Current Topics in Tumor Cell Physiology and Positron-Emission Tomography

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With a Foreword by O. Westphal

With 41 Figures

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Foreword

About ten years ago devices and equipment were developed for producing quantitative images *in vivo* of the distribution of substances with positron-emitting radionuclide label of very short half-life (down to only several minutes). The positron-emitting isotopes can be the most important bio-elements and are, therefore, suitable for the labeling of important physiologic substrates like sugars, amino acids etc. and their synthetic analogues. Their imaging, after distribution *in vivo,* is being performed by PET scanning systems.

It soon became apparent that positron-emission tomography could be very useful in the field of *cancer* biology, diagnostics and therapy. Transport, influx and efflux, metabolism of suitable labeled substrates around and in tumors can be followed over a period of time, thus allowing the localization of tumors and – equally important – the efficiency (or non-efficiency) of any given therapeutic regimen. For this purpose ^{13}N-labeled amino acids, especially glutamate, or ^{11}C- and ^{18}F-labeled glucose derivates were introduced and are already being recommended for the study of special tumors in experimental animals and man, such as brain tumors or osteosarcomas. Some glucose derivatives were developed which differ in their metabolic (enzymatic) fate. In this way, combined application of compounds, like [^{18}F]-2-fluoro-2-deoxy- and [^{11}C]-3-0-methyl-D-glucose are "expected to provide the most important imaging in tumor diagnostics" (M. Hatanaka).

In principle, tumor chemotherapy and other therapeutic approaches can now be followed *continuously.* Non-efficient therapy can be discontinued at an early state! "The information gained could be exploited to develop new strategies for treatment of malignant disease" (R. E. Reiman, G. Rosen et al.).

The costs of the necessary equipment – cyclotron and PET scanner – together with a highly sophisticated infrastructure, including experienced radiochemists, physicists, mathematicians and medically trained people – are, and will probably be, so high that only comparatively few patients may have a *direct* benefit, at least for the next decade to come. "However, research carried out in the course of studying such patients may provide oncologists in other settings with improved drugs, treatment regimens and the techniques necessary to evaluate their effectiveness" (R. E. Reiman, G. Rosen et al.).

This booklet provides knowledge and information about the present state of PET development in the field of cancer. Tumor biochemists and physiologists will certainly be stimulated to develop further suitable positron-emitting substrates by which certain tumor cells and normal cells can be better and better discriminated. Radiochemists will feel stimulated to improve quick and higher-yield procedures for the manufacture of such labeled materials in large enough quantities. More physicians and mathematicians will have to play their role in programming the whole process as well as in the qualitative and quantitative understanding and interpretation of the data obtained.
We are, thus, entering a field which has already proved its potentially high usefulness for the cancer patient, but it is – at the same time – open to further elaboration in almost all aspects of PET. This book is recommended to a broad scientific communitiy. Thanks to the authors for their most valuable reports!

Heidelberg, April 1983

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Introduction

The development of tumor-selective modalities of cancer treatment requires the exploitation of different functional properties of the tumor tissue and its normal environment. The knowledge of typical functional alterations associated with malignancy and the feasibility of their assessment act a key role in the development of therapeutic procedures as well as in the evaluation of the therapeutic efficiency.

Within the last two decades, a large scope of processes on the cellular and molecular level have been described which have been found to be characteristicly determined by malignant transformation. This progress has been attained e.g. in enzymology – reviews of great importance being given by George Weber and Sidney Weinhouse – and in the research of membrane function.

Despite of the accumulated knowledge in these fields, its applications to in-vivo diagnostic methodology has so far not been realized.

Indeed, there are severe obstacles in the in-vivo asssessment of dynamic processes which involve organic substrates: There are at least two biological compartments which have to be separately analyzed for the recording of the radioactive label. Further complication arises from the fact that 'classical' labels like C-14 or H-3 cannot be employed in vivo, since they emit beta radiation. Regarding the elements being essential constituants of organic compounds, there is only one group of isotopes applicable for in-vivo measurements, namely the positron emitters C-11, N-13, O-15, and F-18.

This fact can be taken advantage of, since the physical nature of the positron decay allows a precise quantification of radioactivity in small target volumes distant from the detector by means of positron-emission tomography. On the other hand, the employment of these nuclides is limited to a small number of centers where a cyclotron is available. The very short half life (2–120 min, 20 min for C-11) does not only require an accelerator at the site of application, it also demands special methodology of rapid syntheses for organic compounds.

In the last few years when positron cameras became commercially available, all centers having the facilities at their disposal, have taken intense efforts to make use of positron emitters for physiologic, pathophysiologic and metabolic studies in vivo. Since local alterations of physiology and metabolism are of special relevance to the brain, most work has been dedicated to this organ hitherto.

It is within the scope of this small book to illustrate by means of actual problems in cellular physiology of tumor growth, how an experimental sequence can be formed dealing with biochemistry, dynamic studies in cell culture, and finally with clinical realization by investigations in vivo using positron emitters.
Special attention is attributed to the essential role of specificly altered substrates when particular processes like membrane function are to be quantitated.
On the other hand, from the clinical point of view it is shown that even relatively non-specific informations about local metabolism or substrate availability in tumors, have already proven to be of decisive relevance in the individual therapy control.
Finally, new developments in the field of production and synthesis of short-lived radiotracers are presented.

Heidelberg, January 1984

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