Discussion on the Screening Test of Cancer Chemotherapy
IWAO HIRONO
(Department of Pathology, Nagoya University, School of Medicine.)

Search for tumor-inhibiting agents which has made notable progress these several years, has resulted in the discovery of various useful compounds. Nevertheless, it has been frequently observed by most clinicians that tumor-inhibiting agents used on certain patients become ineffective, though they are efficacious at the beginning of use. Especially, in the treatment of leukemia this phenomenon has most frequently been encountered. Such a phenomenon may be one of the important and fundamental problems in the tumor chemotherapy.

I have carried out successive transplantations of the Yoshida sarcoma by passing tumor cells through animals treated with agents and studied the development of tumor resistance to these compounds. I wish to report here briefly the following observations: 1) the development of resistance to Methyl-bis-(β-chlorethyl)-amine N-oxide (MBAO), 2) effects of other known antitumor agents on the MBAO-resistant variant and 3) behavior of resistant tumor cells carried in serial transplants in the absence of the agent.

Resistance to MBAO always developed sooner or later by any mode of administration of the agent, consecutive or intermittent, intraperitoneal or subcutaneous, and it was found to increase stepwise.\(^1\) The MBAO-resistant variant was proved to be cross-resistant to the other three alkylating agents, namely, Methyl-bis-(β-chlorethyl)-amine, Tris-(β-chlorethyl)-amine and Tris-ethylen-imino-s-triazine, but not cross-resistant to 8-azaguanine, 6-Mercaptopurine, colchicine and X-rays.\(^2\)^\(^3\) To X-rays, especially, the MBAO-resistant variant was more sensitive than the MBAO-sensitive strain. The resistant subline has been carried through 115 successive transfers for above two years in host animals not given MBAO, but no change has been observed in the resistance of these cells to MBAO during this period of transfer through MBAO-free hosts. Consequently, it is apparent that the development of resistance was a irreversible and heritable change. Furthermore, the MBAO-resistant subline has been carried through 4-8 successive transfers in animals treated with colchicine, X-rays, 8-azaguanine, 6-mercaptopurine and H₂O₂. However, the resistance of tumor cells to MBAO has remained unchanged. On the other hand, in order to test whether the resistance to colchicine develops like to MBAO, serial transplantations of the Yoshida sarcoma were performed with the continued treatment through fourteen successive transfer
generations. The development of resistance was not observed, but the sensitivity of tumor cells was somewhat increase. As a possible explanation of this result, it is probable that the doses used were insufficient to act in a selective manner, eliminating susceptible forms and reproducing resistant individuals or that the sensitivity of individual tumor cells to this agent was relatively uniform in the tumor cell population. The mechanism of the development of tumor resistance has not been solved, but from the result mentioned above it may be evident that resistant tumor cells are mutant. In agreement with Law’s opinion (mutation and selection), we assume that the agents used act merely in a selective manner. Consequently, it can be inferred that combined therapy with two or more agents acting independently may be useful for retardation of the development of resistance. In addition, judging from the fact that tumor cells resistant to a certain agent are sensitive or more sensitive than ordinary strain to other unrelated agents, combined therapy is inferred to be useful.


On the Screening Test of Cancer Chemotherapy
KYO KAZIWARA

（１）癌化学療法の Screening 実験については候補薬物（Candidates）をなるべく広く選び出す Primary screening と、この候補薬物について効果と毒性の面から吟味を加える Secondary Screening と、さらに臨床に使用する前に製剤学的検討を加えるべき３つの段階があると考え、このどれもがともに重視すべきものであるとの意見を持ちたい。臨床試用の前には実験室内で可能な観察をつくすべきであろう。

（２）われわれは第一次 Screening には移植性腫瘍を使用する細胞学的判定方法を利用しているが、第一次 Screening において要請されている客観性、定量性、False positive と False negative の率の少ないこと、試料が僅少ですむこと、短期間で判定し得ることなどを考えるとき、検討すべき材料に応じ、また種々の Process に応じて、細胞学的方法以外の方法も利用し得る。たとえば、細菌培養から有効成分を抽出する過程においては抗菌力が活用し得るし、代謝拮抗剤の検討の場合には乳酸菌などを使用してその発育阻止力が検討される。しか