DISPUTANDUM

The Activity of Ibenzmethyzin Hydrochloride Against the Human Transplantable Tumours Human Epithelioma No. 3 and Human Adenoma No. 1

In a recent issue of this journal, GRUNBERG and PRINCE reported the effects of ibenzmethyzin hydrochloride (Natulan®) on 2 human tumours growing in animal hosts[1]. As both the method employed and the results obtained for human adenocarcinoma No. 1 (H.Ad. No. 1) conflict with those of our own laboratory, we deem it necessary to discuss this disagreement.

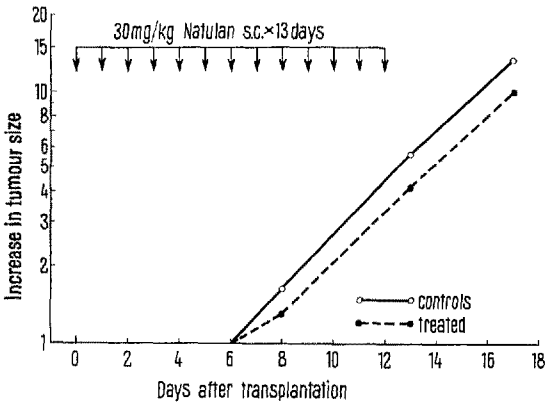
Before proceeding to questions of methodology, mention should perhaps first be made of the nomenclature used in their paper. Both tumours employed were established in laboratory animals by TOOLAN[2], and referred to by her as human epidermoid carcinoma No. 3 and human adenocarcinoma No. 1. Literally altering these neoplasms to 'epithelioma' and 'adenoma' is of no consequence for the evaluation of chemotherapeutic response; nevertheless, the authors have by this means accomplished a change we are all seeking both in the clinic and in the laboratory, viz. producing benign tumours from malignant ones. Their microscopic morphologies and growth behaviours cast no doubt upon their malignant nature.

Turning now from words to deeds, GRUNBERG and PRINCE transplanted H.Ad. No. 1 to the cheek pouch of hamsters divided into groups of 6 and then treated them by injecting the test substance 14 times s.c., beginning immediately after implantation. Growth inhibition was calculated by excising all tumours on day 21 and determining the average difference in weight between control and treated tumours. It has been our experience, however, that the large variability in absolute weight or size between such tumours on any particular measurement day prevents the determination of statistically reliable averages for each experimental group of tumours; more so, to be sure, when only 6 tumours are included per group. Weighing the tumours at a particular time after transplantation assumes that the same amount of *viable* tumour tissue was present at the outset, an assumption rarely realized and usually compensated for statistically by using a large number of measurements. The use of the hamster cheek pouch, which can be everted at will for continuous observation, provides the opportunity of measuring tumour growth rate; for H.Ad. No. 1, this is of an exponential character[3]. Since this type of growth pattern is exhibited by all proliferating H.Ad. No. 1 tumours, regardless of initial tumour size, this then gives us a consistent and predictable criterion for evaluating anti-cancer action, for the average *increase* in tumour size for each experimental group of tumours can be compared to that of the control tumours. Tumour size is determined at regular intervals by caliper measurements of the tumour's length, width, and depth. Each group consists of 15–25 tumours and each experiment is repeated at least twice.

At a dosage causing 20% mortality, which means, in their series, that 1 of 6 animals expired, GRUNBERG and PRINCE reported that the control tumours were 2.3 times larger than those treated with Natulan. Using almost the same therapy regimen, our own results could show a growth inhibition, measured on day 17 post-transplantation, of an unimpressive 24%, when the increase in tumour size of the treated group is compared with that of the controls. In accordance with the slopes of the growth curves for each group (Figure), certainly no improvement in cancerostatic effect is to be expected at any later time.

Acknowledging that different methods may very likely yield different results, we have investigated the effects of Natulan by means of other therapy schedules and application routes. On the basis of our results, to be published in detail elsewhere, we cannot agree with GRUNBERG and PRINCE that ibenzmethyzin hydrochloride is active against H.Ad. No. 1 at a dose permitting a majority of the hamsters to survive. Indeed, this confirms the lack of clinical response reported for this drug in the treatment of solid tumours[4].

The question of the effectiveness of this particular anti-cancer agent in a single tumour system has not been the main objective of this commentary, but rather an evaluation of the methodology that led to such disputable results.



Effect of ibenzmethyzin hydrochloride (Natulan) on the growth rate of H.Ad. No. 1 in the hamster cheek pouch.

Zusammenfassung. Eine kritische Bewertung der von GRUNBERG und PRINCE publizierten Ergebnisse und eigene Versuche lassen an einer deutlichen cytostatischen Aktivität von Ibenzmethyzin-Hydrochlorid (Natulan®) gegenüber H.Ad. Nr. 1 zweifeln. Eine neue Methode zur Erfassung chemotherapeutischer Effekte an Transplantationstumoren in der Hamsterbackentasche wird vorgeschlagen.

D. M. GOLDENBERG and S. WITTE

Cancer Research Laboratory, Department of Medicine, University Clinics, 852 Erlangen (Germany),
8th December 1966.

[1] E. GRUNBERG and H. N. PRINCE, Experientia *22*, 324 (1966).
[2] H. W. TOOLAN, Cancer Res. *14*, 660 (1954); *17*, 418 (1957).
[3] D. M. GOLDENBERG, S. WITTE, B. HINDRINGER and G. HARTMANN, Arzneimittel-Forsch. *16*, 808 (1966).
[4] K. BRUNNER, A. MARTZ, I. KRAKOFF, W. GELLER and G. ESCHER, Proc. Am. Ass. Cancer Res. *5*, 8 (1964). – G. MARTZ, in *Chemotherapy of Cancer* (Ed. PL. A. PLATTNER; Elsevier Publishers, Amsterdam-London-New York 1964), p. 198.