

References and Notes

1. A. L. Turkevich, E. J. Franzgrote, J. H. Patterson, *Science* **158**, 635 (1967); A. L. Turkevich, J. H. Patterson, E. J. Franzgrote, *ibid.* **160**, 1108 (1968); A. L. Turkevich, E. J. Franzgrote, J. H. Patterson, *ibid.* **162**, 117 (1968).
2. M. B. Duke and L. T. Silver, *Geochim. Cosmochim. Acta* **31**, 1637 (1967). This report would suggest that the moon is to some extent internally differentiated. For discussions of the view that basaltic composition does not necessarily imply lunar differentiation, see T. Gold, *Science* **160**, 904 (1968); P. W. Gast, *ibid.* **159**, 897 (1968).
4. J. A. O'Keefe, J. B. Adams, D. E. Gault, J. Green, G. P. Kuiper, H. Masursky, R. A. Phinney, E. M. Shoemaker, *NASA (Nat. Aeronaut. Space Admin.) SP 166* (1968), p. 145.
5. D. E. Gault, J. B. Adams, R. J. Collins, G. P. Kuiper, H. Masursky, J. A. O'Keefe, R. A. Phinney, E. M. Shoemaker, *NASA (Nat. Aeronaut. Space Admin.) SP 173* (1968), p. 233.
6. B. Mason, *Amer. Mus. Novitates No. 2155* (1963).
7. E. D. Jackson and H. G. Wilshire, *J. Geophys. Res.* **73**, 7621 (1968).
8. Publication authorized by the director, U.S. Geological Survey.

11 March 1969

Cyclamates and Human Cells

Stone *et al.* (1), reporting on cytogenetic effects of cyclamates on human cells in vitro, state that a concentration in vitro of 200 μg of cyclamate per milliliter is equivalent to a dosage of 15 g per 75 kg of body weight. This dosage is simply equivalent to a concentration of 15 g per 75 kg of culture medium. There is an implication here, possibly not intended by Stone *et al.*, that a blood concentration of 200 μg of free cyclamate per milliliter can be obtained by an oral dose of 15 g to a man weighing 75 kg. This is manifestly not the case. The absorption of orally administered cyclamate is variable, but is considerably less than 100 percent and, of the amount absorbed, only about 40 percent is free, the remainder being bound to plasma proteins. Also, absorbed cyclamate is rapidly excreted in the urine, so that it is impossible to maintain any particular concentration in the blood for any length of time with a single oral dose. If the cyclamate were ingested over the period of a day, the peak concentrations in the plasma would be lower, with a higher dose being required to achieve a given concentration in the plasma.

In one study by Wiegand, single oral doses of 5 g of sodium cyclamate given to two human subjects resulted in peak concentrations in the plasma of 21.0 and 17.8 $\mu\text{g}/\text{ml}$. This suggests that a

dose of about 50 g would be needed to obtain a plasma concentration of 200 $\mu\text{g}/\text{ml}$ and that, to obtain such a concentration of free cyclamate, a dose of 125 g would be required, 35 times the daily maximum of 3.5 g suggested by the Food and Drug Administration.

ROBERT S. GOODHART

67 Forest Road,
Tenaflly, New Jersey 07670

References

1. D. Stone, E. Lamson, Y. S. Chang, K. W. Pickering, *Science* **164**, 568 (1969).
2. R. G. Wiegand, personal communication.

3 June 1969

Goodhart has correctly pointed out that we did not intend to suggest equivalence between the dosages employed in vitro and blood concentrations of free cyclamate in vivo. What we did point out was that in an average man (75 kg) the dosage in vitro would be equivalent to 15 g of the compound in his body. The problems of absorption, protein binding, and excretion are, therefore, pertinent when comparisons with human intake are to be made, and these have been properly brought up by Goodhart. (i) Actually we have no information on protein-binding of cyclamate in the in vitro systems employed nor whether such binding confers biological activities. With regard to the data offered by Goodhart, information available to us on cyclamate balance studies during daily ingestion in the human is sketchy and variable, with average recoveries, in some instances, being as low as 30 percent. If the low concentrations in the plasma (and interstitial spaces) quoted by Goodhart (Wiegand's data) apply to the low excretors, then cyclamate concentrations in the cells may be relatively high, or possibly even concentrated in specific tissues or cells, such as the bladder and gastrointestinal tract.

Further work may clarify some of the points raised by Goodhart. Our group now has evidence that rats raised on small quantities of cyclamate (substantially less than a daily ingestion of 3 g per 75 kg of body weight) exhibit differences in maze performance as compared to control animals.

DAVID STONE

Worcester Foundation for
Experimental Biology,
Shrewsbury, Massachusetts 01545

Procarbazine: Chemical Immunosuppressant Also Powerful Carcinogen

Stewart and Cohen (1) report that procabazine is an effective immunosuppressant. The implication was that procabazine might be preferred to antilymphocytic serum.

Procabazine (MIH) is a valuable drug in cancer chemotherapy, particularly in certain often fatal conditions such as Hodgkin's disease, malignant melanoma, and bronchogenic carcinoma. Sartorelli and Creasey (2) have reviewed biochemical and pharmacological properties of MIH which bear on the varied biologic and pathologic effects of this compound.

However, it is also important to realize that this compound, and indeed analogous structures, are powerful carcinogenic and teratogenic agents (3). The carcinogenicity appears specifically related to the presence of the benzylmethylhydrazine side chain, also present in the carcinogens azomethane, azoethane, and 1,2-dimethylhydrazine (4). This class of compounds, which, like dialkyl nitrosamines, are metabolized to active carbonium ions (5), is among the most dangerous of carcinogens known. Considering the high degree of carcinogenicity of procabazine, its practical application as an immunosuppressant would seem unwise where extended survival is expected.

J. H. WEISBURGER

National Cancer Institute,
Bethesda, Maryland 20014

References and Notes

1. P. B. Stewart and V. Cohen, *Science* **164**, 1082 (1969).
2. A. C. Sartorelli and W. A. Creasey, *Annu. Rev. Pharmacol.* **9**, 51 (1969).
3. M. G. Kelly, R. W. O'Gara, S. T. Yancey, C. Botkin, *J. Nat. Cancer Inst.* **40**, 1027 (1968); M. G. Kelly, R. W. O'Gara, S. T. Yancey, K. Gadekar, C. Botkin, V. T. Oliverio, *J. Nat. Cancer Inst.* **42**, 337 (1969); J. C. Heuson and R. Heimann, *Europ. J. Cancer* **2**, 385 (1966); D. P. Griswold, Jr., A. E. Casey, E. K. Weisburger, J. H. Weisburger, *Cancer Res.* **28**, 924 (1968); E. Grunberg and H. N. Prince, *Chemotherapy* **14**, 65 (1969); S. Chaube and M. L. Murphy, *Teratology* **2**, 23 (1969).
4. H. Druckrey, R. Preussmann, S. Ivankovic, C. H. Schmidt, B. T. So, C. Thomas, *Z. Krebsforsch.* **67**, 31 (1965); H. Druckrey, R. Preussmann, F. Matzkies, S. Ivankovic, *Naturwissenschaften* **54**, 285 (1967); H. Druckrey, S. Ivankovic, R. Preussmann, C. Landschütz, J. Stekar, U. Brunner, B. Schagen, *Experientia* **24**, 561 (1968).
5. P. N. Magee and J. M. Barnes, *Advan. Cancer Res.* **10**, 163 (1967).
6. I acknowledge valuable discussions with V. T. Oliverio of the National Cancer Institute.

6 June 1969