Mill dressed up in a tight German suit put on back to front. This is well brought out in Cohen's survey. Physician-scientists will derive comfort from the following statement by the same author³: "The measure of confidence that a hypothesis deserves may reasonably be affected, people think, by the results of new experiments to test it, or by discovery of new collateral information about the kinds of variation of circumstances to which it has already been submitted. It seems very paradoxical to suppose that this measure of confidence can be affected merely by changes in human terminology. To suppose the degree of a hypothesis's confirmation to be relative to a certain state of language seems quite out of accord with the normal patterns of scientific discourse, and it is highly doubtful whether scientists would profit by adopting such a supposition."

Language is not a fundamental source of norms for the evaluation of theories about non-linguistic matters: rather it is itself exposed to criticism by standards of extra-linguistic origin.—I am, etc.,

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Potentially Dangerous Forms of Drug Economy

SIR,—The assumed necessity, if not the fashion, of drug economy appears to lead us into forms of pharmaceutical advertising which must give reason for serious concern.

The manufacturers of ampicillin (Penbritin) during the last months have distributed circulars suggesting three effective dosage schemes for bronchitic patients—i.e., (a) prophylaxis, (b) routine treatment, and (c) high-dosage therapy. Whilst there is some documented evidence for the two latter dosage schemes,^{1,2} I am unable to find valid scientific justification for the statement made regarding prophylactic treatment—i.e., "When continuous daily treatment is considered desirable, one capsule (250 mg.) is recommended every twelve hours." True, Oswald³ in a recent review states as follows: "The patients who seem to benefit most are those who are comparatively fit, who have only a small quantity of pus, and who respond to 0.25 g. of tetracycline or ampicillin twice daily," and Francis and his colleagues,⁴ on the basis of three controlled trials for the suppression of both pneumococci and *Haemophilus influenzae* in bronchitic sputum, recommended similar small twice-daily doses of tetracycline which they "have found capable of this with safety." Whilst there is no doubt that pneumococci will be killed by such a dose, May^{1,2} has shown that 6 hours after a dose of 250 mg. of ampicillin the mean sputum level is 0.08 µg./ml., which represents one-quarter of the concentration of ampicillin required to inhibit but not to kill the growth of 50% of *Haemophilus influenzae* strains. It can be assumed reasonably that the level of ampicillin in the sputum will drop to negligible concentrations between the 6th and 12th hour

after a single 250 mg. dose, although, to the best of my knowledge, there is no data in the literature extending May's observations² to 12 hours after a single dose. May suggests that with repeated 6-hourly doses of 250 mg. tissue-ampicillin concentrations are in fact higher than sputum levels, but this does not necessarily hold true for 12-hourly dosage.

It is therefore precisely the safety aspect of small 12-hourly dosage therapy stressed by Francis which must disturb the informed clinical bacteriologist. Cooper *et al.*,⁵ using 250 mg. tetracycline 6-hourly, found strains of *H. influenzae* with increased resistance in the sputum of 2 out of 12 chronic bronchitics after 6 months' treatment. By reason of analogy it is likely, therefore, that the sub-inhibitory doses recommended by the manufacturers of ampicillin for continuous treatment will create conditions in the lower respiratory tract of bronchitic patients similar to those under which bacteriologists can train micro-organisms *in vitro* to acquire resistance to antibiotics.

Much more information should be available before continuous treatment with 250 mg. of ampicillin 12-hourly, or any other presently available antibiotics can be recommended for other than economic reasons. Whilst such a dosage scheme may appear "safe" to clinical investigators at the time of trials, it could in the long run lead to widespread distribution of resistant strains of *H. influenzae* similar to that which has been observed in gonococcus strains, which, no doubt, has been induced by too low therapeutic doses employed over long periods. One of the fundamental principles of antibiotic therapy—i.e., use of maximal therapeutic doses—can only be disregarded at the risk of breeding resistant strains of micro-organisms, and of the ultimate diminished usefulness of the drug thus employed.

More prolonged and intense investigations of both bacteriological and clinical aspects are required before recommendation (a), prophylaxis, of the manufacturers of ampicillin can be accepted by the profession as being in the best interest of bronchitic patients.—I am, etc.,

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- 4 Francis, R. S., in *Some Aspects of Chronic Bronchitis*, edited by F. A. H. Simmonds and L. B. Hunt, 1964. Livingstone, Edinburgh.
- 5 Cooper, A. W., Williamson, G. M., Zinnemann, K., Edwards, G. F., and Thornton, H., *Brit. J. Dis. Chest*, 1961, 55, 23.

Reactions to Intravenous Iron-dextran

SIR,—Dr. I. W. Manson in his recent letter (20 March, p. 794) stated that on the basis of serum folic-acid activity (S.F.A.A.) five cases showed evidence of deficiency, yet no reactions occurred with iron-dextran infusion. From this he concludes that folic-acid deficiency is not necessarily a predisposing factor in triggering off a sensitivity reaction.

It is very doubtful if S.F.A.A. gives any indication of folic-acid status in relation to megaloblastic change, except when deficiency is gross (lesse than 1 mµg./ml.) Dr.

Chanarin and his colleagues (20 February, p. 480) would certainly agree with this statement for, like us, they feel that the diagnosis of megaloblastic change, whether it be frank or transitional, is still a morphological one. One must therefore distinguish between folic-acid deficiency with and without haematological change, and it is in the latter group with changes that we feel reactions are likely to occur.

Of the two reactions reported by Dr. Manson he was able to supply detailed information on one. This patient had a suspiciously low S.F.A.A., but the marrow was still normoblastic. The accompanying table showed that her haemoglobin at delivery was 83%, but by the seventh day of the puerperium it had fallen to 55%. A drop like this is unlikely to be due to iron deficiency alone, and one would suspect that blood loss or infection had complicated the picture. This raises a further point, which should be stressed—namely, the careful selection of all cases for total dose infusion.—I am, etc.,

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Ophthalmic Use of Lasers

SIR,—In their recent article entitled "A Laser Ophthalmoscope for Retinal Phototherapy" (27 March, p. 823), Mr. H. Vernon Ingram, Mr. Neil Manson, and Mr. Desmond Smart provide a summary of the thought and work leading to the developments of lasers, but most surprisingly they fail to mention any of the fairly extensive and earlier ophthalmologic investigations in this field. For this reason I append the following short list of articles which may be of interest to those who wish to pursue further information on the ophthalmic use of lasers.

- (1) Zaret, M. M., Breinin, G. M., Schmidt, H., Ripps, H., Siegel, I. M., and Solon, L. R., "Ocular Lesions Produced by an Optical Maser (Laser)," *Science*, 1961, 134, 1525.
- (2) Zaret, M. M., Ripps, H., Siegel, I. M., and Breinin, G. M., "Laser Photocoagulation of the Eye," *A.M.A. Arch. Ophthalmol.*, 1963, 69, 97.
- (3) Campbell, C. J., Rittler, M. C., and Koester, C. J., "The Optical Maser as a Retinal Coagulator: an Evaluation," *Trans. Amer. Acad. Ophthalmol.*, 1963, 67, 58.
- (4) Campbell, C. J., Noyori, K. S., Rittler, M. C., and Koester, C. J., "Intra-ocular Temperature Changes Produced by Laser Coagulation," *Acta Ophthalmol.*, 1963, Suppl. No. 76, 22.
- (5) Ham, W. T., Williams, R. C., Geeraets, W. J., Ruffin, R. S., and Mueller, H. A., "Optical Masers (Lasers)," *ibid.*, 1963; Suppl. No. 76, 60.
- (6) Zweng, H. C., Flocks, M., Kapany, N. S., Silbertrust, N., and Peppers, N. A., "Experimental Laser Photocoagulation," *Amer. J. Ophthalmol.*, 1964, 58, 353.

It should also be pointed out that the work of the present authors in regard to temperature production following a laser burn is markedly different from the careful study on this subject by Campbell and co-workers (see reference 4). It may interest readers to learn that a number of lasers, including a portable ophthalmoscope model, have been available for the past year in America.—I am, etc.,

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