*Bulletin of Mathematical Biology* (2004) **66**, 1039–1091
doi:10.1016/j.bulm.2003.11.002

# A History of the Study of Solid Tumour Growth: The Contribution of Mathematical Modelling

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A miscellany of new strategies, experimental techniques and theoretical approaches are emerging in the ongoing battle against cancer. Nevertheless, as new, groundbreaking discoveries relating to many and diverse areas of cancer research are made, scientists often have recourse to mathematical modelling in order to elucidate and interpret these experimental findings. Indeed, experimentalists and clinicians alike are becoming increasingly aware of the possibilities afforded by mathematical modelling, recognising that current medical techniques and experimental approaches are often unable to distinguish between various possible mechanisms underlying important aspects of tumour development.

This short treatise presents a concise history of the study of solid tumour growth, illustrating the development of mathematical approaches from the early decades of the twentieth century to the present time. Most importantly these mathematical investigations are interwoven with the associated experimental work, showing the crucial relationship between experimental and theoretical approaches, which together have moulded our understanding of tumour growth and contributed to current anti-cancer treatments.

Thus, a selection of mathematical publications, including the influential theoretical studies by Burton, Greenspan, Liotta *et al.*, McElwain and co-workers, Adam and Maggelakis, and Byrne and co-workers are juxtaposed with the seminal experimental findings of Gray *et al.* on oxygenation and radio-sensitivity, Folkman on angiogenesis, Dorie *et al.* on cell migration and a wide variety of other crucial discoveries. In this way the development of this field of research through the interactions of these different approaches is illuminated, demonstrating the origins of our current understanding of the disease.



## 1. INTRODUCTION

It has been stated recently that 'cancer is now poised to overtake heart disease as the major cause of premature death in the Western World' (Byrne, 1999a). Indeed,

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0092-8240/04/051039 + 53 $30.00/0 

a recent report on worldwide cancer rates by the World Health Organization's International Agency for Research on Cancer (IARC) (Pisani *et al*., 2001) illustrates that North America leads the world in the rate of cancers diagnosed in adults, followed closely by Western Europe and Australia and New Zealand. In 1994 in Britain, for example, one in three were expected to develop the disease over their lifetimes (Imperial Cancer Research Fund, 1994), with a likely increase to one in two by 2010 based on the trends at that time (Perumpanani, 1996). Similarly, a recent publication of the Australian Institute of Health and Welfare (1999) explains that 'at the incidence rates prevailing in 1999 (in Australia), it would be expected that one in three men and one in four women would be directly affected by cancer in the first 75 years of life. Further, an estimated 254 000 potential years of life would be lost to the community each year as a result of people dying of cancer before the age of 75. Cancer currently accounts for 29% of male deaths and 25% of female deaths'.

Reflecting on the seriousness of this disease, Perumpanani (1996) remarks that 'the research community has taken on the challenge posed by cancer on a war footing and this has resulted in recent years in an explosion in our understanding of cancer'. Interestingly, Alberts *et al*. (2002) observe that 'the emphasis given to cancer research has profoundly benefited a much wider area of medical knowledge than that of cancer alone', explaining that 'the effort to combat cancer has driven many fundamental discoveries in cell biology'.

Nevertheless, the study of cancer is not new. Porter (1997) claims that 'breast cancer operations date back to antiquity', giving the example of Aetius of Amida who 'had emphasized that the knife should cut healthy tissue around a tumour and that a cauterizing-iron should stanch the blood'. In a treatise on the history of breast cancer, Olson (2002) further explains that 'medical practitioners the world over, today and eons ago, have struggled with the disease. Egyptians of the New Kingdom—more than 3500 years ago—were the first'. Indeed, Ward (1997) asserts that 'it is clear from various texts of ancient Greece, Egypt and Rome that the early physicians were well aware of the nature of cancer and were capable of making a correct diagnosis and performing successful therapy'.

Clearly the study of tumour growth and the development of anti-cancer therapies are most worthwhile pursuits, having significant potential to enhance quality of life and increase life-expectancies, which may, in turn, yield considerable economic and social benefits.

Notwithstanding recent advances, Gatenby (1998) explains that 'recent research in tumour biology, particularly that using new techniques from molecular biology, has produced information at an explosive pace. Yet a conceptual framework within which all these new (and old) data can be fitted is lacking'. Gatenby and Maini (2003) add that 'clinical oncologists and tumour biologists possess virtually no comprehensive theoretical model to serve as a framework for understanding, organizing and applying these data' noting the necessity to '(develop) mechanistic models that provide real insights into critical parameters that control system dynamics'. Murray (2002) concurs, asserting that 'the goal is to develop

models which capture the essence of various interactions allowing their outcome to be more fully understood'.

Indeed, Byrne (1999a) asserts that 'in order to develop effective treatments, it is important to identify the mechanisms controlling cancer growth, how they interact, and how they can most easily be manipulated to eradicate (or manage) the disease. In order to gain such insight, it is *usually* necessary to perform large numbers of time-consuming and intricate experiments—but not *always*. Through the development and solution of mathematical models that describe different aspects of solid tumour growth, applied mathematics has the potential to prevent excessive experimentation and also to provide biologists with complementary and valuable insight into the mechanisms that may control the development of solid tumours'.

Moreover, experimentalists and clinicians are becoming increasingly aware of the role of mathematical modelling as a new way forward, recognising that current medical techniques and experimental approaches are often unable to distinguish between various possible mechanisms underlying important aspects of tumour growth (Kunz-Schughart *et al*., 1998).

The present paper reviews of some of the important mathematical contributions to the study of solid tumour growth. Owing to the enormous body of theoretical and experimental publications devoted to solid tumour growth in the literature, however, no such review could be comprehensive. Nevertheless, it provides a concise history of the study of tumour growth, discussing some of the most influential mathematical models and their relationship to experimental studies, and illustrating how the field of cancer research has evolved due to these interactions between theoretical and experimental approaches. While the emphasis is primarily on deterministic models, some significant papers which employ stochastic approaches are also noted. Section 2 presents some of the earliest mathematical contributions to the study of solid tumours, beginning with Hill's study of diffusion in tissues (Hill, 1928), and leading to Burton's often-cited paper on tumour growth dynamics as a diffusion problem (Burton, 1966). Section 3 discusses some early theoretical approaches to the study of avascular tumours and multicell spheroids in the wake of Folkman's important discoveries relating to angiogenesis and a prevascular stage of tumour development. Liotta and co-workers' seminal contributions to the theoretical study of tumour invasion and metastasis in the 1970s (Liotta *et al*., 1974a,b,c, 1976b; Saidel *et al*., 1976) are presented in Section 4. The development of mathematical approaches in the 1980s is discussed in Section 5, emphasizing the prominent role of the studies by Adam and Maggelakis (Adam, 1986, 1987a,b; Adam and Maggelakis, 1989, 1990; Maggelakis and Adam, 1990). Section 6 gives an overview of the enormous body of mathematical papers on solid tumour growth published in the 1990s, including those relating to cell migration in multicell spheroids and tumour cords (Section 6.1), multiphase models (Section 6.2), mechanical models and models of residual stress formation (Section 6.3), models of invasion and metastasis (Section 6.4) and models of avascular (Section 6.5) and vascular (Section 6.6) tumour growth.

## 2. The Early Models of Tumour Growth by Diffusion: Hill to Burton

While not applied specifically to the study of neoplastic tissues, some of the early work on diffusion in tissues by Hill (1928) set the scene for many later mathematical models of solid tumours. Hill understood that 'the diffusion of dissolved substances through cells and tissues is a determining factor in many vital processes', and used mathematical approaches to study a number of important physiological processes such as the diffusion of oxygen into a solid where it is consumed by metabolic processes, the outward diffusion of lactic acid from a solid which produces it by metabolic processes and the diffusion of oxygen away from a blood vessel into a region with an oxygen debt.

While diffusion processes would later become an important part of tumour models, the earliest mathematical studies of solid tumours focused purely on growth dynamics. Mayneord (1932), for example, conducted experiments on the effects of X-radiations on the growth of Jensen's rat sarcoma in 1932 and noticed that in the final stages of growth the tumours grew linearly with time, an observation corroborated by the study of spontaneous carcinomas of the mouse reported by Haddow (1938) some six years later. The rate of a tumour's growth was of significant interest at the time since, as Mayneord (1932) explained, 'the mere disappearance or continued growth of the tumours after irradiation afforded a very inadequate criterion of the effect of the radiations'. Since histological examination revealed that active growth was restricted to a thin shell at the periphery of the tumour, Mayneord developed a mathematical model which investigated the effect of different distributions of actively dividing cells. This illustrated that when the entire tissue volume was growing exponential growth was expected, with the growth rate gradually reducing as the region of active growth was progressively restricted to an outer shell of tissue of decreasing thickness, ultimately arriving at a linear growth rate.

As experimental studies on radiotherapy continued, many researchers became interested in the role of the hypoxic tumour cell in the radio-sensitivity of tumours, beginning with the irradiation studies of tumour slices *in vitro* by Cramer (1934) and the *in vivo* studies on tar warts by Mottram (1936), culminating in an influential paper by Gray *et al*. (1955), which first led clinicians to attempt radiotherapy at increased oxygen pressures.

In 1955 Thomlinson and Gray (1955) proposed a mathematical model of the diffusion and consumption of oxygen to supplement an experimental investigation of some types of bronchial carcinomata which grow in solid rods which 'are devoid of capillaries and which comprise cells nourished by diffusion of metabolites inwards from the immediately surrounding stroma'. Large tumours of this kind often consist of necrotic centres surrounded by 'intact tumour cells which appear as rings'. Recognising that 'there must exist a falling gradient in oxygen tension between the periphery and the centre of each tumour cord' and that 'cells which are anoxic at the time of irradiation are generally much less damaged by a given dose of X- or

$\gamma$-radiation than those which are well oxygenated', the investigators appealed to some of the theory developed by Hill (1928) to estimate the critical value of the tumour cord's outer radius for which the concentration of oxygen just reaches zero at the centre. Interestingly, the model showed that 'the scale of the observed histological pattern is of the order to be expected if the supply of oxygen were the limiting factor which determines the onset of necrosis', although the investigators cautiously added that 'this numerical agreement is not advanced as evidence that the cells at the centre in fact die through lack of oxygen', conceding that the role of katabolites had not been considered.

It was Burton (1966), however, who developed a diffusion model which examined both the distribution of oxygen in a spherical tumour 'where the blood supply is completely confined to the surface' and the resulting 'relative radius of the central zone to the total radius', which was then used to explain how the growth curve could fit a Gompertzian expression.

The Gompertzian equation originated from the actuarial model developed by Gompertz (1825), and was applied to the study of growth in biological and economic contexts in 1932 by Winsor (1932). Laird *et al*. (1965) showed that the Gompertzian equation could describe the normal growth of an organism such as the guinea pig over an incredible 10 000-fold range of growth because of the equation's ability to exhibit exponential retardation—a feature not incorporated in other growth equations used in biological contexts at that time such as the allometry equation (Huxley, 1932), the monomolecular equation (Brody, 1945; von Bertalanffy, 1960), and the logistic equation (Robertson, 1923). In addition to using the Gompertzian equation to examine normal growth (Laird, 1965), Laird (1964) illustrated that the growth of a variety of primary and transplanted tumours of the mouse, rat and rabbit could be described very well by the Gompertzian relation.

Several explanations had been advanced for the underlying mechanism of this exponential retardation in tumour growth rates. While Laird (1964) argued that 'considering the data available at the present time, it seems likely that the observed deceleration of tumour growth is due at least in part to an actual increase in the mean generation time during tumour growth', Mayneord (1932) had shown that such a retardation could be achieved by the formation of a necrotic region in the centre of a tumour, gradually reducing the region of active growth to a thin shell at the tumour surface. Burton (1966) favoured Mayneord's explanation, modelling the effects of a diminishing growth fraction, while the mitotic rate of viable cells remained a constant. In addition, appealing to the experimental work by Stainsby and Otis (1961) and Chance (1957), the oxygen consumption per unit volume was considered independent of oxygen tension except below a critical oxygen tension for necrosis where oxygen consumption ceased. In proposing a mechanistic basis for the growth dynamics of the tumour in this way, Burton was also able to overcome the limitations of the Gompertzian relation, predicting growth which closely resembles Gompertzian growth over the 100- to 1000-fold range

of tumour volumes, but ultimately yielding the experimentally-observed linear growth.

## 3. Early Models of Avascular Tumours and Multicell Spheroids

The seminal work on tumour angiogenesis by Folkman (1974) arose from the discovery of dormant avascular tumour nodules *in vivo*. Greene (1961) had observed that the growth of tumour fragments implanted in the anterior chamber of the guinea pig eye ceased because of their inability to acquire a vasculature. Folkman *et al*. (1966) also discovered that tumours implanted in isolated perfused organs could not grow beyond a diameter of three to four millimetres, and observed that neovascularisation of tumour tissue in *in vitro* organ cultures was imperative in sponsoring continued growth (Gimbrone *et al*., 1969). Folkman and Hochberg (1973) were soon able to show that 'cells when removed from a plane surface and forced to grow in three dimensions in spheroidal or ellipsoidal population, will not expand beyond a critical diameter and cell number, regardless of how often new medium is provided or how much open space is made available'. Indeed, several groups of investigators, such as Sutherland *et al*. (1971), had begun to grow multicell spheroids in suspension as an experimental model for the study of *in vivo* nodular carcinomas, a technique which would also be employed by later investigators to study micrometastases and intervascular microregions of larger tumours (Sutherland, 1988).

The emerging interest in both the avascular nodules which precede angiogenesis as well as the multicell spheroid model encouraged various new approaches to the mathematical modelling of solid tumours. [Angiogenesis is, itself, the subject of considerable attention by mathematicians, and will not be addressed further in the present review. See Mantzaris *et al*. (in press) for an excellent recent review of the mathematical modelling of tumour-induced angiogenesis.]

Greenspan (1972) extended the models by Burton (1966) and Thomlinson and Gray (1955) by introducing a surface tension among the living cancer cells in order to maintain a compact, solid mass, and by assuming that 'necrotic cellular debris continually disintegrates into simpler chemical compounds that are freely permeable through cell membranes'. In this way, the tissue volume loss due to necrosis would be replaced by the inward motion of cells from the outer region as a result of the forces of adhesion and surface tension, thereby explaining the existence of a steady-state tumour size. Noting the finding by Sutherland *et al*. (1971) that the mitotic index of proliferating cells tended to decrease with distance from the spheroid surface once the aggregate had reached a critical diameter, Greenspan also assumed that 'a chemical is produced somewhere within the tumour which inhibits the mitosis of cancer cells without causing their death' once the concentration of the chemical reaches a critical level. These effects were

combined in an integro-differential equation for the evolution of the tumour radius, and a reaction–diffusion equation for both the concentration of nutrient and that of the inhibitor.

Two different possibilities were then considered separately. While the first model assumed that the chemical inhibitor was a result of inadequate nutrient supply and a product of necrosis, the second model assumed that the inhibitor was produced purely by the metabolic processes of living cells, with no katabolites associated with necrosis. Qualitatively, the two models predicted some overall similarities in the development of the spheroid, with three distinct growth phases: an initial exponential growth phase, followed by some degree of retardation, culminating in a final phase where retardation by both mitotic inhibition and cell death ultimately gave rise to dormancy. Nevertheless, each of the two models predicted a distinctly different growth pattern prior to arriving at a steady state, an outcome which Greenspan hoped would allow future experiments to distinguish between the two possible sources of growth inhibition. Regrettably, no such experimental work appears to have been undertaken. Greenspan (1974) later published a note which studied a problem of one-dimensional growth incorporating all the important phenomena considered in previous mathematical models (Burton, 1966; Greenspan, 1972), in which it was emphasized that the model could allow the primary source of growth inhibition to be determined from a histological examination of the steady-state cell population.

Glass (1973) was also interested in the role of growth inhibitors in tumour development, developing a mathematical model which predicted patterns of mitotic activity in a growing tumour. This mathematical study was primarily motivated by experimental evidence documented by Weiss (2000), Osgood (1957) and Bullough (1965) which suggested that ‘control of cellular replication in a number of mammalian tissues is at least partially determined by a negative feedback from the tissue itself’ caused by mitotic inhibitors called *chalones*. Importantly, Bullough (1965) and Bullough and Deol (1971) believed that a breakdown in the normal functioning of this chalone mechanism may be responsible for the uncontrolled tissue growth in at least some cancers. Glass therefore developed a simple one-dimensional schematic model which described the patterns of mitotic activity in a growing tumour. Chalones were assumed to be produced uniformly throughout the tissue, which then diffused beyond the tissue boundaries, and decayed. A key modelling assumption was the regulation of growth by a ‘switch mechanism’, where mitosis occurred below a critical value of chalone concentration, and was completely inhibited above this value. In contrast to Greenspan’s work (Greenspan, 1972), no volume loss mechanism such as necrosis was considered, and ‘stable tissue growth’ was assumed to occur when the chalone concentration was less than the mitotic threshold throughout the tissue.

Shymko and Glass (1976) extended this model to two and three dimensions, attempting to determine the effect of different geometries on the pattern and stability of growth, noting the work of Folkman and Hochberg (1973) which illustrated

that tissues cultured in a spheroidal geometry exhibit self-limiting growth while exhibiting unlimited growth as a monolayer.

Greenspan (1976) also extended his own modelling framework to consider the stability to asymmetric perturbations of the spherical shape of an equilibrium-sized tumour, being mindful of the experiments by Sutherland *et al*. (1971) where some cell aggregates disintegrated at a certain stage of development. As in earlier work (Greenspan, 1972), this formulation considered a thin proliferating layer near the surface and a large, central necrotic core, where 'the birth or death of cells produces internal pressure differentials which cause the motion of cellular material'. In defining the solutions of the modelling equations for pressure, nutrient concentration and the radius of the outer boundary as the 'basic state of motion', perturbations from this basic state were considered, with the main result that an aggregate becomes less stable as its size increases, where a function of two model parameters (relating to surface tension, external nutrient concentration, rate of necrotic volume loss and rates of proliferation and nutrient consumption) determines whether or not the aggregate arrives at a steady state before instability to asymmetric perturbations prevails.

The work of Burton and Greenspan was soon extended by Deakin (1975). Although these earlier authors had assumed that the oxygen consumption per unit volume per unit time by the cells was constant, Deakin argued that this behaviour contradicted the experimental evidence presented by Sutherland and Durand (1973) which demonstrated that the viable rim thickness decreases relatively slowly following the onset of necrosis—an observation which was inconsistent with previous model predictions. Appealing to the experimental findings of Froese (1962), Deakin then extended the formulations of Burton (1966) and Greenspan (1972, 1974) to incorporate an oxygen consumption which was proportional to oxygen concentration within critical limits. Beyond an upper critical value of oxygen concentration, oxygen consumption was considered a constant, while necrosis occurred at a lower critical value below which no oxygen would be consumed.

Whereas Deakin's study was restricted to the effect of the non-uniformity of oxygen consumption on the viable rim thickness, McElwain and Ponzo (1977) developed a model which investigated the effect of this non-uniformity on a tumour's growth rate, a model which—like Greenspan's model (Greenspan, 1972)—produced three distinct phases in the tumour's development. In the first phase, oxygen concentration is above the upper critical value everywhere, so that all cells consume oxygen at a uniform rate, giving rise to exponential growth. The growth rate reduces in the second phase as oxygen concentration reduces in the central region, with an associated decrease in the effective proliferation rate and a slowing in the overall growth. In the final phase, the tumour reaches a viable dormant state with an outer proliferating layer, an intermediate layer where overall proliferation is reduced and an inner necrotic core. Significantly, the growth pattern displayed a significant difference from that predicted by Greenspan's model

(Greenspan, 1972), where in some cases, the necrotic core was larger than the outer tumour radius predicted by Greenspan.

Another important aspect of Sutherland and Durand's (1973) experiments was the observation that multicell spheroids could reach a dormant size *without central necrosis*—a result which seemed to suggest a cell loss mechanism other than that postulated by Greenspan (1972). Further, Durand (1976) had detected only a small number of labelled nuclei in the necrotic core of a spheroid which had undergone continuous labelling with tritiated thymidine, which clearly pointed to other cell loss mechanisms even when central necrosis did occur. McElwain and Morris (1978) incorporated these experimental findings in a new mathematical model, heeding the publications by Kerr (1971) and Kerr *et al*. (1972) which demonstrated that apoptosis 'can always be detected in malignant neoplasms'. In this way, previous models were extended to include a constant cell loss rate in the entire viable region, with the consequence that a dormant state could be reached with or without a central necrotic region. In considering apoptosis as a cell loss mechanism, the model by McElwain and Morris (1978) is an antecedent to much of the subsequent mathematical literature relating to tumour development.

Various stochastic models of solid tumour growth also appeared in the literature in parallel with the aforementioned publications. While these will not be reviewed in detail in the present paper, it is important to note that 'since random fluctuations are fundamental to almost all biologic phenomena and particularly so in population processes, the probabilistic or stochastic aspect of evolving populations is essential whenever one considers populations whose size may assume small values. The behaviour of small populations is predominantly statistical, and the random component of the growth kinetics of a population, such as exhibited in the spontaneous extinction in even supercritical growth, may indeed become more important than the average behaviour' (Wette *et al*., 1974a). The interested reader is referred to the papers by Wette *et al*. (1974a,b) for further insight into the early stochastic models of solid tumour growth.

## 4. Early Models of Tumour Invasion and Metastasis: Liotta *et al.*

As explained by Ruoslahti (1996), 'metastasis, the spread of cancer to distant sites in the body, is in fact what makes cancer so lethal. A surgeon can remove a primary tumour relatively easily, but a cancer that has metastasized usually reaches so many places that cure by surgery alone becomes impossible. For that reason, metastasis and the invasion of normal tissue by cancer cells are the hallmarks of malignancy'. In citing the examples of axillary lymph node removal during mastectomy operations by both Marcus Aurelius Severinus in 1632 and Fabricius Hildanus in 1646, Weiss (2000) argues that 'before the basic relationship of metastasis to the primary tumour was recognized, its clinical significance was

appreciated'. Kleinerman and Liotta (1977) claim that the concept of haematogenous tumour cell release as a consequence of vascular invasion was first proposed in the 1800s, with Cruveilier's work (Cruveilier, 1829) in associating primary tumour invasion of local blood vessels with the development of remote metastases, and the later work by Lomer (1883) which recognised the role of circulating free tumour cells in initiating metastases.

Although the study of solid tumour growth had enjoyed considerable popularity among mathematicians, beginning in the early decades of the twentieth century, few insights had been gleaned into 'the factors that determine the onset, mechanism and time course of tumour cell release' (Kleinerman and Liotta, 1977). Indeed, it was not until the 1970s that quantitative experimental work and mathematical models were proposed to elucidate the dynamics of the metastatic process. An experimental model was first developed by Liotta *et al*. (1974a) 'to quantify some of the major processes initiated by tumour transplantation and culminating in pulmonary metastases', by investigating the entry rate of tumour cells into the circulation. The experiments featured a transplantable murine fibrosarcoma—chosen chiefly because of its high haematogenous metastatic propensity and reproducible biological behaviour—which was perfused with an oxygenated, cell-free medium, enabling single tumour cells and tumour cell clumps to be counted from the venous effluent. The study demonstrated the presence of tumour cells (both singly and in clumps) in the perfusate shortly after the appearance of the tumour vascular network, with the concentration of tumour cells increasing quite rapidly initially, and later diminishing. In a later study, Liotta *et al*. (1976a) confirmed these observations, while highlighting the importance of clump size in the metastatic process, since 'larger clumps produce significantly more metastatic foci than do smaller clumps matched for the number of cells'.

Several mathematical papers were published in the wake of these key experimental studies. Saidel *et al*. (1976) proposed a lumped-parameter, deterministic model of the haematogenous metastatic process from a solid tumour, which provided a general theoretical framework for analysis and simulation. As a compartmental model, five sub-populations were considered—tumour cells, vascular surfaces, invading tumour cells on the inner vessel surface, viable tumour cells arrested in pulmonary vessels and pulmonary metastatic foci—thereby providing an overall description of the metastatic process and allowing the relative importance and effective timing of the various steps to be assessed. Among the salient features of the model were the assumption of a Michaelis–Menten form for the processes of tumour cell proliferation and vessel surface formation, which presupposes a limit to both the level of tumour growth stimulation induced by more extensive vascularisation [based on the observations by Tannock (1968)] and the level of induced vascular stimulation. Numerical solution of the resulting suite of five ordinary differential equations yielded results which were in excellent agreement with their experimental counterparts (Liotta *et al*., 1974a). In addition, the investigators considered the effects of various perturbations on the metastatic process—for

example, tumour trauma by either external mechanical massage or by intratumour injection of a saline bolus—to validate the model's behaviour. It is noteworthy that the study corroborated previous findings where showers of circulating tumour cells appeared following tumour manipulation either during operation or in the course of diagnostic procedures (Tyzzer, 1913), since the authors noted that 'in our perfusions tumour massage resulted in a shower of effluent tumour cells resulting in a 10–20-fold higher concentration over control levels'. [This phenomenon was also observed in the authors' previous experimental study (Liotta *et al*., 1974a), where 'tumour massage (resulted in) at least a 10-fold rise over the initial concentration of tumour cells, as well as a higher proportion of large clumps'.] Furthermore, one of the most outstanding aspects of the mathematical model is its ability to distinguish between various mechanisms by which tumour trauma influences the release of circulating tumour cells, illustrating that trauma alone causes metastases to appear earlier without increasing the total number of metastases, whereas when trauma increases the dislodgment rate *and* damages the vessel walls, 'metastases increase more rapidly and are always greater in number than in the unperturbed state'.

A stochastic model of metastases formation was then proposed by Liotta *et al*. (1976b) to complement this mathematical model in order to distinguish amongst tumour clump sizes and the random variation of the populations of clumps and metastatic foci. The authors argued that while great quantities of tumour cells are released into the circulation, less than 0.1% survive to form metastatic foci (Koike, 1964; Griffiths and Salsbury, 1965), making a stochastic description of metastases formation an appropriate modelling framework. In this way, a non-homogeneous, two-dimensional Markov process was intended to 'provide a framework for predicting the development of metastatic foci from clumps in the pulmonary vessels and the probability of no metastatic foci existing after tumour initiation'. Simulation of the dynamics of the metastatic process was then accomplished by combining the numerical solution of the deterministic model given by Saidel *et al*. (1976) with the analytical stochastic model, giving good agreement with experimental data for the mean and variance of macroscopic metastatic foci.

The mathematical framework by Saidel *et al*. (1976) was also extended by Liotta *et al*. (1974c) in a diffusion model which attempted to elucidate experimental data describing temporal changes in tumour cell and blood vessel radial distributions in a host-tissue field transplanted with a fibrosarcoma. Coupled diffusion equations with source and sink terms were proposed in spherical polar coordinates (with spherical symmetry) to describe the density of both the tumour cells as well as the surface area of tumour vessels as functions of time and radial position. In the accompanying experiments, which built on the foundation outlined in Liotta *et al*. (1974a), tumours were examined on a sequence of days after implantation to determine the average radial distribution of tumour cells and tumour vessel surface area as functions of time. Notwithstanding the emphasis on infiltrative, malignant tumours, it may be argued that the underlying mathematical framework, in considering tumour expansion and vessel migration as purely diffusion processes,

is a little limited. Indeed, when very small values of the vascular proliferation rate parameter are assumed, the model equations predict that blood vessels simply diffuse passively into the tumour without any mitogenic stimulation. Nevertheless, in certain parameter regimes, the results of the mathematical model reflect the overall experimental observations quite well, possessing the major trends found in the experimental data, with a peak in the density of blood vessels occurring at the tumour cell migration front, and the peak in tumour cell density moving away from the tumour centre over time.

Liotta and co-workers also published some theoretical work on micrometastasis therapy (Liotta *et al*., 1977) and quantitating tumour cell removal and tumour cell-invasive capacity (Liotta and DeLisi, 1977).

## 5. Mathematical Approaches to Tumour Growth in the 1980s: Adam and Maggelakis

The mathematical models of Adam (1986, 1987a,b, 1989), Adam and Maggelakis (1989, 1990), Maggelakis and Adam (1990) and Landry *et al*. (1982) featured prominently in the mathematical literature pertaining to solid tumour growth published in the 1980s.

Like Glass (1973) and Shymko and Glass (1976), Adam (1986) had noted the important experimental findings on the role of growth inhibitors in tumour development published several decades earlier (Bullough, 1965; Bullough and Deol, 1971; Weiss, 2000). While Glass had assumed that regulation of growth occurred by a discontinuous switch mechanism for the control of mitotic activity with a spatially-uniform production of inhibitor, Adam maintained that a spatially-dependent mitotic control function best reflected experimental observations and warranted further theoretical study. Thus, it was the object of Adam's study (Adam, 1986) to examine the sensitivity of Glass's model (Glass, 1973) to spatially non-uniform inhibitor production, assuming a linearly-decreasing function of distance from the tissue centre. To permit a direct comparison between the models, Adam adopted the dimensionless variable, $n$, defined by Glass to delineate the conditions of stable tumour growth (a variable which related to the critical concentration of inhibitor for growth inhibition and the rates of inhibitor production and decay) as well as much of the schematic nature of Glass's formulation, with no consideration of a necrotic region, and no identification of internal boundaries. In this respect, then, the model represented an intermediate modelling framework between Glass's first model (Glass, 1973) and Greenspan's one-dimensional model (Greenspan, 1974).

In contrast to the work of Glass (1973), this new model predicted that for a given value of the critical dimensionless variable, $n_0$, a finite range of stable tissue sizes exists, which increases monotonically with the value of the dimensionless variable. Qualitatively, then, the model demonstrated the sensitivity of the growth of the tissue to a non-uniform source of inhibitor.

Recognising the importance of considering more realistic geometries to facilitate comparison with relevant experimental studies, Adam soon extended this simple model to investigate the roles of both non-uniform mitotic inhibition and geometry on the stability of growth (Adam, 1987a). Three basic geometric configurations were considered in order to provide a comparison with the work of Shymko and Glass (1976): a thin cylindrical tube where inhibitor concentration depended only on the axial distance from the centre of the tube, a thin cylindrical disc where inhibitor concentration depended only on the radial distance from the centre of the disc, and a sphere where the inhibitor concentration depended only on the radial distance from the centre of the sphere. Notwithstanding the similar *qualitative* results for the three configurations, each geometry gave rise to a distinct relationship between the limiting size of the stable tissue and the dimensionless variable, $n$, illustrating that geometry is also able to affect the stability of growth.

A comparison of these model predictions with the experimental results of Folkman and Hochberg (1973) was then made in a subsequent paper by Adam (1987b). Importantly, an additional parameter was added to the linear spatial variation in mitotic inhibitor concentration to enable an inverse problem to be solved for Folkman and Hochberg's data, thereby yielding the necessary spatial variation of growth inhibitor production to unify theory and experiment. Although the combination of spherical geometry and a certain spatial variation in inhibitor production gave rise to an excellent fit with the published data, Adam cautiously noted that this fit did not prove the necessity of spatial variations in mitotic control to explain such observations. It is particularly noteworthy that the series of mathematical models proposed by Adam (1986, 1987a,b) thus far, in extending the work of Glass (1973) and Shymko and Glass (1976), did not incorporate a volume loss mechanism such as necrosis, so that stability could only occur by complete growth inhibition throughout the tissue—a somewhat incongruous notion in the context of cancer.

Clearly, a consideration of the effects of a necrotic core would be an important extension of these models. While necrosis was later considered in the final paper in this series, it is essential to recognise that the necrotic core was simply incorporated as a source of growth inhibition in this study (Adam and Maggelakis, 1989), rather than representing a mechanism for volume loss. Nevertheless, the model enabled an interesting comparison to be made with the earlier work of Greenspan (1972) in investigating two different sources of growth inhibition: inhibition by diffusion of necrotic wastes, and inhibition via a by-product of processes occurring within living cells. Following Greenspan's approach, a spatially-uniform production was assumed—an important departure from the formulation of the three earlier papers in the series (Adam, 1986, 1987a,b). In other respects, however, the modelling framework was consistent with the earlier papers, employing a decay term in the diffusion equation for the concentration of inhibitor, which was solved, in this case, in spherical geometry. This model illustrated that, in the case of inhibition due to necrotic wastes, an increase in the relative width of the mitotic zone tended to

compromise the stability of the tissue. In the case of inhibition by processes within living cells, on the other hand, an increase in the relative width of the mitotic zone was associated with an increase of the inhibitor production region, and was therefore conducive to greater tissue stability.

Many of the remaining theoretical studies of tumour growth published in this decade, such as those of Landry *et al*. (1982) and Adam and Maggelakis (1990) and Maggelakis and Adam (1990), tended to focus on tumour growth dynamics.

Landry *et al*. (1982) considered the geometric and physical characteristics of multicellular spheroids in a mathematical model which attempted to relate growth rate to easily-measurable parameters such as cell doubling time in monolayer, rate of cell shedding from the spheroid and the depth of the external rim of proliferating cells—phenomena which were investigated in a preceding experimental study (Landry *et al*., 1981). These authors were aware of recent experimental observations which showed that spheroids expanded linearly with time as the spheroids sequestered proliferating cells at the periphery (Yuhas and Li, 1978; Yuhas *et al*., 1978), and later reached dormancy at a maximum diameter (Folkman and Hochberg, 1973; Haji-Karim and Carlsson, 1978). While the model did provide an explanation for the linear growth of multicellular spheroids, as well as a theoretical basis for the experimentally-observed direct correlation between the thickness of the proliferating rim and the spheroid growth rate (Yuhas and Li, 1978), it predicted an infinite linear expansion and was unable to explain the growth saturation of large spheroids. Acknowledging this shortcoming, the authors compared and contrasted the two principal explanations for spheroid dormancy existing in the literature at that time, namely the volume loss associated with the disintegration of cellular debris in the necrotic core (Greenspan, 1972), and the production of inhibitory factors (Glass, 1973; Shymko and Glass, 1976).

Maggelakis and Adam (1990), on the other hand, returned to a consideration of non-uniform growth inhibition in a model which examined the growth rate of a spherically-symmetric prevascular carcinoma when both nutrient consumption and inhibitor production were spatially non-uniform. In this sense, the formulation blended together many of the ideas first proposed by Greenspan (1972), Deakin (1975) and McElwain and Ponzo (1977), although in this case inhibitors were produced only in the necrotic core. Further, based on the work of Mueller-Klieser and Sutherland (1982) which examined the effects of toxic products from the necrotic core on cellular oxygen consumption, an additional parameter was introduced into the model to account for the effects of the inhibitor production on nutrient consumption rate. This formulation bestowed the potential to adopt a four-layered structure, with the development of the spheroid occurring within four distinct phases. In the first phase, all cells could obtain sufficient nutrients, allowing mitosis to proceed normally throughout the tissue. The second phase commenced when nutrient concentration reduced sufficiently in the central region to cause mitotis to decrease there, thereby beginning to slow the overall growth of the spheroid. A two-layered structure prevailed during this phase, with an outer

layer proliferating normally, and an inner layer in which proliferation was reduced. The third phase was a further period of retarded growth where the structure comprised an additional layer of necrosis at the centre, which constituted a volume loss mechanism. While this could give rise to dormancy, further growth ensued if the retardation by necrotic volume loss and consumption decrease was insufficient, giving rise to a fourth phase which could be characterised by either the aforementioned three-layered structure, or a four-layered structure comprising an additional quiescent layer.

The results and implications of this mathematical model (Maggelakis and Adam, 1990) were then presented in a subsequent paper (Adam and Maggelakis, 1990), elucidating the effects of different parameter values on various aspects of the model such as growth rates and overall growth pattern, and distribution of inhibitor concentration.

It is noted in closing that various models relating to oxygenation and radiosensitivity of solid tumours were published during this decade, such as the work of Liapis *et al*. (1982), Arve and Liapis (1988), King *et al*. (1986a,b) and Schultz and King (1987). In addition, some mathematical models of drug transport in tumours such as the models given by Jain and Wei (1977) and Swan (1981) were advanced over a similar time-frame.

## 6. Recent Mathematical Approaches to Tumour Growth: From 1990 to the Present

The 1990s witnessed an explosion in the publication of mathematical papers on solid tumour growth, with many more such papers appearing in this single decade than in all the previous years combined. Not only did the study of both vascular and avascular tumours (along with their *in vitro* counterparts, the multicell spheroids) continue, with the emergence of some new approaches, but various other experimental investigations into tumour biology, such as the internalisation of labelled cells in spheroids, became the subject of mathematical studies. Interesting mathematical contributions to the study of tumour invasion and metastasis were also published during this period, in addition to publications in the inchoate areas of tumour residual stresses and multiphase tumour mechanics.

The following section outlines a selection of such theoretical studies in order to illustrate how this field of research has taken shape and how mathematical modelling has continued to contribute to an enhanced understanding of tumour development over recent years.

**6.1.** ***Cell migration in multicell spheroids and tumour cords.*** In response to the emerging interest in the underlying mechanisms of cell migration, McElwain and Pettet (1993) proposed a mathematical paradigm with which various key experimental findings could be interpreted. Moore *et al*. (1984, 1985), for example, had studied tumour cords—cylindrical ‘cuffs’ of tumour cells surrounding a blood

vessel—using radioactive labelling techniques, and observed that cells tend to migrate from the proximity of the blood vessel towards the outer extremity of the cord, eventually entering the surrounding necrotic zone. Dorie *et al*. (1982, 1986) studied these tumour growth kinetics further using multicell spheroid assays, considering the migration of both single cells labelled with tritiated thymidine and inert polystyrene microspheres in two separate experiments. While both types of probe adhered readily to the surface of the spheroids and gradually migrated inwards, only the microspheres internalized completely, with no microspheres observed in the peripheral region after several days. By contrast, a significant number of labelled cells remained attached to the outer rim after this time, producing a distinctly bimodal distribution.

Since the experiments by Dorie *et al*. (1982, 1986) attempted to clarify whether the internalisation of labelled cells and microspheres was an active or passive process, the model by McElwain and Pettet (1993) incorporated both the passive internalisation due to non-uniform cell proliferation and cell death and the associated pressure gradients, as well as the active migration of cells from a chemotactic response to the gradient of nutrient concentration. While this theoretical framework made predictions which ostensibly reproduced the experimental results reported by Dorie *et al*. (1982), it must be conceded that these results were dependent on a number of controvertible modelling assumptions. In particular, it was assumed that it was only the labelled cells which could migrate actively by chemotaxis, and that these labelled cells do not proliferate. Furthermore, there was no experimental evidence that cancer cells respond chemotactically to nutrient concentrations.

A later model given by Thompson and Byrne (1999) addressed some of these shortcomings, postulating that non-uniform cell proliferation and cell death of the labelled cells were responsible for the different internalisation patterns, rather than chemotaxis. Nevertheless, while the model predicted many of the qualitative aspects of the observed migration of the probes, the limiting distribution of labelled cells was spatially uniform rather than exhibiting the bimodal distribution observed by Dorie *et al*. (1982). In addition, the model required an initial distribution of labelled cells which was entirely internal to the tumour surface, rather than adhering to the surface itself.

Pettet *et al*. (2001), on the other hand, combined many of the ideas proposed by both McElwain and Pettet (1993) and Thompson and Byrne (1999) to propose a novel explanation for the migration of labelled probes in multicell spheroids. Influenced by the experiments by Hughes and McCulloch (1991) and Palka *et al*. (1996) which suggested that the chemotactic response of cells is dependent on cell-cycle phase, these authors maintained that the quiescent cells alone would detect the nutrient concentration gradient and attempt to migrate towards regions of higher nutrient concentration, thereby competing for space with the proliferating cells which continually drive cells towards the spheroid centre. Thus, cells in the quiescent state were assumed to be more ‘chemotactically active’ than their proliferating counterparts. This variation in chemotactic responses predicted a self-sorting

of the cells, with quiescent cells dominating both the innermost region of tissue where nutrient levels are low, as well as the tumour periphery as a result of chemotaxis. Proliferating cells, by contrast, were confined to a comparatively thin shell close to the tumour periphery.

Bertuzzi and co-workers (Bertuzzi and Gandolfi, 2000; Bertuzzi *et al*., 2002, 2003) brought some fresh approaches to the study of cell migration through a consideration of tumour cords. Various experimental investigations of tumour cords have been conducted since the often-cited work of Tannock (1968), Hirst and Denekamp (1979) and Hirst *et al*. (1982, 1991), as well as the influential papers by Moore *et al*. (1983, 1984, 1985). Further, tumour cords represent an interesting subject for theoretical investigation, since their simple cylindrical geometry renders them a tractable subunit of a vascular tumour, which, as a whole, comprises a highly heterogeneous agglomeration of various cell types (both normal and neoplastic, in various phases of the cell cycle) and necrotic regions, permeated by a tortuous and highly fenestrated vasculature (Jain, 1987; David *et al*., 2002; Ruoslahti, 2002).

Bertuzzi and Gandolfi (2000) developed a mathematical model for the cell kinetics in a tumour cord to complement the cell migration data obtained by Moore *et al*. (1984) from two experimental rat hepatomas. In view of the experimental data on the expression of proliferation markers reported by Danova *et al*. (1990) which attests to the presence of quiescent cells in tumours, the model considered the population of viable tumour cells to comprise both proliferating and quiescent cells. In addition, the age—or cell cycle phase—of the proliferating cells was taken into account since this characteristic affects the update of radioactively-labelled DNA precursors during the experimental labelling process. Any variability of phase transit times was neglected, so that all proliferating cells were assumed to undergo the complete cycle in the same time. Moreover, the cells were assumed to behave as a single fluid, with a single velocity field which was independent of cell age and proliferating and quiescent status. In formulating a population model with an assumed cell cycle structure, the model was based on the earlier theoretical work by Gurtin (1973) and Gurtin and MacCamy (1977) on age-dependent diffusion of biological populations. This modelling framework afforded excellent agreement with the experimental data relating to the radial distribution of the labelling index (the fraction of labelled cells after a pulse of tritiated thymidine) published by Moore *et al*. (1984), except in the region adjacent to the blood vessel—a discrepancy the authors argued was likely to be a consequence of assuming a constant cycle time.

Bertuzzi *et al*. (2002) later incorporated a variable cell cycle length in a formulation which built upon the foundation developed by Kendall (1948) and Takahashi (1966, 1968) to represent the cell cycle by a sequence of discrete compartments of cell maturity corresponding to the phases G1 (gap 1), S (synthesis), G2 (gap 2) and M (mitosis). This new model predicted the time evolution of the spatial distribution of the total fraction of labelled cells (LI) and the fraction of mitotic labelled cells (FLM) in order to illuminate the experimental data reported by

Hirst and Denekamp (1979) for the KHH mammary carcinoma. Since the rate of progression through the cell cycle diminished with radial distance from the central vessel because of the decreasing nutrient concentration, the authors maintained that the kinetic differences between inner and outer zones could be masked by the process of cell migration. Indeed, the model studied the effects of cell migration by comparing the predictions relating to the time course of FLM with both the experimental data and the previous analyses by Takahashi (1966, 1968) which neglected spatial structure and cell migration. Although both mathematical models give rise to reasonable correlation with the experimental results for the region adjacent to the blood vessel, only the model given by Bertuzzi *et al*. (2002) yielded an acceptable fit for the observed data in the outermost region of the cord. The authors concluded that a correct analysis of radioactive labelling data from tumour microregions requires the possible cell migration through the regions to be taken into account.

While both the model given by Bertuzzi and Gandolfi (2000) and that given by Bertuzzi *et al*. (2002) neglected the process of cell death within the tumour cord, a subsequent model given by Bertuzzi *et al*. (2003) considered the dynamics of tumour cords under the action of a cytotoxic agent. This model incorporated both a random cell death—either spontaneous or induced by the cytotoxic agent—and a cell death which results from insufficient nutrient availability. Although dependent upon many simplifying assumptions, the model was able to reproduce the qualitative results reported by Tannock and Howes (1973) and Moore *et al*. (1983) relating to the response of tumour cords to a single dose of radiation. It also emphasized the role of the degradation rate of dead cells on the macroscopic response of the tumour mass.

**6.2.** ***Multiphase models.*** The mathematical theory of continua comprising two or more interacting constituents, or *phases*, is well developed, with the combination of the seminal works of Truesdell and Toupin (1960) and Truesdell and Noll (1965) with the more recent publications by Bowen and co-workers (Bowen, 1976, 1980, 1982; Bowen and Wiese, 1969), Passman and co-workers (Passman and Nunziato, 1984; Drew and Passman, 1999) and Rajagopal and Tao (1995) providing a rigorous development of the theory and underlying modelling equations. These approaches have enjoyed considerable success in various areas of industrial applied mathematics over recent decades (Drew, 1971, 1976; Drew and Segel, 1971; Fowler, 1997; Fitt *et al*., 2002), and more recently, in an assortment of biological studies predominantly relating to soft tissues such as articular cartilage and intervertebral discs (Mow *et al*., 1990a; Lai *et al*., 1991, 1993; Snijders *et al*., 1992; Huyghe and Janssen, 1997).

By comparison, the application of multiphase techniques to biological *growth* and the study of tumours is in its infancy, despite a number of important contributions appearing in the literature since the mid-1990s. These models depart from the approaches used in most other biomechanical modelling insofar as the growth

process itself is central to the problem at hand, and necessitates the inclusion of interphase mass exchange in the suite of modelling equations.

Among the first multiphase models of tumour growth was that proposed by Please *et al*. (1998). Noting that the precise underlying determinants of regions of coagulative necrosis had hitherto been neglected in mathematical models of tumour growth, these authors advanced a very simple one-dimensional model of the formation of necrotic regions in growing tumours by considering the role of stresses within the tissue. Two incompressible phases were considered: tumour cells, which were assumed to behave inviscidly, and extracellular water. The process of cell proliferation was regulated by the concentration of oxygen, which was assumed to diffuse rapidly into the tumour from its surroundings. Contrary to many previous models (Greenspan, 1972), no surface tension was introduced to the model, so that the processes of cell proliferation and cell death were the only underlying mechanisms for cell movement. The authors postulated that the extracellular fluid pressure must always be less than or equal to the cellular pressure in a region of live cells, with cell rupture occurring in the event that the extracellular fluid pressure was the greater of the two. In this way, the approach was novel insofar as the onset of necrosis was not dependent upon a critical oxygen concentration, but on the stresses within the tumour.

This formulation was applied to the growth of a tumour in a test tube, with the modelling equations tracking both the upper surface of the tumour, adjacent to oxygen-rich water, and the boundary of the necrotic region. While the tumour growth was initially exponential in this case, the onset of necrosis yielded a linear growth of both the outer boundary of the tumour and the boundary of the necrotic region, with the region of live cells maintaining a fixed thickness.

The authors soon extended this model to include surface tension and a spherical geometry (Please *et al*., 1999), and considered a slow, viscous flow of the cells in a two-phase consolidation model. The assumption relating to the rupture of cells at an elevated interstitial fluid pressure was also elaborated in this paper, which stated that ‘any attempt to induce the extracellular matrix into a state of tension will then result in adjacent cells rupturing as they are ripped from the extracellular matrix and each other’, an assumption the authors believed to be valid for weakened anoxic cells, if not for rapidly proliferating cells.

It is important to note that both this model (Please *et al*., 1999) and its predecessor (Please *et al*., 1998) neglected the interphase drag forces in the equilibrium equation.

By contrast, the full force balance equation—complete with pressure gradients for each phase as well as hydrodynamic drag—was included in a subsequent model by Landman and Please (2001). In addition, this latter paper was influenced strongly by the experimental evidence reviewed by Mueller-Klieser (2000), which pointed to biological mechanisms other than oxygen diffusion and consumption alone in creating a region of necrosis. Moreover, these authors believed the catastrophic rupture of cells due to a tensile intercellular stress to be a weak aspect of

the previous models (Please *et al*., 1998, 1999), preferring the concept of a necrotic region identified by the appearance of voids between cells as neighbouring cells die. Physical constraints on cell density and intercellular pressures were imposed via a linear complementarity condition which allowed necrotic regions to form, grow and shrink.

Assuming spherical symmetry, the model highlighted the role of surface tension in both the possible formation of a necrotic region and the ability of the tumour to reach a steady-state size. In particular, very small values of the coefficient of surface tension prevented a steady state, with linear growth continuing indefinitely. While moderate surface tension permitted a linearly stable steady state, containing a necrotic region of fixed size, a surface tension in excess of a certain critical value gave rise to a compacted tumour with no necrosis, whose steady-state size was independent of the value of the surface tension coefficient.

This two-phase approach to the study of avascular tumour growth was revisited by Breward *et al*. (2002) using a one-dimensional cartesian geometry. While the aqueous phase was assumed inviscid, the viscosity of the cellular phase was considered indicative of the degree of differentiation of the tumour cells, with poorly-differentiated tissue characterised by a reduced intercellular cohesion and, therefore, a lower viscosity than their well-differentiated counterparts. Further, a key feature of this model was the assumption that the pressure in the cellular phase differs from that in the extracellular water phase due to interactions between the cells. Cells could attract each other, due to overlapping filopodia, or repel each other due to the mechanical stress resulting from the deformation of the cell membrane.

A number of interesting predictions emanated from the ensuing solution and analysis of the modelling equations. In the case where the short-range, attractive intercellular forces were inactive, for example, a necrotic core developed, while the live cells were relegated to a thin cortical region adjacent to the tumour periphery which advanced as a travelling wave with an approximately constant propagation speed. Moreover, increasing the viscosity of the cellular phase decreased the speed of the advancing front, which was consistent with the idea that this viscosity correlates with the degree of differentiation of the tumour cells. When the short-range, attractive forces were active, on the other hand, the tumour arrived at a steady state with no mass flux across the free surface, with the mass required for ongoing proliferation coming entirely from the mass relinquished by dying cells.

An similar two-phase theory of avascular tumour growth was soon proposed by Byrne *et al*. (in press). Whereas the former model given by Breward *et al*. (2002) considered interphase exchanges of momentum resulting only from interfacial pressures and ‘Darcy-style’ drag terms, this new model also incorporated the effect on the momentum equations of interphase mass exchange, thereby providing a correct statement of the equilibrium of forces for each phase. Importantly, the development of the suite of modelling equations in both this model (Byrne *et al*., in press) and its predecessor (Breward *et al*., 2002) constitutes a justification for the description of cellular motion as a *diffusion* process [as in, for example, the

models given by Sherratt (1993, 2000) and Gatenby and Gawlinski (1996)], since a 'cell-diffusion' term was shown to be a consequence of interphase drag and the interactions between cells, rather than the hitherto assumed random cell motion.

An extension of this work was later advanced by Byrne and Preziosi (in press) in a model which considered the stress distribution within the tumour, mechanical interactions with the peritumoral region and stress-dependent cell proliferation. Based on the theory of mixtures, a more detailed exposition of the conservation equations was given in this paper in comparison with previous models (Breward *et al*., 2002; Byrne *et al*., in press), appealing to the seminal work of Bowen (1976). Ostensibly, the tumour comprised a solid cellular phase and a liquid phase, but significantly, the constitutive equation deduced for the 'solid' phase was that of a viscous fluid. Moreover, while the model defined the special case where viscous contributions are absent as a 'poroelastic limit', this type of 'poroelasticity' is quite distinct from the usual poroelastic concept of a solid *matrix* permeated by a fluid.

Nevertheless, the model provided some interesting insights into the sensitivity of the tumour's dormant size to the effects of stress-dependent cell proliferation and the application of external loads. While increases in the applied stress at the outer boundary were associated with smaller equilibrium sizes, the sensitivity of the process of cell proliferation to mechanical stresses determined whether or not the tumour evolved to a nutrient-limited equilibrium size or a stress-limited equilibrium size. If the inhibitory effect of mechanical stress on cell proliferation reached a critical value, the tumour could be eliminated.

The recent 'solid-multiphase' models given by Preziosi and Farina (2002) and Araujo and McElwain (submitted-a) currently stand alone in the literature relating to multiphase modelling of tumour growth by including a solid matrix amongst the phases. While the emphasis of the former paper is a derivation of the correct statement of Darcy's law for biological growth problems where interphase mass exchange occurs, the latter model presents a full suite of modelling equations which permit a consideration of *residual stresses*, a topic to be discussed in more detail in the next section. Most significantly, the analysis in the paper by Araujo and McElwain (submitted-a) points to a crucial phenomenological aspect of tissue growth, illustrating that such a process must consist of a coordinated combination of the swelling of the solid (cellular) phase due to the influx of extracellular fluid—which is, in essence, the inverse of the consolidation concept of poroelasticity—and the exchange of mass whereby extracellular fluid is incorporated into the cellular phase. This combination of processes necessitates the inclusion of an additional constitutive postulate which relates interphase mass exchange to the solid matrix expansion amongst the modelling equations in order to close the model. Ambrosi and Preziosi (in press) have referred to the necessity to propose such postulates for velocity or displacement fields as the *closure problem*.

Multiphase approaches are also beginning to be applied to the study of vascular tumours. The recent model by Breward *et al*. (2003) is an extension of these authors' two-phase framework (Breward *et al*., 2002) to include blood

vessels as a third phase. In determining explicitly the pressure exerted by the cells on the blood vessels, an interesting feature of this one-dimensional model is its ability to incorporate vascular collapse when this pressure exceeds a critical value, with the consequence that the local delivery of oxygen is impaired. Such an outcome clearly favours the formation of regions of coagulative necrosis. Mindful of the insights into tumour blood vessel compression and decompression provided by Boucher and Jain (1992) and Griffon-Etienne *et al*. (1999) respectively, the model attempted to explain the recent observations by Brown *et al*. (2002) that in some tumours an almost uniformly vascularised layer of proliferating cells envelops a central necrotic core. Thus, it is interesting to compare this mathematical model (Breward *et al*., 2003) with the recent theoretical studies of tumour vascular collapse by Araujo and McElwain (submitted-b, 2003a,b) which employed the principles of solid mechanics, as well as the early model given by McElwain *et al*. (1979) which determined pressure gradients by Darcy's law.

The multiphase model of capsule formation in tumours by Lubkin and Jackson (2002) is also noteworthy, particularly since, along with the studies by Barr (1989) and Barr *et al*. (1988), it is among the very few attempts to uncover the underlying mechanisms of this important aspect of tumour growth. Indeed, investigators such as Robbins *et al*. (1984) and Ng *et al*. (1992) have noted that the presence of a capsule around tumour often suggests a favourable prognosis. In view of the evidence reported by Ritchie (1970) and Berenblum (1970) that tumours in lumens or on the body surface do not form capsules, one of the foremost current explanations for capsule formation asserts that peritumoral tissue is compressed into a capsule by the expansion of the tumour. For this reason, the mathematical model given by Lubkin and Jackson (2002) attempted to discriminate between the two mechanisms of tumour expansion and host contraction. The tumour was assumed to comprise two interpenetrating phases: an aqueous phase, and a more solid phase consisting of the cells and the remaining, generally fibrous, extracellular components. Nevertheless, *both* phases were assumed to behave as Stokes fluids over the time scale of tumor growth, allowing stresses in the cell–fibre phase to dissipate by permanent deformation. Among the other salient features of the model are the inclusion of a contractility which may arise from a wound-healing response, and a solvation stress, which is a measure of the affinity of one phase for another.

With this relatively simple description of the mechanics of a growing tumour, the model demonstrated that 'it is the expansion of the tumour, coupled with the internal solvation pressure ... which causes the formation of the capsule and the associated elevated interstitial pressure of the tumour'. In addition, the model 'confirmed the high and rising interstitial tumour pressures and the sharp and steepening pressure gradient at its periphery as the tumour grows', which had been observed experimentally by Boucher *et al*. (1991) and Gutmann *et al*. (1992). While contractility was not necessary for the formation of a capsule, the model showed that a host wound-healing response and the associated contractility would produce a denser and better defined capsule, resulting in a much clearer tumour margin.

**6.3.** ***Mechanical models and models of residual stress formation.*** Experimental evidence for the significance and implications of growth-induced stresses in both normal and neoplastic tissues abounds in the literature. Fung (1991), for example, noted the existence of residual stresses in living organs and highlighted the importance of such stresses to physiological functions, asserting that 'in a living organism, the function of its organs depends on the levels of their internal stress and strain'. Taber (1995) emphasizes that 'residual stresses in biological tissues have been observed for a long time' although 'the purpose of these stresses is not well understood'.

In the context of cancer, stresses of various types distinguish neoplastic tissues from their normal counterparts. Extensive experimental evidence attesting to the elevated interstitial fluid pressure (Boucher and Jain, 1992) and oncotic pressure (Stohrer *et al*., 2000) in tumours—even very small tumours (Leunig *et al*., 1992)—has been published by Jain and co-workers, for instance. This interstitial hypertension is thought to arise from the development of the neovasculature (Boucher *et al*., 1996), owing predominantly to both the highly fenestrated nature of tumour blood vessels (Hashizume *et al*., 2000), the paucity of functional lymphatics (Netti *et al*., 1995; Leu *et al*., 2000) and the elevated microvascular pressure linked to elevated solid stresses within the tissue and the accompanying compression of blood vessels (Griffon-Etienne *et al*., 1999). Importantly, interstitial hypertension is believed to be partly responsible for the poor distribution of blood-borne therapeutic agents and low blood flow rate in tumours (Znati *et al*., 1996).

A significant experimental publication relating to the role of stresses in tumour development was that by Helmlinger *et al*. (1997). In these experiments, multicell spheroids were grown in agarose matrices of varying stiffness so that stresses gradually accumulated around the spheroids due to the progressive displacement of the matrix by the growing aggregates. Among the salient results of the study were the reversible inhibition of the spheroid growth, with an apparent threshold stress required for significant growth inhibition, and a resumption of spheroid growth following stress alleviation. In addition, while the net proliferation rate of the cells was not affected by the surrounding stresses, the percentage of proliferating and apoptotic cells both decreased, and cellular density increased with increasing matrix stiffness. Moreover, spatial variations in the surrounding stress field reversibly modulated the shape of the growing aggregates.

Various theoretical papers were published in tandem with these experimental studies, such as the time-dependent model of interstitial fluid pressure using a poroelastic description of the tumour by Netti *et al*. (1995). The model simulated the effect of changes in microvascular pressure and tumour blood flow on interstitial fluid pressure, with the excellent agreement between the model simulations and experimental data suggesting that the model may be helpful for developing strategies to improve high molecular weight drug delivery.

The experiments by Helmlinger *et al*. (1997) were modelled mathematically by Chen *et al*. (2001), in an extension of the model by Landman and Please (2001)

(see Section 6.2). Here, the surrounding agarose gel was assumed to be an isotropic, porous, non-linear elastic medium characterised by a strain energy function so that the stress induced in the gel by the tumour's expansion could be incorporated into the force balance equations, thereby linking it to the tumour's growth. The model exhibited two types of solution, namely a steady state with or without a necrotic core, depending on the induced stresses. The model also predicted that, for a given initial tumour radius, the onset of necrosis would be delayed by increasing gel stiffness, thus reducing the tumour's growth rate and its saturation diameter. In this way, the model had qualitatively reproduced the observations by Helmlinger *et al*. (1997).

A number of key experimental studies of tumour vascular collapse have also appeared in the literature over the past four or five decades—another aspect of tumour biology which is known to be detrimental to anti-cancer therapies (Jain, 1994).

In the study by Eddy and Casarett (1972), for example, the development of a 'tissue growth pressure' around a hamster malignant neurilemmoma in a restrictive transparent cheek pouch chamber was sufficient to compress the weak-walled tumor capillary vessels. Further, in the experiments reported by Goldacre and Sylven (1962), a harmless green dye was injected into the tail veins of mice with transplanted tumours, giving rise to a deep green coloration of the whole animal with the exception of the brain (due to the blood–brain barrier) and the central regions of many of the solid tumours. The investigators concluded that tumours often 'contain substantial regions which cannot readily be reached by blood-borne substances' due to 'some kind of (vascular) collapse'. Another important observation made by Goldacre and Sylven (1962) was that, for each type of tumour used in their experiments, 'the critical factor causing differences in the distribution of dye was mainly the age and to some extent the size of the tumours'. While young tumours were instantaneously coloured throughout with the green dye, the development of green peripheries enclosing white centres was observed to occur at a critical age, suggesting that vascular collapse occurs after a critical period of growth.

It is most striking to compare Goldacre and Sylven's report (Goldacre and Sylven, 1962) with the more recent experiments by Leu *et al*. (2000) in which functional lymphatics were detected only at the periphery of the tumours, the investigators arguing that the paucity of such vessels in the interior was due to the collapse and destruction of the vessels.

From the point of view of theoretical investigation, it is important to recognize that this distinctive spatial pattern of vascular collapse is strongly suggestive of the presence of *residual stresses*, since an elevated hydrostatic pressure exerted by the tumour's surroundings, such as that in the experiments by Helmlinger *et al*. (1997) would give rise to spatially uniform vascular compression. In addition, Boucher and Jain (1992) assert that 'the collapse of tumour blood vessels is probably induced by cancer cells growing in a relatively confined, noncompliant space',

since interstitial fluid pressure and microvascular pressure are approximately equal within tumours.

Nevertheless, despite the numerous analytical studies of incompatible growth in tissues by investigators such as Skalak and co-workers (Skalak, 1981; Skalak *et al*., 1982, 1996), Rodriguez *et al*. (1994), Cowin (1996) and Van Dyke and Hoger (2001), the mathematical modelling of residual stress development in growing tumours is a relatively recent endeavour. Shannon and Rubinsky (1992) published a linear-elastic description of a spherically-symmetric tumour incorporating different spatial distributions of growth strains which were modelled by analogy with thermal expansion. This study yielded the crucial result that in a linear-elastic description of a growing tissue with spherical geometry, any spatial variation in the growth process induces residual stresses. Jones *et al*. (2000) also developed a mathematical model which explored the effect of a spatially-varying growth rate on the distribution of residual stresses within a growing avascular tumour, but extended the framework of Shannon and Rubinsky (1992) by accommodating the continuous nature of the growth process rather than a given fixed growth strain distribution. As a consequence of this measure, however, the model failed to predict a steady-state stress distribution once the tumour had reached its nutrient-regulated equilibrium size and therefore did not truly reflect the growth-induced stresses in an avascular tumour or multicell spheroid. Indeed, the model predicted that the compressive circumferential stresses in the peripheral region of an equilibrium-sized tumour increased approximately linearly with time, with a concomitant linear increase in the difference between the radial and circumferential stresses, the radial stresses being fixed at the boundary itself. In this way, the model given by Jones *et al*. (2000) highlighted the insufficiency of an elastic constitutive law to model continuous volumetric expansion owing to its inability to exhibit stress relaxation.

MacArthur and Please (submitted) addressed this problem by proposing a viscoelastic model of residual stresses in a multicell spheroid—a natural modification of the model given by Jones *et al*. (2000) in view of the substantial body of experimental evidence pointing to the viscoelastic nature of biological tissues (Mow *et al*., 1990b; Fung, 1993; Pioletti *et al*., 1998). These authors used this modelling framework to extend the models of necrosis formation by Please and coworkers (Please *et al*., 1998, 1999; Landman and Please, 2001), allowing necrotic regions to develop under conditions of adverse mechanical stress rather than in regions of low nutrient concentrations.

Intriguingly, Araujo and McElwain (in press-a) were able to show that the stress-relaxation characteristics of a viscoelastic constitutive law may be accommodated in an elastic description of a growing tissue by allowing the growth process to occur *anisotropically*. In associating stress relaxation with the growth term of the constitutive equation rather than the stress response term, this modelling framework heeded the experimental findings by Helmlinger *et al*. (1997) which demonstrated the sensitivity of the directional characteristics of growth to the prevailing stresses with cell aggregates developing as ellipsoids in an orthotropic stress field.

In view of the fundamental role played by the spatial non-uniformity of the growth process in inducing residual stresses, Araujo and McElwain (in press-b) analysed the nature of the induced stresses for different distributions of growth strain in a spherically-symmetric geometry. This analysis uncovered the important result that a distribution of growth strains which decreases monotonically with radius induces stresses which become progressively less compressive with radius, with the circumferential component always less compressive than the radial component. By contrast, a monotonically-increasing distribution of growth strains induces stresses which become progressively more compressive with radius, with the circumferential stress component always more compressive than the radial component. Most importantly, the analysis illuminated the role of anisotropic growth in relieving growth-induced stresses.

These authors later developed mathematical models of Goldacre and Sylven's (1962) experiments (Araujo and McElwain, submitted-b, 2003a) based on the insights gleaned in the former paper (Araujo and McElwain, in press-b), illustrating that a growth strain distribution which increases with distance from the tumour surface *before* collapse, and a growth strain distribution with an internal maximum at the vascular collapse front *following* vascular collapse could reproduce Goldacre and Sylven's observations. A subsequent paper (Araujo and McElwain, 2003b) predicted that oscillations in the steady-state tumour radius could occur from the combination of vascular collapse and the stress-relaxation characteristics of the tissue.

Several other mathematical papers on residual stresses in tumours are noteworthy. Ambrosi and Mollica (2002) considered tumour growth using a combination of hyperelasticity and the notion of 'multiple natural configurations' originally proposed by Rajagopal and Srinivasa (1998). Having developed a general mathematical formulation, the authors considered some simple models, including the spatially-uniform growth of a ductal carcinoma, and the spatially non-uniform growth of a multicell spheroid. This modelling framework was pursued further in a subsequent paper (Ambrosi and Mollica, 2003) which presented numerical simulations of the growth of a multicell spheroid, confirming that residual stresses are generated because of the spatial non-uniformity of the growth process.

Lubarda and Hoger (2002) recently published a general constitutive theory of stress-modulated growth of soft tissues, albeit with an emphasis on pseudo-elastic tissues capable of large deformations, such as blood vessels and muscles. Using the earlier work of Taber and co-workers (Taber and Eggers, 1996; Taber and Perucchio, 2000) and Hoger and co-workers (Chen and Hoger, 2000; Hoger *et al.*, submitted) as a foundation, this study pursued further the technique of a multiplicative decomposition of the total deformation gradient into its elastic and growth components.

**6.4.** ***New mathematical approaches to the study of tumour invasion and metastasis.*** A keen interest in the important areas of tumour invasion and metastasis

has persisted amongst mathematicians over recent years. Indeed, the possibilities afforded by anti-invasion and anti-metastatic strategies in cancer treatment, as discussed by Jiang and Mansel (1996), have bestowed an added preponderance to the subject.

Orme and Chaplain (1996) continued the study of tumour growth and vascularisation commenced by Liotta *et al*. (1974c), contributing various new ideas and modelling assumptions. Whereas the earlier work had proposed coupled diffusion equations with source and sink terms to describe the density of tumour cells and vessel surface areas, this more recent model also assumed that tumour cells react to the presence of blood vessels in a similar manner to that of 'taxis', so that tumour cells move up a gradient of capillary vessels. Moreover, an important novel aspect of the model was the assumption that a necrotic core develops as a consequence of the overcrowding of tumour cells and eventual collapse of blood vessels, in contrast to the hypothesis by Liotta *et al*. (1974c) that necrosis occurs due to the inability of the process of neovascularisation to keep pace with tumour cell proliferation. Moreover, interactions between tumour cells and capillary vessels were considered in more detail, yielding a somewhat more complicated partial differential equation model. In addition to solving these equations by an algorithm which integrated the system by the method of lines and Gear's method, a travelling wave analysis on a slightly simplified form of the equations was conducted, illustrating an advancing front of invading tumour cells which leaves a compressed vasculature in its wake.

The theoretical studies by Perumpanani and co-workers (Perumpanani *et al*., 1996, 1999; Perumpanani and Byrne, 1999; Perumpanani and Norbury, 1999) have made a significant contribution to the recent mathematical literature pertaining to malignant invasion. These models pursued a more detailed phenomenological understanding of tumour cell invasion by incorporating mathematical descriptions of biological processes hitherto neglected from the majority of such studies. They also contrasted strongly with previous mathematical models of cell motility which focused predominantly on the role of angiogenesis.

Motivated by the significant experimental findings reported by Seftor *et al*. (1992) and Aznavoorian *et al*. (1990) on the role of integrins in tumour invasion, Perumpanani *et al*. (1999) developed and analysed a mathematical model of malignant invasion brought about by a combination of proteolysis and haptotaxis. The spatial dynamics of invasive cells were modelled by a directed cell movement up an extracellular gradient, while neglecting random cell motility on the basis of the study by Aznavoorian *et al*. (1990) which reported minimal chemokinetic movement. Following the study by Vaidya and Alexandro (1982), the proliferation of tumour cells was incorporated using the logistic growth equation, while a simple passive degradation described the dynamics of the extracellular matrix. In addition, while the production of protease was assumed to depend on the local concentrations of both tumour cells and extracellular matrix, its decay was assumed to be linear with a specified half-life.

A travelling wave analysis ensued, where the presence of a singular 'barrier' in the phase plane could be identified, such that the phase paths had meaning only on either side of the barrier. However, a particular point on this 'wall' of singularities admitted a trajectory—a point originally described as a 'hole in the wall' by Pettet *et al*. (2000). Importantly, the model admitted a family of travelling waves depending on both the tissue concentration of connective tissue as well as the rate of decay of the initial spatial profile of the invading cells. This model was later analysed further by Marchant *et al*. (2000) who identified the equations as a reaction–advection system, in contrast to the reaction–diffusion equation first considered by Fisher (1937) and Kolmogorov *et al*. (1988)—the Fisher–KPP equation. Marchant *et al*. (2000) showed that whereas the Fisher–KPP was parabolic, the model proposed by Perumpanani *et al*. (1999) was hyperbolic, and may support shocks, or discontinuities in the solution profiles, in addition to the smooth travelling wave solutions presented in the earlier paper (Perumpanani *et al*., 1999). Hence, a previously unnoticed family of solutions for malignant invasion was demonstrated. The study of travelling wave solutions to such haptotaxis-dominated models of malignant invasion has been pursued further in a subsequent paper by Marchant *et al*. (2001).

Another paper by Perumpanani *et al*. (1996) considered the repetitive cycling of the processes of attachment, proteolysis and migration—the sequence of steps referred to by Stetler-Stevenson *et al*. (1993) as the three-step hypothesis—in a mathematical model which explored the ways in which different combinations of these processes are able to produce an invasive phenotype. Thus, the key model variables comprised the concentrations of the invasive cells, non-invasive tumour cells, normal cells, a generic extracellular matrix protein, a generic protease and the product of proteolytic digestion of the extracellular matrix protein. The aim of this one-dimensional continuum model of invasion was to explore the macroscopic implications of various biological hypotheses and to provide a theoretical framework to make predictions about aspects of the system which would not lend themselves to experimental investigation due to either cost or logistic difficulties. Further, since invading cells behave as a front of cells travelling outwards as a wave, the analytical focus of the paper was a study of the nature of this wave and the changes which occur at the tumour/host interface as the wave progresses.

The authors used the results of this mathematical model to make several biological inferences. In particular, it was argued that the movement of cells, as reflected by the wave profile of the invasive cells as well as the speed of invasion, was oscillatory as a result of the simultaneous effects of a haptotactic gradient (encouraging outward movement) and a concomitantly created chemotactic gradient (having a retarding effect). In addition, the average speed of invasion could be determined in terms of the invasive cell kinetics and the coefficient of haptotaxis. Further, the absence of invasion under conditions of high protease expression was explained on the basis of chemotactic gradients. The effects of the diffusivity of the protease on an invading cell were also studied, illustrating that while a small increase in protease diffusivity is conducive to a dramatic increase in tumour invasiveness, a large

increase discourages invasion due to the obliteration of extracellular matrix gradients which guide the cell movement. Perumpanani and Norbury (1999) later considered this mathematical model further, with a particular emphasis on the numerical behaviour of the modelling equations.

Both theoretical and experimental methods were combined in a publication by Perumpanani and Byrne (1999), which illustrated the power of mathematical modelling to provide new and valuable insights into important biological phenomena. In view of the well-documented proclivity of certain primary tumours to metastasize and establish new colonies in specific organs [such as the tendency of colonic carcinomas to spread to the liver (Kuo *et al*., 1995) while breast carcinomas tend to spread to the axillary lymph nodes (Van Lancker *et al*., 1995)], this study attempted to establish whether regional variations in extracellular matrix concentration could contribute to these invasion patterns by exerting a local selection pressure on the invasive cells. For the experimental component of the study, an invasion assay was used to assess the invasiveness of HT1080 tumour cells migrating through a collagen gel, demonstrating a *biphasic* relationship between invasiveness and collagen concentration, with maximum invasiveness at intermediate concentrations of collagen and diminished invasiveness for higher and lower concentrations. Interestingly, the mathematical model developed to study this behaviour yielded the prediction that tumour cell proliferation may also be related in a biphasic manner to collagen concentration, a hypothesis which was then substantiated by a combination of collagen gel invasion and proliferation assays. Moreover, further analysis of the mathematical model suggested that the biphasic dependence of the penetration depth and proliferation of tumour cells on collagen gel concentration may be a consequence of interactions between haptotaxis and cell proliferation.

Over a similar time-frame as the aforementioned studies were published, Gatenby (1991, 1995a,b, 1996a,b), Gatenby and Gawlinski (1996, 2001) and Webb *et al*. (1999a,b) advanced a number of impressive mathematical papers on tumour invasion which contrasted quite markedly with the former publications, investigating alternative mechanistic bases for experimentally-observed behaviour. Since the initial studies by Gatenby (1991, 1995a, 1996b) appealed to methods from population biology in treating tumour cells as an invading species in an otherwise stable 'multicellular ecological domain', it was demonstrated that 'tumour populations, as with any invading population in nature, must directly perturb the environment in a way that facilitates its growth while inhibiting those in the original community' (Gatenby and Gawlinski, 2003). Hence, several acid-mediated tumour invasion models ensued (Gatenby, 1995b, 1996a; Gatenby and Gawlinski, 1996; Webb *et al*., 1999a,b) as a result of the search for tumour-induced perturbations in the tissue environment.

Various experimental observations contributed to this new explanation of tumour invasion. Volpe (1988) and Clarke *et al*. (1988), for instance, had reported evidence that a consistent cellular dynamic in tumours is an evolution away from the differentiated state of the tissue of origin toward one that is more primitive.

Furthermore, Warburg (1930) had observed that an increase in glycolytic metabolism accompanied this evolution despite a concomitant 19-fold decrease in energy production. Gatenby and Gawlinski (1996) held that successful tumour invasion was linked to this inefficiency, postulating that 'transformation-induced reversion of neoplastic tissue to primitive glycolytic metabolic pathways, with resultant increased acid production and the diffusion of that acid into surrounding healthy tissue, creates a peritumoral microenvironment in which tumour cells survive and proliferate, whereas normal cells are unable to remain viable'. A mathematical framework for this acid mediation hypothesis was proposed, giving rise to a system of three coupled reaction–diffusion equations which described the densities of the normal and tumour tissues in addition to the excess concentration of $H^+$ ions—a measure of the tissue's acidity.

The raw data presented by Martin and Jain (1994) relating to *in vivo* interstitial pH profiles for the VX2 rabbit carcinoma and its surrounding normal tissue was then analysed using the model, demonstrating that the data was consistent with the presence and approximate range of the pH gradient extending into peritumoral tissue as predicted by the model. The predicted growth rates of both benign and malignant tumours also compared favourably with clinical observations. In addition, the model highlighted the roles of various biological parameters in the clinically-observed 'crossover behaviour' between non-invasive growth and the development of an invasive phenotype. Most significantly, the mathematical model predicted a number of interfacial structures, including a previously unrecognized hypocellular interstitial gap in some malignancies—a gap which the authors demonstrated through *in vitro* experiments.

Several other interesting contributions to the mathematical study of invasion and metastasis are noted in closing. Chaplain and Sleeman (1993) devised an interesting theory of tumour invasion by supposing that the degree of differentiation of a tumour may be characterised mathematically by a strain energy function, thereby linking the potential for invasion and metastasis to the constitutive nature of the tissue. Here, the cortical layer of proliferating cells enclosing the necrotic core was modelled as a balloon membrane, with the gross internal forces taken into account by an inflationary pressure. This approach afforded an emphasis on the activity of the layer of proliferating cells at the tumour periphery, which may invade the surrounding host tissue. Moreover, the bifurcation from spherical symmetry to an aspherical equilibrium, which may be associated with the onset of local invasion, was considered, with the criterion for bifurcation also expressed in terms of a strain energy function.

A later paper by Sleeman and Nimmo (1998) extended the model of fluid transport in vascularized tumours by Jain and Baxter (1998) to enable a consideration of invasion and metastasis. Introducing a pressure-curvature condition to the tumour periphery, a perturbation analysis was conducted to show how small deviations from spherical symmetry could enhance asymmetric growth, enabling the tumour to invade and metastasize.

**6.5.** ***Further models of avascular tumours and multicell spheroids.*** The study of avascular tumours and multicell spheroids continues to represent a substantial proportion of all mathematical models devoted to solid tumour growth.

Some recent studies have resumed the study of growth inhibitory factors commenced by Shymko and Glass (1976) and Adam (1986, 1987a,b). Chaplain *et al*. (1994), for example, had noted Loewenstein's observations (Loewenstein, 1981) relating to the loss of coupling between tumour cells and proposed that the diffusion of growth inhibitory factors between cells may not be constant. Therefore, in contrast to earlier models (Adam, 1986, 1987a,b; Adam and Maggelakis, 1989) which incorporated only non-linear *production* of mitotic inhibitors, this new model (Chaplain *et al*., 1994) introduced a non-linear, spatially-dependent diffusion coefficient to describe the diffusion of a growth inhibitory factor. In addition, both uniform inhibitor production, as well as the non-linear production term proposed by Britton and Chaplain (1992) and Chaplain and Britton (1993) were considered in this framework. The model demonstrated that the introduction of a non-linear, spatially-dependent diffusion coefficient was sufficient to produce a profile of growth inhibitor concentration which was compatible with experimental findings. Furthermore, since the combination of non-linear diffusion and a non-linear production term was also able to reflect experimental observations, the authors argued that, from a mathematical point of view, it is not possible to distinguish between the effects of non-linear diffusion and non-linear production of inhibitors.

The recent interest in the role of apoptosis (that is, programmed cell death) in tumour growth has also spawned several novel mathematical models. New anti-tumour strategies which focus on apoptosis are emerging (Hickman *et al*., 1994; Darzynkiewicz, 1995; Kastan *et al*., 1995; Thames *et al*., 1996) since, in some cases, a lack of cell death is responsible for neoplastic growth. Byrne and Chaplain (1996a) considered both apoptosis and necrosis as distinct cell loss mechanisms in a model which studied the effects of nutrients and inhibitors on the existence and stability of time-independent solutions for a multicell spheroid.

Experimental evidence attesting to the relationship between cell proliferation and apoptosis (Lynch *et al*., 1986; Raff, 1992; Levine *et al*., 1995), where increases in *both* rates have been observed in some tumours, motivated Byrne (1997a) to develop a mathematical model which studied the effect of time delays on the dynamics of avascular tumour growth. Two types of time delay in the net cell proliferation rate were considered. The first type of delay was regulated by the cell itself (autocrine control) and represented the time taken for the cells to undergo mitosis. The second type of delay, on the other hand, was influenced by neighbouring cells (paracrine control) and represented the time for cells to upregulate the production rate of a particular growth factor and for the growth factor to modify the rate of apoptotic cell loss. Because of these time delays, the tumour's evolution depended not only on its composition at a particular instant, but also on its composition at some earlier time.

The numerical solution of the modelling equations and the accompanying asymptotic analysis demonstrated that the manner in which time delays were integrated into the system was crucial to the tumour's evolution. While the first type of delay did not affect the tumour's limiting behaviour, the second type of delay could dramatically alter the tumour's growth dynamics. Indeed, beyond a certain critical delay time, radially-symmetric steady-state solutions were destabilized, with the tumour volume oscillating in a manner similar to the observations by Lynch *et al*. (1986) on cell number fluctuations.

A subsequent model by Byrne and Gourley (1997) continued the study of the relationship between cell proliferation and apoptosis through a consideration of the internal production of growth factors which regulate apoptotic activity. Here, a growth factor was first produced in an inactive form during cell proliferation, and later activated upon binding to a tumour cell. The inclusion of growth factors in this manner rendered the tumour *history dependent*, so that its evolution depended on its structure at a given time as well as its structure over a *range* of earlier times [rather than at a particular earlier time as in the model given by Byrne (1997a)]. Moreover, growth factors which enhanced apoptosis did not alter the qualitative behaviour of the tumour, while growth factors which suppressed apoptosis could induce asymmetric pulsing of the tumour radius.

The series of papers by Ward and King (1997, 1999a,b, 2000) have made a significant contribution to the recent literature on avascular tumour growth, and are cited often. These are multi-species models, which, despite considering multiple tissue constituents, are quite distinct from the models presented in Section 6.2 since they do not appeal to the theory of porous media and theory of mixtures. [For this reason, they diverge quite markedly from the models by Please *et al*. (1998, 1999) and Landman and Please (2001) in postulating a non-mechanical basis for the formation of necrotic regions.] The first paper by Ward and King (1997) presented a system of non-linear partial differential equations as a continuum model which assumed cells to be either living or dead (depending on the concentration of a generic nutrient), the aim being to make predictions about tumour heterogeneity and growth, without making any *a priori* assumptions about the spatial structure of the tumour. A velocity field developed as a consequence of local volume changes due to cell proliferation and cell death, where, in contrast to previous models, dying cells contracted at a rate which depends on the availability of nutrients. Thus, cell death was a gradual process. Another interesting aspect of the model was its use of a generalized Michaelis–Menten form for the rate constants for cell proliferation and death, building on previous methods to model cell kinetics by investigators such as Lin (1976) and McElwain (1978).

Notwithstanding its inability to model growth saturation since the products of cell death remained within the spheroid without decaying or escaping, this formulation predicted an early exponential growth phase followed by linear growth, corresponding to experimental observations in the intermediate phase of spheroid growth. An additional interesting prediction peculiar to this modelling

framework was the existence of two phases of growth retardation following the exponential growth. The authors used asymptotic analysis to illustrate that the first of these phases was a consequence of nutrient diffusion limitations, with the second retardation coinciding with the formation of a necrotic region. In addition, well-defined tumour regions were predicted, with a distinct viable rim and a necrotic core. Thus, the analysis in this paper offers insights into the time scales of the various stages of growth and the length scales of the various tumour regions.

An extension to the model was soon proposed (Ward and King, 1999a) in order to permit a consideration of growth saturation by incorporating a necrotic volume loss. The model represents an interesting extension to models such as those by Greenspan (1972), McElwain and Morris (1978) and Byrne and Chaplain (1995, 1996a, 1998) where cell death by either apoptosis or necrosis, or a combination of the two, was associated with the contraction of the entire cell volume. Ward and King (1999a), however, considered only necrotic cell death and proposed two distinct mechanisms for the removal of the necrotic debris: leakage and consumption by neighbouring cells. The latter mechanism was postulated on the basis of experimental observations of cells' consuming neighbouring dead cells (having undergone apoptosis), as reported by Kerr *et al*. (1987). Depending on the choice of parameter regime, this measure enabled the long-time solutions to exhibit either travelling waves or growth saturation.

The effects of mitotic inhibitors were investigated in a subsequent model extension, in which it was proposed that during necrotic cell death, a cell dissociates into two different species: basic cellular material such proteins and DNA which may be used by living cells for proliferation and growth, and high molecular weight material which cannot be used directly by other cells and may act as a mitotic inhibitor. Indeed, several growth inhibitory proteins originating in the necrotic core had been identified by a number of investigators including Freyer *et al*. (1988), Harel *et al*. (1984), Iwata *et al*. (1985) and Levine *et al*. (1995), having molecular masses $O(100)$ times that of glucose. While incorporating mitotic inhibition into the model did not alter the qualitative development of the tumour, it did have a pronounced effect on quantitative outcomes such as increasing the propensity for the spheroid to arrive at a steady state (rather than exhibit travelling wave solutions) and causing a reduction in the saturation size. Moreover, the results demonstrated that the inhibitor could act either directly by reducing the mitotic rate, or indirectly by occupying space, thereby reducing the availability of cellular material.

Cell shedding, the process by which cells detach from the surface of a multicell spheroid, became the focus of a further extension of these models. It is noteworthy that this model, along with those by Landry *et al*. (1982) and Casciari *et al*. (1984), is one of the very few theoretical studies to consider this phenomenon. Cell shedding was introduced to the modelling equations by allowing the rate of change of the coordinate of the tumour surface to differ from the surface velocity. Moreover, in view of the observation by Landry *et al*. (1981) that cells are more prone

to detachment during mitosis, the model related the rate of cell shedding to the mitotic rate at the spheroid surface. Including the process of cell shedding in this way was shown to expand significantly the range of parameters for which growth saturation occurred.

Various other mathematical models of avascular tumours are noted in closing. A number of recent models, such as those by Byrne and Chaplain (1996b) and Byrne (1997b, 1999b), for example, have continued the work of Greenspan (1976) on the spherical stability of cell aggregates. A later model proposed by Byrne and Chaplain (1997), on the other hand, comprised some very novel approaches and constituted a quite general formulation for the growth of multicell spheroids. While the model was, in essence, based on the work of Greenspan (1976) in considering the tumour as an incompressible fluid with local cell proliferation and death generating pressure gradients which govern cell motion, these authors made no *a priori* assumptions about the tumour's spatial structure. Moreover, a key aspect of the model was the assumption that the nutrient concentration satisfied the Gibbs–Thompson relation on the tumour boundary, a relation which states that 'the nutrient concentration at a point on the tumour boundary is less than the external concentration by a factor which is proportional to the local curvature there' (Byrne and Chaplain, 1997). This feature was intended to reflect the experimental evidence reported by Miyasaka (1995) and Nagle *et al*. (1994) that cells require energy on the periphery to generate sufficient adhesive forces to maintain a compact tumour mass. [Recall that Greenspan (1976), by contrast, had appealed to a simpler concept of surface tension in order to ensure tumour compactness.] The balance between the internal expansive force due to cell proliferation and the adhesive forces between cells on the tumour boundary then enabled the tumour's potential for invasion to be assessed. This formulation gave rise to a number of free boundaries, explicitly defining the outer boundary, and implicitly defining various internal surfaces (such as the boundary of the necrotic core) as functions of nutrient concentration.

Sherratt and Chaplain (2001) have also developed a novel mathematical approach to the study of avascular tumours, considering continuum densities of proliferating, quiescent and necrotic cells, together with a generic nutrient or growth factor. This framework predicted the development of the characteristic layered structure of a proliferating rim, an underlying quiescent layer and a necrotic core without making any *a priori* assumptions about the spatial structure of the tumour. In this sense, the model extended aspects of the framework developed by Ward and King (1997, 1999a) to consider quiescence. The model also incorporated cell movement based on the phenomenon described by Abercrombie (1970) as 'contact inhibition of migration', where the presence of one cell type limits the movement of another cell type—a measure which was shown to reduce the rate of tumour growth. [Note that this contact inhibition had been modelled previously by Sherratt (1990) in a very simple competition model.] An additional novel feature of the model was that the thin, approximately disc-shaped tumour could be supplied with

nutrients from underlying tissue, a situation which would arise in the context of a tumour growing within an epithelium. The numerical solutions and accompanying analysis illustrated that tumour structure could be altered significantly by this aspect.

The recent model of the early growth of a ductal carcinoma *in situ* of the breast by Franks *et al*. (2003) represents an interesting contrast with the other theoretical studies outlined in this section, applying many of the approaches developed by Ward and King (1997) to the cylindrically-symmetric geometry of the breast duct. The tumour's growth was largely determined by nutrient availability, with growth occurring preferentially down the duct, being the direction of least resistance. In addition, cell movement was described by a Stokes flow constitutive relation. Thus, a system of non-linear partial differential equations was proposed to describe the live and dead tumour cell concentrations, the concentration of fluid within the duct (lumen), nutrient concentration, local velocity and pressure. This modelling framework was then used to study the effects of the tissue viscosity on the shape of the tumour boundary, as well as the extent to which the cells adhere to the duct wall.

**6.6.** ***Further models of vascular tumours.*** A number of noteworthy attempts have been made to model vascular tumour growth on both the microscale and the macroscale, albeit considerably fewer in number when compared with models of avascular tumour growth.

Byrne and Chaplain (1995) developed a model of non-necrotic tumour growth which studied the roles of nutrients and growth-inhibitory factors being supplied to tumour cells by both diffusion and blood–tissue transfer via the vasculature. This was an important contribution to the theoretical study of growth inhibition since, in comparison with the earlier work of Adam (1986, 1987a,b) and Adam and Maggelakis (1990), the consideration of *in vivo* growth permitted an investigation of a much wider range of inhibitory behaviour. The model also departed from earlier work by including apoptosis in the mass conservation equation, being one of only two mathematical models to have considered this cell loss mechanism at that time [the first being the model by McElwain and Morris (1978)]. A further distinguishing feature of this work was a consideration of the variations in dependent variables over both the timescale of nutrient diffusion and the growth timescale, affording insight into the previously unstudied transient behaviour of tumours. [It is noted that this model was later analysed by Cui (2002) and Cui and Friedman (2000).]

Hahnfeldt *et al*. (1999), on the other hand, developed a quantitative theory of vascular tumour growth and treatment response under angiogenic stimulator and inhibitor control by investigating the effects of the angiogenic inhibitors endostatin, angiostatin and TNP-470 on tumour growth dynamics. In this way, a theoretical basis was proposed 'for both describing tumour development and for assessing antiangiogenic treatment alternatives, alone or in combination with conventional therapies'. The results attested to the 'ubiquitous tendency of tumours to exhibit

a growth slowdown with a possible asymptotic approach to a final tumour size, or 'set point" which 'may be understood in terms of the net angiogenic influence upon the tumour becoming more inhibitory over time, independent of any tumour cell-specific details'. In addition, the analysis offered a ranking of the relative effectiveness of the inhibitors.

In contrast to many other studies, Breward *et al*. (2003) proposed a model of the *microscale* within a vascular tumour, considering the interactions between a compliant vessel and the live and dead tumour cells in its vicinity. Here, the oxygen levels in the tumor tissue depended on the spacing of the blood vessels as well as their thickness, with larger vessels supplying greater levels of oxygen. Local cell proliferation and cell death gave rise to pressure gradients which, in turn, caused the blood vessel to open or close. Since the closing of a blood vessel impeded the supply of oxygen, the oxygen tension could vary in response to changes in the local densities of tumour cells.

A poroelastic description of a vascular tumour was developed by Netti *et al*. (1997) in a model which differs from those discussed in Section 6.2 since the growth process itself was not considered. Rather, microscopic and macroscopic descriptions of transvascular and interstitial fluid movement were united in this model, with a view to providing a theoretical tool to complement experimental investigations of macromolecular transport (or drug delivery) in solid tumours. Indeed, the study of drug transport in tumours is a significant area of mathematical modelling in itself and will not be discussed in further detail in the present review. The interested reader is referred to the papers by Jackson (2002), Jackson and Byrne (2000), Baxter and Jain (1989, 1990, 1991, 1996), Netti *et al*. (1995), McDougall *et al*. (2002), Tracqui *et al*. (1995), Adam and Panetta (1995), Panetta and Adam (1995), Wein *et al*. (2002) and Ward and King (2003) for some further examples.

Cristini *et al*. (2003) have recently published a novel formulation of the classical models by Greenspan (1976), McElwain and Morris (1978), Byrne (1997b) and Byrne and Chaplain (1996b), studying vascular tumour growth in the non-linear regime using boundary-integral simulations. Three growth regimes were considered, corresponding to low, moderate and high vascularisation. An interesting outcome of this modelling framework was the prediction that highly-vascularized tumours, in spite of their unbounded growth, would maintain a compact shape without invasive fingering, a prediction corroborated by the recent experimental observations of *in vivo* tumour growth by Nor *et al*. (2001).

The study of a vascularized spherical carcinoma by Adam and Noren (2002) is noted in closing, in which the authors analyse the solutions of the non-linear time-independent diffusion equation arising from a model of a spherically-symmetric vascularized carcinoma with a central necrotic core.

**6.7.** ***Various other mathematical models of tumour growth.*** In addition to the models outlined in previous sections, some recent mathematical papers have

encompassed a number of stages of tumour development, including the avascular and vascular phases, the intermediate period of angiogenesis, and eventual local invasion and metastasis.

The review by Chaplain (1996), for example, discusses these various stages of tumour growth by presenting a variety of mathematical ideas previously published by Chaplain and co-workers (Chaplain, 1993; Chaplain *et al*., 1994). Although many of these modelling approaches have been discussed elsewhere in the present review, Chaplain juxtaposes these models in order to present a unified treatment of the entire process of tumour development.

In a similar manner, Chaplain and Preziosi (in press) present a general discussion of a number of modelling frameworks, including lattice schemes and continuum models comprising either a single phase or multiple phases, for the study of tumour growth at the macroscopic level. Summaries of various aspects of the models given by De Angelis and Preziosi (2000), Anderson and Chaplain (1998) and Anderson *et al*. (2000) are presented to give an overview of the subjects of avascular tumour growth, angiogenesis, invasion and tumour–host interactions. The model given by De Angelis and Preziosi (2000) is particularly noteworthy since it describes the continuous evolution of a tumour from the avascular stage to the vascular stage via the process of angiogenesis.

The study of tumour interactions with the immune system has also attracted an abundance of mathematical models. An overview of this field of research has recently been published by Adam and Bellomo (1997), who present an extensive review of the associated mathematical literature.

## 7. Concluding Remarks and Open Problems

Cancer is a leading cause of premature death in the Western World, and its study dates back to antiquity. This short treatise has presented an overview of the study of solid tumour growth with an emphasis on mathematical modelling, beginning with the early work on diffusion in tissues by Hill (1928) and culminating in the most recent models. The astonishing variety of theoretical approaches—from diffusion models of avascular tumours to multiphase models of vascular tumours, from travelling wave analysis of tumour invasion to models of cell migration by chemotaxis in multicell spheroids, from multi-species fluid models to single phase viscoelastic models, from stochastic models of metastases formation to multiphase models of necrosis formation—attest to the incredible complexities of the biological and physiological processes underlying solid tumour growth and invasion at molecular, cellular and macroscopic levels. Importantly, this overview has interwoven these theoretical studies with the relevant experimental investigations, illustrating the crucial relationship between these different approaches, demonstrating how the field of cancer research has evolved through their interactions and elucidating the origins of our current understanding of the disease.

The majority of mathematical models of solid tumour growth seem to have appeared in the literature since 1990, although many of these have extended the basic frameworks developed by investigators such as Greenspan (1972, 1974, 1976), Burton (1966) and McElwain and co-workers (McElwain and Ponzo, 1977; McElwain and Morris, 1978) in previous decades. Mathematical models continue to appear in the literature at an extraordinary rate. Indeed, the lacunae in our understanding of tumour growth and invasion necessitate a sustained input by mathematicians into current and future investigations, and provide the impetus for a continuing stream of new projects in mathematical oncology and ongoing collaborations between mathematicians and experimentalists. As explained by Gatenby and Gawlinski (2003), 'it is clear from centuries of experience in the physical sciences that the complex dynamics of systems dominated by non-linear phenomena such as carcinogenesis cannot be determined by intuition and verbal reasoning alone. Rather, they must be computed through interdisciplinary, interactive research in which mathematical models, informed by extant data and continuously revised by new information, guide experimental design and interpretation'.

For this reason the relationship between theory and experiment is a crucial one, and one which will guide the progress of cancer research in the future.

At the present time, the open problems in the study of tumour development are legion. For instance, an understanding of the phenomenological determinants of cell migration (discussed in Section 6.1), and whether it is an active or passive process, is lacking. Furthermore, the question of the nature of tumour cell migration is central to a number of consequential phenomena such as tumour invasion. If cell migration should prove a passive process, then invasion models such as those of Gatenby (1995b, 1996a), Gatenby and Gawlinski (1996, 2001, 2003) and Webb *et al*. (1999a,b) would seem the more plausible and warrant further development and study. If migration be an active process, on the other hand, a whole new field of study would open in the quest to identify the agents responsible for the migration and their manner of influence. An active cell migration would endow the tumour invasion models given by Perumpanani and co-workers with added standing (Perumpanani *et al*., 1996, 1999; Perumpanani and Byrne, 1999), so that models of this type could offer crucial insights into future experimental studies and give rise to much-needed predictive tools.

The collapse of tumour blood vessels is another poorly-understood phenomenon, and one which is of fundamental importance to the administration of anti-cancer agents. The most striking experimental illustration of vascular collapse seems to be the classic work of Goldacre and Sylven (1962) published in 1962. The publications by Brown *et al*. (2002) and Leu *et al*. (2000) offer more recent examples, although the nature of these experiments did not allow the investigators to make a positive link between the observed macroscopic behaviour and vascular collapse. Very few mathematical models have been developed to explain the collapse of tumour vessels. Araujo and McElwain (submitted-b, 2003a,b),

Breward *et al*. (2003) and McElwain *et al*. (1979) have proposed very different mathematical paradigms for the genesis of tissue stresses and the accompanying patterns of collapsed blood vessels.

Central to an understanding of tissue stress evolution is the necessity to identify the precise constitutive nature of growing tumour tissues—a characteristic which must be determined through future experimental study. The overwhelming majority of mechanical models of tumours consider the model to be an incompressible fluid [such as the model by McElwain *et al*. (1979)], or a mixture of such fluids [such as the model by Breward *et al*. (2003)], either incorporating or neglecting viscosity. Breward *et al*. (2002, 2003) have extended the potential scope of multiphase fluid models given by incorporating cell–cell interactions which bestow more active properties to the constitutive nature of the cellular phase than previous fluid models. Araujo and McElwain (submitted-a,b), on the other hand, emphasise the importance of considering residual stresses, which necessitates a consideration of the solid characteristics of tissues. It is essential to recognise that each of these different approaches rely on vastly different phenomenological assumptions to reproduce the patterns of vascular collapse demonstrated by Goldacre and Sylven (1962) and Brown *et al*. (2002), highlighting the fact that the associated underlying mechanisms are, as yet, not understood. 1g Necrosis formation is also a very poorly-understood aspect of tumour development. While most mathematical investigators have attributed the presence of necrosis purely to depressed levels of oxygen or other vital nutrients, Please and co-workers (Please *et al*., 1998, 1999; MacArthur and Please, submitted) have argued that mechanical factors are paramount. At the present time, experimental studies have been unable to offer sufficient insights to distinguish between these possibilities. The distinction is certainly an important one, since the formation of necrotic regions appears to correlate with tumour aggressiveness, and further insights into necrosis formation may yield fresh information on invasion and metastasis.

Future combinations of ingenious experimental designs and astute mechanistic mathematical models will be imperative to elucidate these and other enigmas.

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*Received 15 September 2003 and accepted 6 November 2003*