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Chairman's Summary of Session A

Compared to the oxidative metabolism of drugs and other xenobiotics the reductive processes lead more often to an activation and to potentially toxic intermediates. Owing to the strong negative redox potential of the living cell, a variety of organic compounds like quinones, nitro-, nitroso-, or azo derivatives, N-oxides or polyhalogenated aliphatics can undergo reductions. However, unlike the reductions of carbonyl compounds which are catalyzed by two-electron transfers directly from pyridine nucleotides via dehydrogenases, these reductions mostly occur by stepwise one-electron transfer reactions and therefore involve radical intermediates. Because of their high reactivity, radicals can rearrange or dimerize, but also can abstract hydrogen atoms or, most important, can combine with molecular oxygen. As a consequence, radical chain reactions are initiated which produce a host of different radical species. Although the chemical nature of these radicals and their reactivities are not yet well understood, it is evident that the macromolecules of the cells, especially unsaturated phospholipids and DNA, are attacked by such reactive species and thereby cause pathological conditions.

It is interesting that one very often finds the enzyme NADPH-ferricytochrome reductase involved in the reduction process, probably because of the unspecificity for its acceptors which can be quinones or iron complexes. Another important factor is a low redox potential of the flavin prosthetic groups. Other oxidoreductases that share this property are xanthine oxidase (or dehydrogenase) as well as the various electron transport enzymes involved in photosynthesis and respiration.

In spite of some knowledge of the biochemical background of reductive processes for xenobiotics the situation in an intact cell or even a whole organism is much more difficult to assess. It is not only the redox potential of a given compound that determines its reductive pathway but more so the availability of the reducing enzymes, the energy status or the oxygen tension. In addition, the antioxidant or the radical scavenger potential given by the concentration of vitamins A, C and E as well as glutathione have a considerable influence on the radical intermediates formed. Each cell type is different in this respect, which requires extensive studies on isolated cells to unravel the reductive fate of a compound in an organism, not to forget the participation of symbiontic or invading microorganisms.

On the other hand, it is this diversity in cell metabolism that may provide conditions for a selective chemotherapy in diseased states, a goal well worth the combined efforts of synthetic chemists, biochemists, radiation chemists, biologists and physicians present at this symposium.

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