tion, and I did *not* contend that it is "legitimate in biology." I did not use it at all in this connection. The pertinent question, and the one I did use, is "What for?"—that is, what useful function is related to the characteristics under study? Such functions and their usefulness to the organism can be directly observed and tested. In this context it is thus sensible and fully scientific to say, for example, that green leaves are for photosynthesis, and in this formulation classical teleology is not involved at all.

The comment by Portz helpfully adds to but does not contradict what I wrote. In an attempt to cover so much in one essay, it obviously was not practical to characterize the whole Greek contribution. Singling out Platonic idealism and Aristotelian teleology as having had a major impact on the subsequent history of philosophy and science follows much historical authority superior to my own. Surely we all agree with Portz that not all ancient Greeks were Platonists and that Aristotle had solid accomplishments not directly related to his views on teleology.

I would prefer a somewhat different form of expression, but I find myself in agreement with much in Sinnott's comments. In his present letter, however, he of course has not covered all the ground traversed in long earlier studies, notably in his thoughtful and beautifully written books *Two Roads to Truth* (1953) and *The Biology of the Spirit* (1955). (Incidentally, I have not been frightened away by the word "purpose" and have carefully studied those and other works by Sinnott.) In them he did plainly express the opinion that the apparent purposefulness of organisms has not been adequately explained by science and that another approach, involving religion, is likewise necessary. The statement in his present letter that differences of opinion in this respect are not biological matters reflects just the point I was making when I mentioned him as a scientist who has gone outside the field of science in seeking explanations of some phenomena.

D'Arcy Thompson's forebodings, cited by Wharton, have not proved to be justified. When Thompson wrote *On Growth and Form* (first published in 1917) the explanatory theory of adaptation in its current form did not yet exist. It was just beginning to be clear when he revised that book, but he was completely unfamiliar with it. (The revision was published in 1942, Thompson's 83rd year; the date 1952 cited by Wharton is perhaps that of a reprint.) All of us who knew him hold D'Arcy Thompson's memory dear and enjoy and admire his great book, but he was not a student of, or even interested in, 20th century evolutionary theory. It has certainly neither arrested nor prejudiced discovery—quite the contrary!

Wharton's suggestion that I should have adopted a simple definition of science is puzzling. His own definition is both longer and more technical than the one I gave. Moreover, it virtually excludes biology, as such, from the field of science. It thus illustrates one of my points: the tendency of some biologists to abrogate their own field in favor of physical science.

The relevance of Wharton's remarks on Harvard is still more puzzling. The populous biological community here has special provisions of one sort or another for instruction and research on such diverse subjects as electron microscopy and orchids, to name only two. Yet we do generally manage a fair degree of integration and cooperation. That we can provide some support for graduate study in evolutionary biology, as well as in almost all other aspects of the life sciences, surely should be cause for congratulation rather than alarm. I do not have the slightest idea what "the primrose path of dualism" may be, or what it has to do with any of this, and so cannot speak to that subject.

Finally, I must express regrets that I have not been able to fill all of the requests for reprints of my article.

G. G. SIMPSON
Museum of Comparative Zoology,
Harvard University,
Cambridge, Massachusetts

Choice of a Cell System for Vaccine Production

The paper on "Continuously cultured tissue cells and viral vaccines" [*Science* **139**, 15 (4 Jan. 1963)] is open to several criticisms. The statement, ". . . continuously cultured cells eventually develop characteristics suggestive of malignant change" is particularly debatable.

This statement recurs frequently in the committee report and may well apply to cultured mouse cells (*1*) but its antithesis has been demonstrated for human cells in these and in other laboratories (*2, 3*). Alterations in vitro to heteroploidy may or may not be associated with malignancy but human cell strains are readily available which have not altered. The use of such unaltered human diploid strains would entirely circumvent this problem.

For human cells grown in vitro to develop ". . . characteristics suggestive of malignant change" (alteration) is a rare and fortuitous event. Almost all cell populations cultivated in vitro from primary tissue terminate within periods of time varying from a few days to about 12 months. Of the perhaps thousands of opportunities to detect alterations in normal human cells in the last 15 years, only 50 successes have been reported (*4*). To our knowledge, no indefinitely cultivable cell population exists which lacks aberrations in chromosome number or form. Until the work on morphologic and karyologic alteration by viruses (*5*) and its recent extension to human cells (*6*), no one had reported conditions under which diploid (unaltered) cell populations could be *reproducibly* altered in vitro to heteroploid cells. For this reason the finding that oncogenic viruses such as polyoma and SV_{40} are capable of reproducibly altering normal diploid cell populations has proved to be a significant development in the field of viral oncogenesis. The aforementioned statement ". . . continuously cultured cells eventually develop characteristics suggestive of malignant change" implies the inevitability of malignant change. If alteration were a certainty, then the demonstration of these viral-induced alterations would be trivial. Thus, the fundamental distinction between the two kinds of in vitro cell populations (unaltered and diploid vs. altered and heteroploid) has been largely ignored (*3*). This is evident in the report when the three types of cell cultures to be considered are defined. Human diploid cell populations which, in our opinion, have the greatest potential for use in human virus vaccine production (*7*) would, by those definitions, be excluded.

When human diploid cell strains *are* considered in the report, the criticisms of their use for human virus vaccine production are, with one exception, without foundation. In referring to the human diploid cells the report states that ". . . the resultant cell populations are heterogeneous, which means that

they are not precisely characterized genetically or otherwise and may be subject to random fluctuations in properties." The cells composing a human cell strain have the karyotype of the tissue of origin (*2*, *3*). How could human cells be shown to be more "precisely characterized genetically" than to demonstrate that, with the exception of the same small percentage of cells shown to be tetraploid in vivo and in vitro, all of the cultured cells examined have 46 chromosomes?

We do not imply that chromosomal uniformity means that each cell in a human diploid cell population or any cell population is identical biochemically with each of its sister cells. If this were considered to be such a strong objection, then the technique of cloning proposed in the report as an advantage to circumvent such a criticism of the heteroploid cell lines derived from normal tissue could just as well be used for the human diploid cell strains. It has been demonstrated that the human diploid cell strains can be cloned (*2*, *3*). Moreover, what advantage would there be to clone what is referred to in the report as "stabilized cell lines" (heteroploid cell lines)? Published studies (*8*, *9*) have shown that cloning of heteroploid cells is limited by the rapid reemergence of a range of chromosomal types among the progeny of the cloned cell. Clearly then, "stabilized" is one word that, if used at all in discussions of in vitro cell populations, should be more aptly descriptive of a diploid cell population than of a heteroploid cell line. Furthermore, the report's use of the terms "mixed" or "heterogeneous" for human diploid cell strains is more properly applicable as a criticism of use of the heteroploid cell lines since numerous publications have shown that heteroploid populations are (i) "heterogeneous" (ii) "not precisely characterized genetically" and (iii) "subject to random fluctuations in properties."

It is somewhat puzzling that the report defines a "stabilized cell line" to be ". . . the progeny of cells from as nearly a homogeneous tissue source as possible, e.g., from a single individual and from one organ of that individual, descended asexually in artificial culture media long enough to achieve reasonable stability in desired selected characteristics." The existent human diploid cell strains (*3*, *7*, *10*) were derived from tissue defined exactly as for the source of the "stabilized cell lines." The "stabilized cell lines" do not "achieve reasonable stability" since their chromosome number per cell is widely variable while the diploid human cells contain 46 chromosomes. In fact, biochemical and morphological variants can be selected as sublines from so-called "stabilized cell lines" (*8*, *11*). Even virus susceptibility has been demonstrated to vary within such populations (*12*).

The committee also points out that any candidate cell shall be tested for "oncogenicity when transplanted into suitable hosts." On the one hand they indicate that this should be one "criterion for control" and on the other hand, that ". . . as a rule in rapidly growing long-term cultures even cells originating in normal tissue become capable, when transplanted under appropriate conditions into histocompatible or other suitable hosts, of progressive multiplication into neoplasms leading to death of the recipients." We fail to see why this danger does not lead to the conclusion that the heteroploid cell lines should be rejected from consideration. No consideration is given to the fact that the human diploid cell strains when inoculated into the hamster cheek pouch or terminal human cancer patients do *not* "develop local growths which have the morphological characteristics of malignancy" (*3*, *7*, *10*).

Another advantage of heteroploid cell lines cited in the report is that "some stabilized cell lines cultivable in chemically defined media can support the replication of any one of at least 15 viruses." Published studies (*3*, *10*, *13*) show that a human diploid cell strain is susceptible to almost 100 human viruses including the entire Rhinocoryza group, many of which cannot be isolated or grown in "stabilized cell lines" or primary monkey kidney, and most of which were first discovered by utilizing a human diploid cell strain.

Thus, the single advantage remaining for the utilization of heteroploid cell lines for vaccine production referred to in the report is that this type of cell population can be grown in chemically defined media. Although the human diploid cell strains are not presently cultivable in chemically defined media, they *can* be prepared for vaccine production (*7*) exactly as primary monkey kidney and chick cells are grown in current manufacturing procedures. Nevertheless, the total research efforts directed toward growing human diploid cell strains in chemically defined media have, since their recent recognition, been minimal. Is it then preferable to produce a human virus vaccine in heteroploid cells grown in chemically defined media which "as a rule . . . when transplanted . . . become capable of progressive multiplication into neoplasms . . ." than in karyotypically normal cells grown in chemically undefined media?

LEONARD HAYFLICK
PAUL S. MOORHEAD
Wistar Institute of Anatomy and Biology, Philadelphia 4, Pennsylvania
CHARLES M. POMERAT
Pasadena Foundation for Medical Research, Pasadena, California
T. C. HSU
M. D. Anderson Hospital and Tumor Institute, Houston 25, Texas

References and Notes

1. K. H. Rothfels and R. C. Parker, *J. Exptl. Zool.* **142**, 507 (1959).
2. T. T. Puck, S. J. Cieciura, H. W. Fisher, *J. Exptl. Med.* **106**, 145 (1957); H. Moser, *Experientia* **16**, 385 (1960).
3. L. Hayflick and P. S. Moorhead, *Exptl. Cell Res.* **25**, 585 (1961).
4. L. Hayflick and P. S. Moorhead, in *Handbook on Growth* (Federation Am. Soc. for Exptl. Biology, Washington, D.C., 1962).
5. H. Rubin and H. M. Temin, *Federation Proc.* **17**, 994 (1958); M. Vogt and R. Dulbecco, *Proc. Natl. Acad. Sci. U.S.* **46**, 365 (1960); K. K. Sanford, T. B. Dunn, A. B. Covalesky, L. T. Dupree, W. R. Earle, *J. Natl. Cancer Inst.* **26**, 331 (1961).
6. H. Koprowski, J. A. Ponten, F. Jensen, R. G. Ravdin, P. S. Moorhead, E. Saksela, *J. Cellular Comp. Physiol.* **59**, 281 (1962); H. M. Shein and J. F. Enders, *Proc. Natl. Acad. Sci. U.S.* **48**, 1164 (1962).
7. L. Hayflick, S. A. Plotkin, T. W. Norton, H. Koprowski, *Am. J. Hyg.* **75**, 240 (1962).
8. E. H. Y. Chu and N. H. Giles, J. *Natl. Cancer Inst.* **20**, 383 (1957).
9. T. C. Hsu, *Intern. Rev. Cytol.* **12**, 69 (1961).
10. Report by the Scientific Group on the Human Diploid Cell to the director general, World Health Organization, Geneva (MHO/PA/140.62).
11. W. Szybalski and M. J. Smith, *Proc. Soc. Exptl. Biol. Med.* **101**, 662 (1959); G. G. Rose. *Texas Rept. Biol. Med.* **20**, 308 (1962); I. Lieberman and P. Ove, *Proc. Natl. Acad. Sci. U.S.* **45**, 867 (1959).
12. M. Vogt and R. Dulbecco, *Virology* **5**, 425 (1958).
13. V. V. Hamparian, A. Ketler, M. R. Hilleman, *Proc. Soc. Exptl. Biol. Med.* **108**, 444 (1961); M. R. Hilleman, V. V. Hamparian, A. Ketler, C. M. Reilly, L. McClelland, D. Cornfeld, J. Stokes, Jr., *J. Am. Med. Assoc.* **180**, 445 (1962); A. Ketler, V. V. Hamparian, M. R. Hilleman, *Proc. Soc. Exptl. Biol. Med.* **110**, 821 (1962); D. A. J. Tyrrell, M. L. Bynoe, F. E. Buckland, L. Hayflick, *Lancet* **2**, 320 (1962); K. M. Johnson and L. Rosen, *Am. J. Hyg.* **77**, 15 (1963).

The report of the Committee on Tissue Culture Viruses and Vaccines evaluates the risks involved in employing continuously cultured cells for the production of viral vaccines. It is concluded that if there are no unfavorable indications then it would be reasonable to undertake a five-stage expanding test program for the resulting vaccine material, as a prerequisite to approval for inoculation of the population at large.

It is recognized in the report that it will be difficult to evaluate the risk of

inducing cancer, due to possibly undetected agents arising in the degenerative processes that usually seem to occur in long-cultured tissues. The trouble is that, with our present methods, it would take a lifetime to be absolutely sure. Accordingly, it seems appropriate to propose a new national policy. We must consider the idea of avoiding exposure of the *entire* population to *any* new viral material so derived, except in the event of an overwhelming emergency.

Therefore, until we better understand the situation vis-a-vis the possible viral etiology of delayed degenerative disease, universal inoculation by a vaccine derived from continuous culture of cells from a single individual source, organ, or even species, should be prohibited. The public can be protected by use of separately derived preparations in distinct geographic areas.

The same policy might be considered in connection with material derived by different routes from the same viral source. One might even consider such reservations in connection with any particular method of preparation.

For each method involving a single source, or kind of source, there is a certain risk of disaster for all those inoculated. From the public health point of view, we must regard a 1/1000 risk of universal disaster as worse than a 1/1000 risk of individual disaster. This should be considered against the fact that one does obtain greater assurance from the more massive testing possible with a single uniformly derived preparation. As the number of vaccines grows, the chance of a serious error must also increase; we can expect to accumulate soon a large selection of vaccines and other preparations for many diseases, some of relatively small importance to the general public health picture. Rather than risk universal disaster from any one of these, we would do better not to "put all our eggs in one basket"; a more rational approach would be to divide the population into a great latin square experiment.

One must recognize that it is not yet within our means to say that any product is perfectly safe. The problem is serious enough for those drugs which are likely to reach a large percentage of the population. It is critical for those agents like vaccines which are intended to reach everyone—as in the case of atmospheric radiation, the ubiquitous food additives and others—and one must have extreme standards. Although inconvenient and expensive, alternatives such as regional use of different agents must be considered. Whatever the results of short-term safety studies, these matters always remain experimental on some level, as does evolution itself.

MARVIN MINSKY
Massachusetts Institute of Technology, Cambridge

Radiation Exposure Records

Title 10, part 20, of the Code of Federal Regulations includes the following rule (section 20.404): "Each licensee shall furnish to the former employee a report of the former employee's exposure to radiation as shown in records maintained by the licensee." There are many other references to records of exposure that have been given important legal status not only in the regulations of the Atomic Energy Commission but in most of the regulations which the various states have adopted or are in the process of adopting. It was only after considerable debate during the process of transferring regulatory responsibilities from the federal government to the city of New York that the city health department prevailed upon the AEC to allow it to require that such personnel-monitoring records be given to "so called" overexposed employees *only* if the Commissioner of Health were to decide that the action is appropriate.

It should be obvious to the initiated that the radiation-dose figure given by a number read from a film densitometer represents only one item of data among many that can be of value to an expert in estimating the exposure. The exposure itself usually cannot be expressed in simple terms. An estimate of exposure represents an attempt to express the degree to which different parts of the body have been exposed to ionizing radiation in terms of the recommended limits for the various critical organs. Whether or not the monitoring device was worn properly, exactly where it was worn, the movement of the wearer with respect to the radiation source or sources with which he worked, the extent of local shielding (particularly with respect to the location of the monitoring device), and the type and energy of the radiation or mixture of radiations to which the wearer was exposed all enter into the determination, by experts, of the extent to which various body organs of the person under consideration were exposed to radiation. Most of these additional data *cannot* be determined by examining the film.

The health physicist would do well to acquaint himself with the experience of the medical profession under somewhat similar circumstances. There have been many legal efforts in which unqualified persons, such as lawyers, have sought to obtain and use isolated clinical data for the purpose of establishing the existence of a physical illness or injury. A medical x-ray film has been found by the courts on many occasions not to be admissible as a record of a patient's physical condition, but it is a part of the clinical data that help a properly trained person (a radiologist) determine the condition of the patient. Most attempts in court to obtain posession of an x-ray film from the radiologist have failed. Films from personal dosimeters and the related records should be treated similarly. If any record is needed, it should be in the form of an opinion or report by a person qualified to evaluate the complete exposure history of the person involved.

Careful and regular recording and summation of the estimated radiation received by a piece of photographic film and entering of the total on an individual's personal record for all time, as representing the extent to which his various critical organs have been exposed to radiation, should *not* be required. Such records have been given an exalted importance to which their doubtful validity does not entitle them. The admission of such records in litigation could result—and has, in the opinion of many experts, resulted—in a miscarriage of justice.

The professional health physicist should defend aggressively the position that the radiation exposure of an individual is a result to be determined by experts on the basis of a study of all the available data. It cannot, in most cases, be reasonably represented by a number read from a film badge or other instrument carried by the person in question.

It is not my intent to discourage monitoring by film badges or other devices. Such programs are of unquestionable value when they are conducted with discrimination. Film badges should be recognized for what they are—a useful tool in the hands of a radiation specialist, not a substitute for a specialist, even when in the hands of a good technician.

HANSON BLATZ
Office of Radiation Control, New York