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Symposium Summary and Closing Remarks

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The title of this symposium needs perhaps a more precise definition. Tumor resistance may mean resistance of tumors to host factors or therapy, or it may mean resistance of the host to aetiological agents, the process of carcinogenesis or to tumor cells.

Resistance of the host may depend on exogenous as well as endogenous factors. According to the estimate of cancer epidemiologists about 70% of all cancers are due to environmental factors, but only 30% are thought to be preventable. The presence or absence of environmental carcinogens has strictly speaking nothing to do with the problems concerning resistance. However, the presence or absence of cancer promoting or inhibiting factors in the environment may explain variations in the response to environmental carcinogens. Thus, asbestos, nutritional components and other factors mentioned by dr. Ole Møller Jensen may account for variations in the resistance or the susceptibility to cigarette smoking, nitrosamine precursors and other aetiological agents.

In most cases geographical variations in the cancer incidence lack a final explanation. The high incidence of stomach cancer in Japan as compared to the West may possibly be explained by differences in the environment. Howerver, the changes reported by Dr. Osamura in the rate of differenctiated to non-differenctiated carcinomas in the F-labile area of the stomach indicate the existence of a natural resistance to the more differentiated types of carcinomas in certain regions of the stomach.

More directly related to the problem of resistance of the host are the genetically determined diferences in the metabolism of carcinogens, leading to their activation or detoxification, and in DNA repair mechanisms. Epidemiology might help to clarify some of these factors. The acetyltransferase phenotype studies mentioned by Dr. Ole Møller Jensen are an important example of this type of research.

Age is another factor which plays a role. The age dependency of cervix cancer with a maximum at the menopause as described by Dr. Møller Jensen suggests a hormonal regulation of the susceptibility to this type of cancer. On the other hand the constant increase of the incidence of colonic cancer with age raises the question whether immunological factors may be of importance. However, experiments published by Dr. Ebbesen - but not reported at this symposium - indicate that the increased susceptibility of senescent tissues to carcinogenic stimuli may be an inherent characteristics which is not related to the immunocapacity of the host.

Age was also mentioned by Dr. Arimori as a risk factor to make a poor prognosis in the treatment of acute leukemia. Certainly, decreased resistance

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to residual leukemic cells could be the explanation for this age dependency.

In Dr. Hata's report a somewhat unexpected influence of age on the growth of neuroblastomas was described. The more rapid growth of these tumors in children above 1 year of age could theoretically be due to an immunostimulation, but Dr. Hata's transplantation experiments in nude mice did not support this theory.

Among the various factors which might influence host resistance to cancer the immunological defence has attracted the greatest interest, which primarily has been centered around the specific autoreactions. However, we have come to the point, where we have to admit that our various in vitro methods in the case of apparently spontaneous tumors to a great extent have failed to demonstrate the specificities which are characteristic of many experimentally induced and transplanted animal tumors. This has been discouraging and lead to some pessimism. However, I agree with Dr. Eva Klein when she says that this is not the end of the tumor immmunology. On the contrary we are only at the beginning, and I should like to add a small piece of warnig against what I will call the undulating scientific development. Since the war we have experienced numerous waves of scientific fashions such as cancer chemotherapy, nucleic acid chemistry, tumor virology, tumor immunology, and lately environmental carcinogenesis. Certainly these waves of research have contributed significantly to our knowledge and our understanding of cancer. However, if we concentrate all our efforts in the fields of research which are temporarily sucessful, then we may be badly equipped to start new research, when the wave hits new coasts of unknown land which defy all attempts of exploration until a new technology or completely new scientific horizons have been discovered.

During this symposium we have only heard little about the specific immune reactions. A new approach to specific immunization against MC-induced tumors was described by Dr. Tachibana who used somatic hybrid cells made by cell fusion of MC-induced primary tumor cells with 2-azaguanine-resistant L-cells. However, inoculation of the hybrid cells in tumor-bearing hosts evoked enhancement of tumor growth which, however, was suppressed by admnistration of the hybrid cells in an appropriate combination with cyclophosphamide. In sera from mice with enhanced tumors Dr. Tachibana found an elevated level of blocking factors.

In our laboratory Dr. Laursen has demonstrated the possibility of inducing enhanced tumor growth through prior intestinal immunization. He also reported experiments in which cyclophosphamide facilitate induction of immunological enhancement in mice. Immunofluorescence studies on sera from the experiments demonstrated that enhancing sera contained interfering factors (IF) able to reduce the antigenicity of the immunizing cells detectable with an isoantiserum. IF was found to share properties with immunoglobulins of the IgG class. Evidently, further studies are needed to clarify the factors controlling the development of tumor resistance or enhancement after specific immune stimulation.

The ascites tumor studies by Dr. Laursen was derived from "spontaneously" transformed C3H mouse fibroblasts propagated in vitro. The antigenicity of these cells as well as of "spontaneously" transformed ST/a mouse

fibroblasts has been studied in greater detail. As reported by myself during this conference, in vitro studies of serum and cell mediated immunity indicate that the expression of the viral protein gp70 on the surface of the transformed cells at least to a great extent may account for the immunological cross-reactions between a number of "spontaneously" transformed cell lines propagated in vitro. However, these experiments failed to explain the protection against secondary challenge with an ST/a mouse leukemia (SABAL) and with Ehrlich ascites tumor cells observed in mice preimmunized with the "spontaneously" transformed tissue culture cells.

As pointed out by Dr. Klein certain cultured cell lines are highly sensitive to the NK effect of lymphocytes from immunized donors provided they have been derived from the same species. Furthermore, Dr. Baldwin's studies of the host cells infiltrating tumors either growing progressively or undergoing rejection as well as his studies of regional lymph modes reveal that NK cells and/or macrophages may be the final effector cell also under in vivo conditions.

This is supported by the two interesting papers presented by Dr. Kärre and Dr. Habu. The correlation described by Kärre between resistance to various mouse leukemia and the NK-activity in the beige mutant of C57 Bl mice (bg/bg) and its phenotypically normal heterozygous littermate (+ /bg) as well as in beige-nude mice suggests that NK-cells may be responsible for the elimination of small numbers of tumor cells in the intact syngeneic host. In agreement with this conclusion Dr. Habu reported that the injection of anti-asialo GM1 - which in the presence of complement selectively eliminated NK-cells in vitro - abolishes the NK-activity in nude mice in vivo and increases the rate of tumor takes, growth and metastasis in these animals.

It is to be expected that more knowledge of the in vivo role played by NK-cells will accumulate in the future. Dr. Ueyama's studies of the growth rate of a human gastic carcinoma in nude mice with different genetical backgrounds seem to represent an interesting model, which may be further improved when sufficient back-crosses have secured well defined strains of nude mice. So far this model has not revealed any correlation between NK-activity and the growth rate of human turmors.

Dr. Kristensen has previously reported that patient lymphocytes mixed with cultured human melanoma cells decreased the number of tumor takes in nude mice and increased the latency period. However, the growth rate of the tumors was not influenced. Furthermore, in the microcytotoxicity assay, a stimulatory effect exerted by nonsensitized spleen cells derived from nude mice was observed on the growth of human tumor cells which were tumorigenic in nude mice. In contrast, the growth of non-tumor-producing cell lines (malignant and non-malignant) was inhibited by identical effector cells. Evidently, furhter research is required before all factors controlling the growth of human cells in nude mice have been revealed. Reconstitution experiments as described by dr. Povlsen may be useful in this connection.

Dr. Baldwin presented two models which illustrate the possible mechanism of NK-cells activation against non-immunogenic and immunogenic tumors. Whether T-cells play a role in the former case is unknown. However, in latter case, it seems likely that the reaction between tumor cell

and T-cell may activate macrophages to stimulate the NK-activity. This possibility was also described by Dr. Klein as transactivation, i.e. the activation in additional cells that do not participate in the specific reaction, during the event of antigen specific recognition in a lymphocyte population.

Transactivation may account for the lack of correlation between the in vitro and in vivo studies reported by myself. It is conceivable that even a moderate expression of viral antigen (gp70) on the surface of STABAL and Ehrlich cells may trigger a cellular response in vivo involving cytotoxic T-cells, as well as macrophages and NK-cells, which is strong enough to protect the host against these two ascites tumors.

The role played by NK-cells in the natural defence against human tumors is not yet clear; but the cytotoxic activity of control lymphocytes in numerous microcytotoxicity assays indicate that natural-killing may play a significant role. Thus, the characterization of the cells responsible for this autoreaction has become an important task. According to Dr. Kristensen the killing activity is most pronounced in the non-T fraction, but if only Fc-receptor bearing cells are included no differences could be demonstrated between the natural-killing activity of human T and non-T lymphocytes. The importance of the Fc-receptor was examined in blocking experiments with soluble immune complexes or IgG split products. Blocking with Fc portions was never complete, suggesting the presence of a residual cytotoxicity which is not mediated through the Fc-receptors.

The sensitivity of tumor cells to NK-activity may vary for many reasons which future research will have to clarify. The interest will primarily be directed towards the surface membrane of the malignant cells. However, Dr. Ebbesen's demonstration of an increased susceptibility of skin fibroblasts from patients suffering from Hodgkin's disease to the lytic effect of autologous lymphocytes raises the question whether neoplasma has a general effects on cellular interaction. Further studies are required before more than pure speculative explanations can be offered.

Tumor resistance is too large and too important a field to be covered completely in a short symposium like this one. However, I think that we have had the opportunity to discuss some very interesting aspects of the problem including a number a new observations which may be helpful in our attempts to explore the shores of the unknown land which have brought the good ship "Tumor Immunology" to anchor - temporarily I am sure - to take bearing of the final goal the discorvery of the mechanism of selfdefence against neoplasia. At the same time the symposium has given us an inspiring opportunity to establish a personal contact between Japanese and European scientists. For this I should like to thank the Tokai University and the Tokai University European Center very much indeed.