Introduction

A series of non-connected facts are difficult to remember. The pre-war German chemistry textbooks that were still in common use in my student times contained such an agglomeration of facts. In contrast, the mechanistically oriented Anglo-Saxon textbooks were a pleasure to read. They taught us the underlying principles into which facts fitted quite smoothly. Ever since, I have had a foible for mechanisms, the little brother of the 'laws' that physicists enjoy in their profession. Mechanisms are only concepts, and we should not adhere to them without reservations, otherwise we get trapped by our prejudices. Our unjustified bias for a certain concept has been brought to the point by the German physicist and aphorist *Georg Christoph Lichtenberg* (1742-1799) in his '*Sudelbücher* (entry L 674)': "*Bei den meisten Menschen gründet sich der Unglaube in einer Sache auf den blinden Glauben in einer anderen*", that is, "with most people, the disbelief in something is based upon a blind belief in something else". The development of new concepts is a major contribution to progress in science, and work that leads to mechanistic concepts is presented here with some preference. However, according to *Alfred Popper*, mechanisms or any other concepts in science can never be proved; they can only be falsified. A mechanism may be called 'accepted' as long no experiment has been thought of and has been carried out that could falsify the present view. It is hoped that the mechanistic formulations given in this book will trigger further research by trying to falsify them and will thus lead to a much better understanding of free-radical-induced DNA damage and repair.

Mechanistic aspects can only be adequately dealt with when the complexity of the system is reduced to the essential, and the reader will see that there is a strong emphasis on DNA model systems such as the free-radical chemistry of nucleobases, nucleosides and nucleotides. Increasingly, compounds are synthesized, even up to the double-stranded oligonucleotide level, that allow the generation of a specific radical, e.g., by photolysis. This is an important breakthrough as far as mechanistic studies are concerned. Yet most of our present knowledge of the free-radical chemistry of DNA and its model systems has been obtained by radiation-chemical techniques (induced by attempts to improve radiotherapy and by radiation protection concerns). Obviously, the reactions of a given radical does not depend on its mode of generation, and it has been tried throughout the book to extract from these data the more general aspects of DNA free-radical chemistry rather than those particular to radiation-chemical effects. This, of course, had to lead to a suppression of some very fine radiation-chemical studies, notably in the area of low-temperature EPR. Moreover, some of the excellent biochemical studies such as details of the site-specificity of a given free-radical reaction did not find an adequate discussion. Space just did not permit this.

Some of the different chemistry of DNA as compared to its low-molecular-weight model compounds is due to the fact that DNA is a polymer, and some aspects of polymer free-radical chemistry are dealt with in a separate chapter. The special properties of dsDNA allow hole and electron transfer to trapping sites. This is an area that attracts very strong attention at present, and the level of understanding is already very high.

One way of oxidizing selectively the Gua moiety of DNA is the use of inorganic radicals having the right redox potential. A small chapter is devoted to such free-radical probes.

A number of anticancer drugs that kill cells by destroying their DNA via free radicals are used in the clinic. They show a most remarkable chemistry. Some of it is fairly well understood. Where important open questions remain, attention is drawn to these in order to elicit future studies that are urgently needed for a better understanding of the underlying mechanistic principles.

Free-radical-induced reproductive cell death is the basis of radiotherapy, and it is obvious that the main problem of this approach to fight cancer is to target the ionizing radiation to the tumor in order to prevent damage to healthy tissue. This is a most difficult if not impossible task. Radiation modifiers that sensitize the tumor cells and protect healthy tissue are considered for improving treatment regimes in radiotherapy, and the underlying mechanistic principles are addressed.

Free radicals, notably the superoxide radical, are by-products of the cellular metabolism and transition-metal ions seem to play a role in causing DNA damage in vivo. This may lead to mutations and eventually to cancer, and some of the phenomena of aging have also been attributed to free-radical-induced DNA damage. We are still far from understanding these reactions in sufficient detail, but the reader will find chapters on peroxyl radical chemistry and on some aspects of the involvement of transition-metal ions in free-radical reactions on which future work may be based.

Cells have two defense systems to cope with free-radical DNA damage that work on very different time scales: the fast 'chemical repair' by thiols that occurs at the stage of DNA free-radicals and the slow enzymatic repair that only sets in once the damage is fully set. The present book deals in some detail with the chemical repair. To discuss the even more important enzymatic repair would have exceeded the space allocated to this book, and enzymatic repair is only briefly touched on.

It is impossible in a book of a scope as wide as the present one to refer to all studies that may be relevant to a certain topic, but the many references that are given here will allow the reader to find an entry into the wider literature.

In science, there is a hierarchy of questions: (i) 'what', (ii) 'how', and (iii) 'why'. The report of a given fact, e.g., the determination of a series of products and their yields, only answers the question 'what'. Additional kinetic studies raise our level of understanding, as it answers the question 'how'. The ultimate scientific question, 'why', has as yet rarely been answered, but this level of knowledge is a prerequisite for being able to predict a certain reaction without too many flanking experiments. Thus, it will be one of the main goals of future research to strive for an in-depth theoretical understanding. This, of course, has to be based on our present (and future) experimental data, and it is one of the intentions of this book to provide the necessary information in a compact form.

DNA research is a very multidisciplinary field, with contributions by biologists, biochemists, chemists, physicists and theoreticians. Hence, the presentation given here should be at a level that it can be understood even when the educational background is not chemistry. In parts, this goal may not have been fully reached, but at other instances it may have led to some oversimplifications. I ask for apologies. Yet, in the 1920s, nuclear physicists enjoyed discussing that *Wahrheit* and *Klarheit* (truth and clarity) may be a conjugate pair connected in a similar way as are position and velocity by the *Heisenberg* uncertainty principle. Thus, it seems not to be possible to make a given point clear without deviating from the truth, and this is comforting in view of some unavoidable oversimplifications.