken line. The data are shown as number of cells (N) at 30 minute intervals (a), mean rates (b), mean specific rates (c) and normalized mean specific rates (SGR%) (d) for 30 minute periods (after Stebbing et al. 1984).

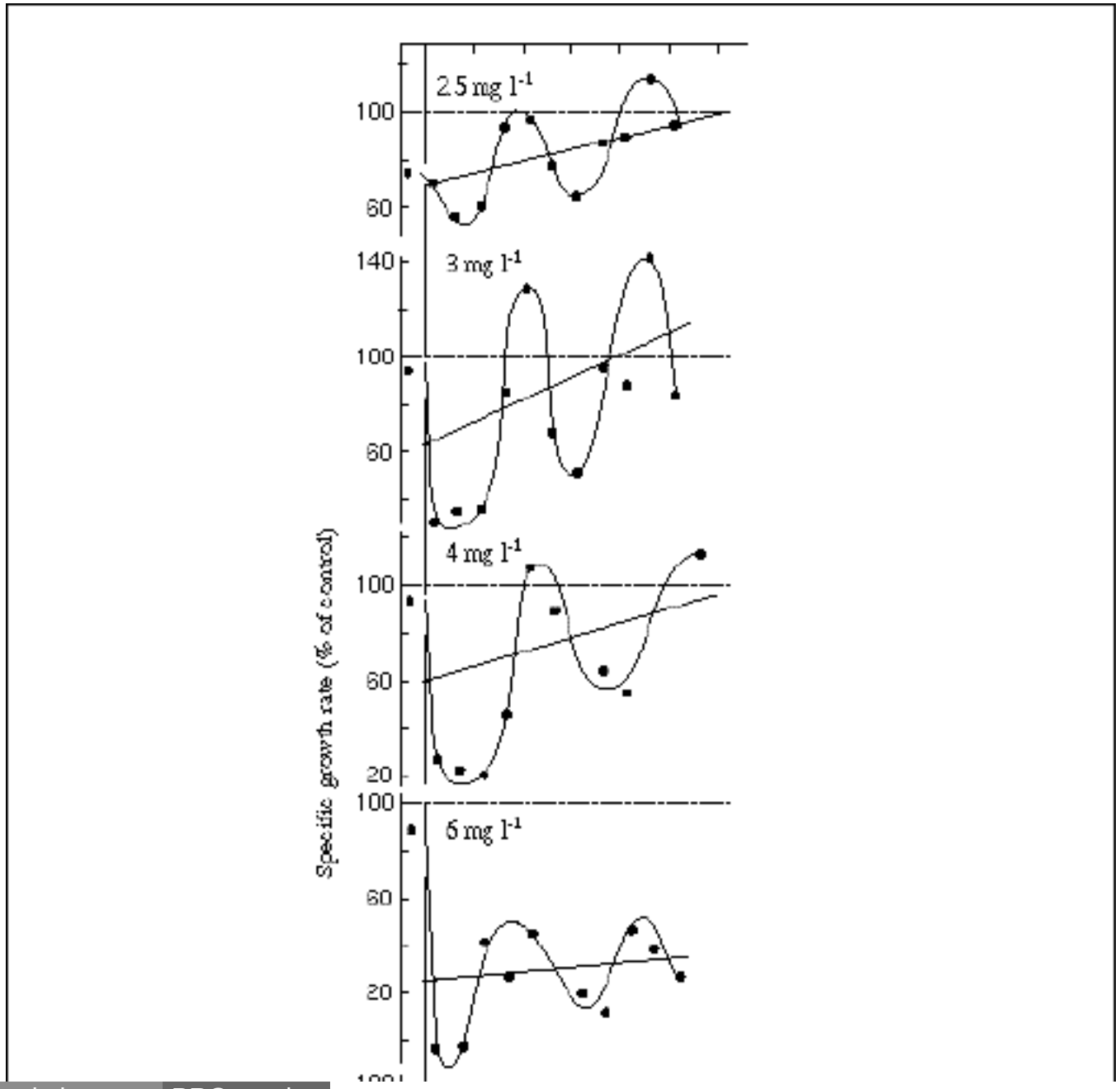
2. Perturbing the controlled process. The most important feature of experiments to study the behavior of feedback mechanisms is the need to perturb the controlled process by imposing a load; then to observe the resultant behavior of the system over time. The process must be deviated from its equilibrium rate in order to activate the mechanism that regulates it, since the behavior of a control mechanism in equilibrium tells little of its

properties. In the experiments cited here, the perturbation was provided by low levels of cadmium on the gr owth of cultures of the marine yeast *Rhodotorula rubra* . Graphs show the different ways of expressing the same growth data summarized above (Figure 3); there are two curves on each graph, one indicating the growth of the control and the other that of the experimental treatment. Each successive method of presenting the growth data has the effect of revealing more clearly the variations in growth rate of the experimental group, while also making the rates for the unperturbed controls more constant (Figures 3 a-c).

3. Filtering out the signal. Use of SGR thus has the effect of magnifying the "signal" relative to the experimental group. At the same time the background trend of the controls, which here constitutes "noise", has been reduced. The final step to remove experimental variability is to use the principle of the "active filter" to fully separate signal from noise, by simply expressing the SGR of the experimental group as a proportion of that of the controls (SGR%). The data then appear as shown in Figure 3d. It can now be seen that the data points follow a series of regular fluctuations, with a trend indicating recovery over time. A regular oscillatory cur ve can now be superimposed on the dat a. The frequency of rate determinations t o adequately define the oscillations is a critical balance between increasing t heir number (which should be no less than 5 and pref erably more per cycle) and reducing frequency of deter minations to improve the precision of SGR determinations. This method of growth analysis has the effect of magnifying variability of the data 20 - 30 t imes. While in this example raw counts may have standard er rors of <0.5%, SGRs calculated from such densities have standard errors of over 10%. I n c reasing count frequency has the same effect in causing a sharp decrease in precision. Much care has to be taken ther e f o re in optimizing the frequency of determinations in relation to the frequency of oscillations, while main- taining precision.

4. The overall pattern. When a number of experiments of this kind are considered together (Figure 4), it can be seen that there is an instructive pattern in the data reflecting the behavior of a control mechanism responding to various loads. With increasing levels of cadmium, the initial decrease in SGR% becomes greater, oscillating about an upward trend line indicating recovery in the lower concentrations and restoration of SGR to that of the controls. At low concentrations (2.5 and 3.0 mg/l^{-1}) recover y is rapid, while at higher concentrations (4.0 mg/l^{-1}) restoration of the SGR to that of the control takes as long as the duration of the experiments (6h). At 6 mg/l^{-1} the large initial fall in SGR and oscillation about a lower level suggests recovery may not occur. At 8.0 mg/l^{-1} there is a similar initial drop, which is not followed by oscillations indicating that the control mechanism has been saturated or is overloaded.

When compared with a typical concentration-response curve for mean SRG%, 4, 6 and 8 mg/l^{-1} provide the downward arm of the curve from a threshold of overall inhibition at about 2 mg/l^{-1}. This is the same range of concentrations marking the transition from tolerable loading to overload of the growth control mechanism.



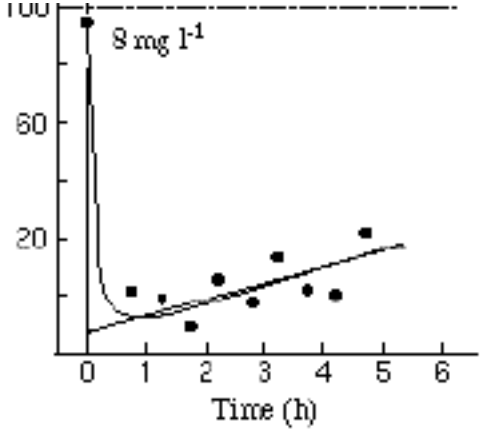


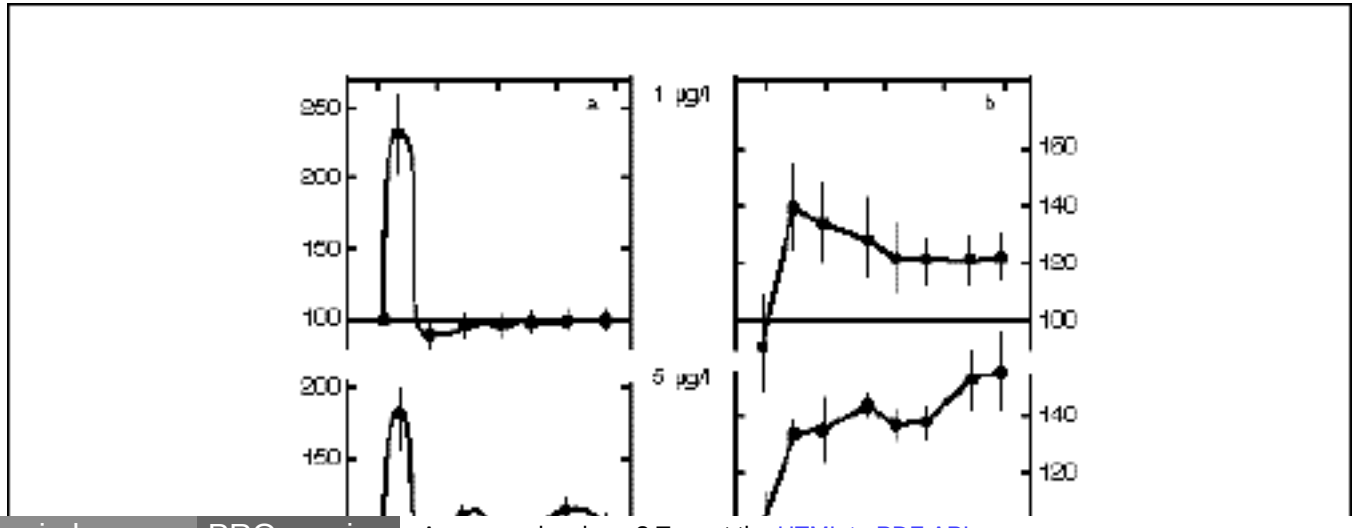
Figure 4. Data for experiments with marine yeast (*Rhodotorula rubra*) exposed to a range of cadmium concentrations. Trend lines are superimposed indicating recovery at lower and overload at higher concentrations (after Stebbing et al. 1984).

In the colonial hydroid *Laomedea flexuosa* experiments over a range of copper concentrations show similar features (Figure 5a), although here growth rates of colonies are much slower and the experiments last 16 days rather than 6 hours. Nevertheless, the data expressed as SGR% indicate similar behavior. There are subtly different features, partly due to the wider range of loadings represented by concentrations of 1 to 50 µg/l^{-1}. At the lowest concentration equilibration is rapid and after an initial oscillation SGR% is quickly restored to that of the controls. At the highest concentration overload is immediate, growth quickly becomes negative and the colonies die. Between these two concentrations SGR% oscillates instructively suggesting features of the control mechanism.

Initially there is an overshoot which is most marked at the lower concentrations, suggesting that the contr ol mech-anism responds maximally to any perturbation at first and only later does the response become proportional to loading due to copper. This feature is not seen in the *Rhodotorula* data, but may have adaptive significance. It is also apparent that amplitude decreases with time following perturbation, as SGR% is restored to that of the controls. Recover y or adaptation occurs at all the lower concentrations (1 - 15 µg/l^{-1}). The data are again presented as SGR% (Figure 5a), and also as colony size as % of controls (Figure 5b) indicating the cumulative increase as a result of variations in rate. Thus it can be seen that at 1 µg/l^{-1} the initial over-correction in SGR results in an increase in size, as it does at 5 µg/l^{-1}, but the most significant increases in size at 5 and 10 µg/l^{-1} result from sustained

fluctuations in SGR% slightly above those of the control colonies. As a consequence these colonies ther efore become progressively larger than the control colonies.

Such over-corrections in SGR%, whether transient or sustained, contribute to cumulative increases in biomass, causing hormesis and the characteristic beta-cur ve that characterizes it. It follows that hormesis is due to the behavior of the control mechanism in response to low levels of inhibitor y load. The responses of the control mechanism not only compensates fully, but overcorrect, resulting in the stimulation of growth in response to exposure to an inhibitor. There are two features of the oscillatory behavior that result in the mean SGR exceeding that of the controls. The first is the initial over-correction, seen in *Laomedea,* but not in *Rhodotorula* . The data (Fig. 5a) indicate that load-proportional control only follows an initial response that is maximal irrespective of toxic load. The consequence of such behavior is seen in Figure 6 which shows the cumulative growth in colony size against concentration over time. As variations in specific growth rates have their effect on biomass (Figure 5), the typical beta curve can be seen to emerge (Figure 6), resulting in the characteristic curve with which this article began. Thus the unexpected experimental results which first brought the paradox to my attention (Figure 1) have been explained by demonstrating the behavior of growth control mechanisms whose currency is the SGR. Clearly fluctuations in SGR that, averaged over time, are less than the controls will result in growth inhibition, while those that on average are greater than the controls will result in stimulation (Figure 5b). It is proposed that hormesis is a by-product of the behavior of growth control mechanisms, due to regulatory over-corrections to low levels of inhibitor y challenge (Stebbing, 1987).



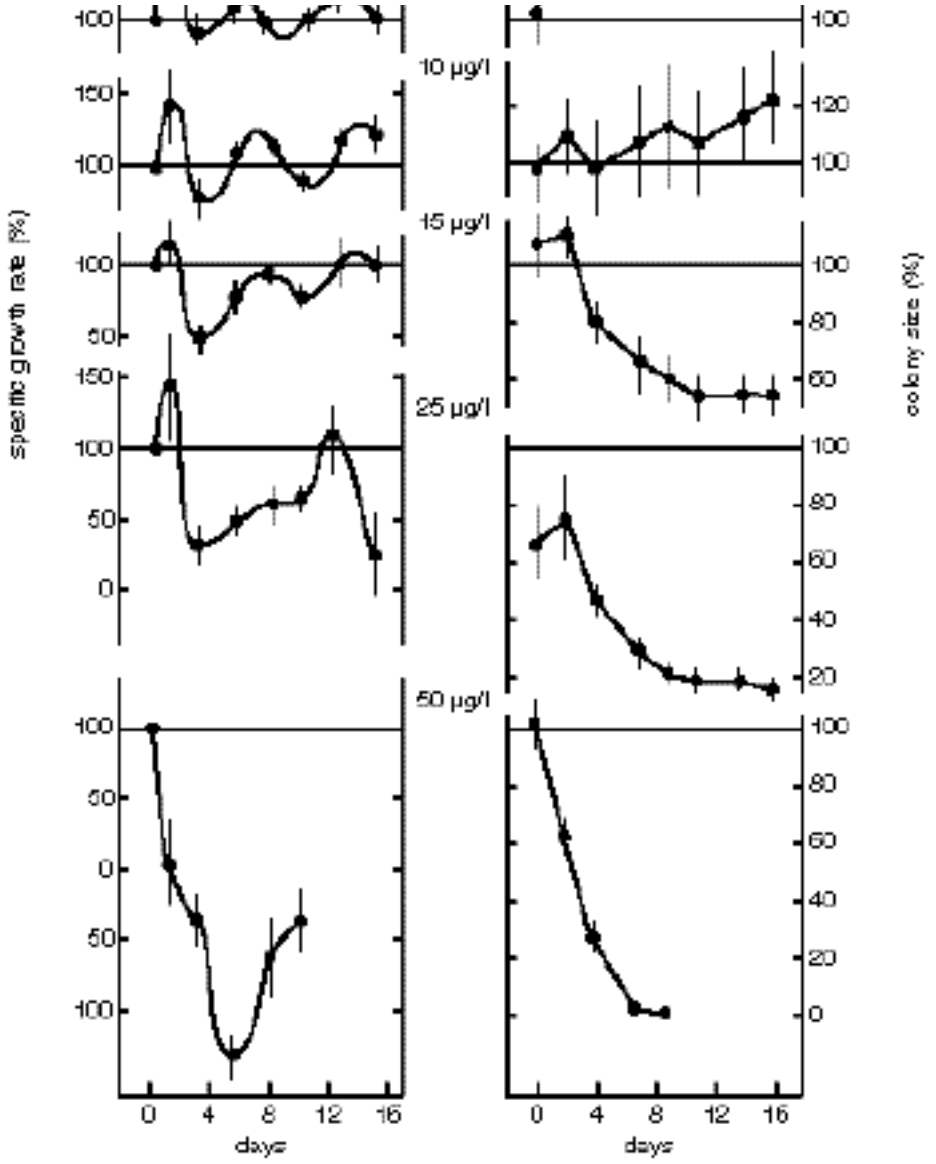


Figure 5. Data for experiments with marine yeast (*Leucosporidium*) exposed to a range of copper concentrations. (a) data expressed as normalized specific growth rates (SGR %), (b) data as normalized colony sizes (after Stebbing et al. 1984).

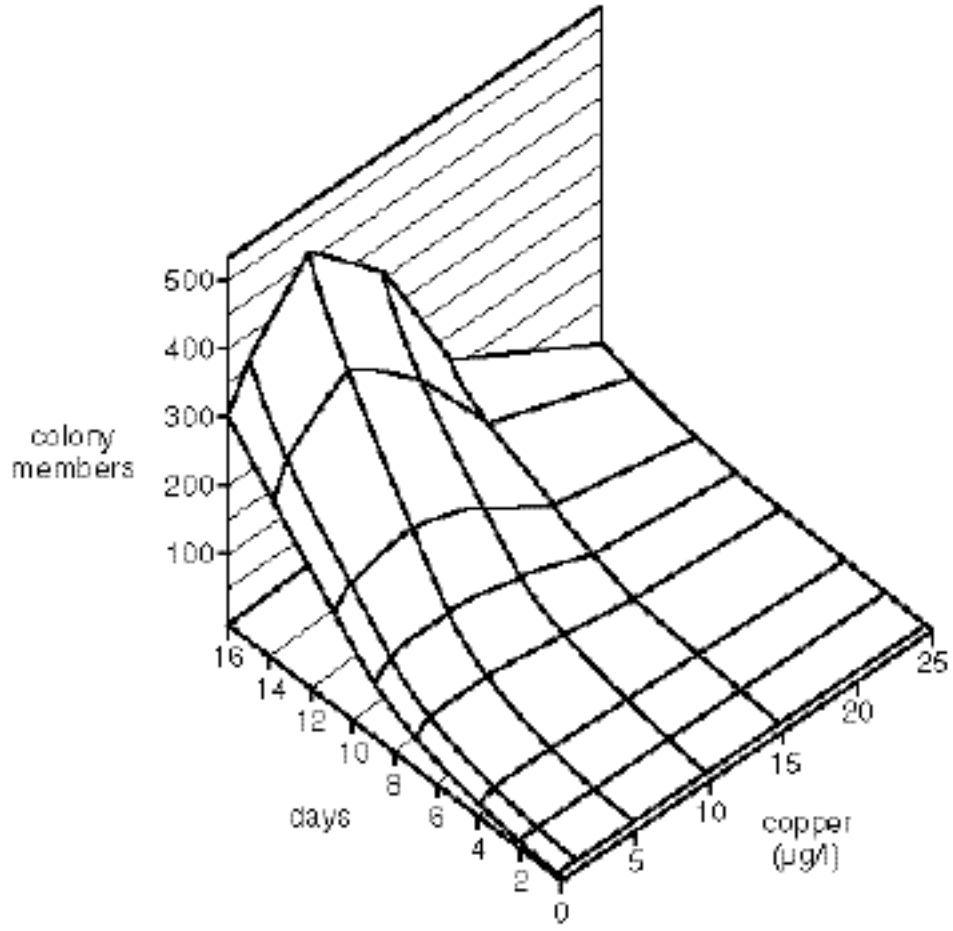


Figure 6. Experiments with marine hydroid (*Laomedea flexuosa*) exposed to a range of copper concentrations. Data are plotted as cumulative colony growth showing the progressive emergence over time of the beta curve given in Figure 1 (after Stebbing, 1981).

DISCUSSION

Circumstances under which the control mechanism overcorrects can be interpreted as actually or potentially advantageous to counteracting loads on a control mechanism. For instance, should a sudden increase in loading occur from a lower level that has been sufficient to elicit such an over-correction, the likelihood of overloading by the higher loading is reduced. Thus it seems that over-correction is the best strategy on first exposure to low loadings, since in effect it anticipates the possibility of higher loadings. Often this may be unnecessary, but it is unlikely to be disadvantageous, so it may well have evolved to behave in this way. The second and principal cause of growth

hormesis is due to a sustainable upward shift in the level about which SRG oscillates such that the average rate exceeds that of the controls (see 5 µg/l^{-1} -1 in Figure 5a). Thus the size of colonies relative to the controls becomes progressively larger (see 5 µg/l in Figure 5b) resulting in hormesis.

It has been suggested that one mechanism by which tolerance is acquired in clonal hydroids (Stebbing, 1981a) and in other species may be due to adjustments of the growth control mechanism to the *required growth rate* (see Figure 2) in response to sustained load. Thus it may be that hormesis is linked directly to the acquisition of tolerance of toxic exposure by adaptation of growth control mechanisms. This is a readily tested proposition, since it suggests that those levels of toxic loading that cause greatest hormesis will also be likely to r esult in acquired tolerance. The existence of a control mechanism that regulates growth has important implications for the interpretation of concentration-response curves (Figure 1), quite separately from an interpretation of hor mesis. What is of interest to toxicologists generally is to interpret the point of downward articulation in such curves at which toxic inhibition occurs. The behavior of the control mechanism that counteracts inhibition provides a ready explanation, in that at lower concentrations than the threshold of inhibition, the control mechanism operates effectively to counteract fully the inhibitory load imposed by the toxic agent. For example, at concentrations less than 0.5 µg/l^{-1}, copper does not activate the control mechanism, as is evident from the absence of any oscillatory behavior.

Between approximately 1 and 10 µg/l^{-1} the control mechanism ef fectively counteracts or overcorrects the effect of copper, as is apparent from its behavior seen in Figure 5. Even at 15 µg/l^{-1} recover y of growth rate to equilibrium at its initial level is eventually achieved. However, at higher concentrations, corresponding to the lower part of the downward arm of the concentration-response curve (Figure 1), the control mechanism becomes saturated by the overwhelming inhibitory load. As before, it seems that the action of the control mechanism provides an explanation for the principal fea- tures of the concentration-response curve. Low levels of toxic inhibition are fully counteracted until the capacity to neutralize is saturated, the inhibitory threshold is exceeded and the onset of sustained inhibition of growth follows. Although such behavior has been demonstrated in a number of organism systems from different taxa (protozoa, diatom, yeast, hydrozoan), the specific feedback mechanism(s) among the many responsible for biosynthesis are not known. Nevertheless there seems little doubt that the obser ved oscillatory behavior represents the output of contr ol mechanisms, since so many features of the behavior can best be explained in this way. For example: 1. The overall behavior from many data sets, using a range of organism systems and growth inhibitors,

resembles in a number of respects that of an under-damped control mechanism. The most characteristic is the oscillatory behavior following low levels of perturbation, fluctuating with decreasing amplitude as equilibrium is restored (Stebbing, 1981a & b; Stebbing, Norton & Brinsley, 1984; Stebbing & Brinsley, 1985).

2. The experimental data show other characteristic features of control mechanisms, such as "relaxation stimulations" (Stebbing, 1981a), where increased SGR% follows the removal of an inhibitor y load to which the control mechanism has accommodated. The magnitude of the relaxation stimulation is a function of the load to which there had been equilibration.

3. The phenomenon of *catch-up growth* (Prader et al., 1963), where growth rate increases upon removal of some growth inhibiting disease or influence, is most readily explained as consequence of relaxation stimulation upon removal of a load to which there had been equilibration, rather than a need to r esume some predetermined trajector y on a growth curve.

4. Simulation models based on control system theory reproduce most of the features of the experimental data (Stebbing & Hiby, 1979; Norton & Stebbing, 1984).

The hypothesis is that hor mesis is the cumulative consequence of transient and sustained over c o rrections by rate-regulating control mechanisms to low levels of inhibitory challenge. Thus hormesis is a by-product of normal r e s p o n ses of biological systems that counteract the effects of inhibit ors. It is unclear how this explanation of growt h hor m e s i s might help to explain other kinds of hormesis since the definition is not limited to growth. Nevertheless, some general points can be made in extending these ideas to other examples:

1. There are likely to be adaptive or homeorhetic responses to perturbations of all kinds. Organisms appear pre-adapted to many noxious stimuli, by responding in a generalized fashion to the changes in the controlled process, independently of any more specific response to the agent that causes it. Homeostatic and homeorhetic control mechanisms abound in all biological systems, responding autonomously to exogenously-induced changes in the states or rates they regulate. It is inevitable that aspects of the behavior of such systems will permeate those sciences like toxicology that are concerned with responses to imposed perturbation. It seems likely that hormesis, *catch-up growth* and acquired tolerance are such features.

2. The removal of toxic load to which there has been t ime to allow equilibration also causes a marked if t ransient stimulation to growth rate (Stebbing, 1981a). While such stimulations do not contribut e to the beta cur v e s described here, which are all due to constant loadings, such *relaxation stimulations* nevertheless result in i n c reased growt h as a related consequence. It f ollows that growth will be maximized by fluctuating loadings on control mechanisms that first apply a low level of inhibitor y loading, to which equilibration occurs, before then removing it. Conversely it must be assumed that constancy of conditions are unfavorable in seeking to maximize g rowth.

3. It is clear that there is a richness of interpretation and explanation that becomes possible by analyzing growth data, using the method described here, that is not possible using cumulative data alone. The analogy with travel as a rate-controlled process and how little cumulative distance traveled helps interpret the nature of the journey hold true. It appears that traditional methods of growth analysis, based as they are on the analysis of raw cumulative data, tend to obscure rather than reveal evidence of the behavior of growth as a process. Interpretation of growth hormesis is only possible from data that reveal growth as a rate-controlled process. It has been noted that hormesis has had an interesting histor y, but the following quotation clearly shows that the workings of control mechanisms were also anticipated. It is curious that over a century ago Herbert Spencer (1862) described in his "First Principles" the action of just such a control mechanism, anticipating their behavior and its interpretation. It is interesting to quote him in full:

"...any disturbing force that works an excess of change in some direction is gradually diminished and finally neutralized by antagonistic forces, which thereupon work a compensating change in the opposite direction, and so after more or less of oscillation, restore the medium condition."

REFERENCES

Calabrese, E.J. & Baldwin, L.A., The dose determines the stimulation (and poison): development of a chemical hormesis database. International Journal of Toxicology, In press

Davis, H.C. & Hidu, H., 1969. Effects of pesticides on embryonic development of clams and oysters and on survival and growth of the larvae. Fish Bull. Fish W ildl. Serv. U.S., 67: 393-404.

Hayes, W.J., 1975. Toxicology of Pesticides. Baltimore, Williams and Wilkins.

Hueppe, F., 1896. The Principles of Bacteriology. Chicago Open Court.

L u c k e y, T.D., 1956. Mode of action of antibiotics evidence from germ - free birds. In: 1st International Conference on the Use of Antibiot ics in Agricult ure. p135. National Academy of Sciences, Washington DC.

M i l l e r, W.S., Green, C.A. & Kitchen, H., 1945. Biphasic action of penicillin and other similiar sulphonamides. Natur e , Lond., 155, 210-211.

Norton, J.P. & Stebbing, A.R.D., 1984. Measurement and interpretation of growth rate oscillations in a marine yeast. In: Oscillations in Physiological Systems, pp. 67-71. The Institute of Measurement and Control

Prader, A., Tanner, J.M., Harnack, G.A., 1963. Catch-up growth following or starvation. Journal of Paediatrics, 62: 646-659

Schultz, H., 1888. Ueber Hefegifte. Pflugers Archiv fur die gesamte Physiologie des Menschen und der Tierre, 42, 517-541.

Southam, C.M. & Ehrlich, J., 1943. Effects of extracts western red cedar heartwood on certain wood-decaying fungi in cult u re. Phytopathology, 33: 5517-524.

Spencer, H., 1862. First Principles. London: Watt.

Stebbing, A.R.D., 1976. The effects of low metal levels on a colonial hydroid. Journal of the Marine Biological Association of the United Kingdom, 56: 977-994.

Stebbing, A.R.D., 1981a. The kinetics of growth control in a colonial hydroid. Jour nal of the Marine Biological Association of the United Kingdom, 61: 35-63.

Stebbing, A.R.D., 1981b. Hor mesis - stimulation of colony growth in Campanularia flexuosa (Hydrozoa) by copper,

cadmium and other toxicants. Aquatic Toxicology, 1: 227-238.

Stebbing, A.R.D., 1982. H ormesis the st imulation of growth by low levels of inhibitors. Science of the To t a l E n v i ronment, 22: 213-234.

Stebbing, A.R.D., 1987. Growth hormesis: a by-product of control. Health Physics, 52: 543-547.

Stebbing, A.R.D. & Brinsley, M.D., 1985. The effects of load and stress induced by cadmium on the growth of yeast. In J.S. Gray & M.E. Christiansen (Eds) Marine Biology of Polar Regions and Effects of Stress on Marine Organisms. pp. 577-583. London: Wiley.

Stebbing, A.R.D. & Hiby, A.R., 1979. Cyclical fluctuations in the growth rate of stressed hydroid colonies. In E. Naylor & R.G. Hartnolls (Eds), Cyclic Phenomena in Marine Plants and Animals: pp. 165-172. Oxford: Pergamon. Stebbing, A.R.D., Norton, J.P. & Brinsley, M.D., 1984. Dynamics of growth control in a marine yeast subjected to perturbation. Journal of General Microbiology, 130: 1799-1808.

Townsend, J.F. & Luckey, T.D., 1960. Hormoligosis in pharmacology. J. Am. Med. Assoc., 173: 44-48. Waddington, C.H., 1977. Tools for Thought. London: Jonathan Cape.