CERUTTI

First we'd like to discuss questions which are directly relevant to the lectures of this morning, very shortly, only burning questions are being accepted. Then I'd like to ask 5 speakers to give the short presentations for which they have signed up and which are relevant to the topic of the round table discussion for this afternoon. In the third part I'd like to discuss with you the possible role of DNA repair for interindividual differences in cancer susceptibility. Maybe we can come up with some recommendations of what system could be used to explore this question. For the fourth topic, it has been suggested that we discuss radical mechanisms which might be involved in human carcinogenesis.

Short questions relating directly to the lectures of this morning:

LEWIS

I was interested in the role of the active oxygen in the diseased states in which most of the tumors seem to come from the immunocompetent cells. The role of the active oxygen, especially hydrogen peroxide, in the killing of intracellular bacteria is well known. It also may be a very important mechanism in macrophage mediated cytolysis of tumor cells. Could it not possibly be in some of these diseases, and I understand that these people frequently die from infection, that just by encountering of bacteria, they are continually and chronically damaging the DNA of their immunocompetent cells. These mechanisms you described could be easily tested or has this been tested already?
This is a very interesting comment. The word I liked best in your comment is 'chronic'. I think the chronic exposure which is typical for inflammation and some of the rheumatoid diseases I mentioned this morning could well play a role in tumor promotion and progression and possibly even in initiation.

Phil Lawley and his collaborators have been looking at immunodeficiency diseases over the last few years. For information, they are fairly convinced now that a large number of these patients are defective in O₆-methyl-guanine excision. While we have been at some pains to try and play down the cry 'repair' here comes 'repair' throwing itself out at another level.

Something which I find particularly striking in the chromosome breakage disorders: so many apparently unrelated abnormalities have been discovered on the molecular level. This is hard to explain on the basis of a single gene mutation. Some mechanism of the type mentioned by Dr Lewis could be involved. For example a deficiency in detoxification of active oxygen species may result in chronic macro-molecular damage. This could result in partial enzyme deficiencies rather than total lack of a function.

As you have been pointing out the damage may be ubiquitous but the diseases are well defined. The clinical characteristics fall into certain categories, for instance we talk glibly about xeroderma pigmentosum patients having neurological abnormalities (and so do ataxia teangiectasia patients) but the specificity of the type of abnormality is much different in the two of them. We are really at a loss to explain this specificity particularly in view of a general mechanism of damage.

I totally agree. I would like to stress we are not proposing that the abnormality in oxygen metabolism which apparently exists in these diseases represents the primary genetic defect in these diseases. It may be a secondary expression of the pathology in these diseases, however.

The tissue specificity of the reaction to injury, may be very different for neural tissue, but back to the immune system, these tumors do seem to be specific. I don't mean to offer the solution,