tainly be surprising if it were discovered that there is no common basis to the various control mechanisms of the various tissues. Mitosis itself is such a uniform process wherever it is found that the pattern of its control may be equally uniform, although, of course, it may be expected that each tissue will show its own specific variation within that pattern.

In the cycle of cell-growth and mitosis there is one period of outstanding interest and importance, and it is unfortunately the one about which least is known. This is the period here defined as the dichophase, the phase of unknown duration within which the decision is reached whether the cell's synthetic machinery shall be directed towards differentiation or towards preparations for yet another division.

The only slight information that can be deduced about the dichophase and about differentiation itself comes from the results of experiments on wounding and on 'compensatory hypertrophy'. In such experiments cells which have previously committed themselves to differentiate are seen to reverse this decision and to prepare once more for mitosis. The impression is gained that most cells that are not so highly differentiated that they can never again divide are in fact normally held in the differentiated state by some factor which, when it is withdrawn, releases the cells to revert back through the dichophase to their basic activities of growth and mitosis. After wounding and in 'compensatory hypertrophy' such a withdrawal is only temporary, and there is some evidence to support a hypothesis that the factor withdrawn may in fact be the chalone which is specific to the tissue in question[5,15,19]. On this argument the chalone may prove to be a basic part of the mechanisms both of differentiation and of mitosis inhibition, if indeed these mechanisms can be separated. Also on this argument differentiation may be regarded as an unstable state.

It may be noted incidentally that some indication of the speed with which a differentiated cell can return to the dichophase has been recorded for rabbit lens epithelium by Harding and Srinivasan[22], who have found that thymidine-incorporating cells first appear in the vicinity of a wound about 14 h after injury. This period may be roughly similar to that in epidermis, but other tissues, such as mouse hypodermis and mouse ear cartilage[7], probably take much longer. Whether such information gives any indication of the time normally taken to pass in the reverse direction from dichophase to the fully differentiated condition is, of course, debatable.

In a tumour, the undifferentiated condition shown by the cells is permanent. Theoretically this sort of change might occur in several ways: on the chalone hypothesis it could be due either to a failure to produce sufficient chalone or to a failure to react to what chalone is present. In either case, the failure might be one of degree only: the more complete it is, the more cells might be expected to dedifferentiate, the higher might be the mitotic rate, and the shorter might be the various phases of the cycle of cell growth and mitosis.

However, until a much clearer understanding has been obtained in normal mammalian tissues of the manner of control of the various cycle phases, of the factors that determine the choice made in the dichophase, and of the manner in which a differentiated cell is maintained in that condition, it is of little value to speculate on the conditions that may exist within cells that have suffered a pathological change.

Note added in proof. Since this article was written an important discovery has been reported by Pilgrim, Erb and Maurer (following article, p. 863). They have provided the first indication that in certain tissues not only may there be a diurnal rhythm in the number of cells in mitosis but also a similar rhythm in the number of cells in the phase of DNA synthesis. However, the available evidence is against their conclusion that the diurnal mitotic rhythm may be the delayed consequence of the diurnal rhythm in DNA synthesis. It appears more probable that there may exist two highly sensitive points in the mitotic cycle, the first during the transition from dichophase to prosphase (or to DNA synthesis) and the second during the transition from antephase to mitosis. It is now extremely important to discover whether both these points are sensitive to the inhibitory action of the same mitotic control mechanism.

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[1] Defendi, V., and Manson, L. A., *Nature*, **198**, 359 (1963).
[2] Gelfant, S., *Exp. Cell Res.*, **26**, 395 (1962).
[3] Leblond, C. P., and Walker, B. E., *Physiol. Rev.*, **36**, 254 (1956).
[4] Bertalanffy, F. D., and Lau, C., *Intern. Rev. Cytol.*, **13**, 357 (1962).
[5] Bullough, W. S., and Laurence, E. B., *Symp. Zool. Soc. Lond.*, **12** (in the press).
[6] Bullough, W. S., *Biol. Rev.*, **27**, 133 (1952).
[7] Bullough, W. S., and Laurence, E. B. (unpublished).
[8] Lesher, S., Fry, R. J. M., and Kohn, H. I., *Exp. Cell. Res.*, **24**, 334 (1961).
[9] Cattaneo, S. M., Quastler, H., and Sherman, F. G., *Nature*, **190**, 923 (1961).
[10] Fry, R. J. M., Lesher, S., and Kohn, H. I., *Nature*, **191**, 290 (1961).
[11] Fry, R. J. M., Lesher, S., and Kohn, H. I., *Exp. Cell Res.*, **25**, 469 (1961).
[12] Sherman, F. G., Quastler, H., and Wimber, D. R., *Exp. Cell Res.*, **25**, 114 (1961).
[13] Bullough, W. S., and Laurence, E. B., *Proc. Roy. Soc.*, B, **154**, 540 (1961).
[14] Bullough, W. S., and Laurence, E. B., *The Biology of Hair Growth*, edit. by Montagna, W., and Ellis, R. A., Chap. 8 (Academic Press, New York).
[15] Bullough, W. S., *Biol. Rev.*, **37**, 307 (1962).
[16] Bullough, W. S., and Laurence, E. B., *Exp. Cell Res.*, **21**, 394 (1960).
[17] Bullough, W. S., and Laurence, E. B., *Exp. Cell Res.* (in the press).
[18] Gelfant, S., *Exp. Cell Res.*, **16**, 527 (1959).
[19] Bullough, W. S., and Laurence, E. B., *Proc. Roy. Soc.*, B, **151**, 517 (1960).
[20] Bertalanffy, F. D., *Nature*, **198**, 496 (1963).
[21] Voutilainen, A., *Acta Path. Microbiol. Scand.*, supp. IX *C* (1953).
[22] Harding, C. V., and Srinivasan, B. D., *Exp. Cell Res.*, **25**, 326 (1961).

Without making detailed comments on Prof. Bullough's communication, or on the very general scheme he proposes, we would like to rectify some of his statements presented in reference to our own communications.

(1) Prof. Bullough's statement in the initial paragraph is incorrect in minimizing the basis of our conclusions since, in addition to four tumour cell lines, we have tested three strains of human diploid cells which, by any criteria we can consider, are neither "aberrant" nor "pathological".

(2) While, of course, little is known about all the various factors involved in the preparation for mitosis of tumour and normal cells, it is still true that the wealth of information which has been collected during the past few years concerning the periodicity and length of DNA synthesis certainly permits some general statement.

(3) It is quite true that the *primum movens* of cell division must occur before, and not at the time of, initiation of DNA synthesis. The time of action and the nature of this *movens*, notwithstanding the elegant names and speculations of Prof. Bullough, are still completely unknown. Since we were concerned with what we were able to determine and measure, we chose the occurrence of certain biological events leading to the beginning of DNA synthesis as the time at which the decision to enter replication is irrevocably taken by a cell under normal conditions.

(4) Our communication was not intended to be a review, and the results in the table were selected with that in mind. Since results in numerous other publications dealing also with 'long generation time' cells have not contradicted our hypothesis, it seemed useless to list a long series of references. The case of the mouse skin was purposely omitted since there are conflicting reports on this 'complex situation' which cannot be resolved at the present time without the further work of interested workers.

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