With the help of this check list both of us have independently examined all the reports of therapeutic trials to be found in the issues of four British journals published between January 1 and June 30 in 1966 and 1969. The assessments made by the two observers largely agreed, though they sometimes differed on points in sections 2 to 4. These differences in opinion most often arose from ambiguities in the description. In the two weekly journals, 83% of the 82 reports published and in the monthly journals, 46% of the 59 reports published were acceptable or probably acceptable ($\chi^2=21{\cdot}6$, 1 d.f., $P<0{\cdot}01$). Furthermore the weeklies showed greater improvement in this respect between 1966 and 1969 than the monthlies.

The check list may be of help in the preparation of therapeutic trials and of reports describing them, in editorial offices, and in the assessment of claims made for drugs and other therapeutic measures. Copies may be obtained by writing to A. H.

† WHO fellow. Permanent address: Department of Pharmacology, University of Ceylon, Colombo.

Drug-induced inhibition of tumour cell dissemination

KAREN BURRAGE, K. HELLMANN* and A. J. SALSBURY, *Cancer Chemotherapy Department, Imperial Cancer Research Fund, London, W.C.2, and Haematology Department, St. Bartholomew's Hospital, London, E.C.*1

A characteristic feature of cancer and one of its major problems is dissemination of malignant cells from the primary growth. Attempts to discover drugs specifically to inhibit this dissemination have not, however, received much attention; perhaps because of inadequate experimental models. Recent work (Hellmann & Burrage, 1969) has shown not only that the Lewis lung carcinoma (3LL) may be a useful test system for tumour cell dissemination, but that there may be drugs which can control the appearance of metastases without overt influence on the development of the primary growth.

The 3LL carcinoma has now been used to study the effects of a number of bis-diketopiperazines, a new class of cytostatic agents (Hellmann, Newton, Whitmore, Hanham & Bond, 1969; Creighton, Hellmann & Whitecross, 1969; Hellmann & Field, 1970) and more particularly the mechanism of metastasis inhibition by one of them, ICRF 159, (±)-1,2-bis(3,5-dioxopiperazin-1-yl) propane. Cyclophosphamide, a well known inhibitor of cell division, has been studied for comparison.

Inhibition of metastases by cyclophosphamide paralleled inhibition of the primary growth, but ICRF 159 inhibited pulmonary metastases at doses which gave only slight inhibition of the primary growth as judged by weight differences.

Daily microscopical examination for 14 days of blood concentrates and lung sections from untreated mice inoculated with 3LL showed that pulmonary metastases developed rapidly from the ninth day onwards, but malignant cells could only be detected in the blood from day 10 onwards. In the treated mice, however, no malignant cells were seen in the blood at any time and no pulmonary metastases developed.

Primary tumours from treated and untreated mice were then examined microscopically. In untreated mice the actively growing border of the tumour was permeated with innumerable thin-walled vascular spaces. In striking contrast in the treated mice the same part of the tumour contained well formed discrete blood

vessels which were relatively few in number and whereas in the untreated tumours blood was in direct contact with malignant cells, in the treated mice it was not.

It is not yet clear whether the apparently better development of the vasculature in the treated animals is due to the slight retardation of tumour growth thus permitting the vessels more time to develop, or whether the influence of the drug is at the more fundamental level of the growth pattern of the tumour.

REFERENCES

CREIGHTON, A. M., HELLMANN, K. & WHITECROSS, S. (1969). Antitumour activity in a series of bisdiketopiperazines. *Nature, Lond.*, **222,** 384–385.

HELLMANN, K. & BURRAGE, K. (1969). Control of malignant metastases by ICRF 159. *Nature, Lond.*, **224,** 273–275.

HELLMANN, K. & FIELD, E. O. (1970). The effect of ICRF 159 on the mammalian cell cycle: significance for its use in cancer chemotherapy. *J. natn. Cancer Inst.*, in the Press.

HELLMANN, K., NEWTON, K. A., WHITMORE, D. N., HANHAM, I. W. F. & BOND, J. V. (1969). Preliminary clinical assessment of ICI 159 in acute leukaemia and lymphosarcoma. *Br. med. J.*, **1,** 822–824.

Inhibition of alcohol dehydrogenase by aminophenoxyalkanes: a possible mechanism of their retinotoxicity

R. H. NIMMO-SMITH (introduced by O. D. STANDEN), *Biophysics and Biochemistry Laboratory, Wellcome Research Laboratories, Beckenham, Kent*

Numerous *p*-aminophenoxyalkanes have a powerful chemotherapeutic effect in experimental schistosomiasis (for example, Raison & Standen, 1955; Caldwell & Standen, 1956). To varying degrees they can also induce a retinopathy in monkey, cat and dog but not in rodents (Edge, Mason, Wien & Ashton, 1956; Goodwin, Richards & Udall, 1957) and can prevent regeneration of rhodopsin in the dark-adapting frog (Goodwin, Richards & Udall, 1957).

A third characteristic of these compounds is their ability to inhibit alcohol dehydrogenase (ADH), some of them at concentrations as low as 0·1 μM. Inhibitory potency of representative compounds has been measured *in vitro* with ADH of horse liver as the main test enzyme; some of the more important results have been confirmed with ADH of ox retina. Results from these experiments have been compared with the relative abilities of the same compounds to inhibit resynthesis of rhodopsin in the intact frog and to cause blindness in the cat, as described by Goodwin, Richards & Udall (1957), Collins, Davis, Edge & Hill (1958) and Goodwin & Richards (personal communication).

The effects of several types of structural alteration to model compounds upon their biological activities will be described. Inhibitory potency against ADH and ability to produce ocular damage were found always to change in the same direction and to a similar extent.

Alcohol dehydrogenase is regarded as playing an essential role in the visual cycle (Wald & Hubbard, 1960), catalysing the equilibrium between retinal and retinol. It is suggested that inhibition of this enzyme by aminophenoxyalkanes may be a primary biochemical lesion associated with their retinotoxicity.

I am very grateful to Drs. L. G. Goodwin and W. H. G. Richards for letting me use some of their unpublished data.