

# Stochastic Model for Abnormal Clone Spread through Epithelial Basal Layer

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The induction of a tumour in the basal layer of an epithelium has been simulated by computer. The primary assumption is that tumour growth begins when a single abnormal cell divides faster than surrounding normal cells by a factor  $\kappa$ , the "carcinogenic advantage".

THE generative mass in the epithelium is located in the basal layer, above which are differentiated cells, thought to secrete chalone<sup>1</sup>, that diffuses back to the basal layer to control cellular divisions. It was thought that when a basal cell divided, one daughter cell remained, while the other was pushed up among the differentiated cells. Leblond *et al.*<sup>2</sup>, however, found that radioactive thymidine remained longer than anticipated in the basal layer, indicating that both daughter cells remained in the basal layer and displaced a neighbouring cell. This sidewise splitting is substantiated by mitotic patterns, tending to cluster in the basal layer.

Bjerknes and Iversen<sup>3</sup> have suggested a possible mechanism for tumour induction, in which a basal cell becomes less sensitive to chalone. Since the clone derived from this cell would divide faster than its neighbours, the tumorous cells would push their neighbours out and gradually usurp the entire basal layer.

Cells tend to pack into layers in a honeycomb pattern; sometimes almost perfectly, more often only approximately. Our computer simulations assume a precise honeycomb distribution. We started each realization with a single abnormal cell, which we postulated to divide  $\kappa$  times as fast as the normal cells: we call  $\kappa (> 1)$  the "carcinogenic advantage". Sometimes, by chance, the entire abnormal clone will be pushed out of the basal layer; the probability of such a regression is  $1/\kappa$ , and is virtually the only mathematically rigorous result we have obtained.

## Computer Simulations

For the complementary situation, where the abnormal clone takes hold, the computer printed out a picture of the basal layer configuration when first there were 100, 400, 900 or 1,600 abnormal cells in this layer. Fig. 1 shows three sequences of such pictures: normal cells are indicated as dots and the abnormal ones as circles (the boundary between normal and abnormal cells has been drawn in). The first column (Fig. 1) shows the situation where  $\kappa$  is so large that the abnormal cell always pushes out the normal one and regression is impossible. Note that from time to time enclaves of normal cells are engulfed by the abnormal, but that the opposite cannot happen. There are no abnormal islands off by them-

selves, as this would require the normal cells to cut off an abnormal peninsula, which cannot happen since the normal cells never win out here.

The middle column (Fig. 1) shows the development of the process when  $\kappa = 2$ . Half the patterns now regress and this sequence of pictures shows one that has taken hold. The enclaves are now larger and take longer to fill in. Also, there are now islands of abnormal cells, notwithstanding the fact that the configuration was started with a single abnormal cell.

The right column (Fig. 1) is particularly instructive. Here  $\kappa = 1.1$ , so that for every series of pictures like this, there will be on average ten that ultimately regress. This sequence looks far more invasive than does that of Fig. 1, which has more the appearance of a carcinoma *in situ*. Our model implies that the infiltrating patterns traditionally associated with cancer growth may be as much due to counter-invasion of the abnormal by the normal cells, as to invasion of the normal by the abnormal cells.

## Mathematical Background

In our computer patterns, abnormal cells are often completely surrounded by abnormal cells; if an interior cell divides, an abnormal cell will be pushed out of the basal layer and replaced by another abnormal cell. The configuration in the basal layer will be unaltered, as is the case when a normal cell, entirely surrounded by normal cells, divides. Therefore configuration changes can only occur along the periphery, where abnormal cells exert a thrust of  $\kappa - 1$  against their normal neighbours. Hence, calling  $N$  the total number of abnormal cells and  $n$  the number of peripheral abnormal cells,

$$dN/dt = (\kappa - 1)n \quad (1)$$

One would expect  $n$  to be proportional to  $N^{0.5}$ , but it turns out that the dimension that must be assigned to the periphery is not 1, but roughly 1.1, so that the exponent on  $N$  becomes 0.55 rather than 0.5. We have been unable to evaluate this quantity mathematically, but there can be no question that it is effectively correct, as indicated by graphs of the expected value of  $n$  as a function of  $N$ . It is unusual to find fractional dimension<sup>4,5</sup> arising so naturally in an applied problem. The reason here is apparently that the periphery has an inherent crinkliness, which persists on an absolute scale, while the overall figure is growing in size. What is perhaps more surprising is that the dimensionality of the periphery is independent of  $\kappa$ : for values of  $\kappa$  close to unity, the periphery ought to have been of correspondingly higher dimension. However, an extensive series of realizations, each resulting in a sample of size thirty, indicates that the mean first-passage time to a total of  $N$  abnormal cells is given very accurately by the expression

$$\bar{t} = 1.25 N^{0.45}/(\kappa - 1) \quad (2)$$

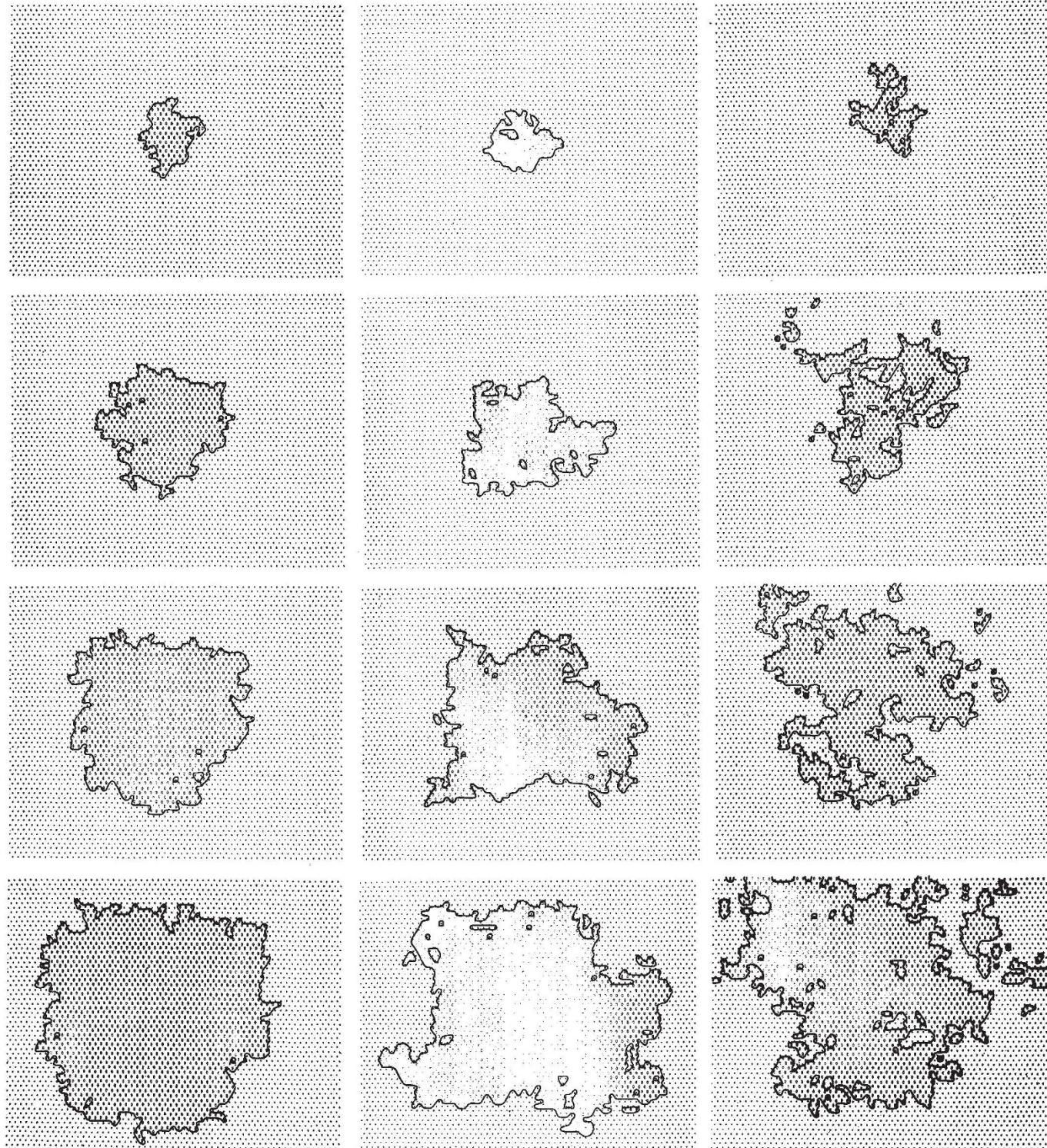
where the time unit is the mean division time for the normal cells. If we take this to be three diameters, which is in accord

with inferential evidence, and assume that  $N=50,000$  results in a clinically manifest growth (measuring some 2 mm in diameter), then with  $\kappa=1.1$  this formula yields a mean induction period of over 13 yr for a tumour beginning from a single cell. Even if we assume that the abnormal cells divide twice as fast as the normal, which seems rather extreme, the induction time is still about 1.33 yr.

There exist two other regular tessellations of the plane: by squares and by triangles. We have also examined the spread of abnormal cells through these configurations and the conclusions remain effectively the same, the only difference between

them being the fact that the abnormal cells push out about 20% slower through the square than through the hexagonal lattice, and some 10% slower through the triangular than through the square. The behaviour is clearly a property of the plane itself, rather than the specific lattice in question.

In our simulations, the basal layer is represented by an  $80 \times 80$  array in the computer memory. To avoid unimportant and tedious boundary effects we have folded the configuration onto a torus, and identified the top, bottom, left and right edges. To render the process Markovian, we have assumed exponential distributions of division times for both normal



**Fig. 1** Configurations of normal and abnormal cells in the basal layer. Abnormal cells, shown as circles, are postulated to divide  $\kappa$  times as fast as normal cells (dots). Cells breed true and, whenever a cell divides, one of the six nearest neighbours, chosen at random, is pushed out so there is room for both daughter cells. The three columns show the configurations when there are, for the first time, 100, 400, 900 and 1,600 abnormal cells. In the left column,  $\kappa=\infty$ ; in the middle,  $\kappa=2$ ; and in the right,  $\kappa=1.1$ .

and abnormal cells. This makes the probability that a normal cell will divide in the time interval  $(t, t + \Delta t)$  equal to  $\Delta t$ , irrespective of the time since its last division. For the abnormal cells, the corresponding probability is  $\kappa\Delta t$ .

The development of the process in time depends solely on the state of the configuration at one given time. All links joining neighbouring normal and abnormal cells are equally likely to "break" in unit time. The normal neighbour is replaced by an abnormal daughter cell with probability  $\kappa/(\kappa + 1)$ ; with a complementary expression for the probability that the abnormal neighbour is replaced by a normal daughter cell. Such a growth process with  $\kappa = \infty$  was considered some years ago by Eden<sup>6</sup>, although he did not have the necessary experimental evidence to recognize it as a possible model for tumour growth. On the strength of limited computer simulations, he made the obvious conjecture that the exponent in equation (2) might be 0.5.

We simulated the process by retaining in the computer memory a list of boundary points and updating this list whenever a change in the configuration took place; adding and deleting as necessary. It was then possible to obtain realizations with  $\kappa$  only slightly greater than unity, which would have been prohibitively time-consuming if we had had to scan the entire array periodically. Solutions of such problems are not strongly dependent on the specific distribution of division times postulated<sup>7</sup>. In particular, the exponent in equation (2) is a consequence of the curious diffuseness of the boundary, which is in no way dependent on the specific distribution assumed.

### Critical Discussion

Although we have supposed the carcinogenic advantage to reside in a higher rate of cellular division than normal, one might (O. H. Iversen, personal communication) equally well postulate, for example, that the advantage lay in a stronger

adherence of the abnormal cells to the basement membrane: the conclusions would not be materially changed. The motility of cancer cells is thought to give cancers their invasive appearance, but our contention is that this is not necessary to account for patterns which seem to us to be more evocative of an evenly balanced contest. The same patterns have been adduced as evidence for a multi-cell origin of tumours. Here again, this is unnecessary, although we certainly do not rule them out. Indeed, to harmonize equation (2) with skin-painting experiments on mice, several hundred initial "hits" must be assumed to reduce the latent periods to a reasonable period. This is certainly not an implausible assumption within the experimental limits.

Our model is non-specific; it does not even distinguish between benign and malignant growths. We have studied the basal layer only and have said nothing about subsequent tumour growth. We envisage that any abnormal growth, even a papilloma, requires a broad and substantial foundation in the basal layer.

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# Infall of Matter in Galaxies

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Arguments based on the existence of intergalactic matter are advanced to show that this matter may interact with and be accreted by galaxies to produce observable consequences. The diversity of the phenomena that results from such processes offers a possible understanding of some of the properties of extragalactic systems.

THE most striking result of surveys of the distribution and motions of neutral hydrogen away from the galactic plane<sup>1-3</sup> is the discovery of several high velocity hydrogen clouds or concentrations, nearly all having negative (approaching) radial velocities of up to about 200 km s<sup>-1</sup>. Oort<sup>4</sup> believes that the clouds represent material of local origin which has left the galactic plane and is being pushed back into it by infalling

intergalactic matter. It seems equally plausible, however, to suppose that we are observing the infalling matter itself, which is initially ionized but recombines into neutral clouds when it is decelerated and compressed by interaction with gas near the galactic plane. Both assumptions lead to similar estimates for the rate of infall of material into the galactic plane. I shall adopt the estimate given by Oort<sup>4</sup>, which is equivalent to a rate of about  $25 M_{\odot}$  pc<sup>-2</sup>/10<sup>10</sup> yr, if the material is 70% hydrogen. If the infall is assumed to occur uniformly over a disk of radius 15 kpc, the total infall rate for our Galaxy is about  $2 M_{\odot}$  yr<sup>-1</sup>.

This accretion rate requires a fairly high density of intergalactic material outside our Galaxy. There is no conclusive evidence for the existence of intergalactic matter, but several observations suggest its presence. X-ray observations<sup>5</sup> are consistent with an intergalactic medium having a temperature of about  $2-3 \times 10^6$  K and a density of the order of  $10^{-29}$  g cm<sup>-3</sup>. The spectra of distant quasars often show numerous absorption lines which, according to Silk<sup>6</sup>, can be produced by relatively cool intergalactic clouds with temperatures between  $2 \times 10^4$  and  $10^5$  K. There has also been speculation that the "missing