Proc. R. Coll. Physicians Edinb. 1995; **25:** 96–104

CHAOS: A MECHANISM FOR HUMAN DISEASE*

W. M. Bisset, Department of Child Health, University of Aberdeen

INTRODUCTION

'In the beginning God created the heaven and earth and the earth was without form or void and darkness was on the face of the deep'.

Genesis, Chapter 1; Verse 1

The Bible tells us that at the time of the creation there was great disorder and darkness over the earth. As the earth developed it became more ordered and life as we know it today evolved.

In 1681, Sir Thomas Burnett, depicted the history of the earth in his publication *Telluris Theotia Sacra.* He saw the earth initially as a chaotic liquid which evolved through the phases of the pristine earth and flood into the earth as we know it today. He predicted that in the future, following the conflagration and the millennium, the ultimate fate of the earth was as a star. Again there is the clear vision of a world where order has arisen from the chaos of creation.

During the 17th, 18th and 19th centuries scientists tried to understand how the order of the natural world which they saw around them had arisen and promulgated scientific laws to describe and predict the behaviour of the universe. Prominent among these was Isaac Newton who in 1687 published his *Mathematical Principles of Natural Philosophy* which outlined the laws of movement and of gravity. The work of Newton and other scientists led to a view of the world which described how order had arisen out of the disorder of creation,[1] and in which natural events were governed and predicted by mechanistic laws. This view soon extended into medical science where order became equated with concepts of health and disorder with disease.

The Newtonian view of the world has been overtaken during the 20th century by the emergence of quantum physics and the theory of relativity and by a greater realisation of the uncertainties and difficulties of predicting the behaviour of the physical world. More recently, efforts to understand and predict the behaviour of a whole range of turbulent and apparently random natural events, ranging from tornados to population explosions, has led to the development of so-called 'chaos theory'.[2,3] Chaos theory has provided new models to explain why and how complex and chaotic activity may arise from apparent order, why natural events and systems may fail to behave in a regular, predictable manner and why the consequent irregularities which arise in natural systems make the prediction of future events very difficult. Chaos theory has also led to an appreciation that apparently disordered and unpredictable natural events do in fact contain an internal and predictable complex order which is clearly distinguishable from either regular cyclical activity or random noise. This complex, but ordered activity is referred to as 'chaos'—an unfortunate term since it erroneously suggests a vision of complete disorder. Although chaos is a universal phenomenon, its role and importance in health and disease is only now becoming appreciated.

*The Twentieth Croom Lecture delivered at the Symposium on *Medicine Through the Age Groups: Paediatrics to Old Age* held in the College on 15 October 1993.

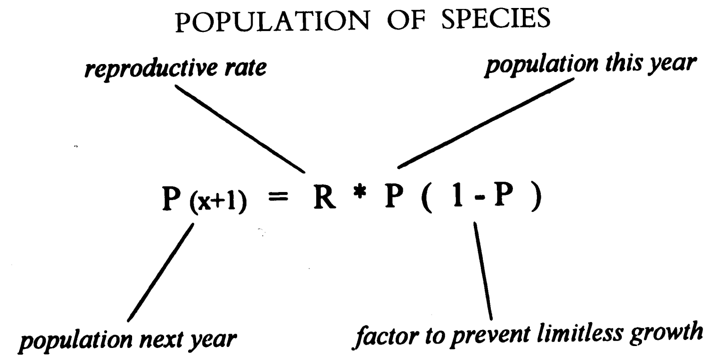

FIGURE 1

The equation devised by May[4] to model the growth of a population with time. This represents a simple feedback system in which future growth is limited by the population of the previous year. The value 1 represents the maximal theoretical population. The result of applying this model over repeated generations for differing reproductive rates (R) is shown in Fig. 2.

The behaviour of a chaotic system

One of the earliest researchers into chaos in biological systems was Robert May, an ecologist working at Princeton, USA.[4] His interest was in the population size of animal species and how this was affected by changes in reproductive rates. He derived a simple equation (see Fig. 1) to predict the population of a given species in successive generations. The population for the subsequent year was a function of the reproductive rate, the present population and the theoretical maximum population which was designated as 1. The recursive nature of this equation, represents a continuous feedback process that is not dissimilar to the controlling mechanisms seen in many physiological systems. May found that with low reproductive rates (1–2.7), after a number of generations, a steady population level was maintained but if the reproductive rate was increased (3–3·5) the system became unstable, oscillating between two or four different population levels and, at even higher reproductive rates ($>3{\cdot}6$), the behaviour of the system became very unpredictable with major fluctuations in the population from one year to another (Fig. 2). These remarkable fluctuations which have arisen in a simple system with only three variables illustrate the phenomenon of chaos. Another feature of May's findings was that where the reproductive rate of a species was low, small changes in the reproductive rate made very little difference to the ultimate population. However in the period where there were higher reproductive rates, very small changes in reproductive rates had dramatic effects on the population from one generation to the next. In the same way small changes in parameters may under certain conditions have dramatic effects on the control and stability of physiological systems.[5,6] The characteristics of a chaotic system are summarised in Table 1.

Detecting chaos

Recordings from physiological systems made on chart recorders are an example of a one dimensional time series. Simple time series traces of chaotic systems look outwardly irregular and it can be very difficult if not impossible to see any signs of regularity within the signal. By digitising these one dimensional recordings it is possible to display the same data in two or more dimensions, using the technique of time lagging. By plotting the recording against a copy of itself delayed in time (altered phase), a two dimensional representation of the signal is

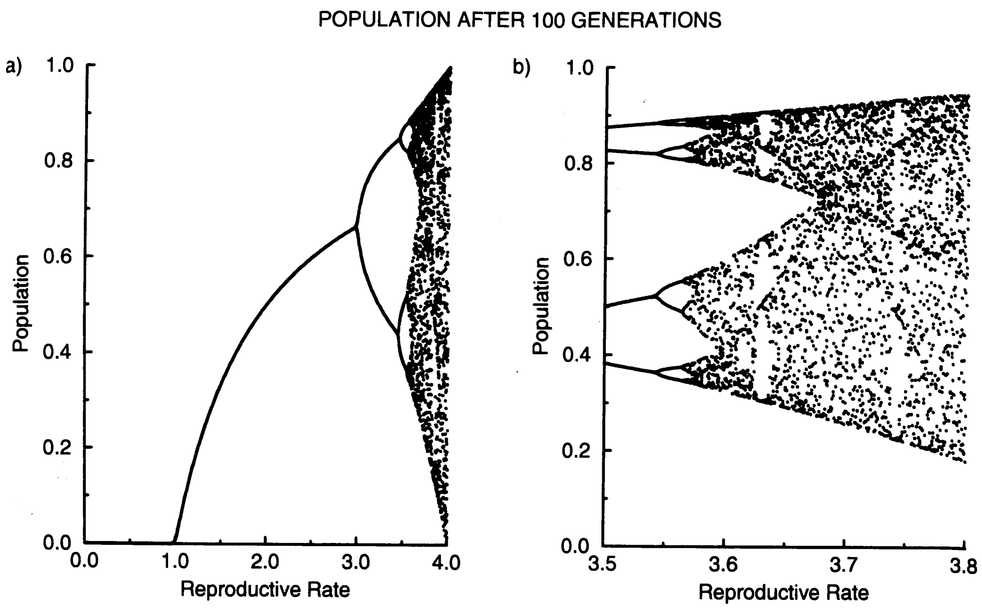

FIGURE 2

The final population, using the formula in Table 1, after 100 generations, with a reproductive rate between 0 and 4. (a) When the reproductive rate is <1 there is eventual extinction of the species, between 1 and 2·7 there is an increase in the final population and above 2·7 there is instability from year to year with initial bifurcation followed by chaos. (b) Magnification of the same data as in (a) from 3·5 to 4 clearly shows the complex patterns of activity which can develop in an apparently simple model of a biological system.

TABLE 1
The characteristics of a chaotic system

(1)	non-linear system
(2)	show period bifurcation as prelude to chaos
(3)	have irregular periodicity
(4)	are exquisitely sensitive to initial conditions

obtained. If necessary, this process can be repeated in multiple dimensions. Using this method of analysis, the internal order of apparently disordered one dimensional data can be identified and represented. An example of this is shown in Fig. 3 where a trace of a chaotic region of the equation shown in Fig. 1 is plotted in both one and two dimensions. The first, one-dimensional plot, shows apparently disordered fluctuations in population size, while the second 'altered phase' graph, plotted in two dimensions, shows clearly how the same data is confined within an ordered pattern. This geometric pattern in which the chaotic signal is confined is referred to as a strange attractor. This is an example of a system with a fairly low level of chaos whose order can be demonstrated by embedding the data in a small number of dimensions. In more complex systems, the data can be embedded in higher dimensions and analyses by computerised techniques to reveal any underlying order. Through this technique[7,8] which is referred to as correlation dimensional analysis, it is possible to define the number of state variables needed to describe the steady state behaviour of a time series. Regular signals, such as a sine wave, have a dimension of 1, while chaotic systems are characterised by a non-integer dimension >1 with more chaotic systems having increasing dimen-

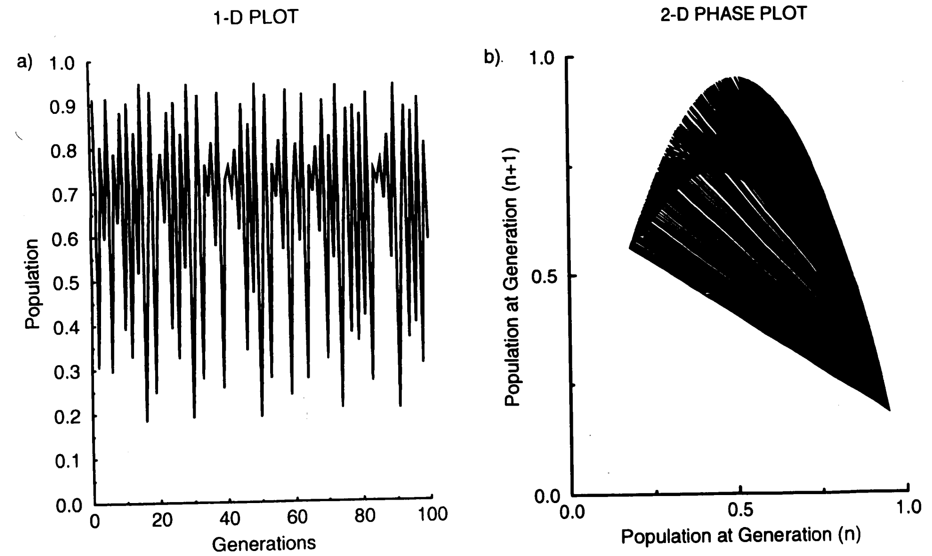

FIGURE 3

(a) A time series plot, calculated from the formula in Table 1, for a reproductive rate of 3·7, shown over the first 100 generations. Their is an apparently random variation in population from one year to the next. (b) If the same data (over 500 generations) is presented as a 2 dimensional phase plot (x against x+1) the order within the data can be clearly seen.

TABLE 2
The techniques used to detect and measure chaos in physiological time series

Technique		*Result*
1. Examination of time series		bifurcation irregularity
2. Phase plotting		strange attractor
3. Dimensional analysis	*regular*	integer
	chaos	non integer
	noise	infinity

sions. With a truly random signal (i.e. noise), it is impossible to show evidence of order, irrespective of the number of dimensions used to model the system, because its correlation dimension is infinity. It is therefore now possible by examining time series and using the approach outlined in Table 2, to differentiate between order, chaos and noise. These techniques provide an opportunity for widening our understanding of how complex systems are controlled and how small changes in initial conditions can have a major influence on the behaviour of biological systems.

Chaos in physiological systems

If chaos theory is to be used to develop new models of human disease, the role of chaos in physiological control systems will need to be understood. Control systems which show feedback or involve interaction between excitable cells have many of the characteristics needed for the development of complex and chaotic behaviour.[9,10] The effect of feedback on the ecological model shown in figure 1, illustrates clearly how changes in the initial values of feedback parameters can generate very complex responses in simple system. Glass and Mackay have shown that the white blood count in patients with chronic myeloid leukaemia varies with an apparent period of 70–80 days.[11] Closer examination however reveals that this variation is not regular and they have suggested that the irregularity in the blood count arises through chaotic mechanisms. Although the exact defect responsible for this activity is not known, it has been postulated that disruption to normal feedback controls may be responsible. As already shown in the example of population growth,[4] very small changes in feedback parameters can have major effects on the dynamics of control processes. In the leukaemic patient such changes have a very dramatic disruptive effect on the mechanisms which normally maintain steady white cell numbers.[12] The same authors have also suggested that the efficacy of medical treatment may also be effected by the unpredictable variability in white cell number and that the timing of treatment, relative to the blood count may be of importance. The possible role of chaos in voluntary human control was investigated by Beuter who developed a system for modifying the time delay in the feedback loop between the subject's eye and finger.[13] The position and movement of a subject's finger was sensed by transducers and displayed, after a defined time lag, on the screen of an oscilloscope. The subject was then asked to maintain the finger in a steady position while observing the movement of their finger indirectly on the oscilloscope. The oscilloscope was used to introduce a lag time between the actual movement of the finger and its display on the screen. When the time lag in the visual feedback pathway was increased, increasing tremor and eventually chaotic movement was induced in the subject's finger. The author postulated that this model was analogous to the situation in Parkinson's disease where disease of the nigra striatal system leads to a similar delay in feedback of normal physiological cues and development of the typical tremor. Traces made of movement of patients with Parkinson's disease were very similar to those observed in the experimental model.

Excitable cells are characterised by having an intrinsic rhythm which can be perturbed either by electrical stimuli from an external source or from an adjacent excitable cell. Such cells are seen in the myocardium of the heart, in neurones within the central and autonomic nervous system and also within smooth muscle cells in vascular and intestinal tissues. Experiments have shown that in embryonic myocardial cells this normal spontaneous rhythmic activity can be perturbed by the injection of electrical current and depending on the magnitude and the phase of the stimulus (timing relative to the spontaneous activity) it is possible to induce chaos in this normally regular system.[14] Similarly it was also shown that the injection of a very large current could revert a chaotic system to a regular rhythm. This behaviour in a model of excitable cellular activity is not dissimilar from the circumstances of ventricular fibrillation (VF) that may be induced in a patient who is cardioverted during the incorrect phase of the cardiac cycle or to the use of defibrillation as a tool to convert a patient from VF back to sinus rhythm.[15,16] The transition of the system from one steady state to two steady states (bifurcation) and then to chaos is seen in the electrical activity of the heart where there may be a transition from a steady heart rate to steady variation in the heart rate (bigemini), then with increasing irregularity leading to fibrillation or chaos.[5,6]

Similar evidence had been found for the involvement of chaotic mechanisms

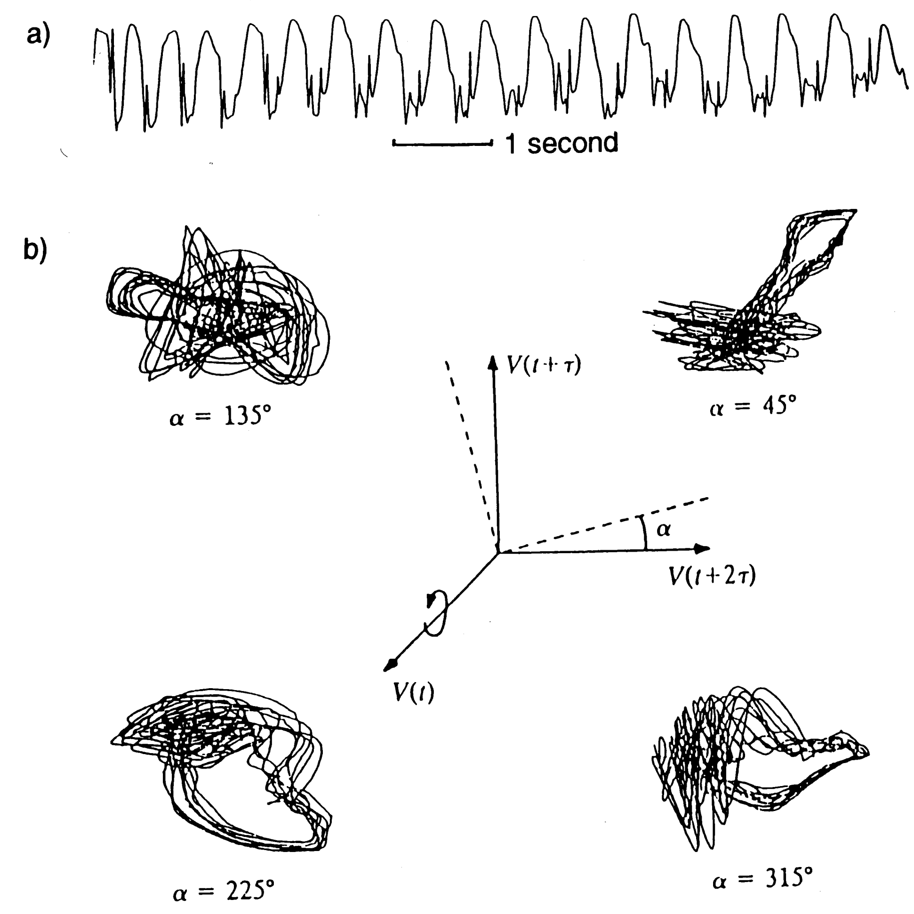

FIGURE 4

(a) An EEG trace from an adult during a petit mal attack. (b) A 3 dimensional phase plot of the same data as (a) clearly shows order within the attractor. The data is viewed from different angles and represented in 2 dimensions. This attractor has a correlation dimension of 2.1. Reproduced with the permission of A Babloyantz.[17]

in other excitable systems including electroencephalographic activity in petit mal seizures, which has the features of low dimensional chaos (Fig. 4),[17] and electrical activity of the human stomach.[18]

Chaos and health

The assumption that instability or chaos in physiological systems equates with disease is probably incorrect. In health, the ECG the EEG and the EGG (electrogastrogram) all show some degree of chaos. In 1987, Goldberger[15,19] postulated that the presence of chaos may facilitate change in some physiological systems. This hypothesis is supported by experiments which have shown that the degree of chaos in heart rate variability decreases after severe myocardial infarction and is a predictor of poor prognosis. It has similarly been shown that during organ rejection following cardiac transplantation,[20] heart rate variability and the degree of chaos in cardiac electrical activity is reduced. Similarly the EEG in health generally shows high-dimensional chaos which steadily reduces as we sink into sleep. In epilepsy the EEG becomes more organised and the level of chaos falls as

FIGURE 5

Titian's 'The Three Ages of Man'. Duke of Sutherland Collection, on loan to the National Gallery of Scotland. Reproduced with the kind permission of His Grace.

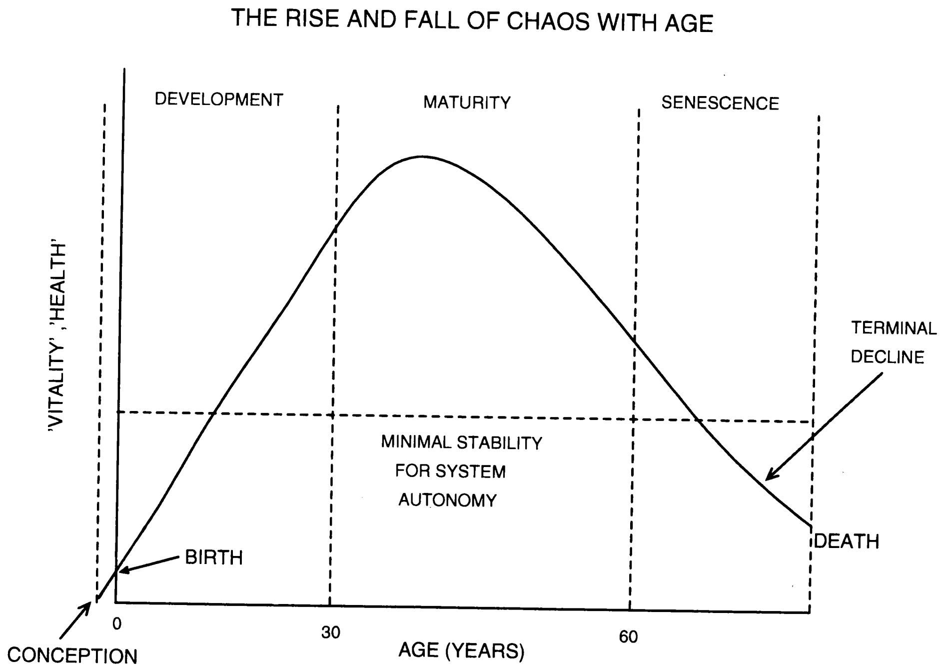

FIGURE 6

A schematic representation of life, devised by F. E. Yates.[21] During development, increasing complexity and chaos in physiological control leads to increased health and resistance to insult. With increasing age this chaos is lost and resistance to disease falls. Reproduced from[26] with the permission of Springer Publishing Company, Inc., New York 100012. ©

neurones start to discharge in synchrony. It seems clear therefore that in some physiological systems such as the brain and heart, chaos is a normal physiological feature and that loss of this inherent variability may compromise normal function.[17] The previous use of linear techniques such as frequency analysis by Fourier transformation, which is based on the expectation of finding sinusoidal activity, has led to flawed 'mechanical' models of physiological control systems which underestimated their complexity. The application of chaos theory to biology provides the opportunity for realising the true complexity of physiological control systems.

The role of chaos within individual cells and in individual organs such as the heart or the brain has been described above. The concept can however be extended to examine the function and behaviour of the individual as a whole and, as has already been described, to the growth of a whole population. Although the scale is different, the interaction and feedback from many individual components within the system determines the behaviour of the whole. In Titian's 'The Three Ages of Man' (Fig. 5), the major differences in both form and behaviour which occur in all humans as they develop and age, can be clearly seen. Between the time of conception, our birth and eventual death there are a great many changes, not only in our outward physical appearance but also in the nature and complexity of the many controlling systems whose combined action maintains health. It has been postulated[21] that as we develop and mature, healthy development is associated with an increasing level of chaos in each of our chaos in this normally regular system.[14] Similarly it was also shown that the component physiological systems. A certain level of chaos, or as Yates[21] described it, 'vitality and health', is needed before the individual can function independently (Fig. 6). Indeed, there is preliminary evidence that in the very young infant, normal healthy development is synonymous with increasing complexity and flexibility of control.[22–24] With increasing age however, there is loss of complexity of control leading to a steady downhill course that ultimately ends in death. This hypothesis is supported by the fact that the complexity, of both anatomical structure and physiological control, gradually reduces with increasing age.[25] The loss of heart beat variability, variability in the spectral range of the EEG and the branching structure of neuronal dendrites are just a few examples of this phenomenon.

CONCLUSIONS

When we measure physiological variables our eye is generally drawn to the regular patterns of activity and tends to ignore irregular activity which may be difficult to describe or to quantify. With the applications of chaos theory it is clear that there is irregularity in most physiological controls which has been previously disregarded but may in fact contain much valuable information about the system under study. It is now possible to analyse this in a meaningful manner and much data which was previously destroyed or disregarded can now be interpreted. Much of our present understanding of medicine and physiological control has now to be redefined. The relatively simplistic version current up till now no longer adequately represents how the human body responds in health and disease. Chaos appears to be an intrinsic part of normal physiological control and with the increasing application of chaos theory to research our previous conceptions have to be re-examined. Chaos theory offers the potential to enhance further our understanding of the factors which control and influence the development of both health and disease in the human.

REFERENCES

[1] Stewart I. Chaos from Order. In: Stewart I, ed. Does God play dice? London: Penguin Books, 1989; 5–22.
[2] Gleick J. Chaos: making a new science. London: Sphere Books 1988.
[3] Hall N ed. The New Scientist Guide to Chaos. London: Penguin Books 1992.
[4] May RM. Simple mathematical models with very complicated dynamics. Nature 1976; **261:** 459–67.
[5] Karagueuzian HS, Mandel WJ, Arrhythmias, proarrhythmias, and nonlinear dynamics: An orderly invitation of chaos to cardiology. *Curr Opin Cardiol* 1992; **7:** 3–7.
[6] Denton TA, Diamond DA, Helfant RH *et al.* H. Fascinating rhythms: A primer on chaos theory and its applications to cardiology. *Am Heart J* 1990; **120:** 1417–40.
[7] Grassberger P, Procaccia I. Measuring the strangeness of strange attractors. *Physica* (9D) 1983; 189–208.
[8] Theiler J. Efficient algorithm for estimating the correlation dimension from a set of discrete points. *Phys Rev A* 1987; **36:** 4456–62.
[9] Mackey MC, Glass L. Oscillation and chaos in physiological control systems. *Science* 1977; **197:** 287–9.
[10] Goldberger AL, Rigney DR, West BJ. Chaos and fractals in human physiology. *Sci Am* 1990; **Feb:** 35–41.
[11] Glass L, Mackey MC. The rhythms of life. Princeton: Princeton Press, 1988.
[12] Fisher GV. An introduction to chaos theory and some haematological applications. *Comp Haematol Int* 1993; **3:** 43–51.
[13] Beuter A, Labrie C, Vasilakos K. Transient dynamics in motor control of patients with Parkinson's disease. *Chaos* 1991; **1:** 279–85.
[14] Glass L, Zeng WZ. Complex bifurcations and chaos in simple theoretical models of cardiac oscillations. *Ann NY Acad Sci* 1990; **591:** 316–27.
[15] Goldberger AL, West BJ. Applications of non-linear dynamics in cardiology. *Ann NY Acad Sci* 1987; **504:** 195–213.
[16] Garfinkel A, Spano ML, Ditto WL, Weiss JN. Controlling cardiac chaos. *Science* 1992; **257:** 1230–1235.
[17] Babloyantz A, Destexhe A. Low-dimensional chaos in an instance of epilepsy. *Proc Natl Acad Sci* 1986; **83:** 3513–7.
[18] Bisset WM, Ravelli A, Devane SP, Milla PJ, Disease of gastrointestinal smooth muscle increases chaotic myocyte activity. *J Pediatr Gastroenterol Nutr* 1992; **15:** 354.
[19] Pool R. Is it healthy to be chaotic? *Science* 1989; **243:** 604–7.
[20] Zbilut JP, Mayer-Kress G, Geist K. Dimensional analysis of heart rate variability in heart transplant recipients. *Mathematical Biosci* 1988; **90:** 49–70.
[21] Yates FE. Self-organising systems. In: Boyd CAR, Noble D, eds. The logic of life. The challenge of integrative physiology. Oxford: Oxford University Press, 1993; 189–218.
[22] Schechtman VI, Harper RM, Kluge KA *et al.* Correlations between cardiorespiratory measures in normal infants and victims of sudden infant death syndrome. *Sleep* 1990; **13:** 304–17.
[23] Gough NAJ. Fractal analysis of foetal heart rate variability. *Physiol Measurement* 1993; **14:** 309–16.
[24] Chaffin DG, Goldberg CC, Reed KL. The dimension of chaos in the fetal heart. *Am J Obstet Gyncol* 1991; **165:** 1425–9.
[25] Lipsitz LA, Goldberger AL. Loss of 'complexity' and aging: Potential applications of fractals and chaos theory to senescence. *J Am Med Assoc* 1992; **267:** 1806–9.
[26] Yates PE. Ageing as prolonged morphogenesis: a topological sorcerer's apprentice. In: Kenyon GM, Birren JE, Schroots JJF, eds. Metaphors of aging in science and the humanities. New York: Springer Publications, 1991: 199–218.

Proc. R. Coll. Physicians Edinb. 1995; **25:** 105–117

MANAGEMENT OF HYPERGLYCAEMIC EMERGENCIES*

Sally M. Marshall and K. G. M. M. Alberti, Department of Medicine, University of Newcastle upon Tyne

Acute metabolic decompensation of diabetes leading to life-threatening hyperglycaemia and dehydration with or without ketoacidosis continues to occur commonly despite higher awareness amongst the general public, health care professionals and people with diabetes. Data from the USA suggests an annual incidence of diabetic ketoacidosis (DKA) of 3 to 8 episodes per 1000 patients with 20–30 per cent of new cases presenting in ketoacidosis.[1] A rate of 1.3–2 episodes per 100 patient years was reported by the Diabetes Control and Complications Trial Research Group.[2] The frequency of hyperosmolar non-ketotic coma is about 10 per cent that of ketoacidosic coma. Mortality remains considerable at 5–10 per cent and has changed little over the last 20 years. A significant proportion of deaths are avoidable with careful and experienced management.[3] Some deaths particularly in non-ketotic hyperglycaemic emergencies, are due to the underlying precipitating illness rather than the metabolic upset and there is considerable increase in mortality in the elderly.[4]

PATHOPHYSIOLOGY

The hallmark of diabetic ketoacidosis and non-ketotic hyperglycaemia is an absolute or relative deficiency of circulating insulin. In C-peptide negative diabetic patients, lack of insulin leads to a rapid rise in hepatic glucose output,[5] with an initial fall in insulin-dependent peripheral glucose uptake due to a failure to mobilise GLUT-4 glucose transporters.[6] Blood glucose concentrations rise until glucose disposal again equals glucose input.[5] This occurs at around 16 mmol/l. The fall in insulin-dependent glucose utilisation is compensated for by concentration driven glucose uptake which is insulin-independent and by glycosuria. Further rises in blood glucose concentration occur due to the stimulation of gluconeogenesis and inhibition of peripheral glucose uptake by cortisol, the catecholamines and glucagon acting as counter-regulatory hormones. Glucagon is of particular importance; circulating levels rise in insulin deficiency despite hyperglycaemia,[7] the rises in cortisol and catecholamines occur later. Hyperglycaemia *per se* decreases peripheral glucose utilisation[8,9] and residual insulin secretion,[10] creating a vicious cycle of increasing plasma glucose concentration. Hyperglycaemia leads to dehydration, and eventually hypotension, as well as loss of electrolytes through osmotic diuresis. The dehydration further worsens the hyperglycaemia through poor tissue perfusion, reducing glucose uptake further, and delaying absorption of any remaining subcutaneous insulin.

Insulin deficiency coupled to high circulating levels of counter-regulatory hormones results in unrestrained lipolysis, with a large increase in the supply of non-esterified fatty acids (NEFA) to the liver. Lack of insulin and high glucagon levels combine to switch NEFA metabolism from re-esterification to oxidation,

*Based upon a lecture deliveredby K. G. M. M. Alberti at the Symposium on *Medicine through the Ages: Paediatrics to Old Age* held in the College on 15 October 1993.