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2. Electrophoretic results were obtained by vertical starch-gel electrophoresis in 12 to 13 percent Connaught hydrolyzed starch; the following electrode and gel buffers were used. For PHI and XDH, the electrode buffer consisted of 0.5*M* tris, 0.5*M* H_3BO_3, 0.016*M* EDTA, *p*H 8.0; and the gel buffer consisted of a 1 : 4 dilution of the electrode buffer with distilled water. For PGM and IDH, the electrode buffer consisted of 0.1*M* tris, 0.1*M* maleic anhydride, 0.0084*M* EDTA, 0.01*M* $MgCl_2 \cdot 6H_2O$, and sufficient NaOH (~ 0.124*M*) to bring the *p*H to 7.45; and the gel buffer consisted of a 1 : 9 dilution of the electrode buffer with distilled water. This buffer system was also used for PHI, and gave better resolution of species I and Ia PHI, and species III and IIIa PHI. For MDH and α-GPDH, the electrode buffer was 0.223*M* tris, 0.086*M* citric acid, and sufficient NaOH (~ 0.028*M*) to bring the *p*H to 6.45; and the gel buffer was 0.016*M* tris, 0.0104*M* citric acid, and sufficient NaOH (~ 0.002*M*) to bring the *p*H to 6.85. Individual worms with their guts cleared were homogenized in an extractant containing 0.01*M* tris, 0.0072*M* HCl, 0.001*M* EDTA, $5 \times 10^{-5}M$ NADP, 0.25*M* sucrose, *p*H 7.3. Staining mixtures were as follows: for PHI, 100 ml of 0.05*M* tris-HCl buffer, *p*H 8.0, 4.0 ml of 0.12*M* $MgCl_2 \cdot 6H_2O$, 40 mg of MTT tetrazolium, 100 mg of D-fructose 6-phosphate, 30 mg of NADP, 10 mg of phenazine methosulfate (PMS), and 50 units of glucose-6-phosphate dehydrogenase (Sigma type XI); for XDH, 100 ml of 0.1*M* tris-HCl, *p*H 8.0, 2 ml of 0.12*M* $MgCl_2 \cdot 6H_2O$, 100 mg of hypoxanthine, 30 mg of nitro blue tetrazolium, 10 mg of MTT tetrazolium, 50 mg of NAD, 5 mg of PMS; PGM, 100 ml of 0.05*M* tris-HCl, *p*H 8.0, 5 ml of 0.12*M* $MgCl_2 \cdot 6H_2O$, 150 mg of α-D-glucose 1-phosphate, 10 mg of MTT tetrazolium, 10 mg of NADP, 4 mg of PMS, 50 units of glucose-6-phosphate dehydrogenase (Sigma type XI); IDH, 100 ml of 0.1*M* tris-HCl, *p*H 7.0, 1 ml of 0.12*M* $MgCl_2 \cdot 6H_2O$, 125 mg of trisodium isocitrate, 30 mg of nitro blue tetrazolium, 30 mg of NADP, and 2 mg of PMS; MDH, 4.02 g of L-malic acid, 0.758 g of tris, 162 ml of distilled water, sufficient 4.0*M* NaOH to bring the *p*H to 7.05 (~ 14.0 ml), 48 mg of KCN, 75 mg of NAD, 50 mg of tetra nitro blue tetrazolium, and 5 mg of PMS; for α-GPDH, 100 ml of 0.05*M* tris-HCl buffer, *p*H 8.5, 180 mg of EDTA, 20 mg of nitro blue tetrazolium, 30 mg of NAD, 800 mg of DL-α-glycerophosphate (disodium salt), and 5 mg of PMS; the PMS is added after the gel has been staining for 90 minutes in the dark.

3. The mobilities of the most common PHI alleles (relative to 1.0 for PHI species I fast homozygote), and the numbers of alleles (parentheses) are: species I, 1.0 (2); species Ia, 1.04 (2); species II, 0.60 (1); species IIa, 0.77 (1); species III, 0.36 (2); species IIIa, 0.34 (2). The range of mobilities for the XDH alleles for each species, and the number of alleles (parentheses) are: species I, 1.05 to 1.31 (11); species Ia, 0.87 to 1.07 (6); species II, 0.89 to 1.14 (8); species IIa, 0.54 to 0.61 (4); species III, 1.33 to 1.60 (9); species IIIa, 0.97 to 1.13 (7). It is apparent that the XDH alleles for species I, species IIa, and species III are unique, while the mobilities of the XDH alleles in species Ia, II, and IIIa show considerable overlap. However, within each species XDH heterozygotes are only found between alleles with similar mobilities. If XDH alleles do not assort independently within each species as we have defined them, then the identity of XDH with similar mobilities between species seems doubtful. Species III shows a complete lack of PGM and IDH activity (at both loci). The mobilities of the most common PGM alleles (relative to PGM species I fast band) and the number of alleles (parentheses) in the other five species are: species I, 1.0 (1); species Ia, 1.0 (1); species II, 0.57 (1); species IIa, 0.67 (1); species IIIa, 0.50 (3). The mobilities of the most common IDH-1 alleles (relative to PGM I fast band) and the number of alleles are: species I, 1.14 (1); species Ia, 1.07 (2); species II, 1.09 (2); species IIa, 1.13 (1); species IIIa, 0.90 (1). The mobilities of the most common IDH-2 alleles (relative to PGM I fast band) and the number of alleles are: species I, 0.96 (3); species II, 0.79 (2); species IIa, 1.01 (1); species IIIa, 0.44 (2). The mobilities of the most common MDH-1 alleles (relative to MDH-1 species I) and the number of alleles are: species I, 1.0 (1); species Ia, 1.01 (1); species II, 1.02 (1); species IIa, 1.02 (2); species III, 1.04 (1); species IIIa, 0.71 (1). The mobilities of the most common MDH-2 alleles (relative to MDH-1 species I) and the number of alleles are: species I, 0.72 (2); species Ia, 0.71 (2); species II, 0.59 (2); species IIa, 0.61 (2); species III, 0.59 (2); species IIIa, 0.29 (2). The mobilities of the most common α-GPDH alleles are: species I, 1.12 (1); species Ia, 1.09 (1); species II, 1.06 (1); species IIa, 1.02 (1); species III, 0.67 (1); species IIIa, 0.88 (1). These mobilities are repeatable and consistent and have been determined for at least several hundred individuals, except as noted for species IIa in (*15*).

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16. The egg number per brood is highly dependent on the amount of food available. For each species, the low end of the quoted range represents counts from laboratory individuals in cultures where food was not abundant. The high end of the range for each species is representative of field-caught animals.
17. Supported by NSF grants GA 35393 and GA 40144. Contribution 3447 from the Woods Hole Oceanographic Institution. We thank J. Ashmore A. White for technical assistance.

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Models of Carcinogenesis as an Escape from Mitotic Inhibitors

Abstract. *Diffusible mitotic inhibitors are assumed to govern proliferation of normal cells. Cancer cells may escape regulation by failing to either recognize or secrete inhibitors. In the latter case, probabilities and expected times for reaching a critical clone size are given. Patterns of proliferation will depend on whether the inhibitor concentration is locally or systemically determined.*

In an adult animal, many tissues, such as skin, liver, or bone marrow, can respond to unusual loss of cells by increased cellular proliferation, which restores the tissue to normal size. Mechanisms that inhibit such proliferation in normal tissue, yet permit it in wounded tissue, are not well understood, but may include mediation by mitotic inhibitors (*1–3*) which are secreted by cells of the affected tissue. Such factors have been called "chalones" (*4*) but have not been isolated in pure form.

It has been suggested (*3, 5, 6*) that these factors are homeostatic mechanisms that serve to regulate proliferation of cells in normal tissues and that cancer cells have somehow escaped these normal control mechanisms. In this report we suggest that in a simple model of mitotic inhibition by diffusible factors, the competition between normal and cancer cells will strongly depend on the type of tissue involved and on the mechanism whereby the cancer cells escape regulation.

To make the arguments clear, let us adopt a simple model of inhibitor action. Assume that some or all cells in a tissue secrete inhibitor molecules and that (possibly other) cells in the tissue recognize the inhibitor concentration in their vicinity such that a high concentration will reversibly inhibit mitosis. A central question is what determines the inhibitor concentration near the responsive cells. In a tissue such as skin, inhibitors must be largely distributed by diffusion so that the local concentration will be determined by the nearby source (number of nearby secreting cells), by the diffusion properties and geometry of the tissue, and by the lifetime of the molecules against metabolic degradation or loss to the circulatory system. Such a tissue could respond to a local loss of secreting cells by local proliferation so that such a mechanism could regulate the local thickness of skin (*7*). Simple mathematical models (*8–10*) have confirmed this behavior. We shall say that in such tissues the control is local or diffusive.

Rather different considerations must determine the inhibitor concentration in such organs as the liver (*11*) or bone marrow (*12*), where cells throughout the tissue respond with increased proliferation to any substantial loss of tissue cells. In such tissues we assume that inhibitor molecules circulate throughout the body and that their concentration is more or less uniform in the tissue, being largely determined by their source strength (number of secreting cells in the whole tissue) and by their lifetime against metabolism and excretion. In such a tissue, we shall say that control is systemic. Simple mathematical models

Table 1. Effects of mutant cells with altered inhibitor recognition, secretion, or metabolism are shown for tissues subject to local or systemic regulation of mitosis.

Properties of mutant			Effects in tissue	
Recognition	Secretion	Metabolism	With local, diffusion control	With systemic control
Reduced	Normal	Normal	Mutant cells will proliferate. Compact mass of mutant cells must induce vascularization to grow larger than ≈ 1 mm.	Mutant cells will proliferate. Normal cells inhibited by high inhibitor concentrations.
Reduced	Reduced	Normal	As above. Possible hyperplasia of adjacent normal cells.	Mutant cells will proliferate. Hyperplasia of normal cells likely as mutant cells displace normal ones, lowering inhibitor concentrations.
Normal	Reduced	Normal	No selective advantage of isolated mutant, but if, by chance, a large clone develops, mutant cells therein will find a lower inhibitor concentration and proliferate. Critical clone size, long latency. Vascularization barrier remains. Possible hyperplasia of adjacent normal cells.	No selective advantage of mutants and no tendency to proliferate.
Normal	Normal	Increased	As above.	As above.

of systemic control have also been constructed (*5, 13*).

No doubt the model described above is oversimplified. It neglects heterogeneity of cells in a tissue and a plethora of positive growth control factors, which are under study (*3, 14*). In addition, in many tissues it is likely that both local and systemic controls are operative. Nevertheless we suggest that the model, with a distinction between diffusive and systemic control, is useful for clarifying concepts.

Suppose a nascent cancer cell arises in a tissue which is under regulation by a diffusible mitotic inhibitor. How might it escape regulation? The simplest possibility is that the mutant cell, as we shall designate it, fails to recognize the inhibitor. For example, the mutant cell might have altered receptors for binding inhibitor molecules or might fail to respond to such binding. However, there are other possibilities. In particular, the mutant cell might fail to secrete the inhibitor or it might metabolize the inhibitor with abnormal rapidity. In these cases, we will also see that it is sometimes possible for the mutant cells to escape regulation. In addition, combinations of abnormal recognition, secretion, and metabolism may be considered. Results of the following discussion are summarized in Table 1.

Consider first a mutant cell which is not mitotically inhibited by normal concentrations of inhibitor. In a regulated tissue it would have an immediate selective advantage and begin to proliferate. If the mutant cells secrete inhibitor normally, then the concentration in the tissue will not be affected by proliferation of mutant cells, so that the mutants can continue to proliferate while the normal cells remain regulated. If the proliferating cells remain as a compact, unvascularized cell mass, net growth will be arrested when the cell mass reaches such a radius (≈ 1 mm) that the diffusion of nutrients and oxygen is unable to sustain proliferation in the interior of the cell mass (*15*). Further growth may then require that cells produce new factors, such as tumor angiogenesis factor (*15*) or plasminogen activating factor (*16*), which lead to vascularization of the cell mass or otherwise promote nourishment of the mutant cells. If the mutant cells do not remain as a compact mass, they may not need to elaborate such factors in order to proliferate indefinitely.

In a tissue subject to systemic control it is important whether or not mutants that fail to recognize inhibitor continue to secrete inhibitor molecules. As the mutant cells proliferate, it is likely that normal cells will begin to suffer because of nutritional deprivation, crowding, or other reasons, and if the mutants do not secrete inhibitor, or secrete at reduced rates, then the overall rate of secretion will fall. Therefore the concentration of inhibitor will fall and the normal cells will begin to proliferate. Under these conditions there will be competition between the normal and mutant cells in which the outcome is uncertain, since the mutant cells have no decisive mechanism for shutting off normal cells. If the mutant cells do not metastasize to other tissues, the result could be chronic hyperplasia of both normal and mutant cells. If, however, the mutant cells continue to secrete inhibitor, they could continue to expand at the expense of the normal cells until the normal cells were largely eliminated, with perhaps lethal consequences.

For acute myeloblastic leukemia, a model has been developed (*17, 18*) in which mutant cells are effectively assumed to secrete inhibitors at a normal rate. In lymphoid cell lines that have been examined, some appear to secrete inhibitors (*19*) while others do not (*20*). Evidence has been presented (*21*) that chloroleukemia in rats can be arrested by exposure to a granulocyte chalone, and it has been suggested (*22*) that multiple myeloma cells secrete a lymphocyte chalone which inhibits normal levels of antibody production. It would be interesting if the clinical severity of leukemias could be correlated with inhibitor secretion of the mutant clone. Data concerning such a correlation would be of great value for testing this model.

Since mutant cells that fail to recognize inhibitors pose such a severe threat to an animal, there may be special defense mechanisms against such cells. For example, cells that do not bind inhibitors may be favored targets for immunological surveillance. Alternatively, an ability to bind inhibitors may be closely coupled with an ability to respond to growth-stimulating factors (*23*). In any case it is of interest to consider other mechanisms for escape from inhibitor regulation.

Consider a mutant cell that recognizes inhibitor concentrations normally, but fails to secrete the molecules. The single mutant cell will find itself in tissue with normal concentrations of inhibitor and hence have no appreciable advantage over normal cells. Suppose, however, that by chance the cell grows into a clone of significant size. In a tissue with diffusive control, the inhibitor concentration inside the mutant clone will become depressed. (We assume that the inhibitor is metabolized by mutant cells at a normal and appreciable rate.) The mutant cells will then enjoy a selective advantage over normals, although they will still

face the vascularization barrier noted earlier.

In order to estimate the probability and time for a single cell to become by chance a macroscopic clone, consider a birth and death process in which each cell has probability p of dividing to produce two identical new cells and probability $(1 - p)$ of dying or of becoming irreversibly committed to a nondividing state. For normal cells in a tissue that is not undergoing net growth, $p = ½$. The probability, $P(N)$, that a single cell ever becomes a clone of N proliferating cells is then found as the solution of a "gambler's ruin" problem (*24*)

$$P(N) = \frac{[(1 - p)/p] - 1}{[(1 - p)/p]^N - 1} \quad (1)$$

This probability is shown in Fig. 1a, where we see that (i) for $p > ½$, the probability of exceeding N cells is nearly independent of N, being given by $(2p - 1)/p$, (ii) for $p < ½$, probabilities are exceedingly small unless $N \lesssim 10^3$, and (iii) in the region of selective neutrality, $p \simeq ½$, a wide range of probabilities is found depending on the precise values of p and N.

The expected time to first reach N may be estimated (*24*, p. 480) by letting the proliferation continue beyond N. The probability of having N cells present $(N > 1)$ will start from zero at time zero and will increase and go through a maximum as time increases. Letting $T(N)$ denote the time of this maximum, measured in cell cycle times, we find

$$T(N) = \frac{1}{|2p - 1|} \ln \left\{ \frac{N + [N^2 + 4s(s - 1)]^{1/2}}{2s} \right\} \quad (2)$$

where $s = p/(2p - 1)$ for $p > ½$ and $s = (1 - p)/|2p - 1|$ for $p < ½$. We shall use this time as an estimate of the time to first reach N (*25*). The time $T(N)$ is shown in Fig. 1b, where it is apparent that very long times are to be expected for $p \simeq ½$ and $N > 10^3$.

What evidence can be cited for the failure of inhibitor secretion to be associated with malignancy? First, a few malignant cell lines have been reported (*20, 26*) to be deficient in inhibitor content, but inhibited by diffusible factors from normal cells. Second, tumor cells often fail to propagate when injected, even in large numbers, intravenously or intraperitoneally as circulating individual cells, but do propagate when injected as a localized cell mass, with much smaller total cell numbers (*27*). This could be because the injected cells require a conditioned environment, such as one in which they have been able to reduce local inhibitor concentrations to below normal values. In addition, in the two-stage model of chemical carcinogenesis of the skin (*28*), it is possible that the action of the "promoter" is simply to expand the mutant clone to a critical size. Finally, it is tempting to acribe the very long delay times (~ 20 years) (*29*) that are typically observed between radiation and the resulting clinical solid cancers to the long times, $T(N)$, required to produce a critical clone size. Of course, a critical clone size does not necessarily demonstrate the importance of mitotic inhibitors. It could equally well be explained by a secretion by the mutant cells of positive, growth-stimulating factors, which must accumulate to some critical concentration before they are effective.

Estimates of the number of cells, N, in a critical clone may be made in a number of ways. One could estimate the distance over which the inhibitor molecules might diffuse in some reasonable amount of time, say a few hours. For inhibitors of

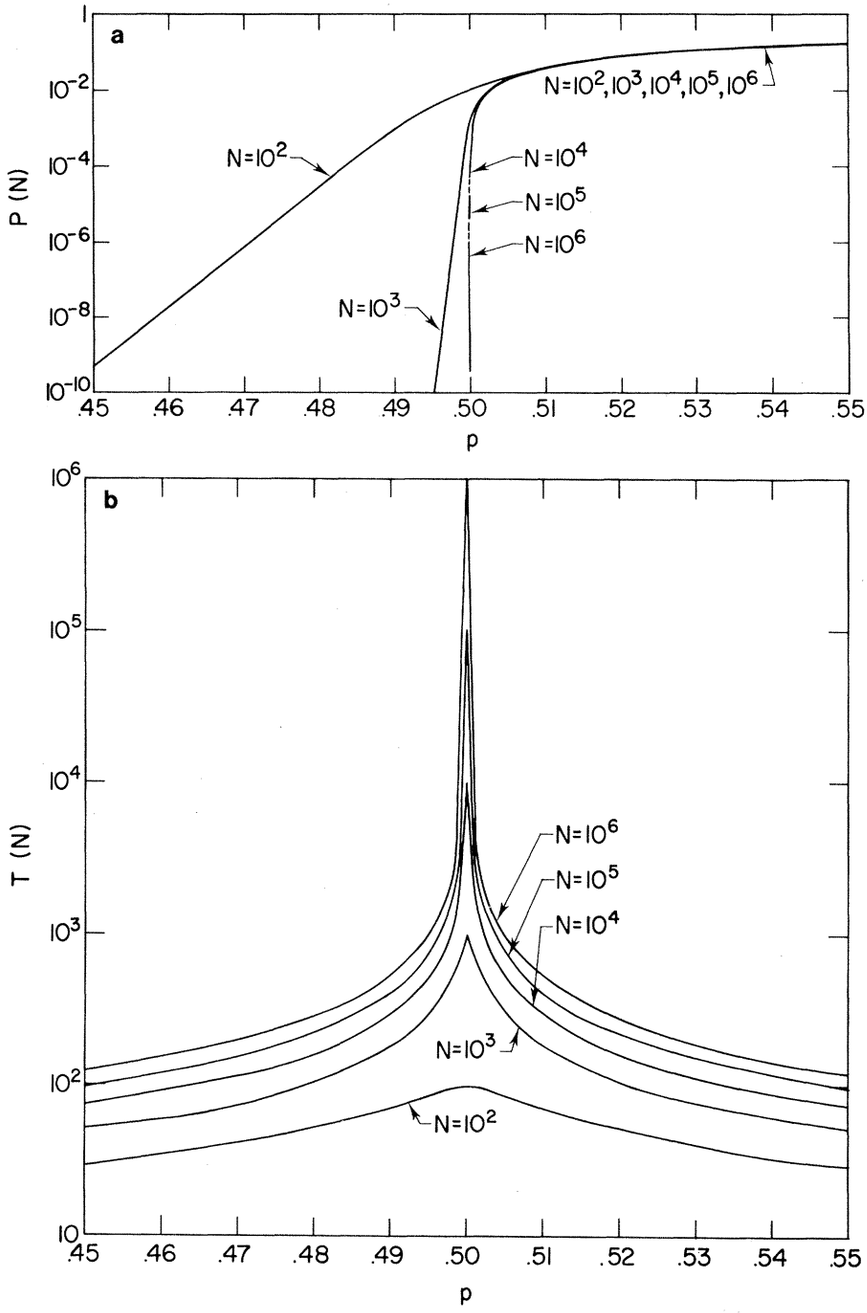

Fig. 1. (a) Probability for a clone to reach N cells for the simple birth and death process in which p is the probability of mitosis and $1 - p$ is the probability of death. For $p = ½$, $P(N) = 1/N$. (b) Expected time (approximate) for a clone to reach N cells in the simple birth and death process. Time is measured in cell cycle times. For $p = ½$, $T(N) = N - 1$.

low molecular weight [~ 2000 daltons (*2*)], the considerations would be much the same as for diffusion of morphogens in embryogenesis, in which case distances $\lesssim$ 100 cell diameters have been estimated (*30*). A clone spanning such a distance would have $N \leq 10^6$ cells. An alternative approach is through data on the number of tumor cells required for localized cancer induction with high probability. Numbers of cells between 10^4 and 10^6 are frequently used (*27*). We conclude that N may be in the range 10^3 to 10^6 cells.

An increased rate of inhibitor metabolism by mutant cells would also lead to a locally reduced inhibitor concentration, so that, at least qualitatively, the effects would be similar to reduced secretion and need not be separately considered.

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Sex Differences in Cognition: A Function of Maturation Rate?

Abstract. *Regardless of sex, early maturing adolescents performed better on tests of verbal than spatial abilities, the late maturing ones showed the opposite pattern. Those maturing late were more lateralized for speech than those maturing early. Sex differences in mental abilities, it is argued, reflect differences in the organization of cortical function that are related to differential rates of physical maturation.*

Discussions about the origins of sex differences in behavior have usually focused on obvious dichotomies, such as nature versus nurture and male versus female. However, the sexes can also be arrayed along continuous biological dimensions. Examining data from this point of view might yield more information about the mechanisms of sex differences than do dichotomous comparisons of male and female.

One such dimension is maturational rate; females generally attain physical maturity at an earlier age than males (*1*, *2*). Therefore, I hypothesized that this biological variable would be systematically related to mental abilities for which sex differences have been repeatedly demonstrated: (i) verbal ability (fluency, articulation, and perceptual speed), at which females have been reported to excel, and (ii) spatial ability, at which males have been reported to excel (*3*).

Several authors have proposed relationships between verbal and spatial ability and the organization of higher cortical functions. Buffery and Gray (*4*) have argued that earlier and stronger lateralization of language in females facilitates verbal ability and that bilateral representation of space in males facilitates spatial ability. Alternatively, Levy (*5*) has postulated that intraindividual differences between these abilities reflect differences in the degree of specialization of language in the left cerebral hemisphere. That is, bilateral mediation of language increases the probability that language will interfere with spatial processing, which is presumed to be the province of the right hemisphere. Recent data indicating that speech is more lateralized among adult males than females (*6*) are consistent with the Levy hypothesis (*5*).

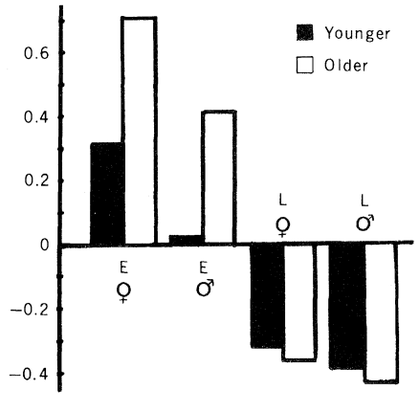

Fig. 1. Mean values of difference scores for each grouping of sex, maturation, and age level. Positive values indicate that the verbal score is greater than the spatial score, and negative values indicate that the spatial score is greater than the verbal score.

In this study, both verbal and spatial performance and lateralization of linguistic processing were examined in relation to sex and maturational rate. Two hypotheses were tested. Along a continuum of rate of maturation, and regardless of sex, (i) so-called early maturers perform better at verbal than spatial ability, and so-called late maturers perform better at spatial than verbal ability; and (ii) early maturers are less lateralized for speech perception than late maturers. The results of the study support these two hypotheses.

A sample of early and late maturing adolescents was selected at two age levels, which were chosen to maximize the observable physical variability and so differed for boys and girls. Girls 10 and 13 years old and boys 13 and 16 years old from a middle-class Caucasian population were examined medically and rated according to the Tanner criteria for staging secondary sexual characteristics, which are a good indicator of general