Human Tumor Markers

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Biology and Clinical Applications

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PREFACE

The development of cancer is an insidious process, that very often takes a number of years before becoming clinically evident, and no current technique, of any kind, is as sensitive and specific as to detect tumors smaller than one billion of cells. As a consequence, the disease is usually diagnosed in an advanced state, when it is beyond the reach of therapeutic strategies. This is the main obstacle to secondary prevention aimed at reducing the mortality from cancer.

The last decade has seen an explosion of reports dealing with tumor markers, i.e., simple, inexpensive and non-invasive tests able to detect a precocious signal of a neoplasia. Unfortunately, the elation that greeted many reports was often followed by disappointment, because what at first sight seemed to be promising turned out to be applicable only to a limited number of cases. The most probable cause of these failures is that cancer is a multitude of neoplastic diseases in which a number of endogenous and exogenous etiologic factors are involved, either simultaneously or at different times. Therefore, no one single test will be able to diagnose all neoplastic diseases.

Throughout the world scientists involved in both basic and clinical biomedical research are making efforts to identify peculiar aspects of the transformed phenotypes in order to use them as precocious signals of neoplasia. It must be said, however, that despite the great progress that has been made over the last few years, the early diagnosis of cancer is still, with a few exceptions, out of our reach. It is conceivable that a breakthrough will only be seen when the biology of the tumor cell is fully elucidated. In other words, only when the intimate mechanisms of cell transformation are clarified, will we have access to the true signals of a nascent or ongoing neoplastic process.

It was this line of thinking that prompted the 3rd International Congress of Human Tumor Markers that was held under the auspices of the International Academy of Tumor Marker Oncology and of the University of Naples in Lacco Ameno d'Ischia on April 23-26 1986. This volume contains the Proceedings of the Conference in the form of 61 papers that covered the following topics: Molecular Biology of Tumors, Tumor Antigens, Immunochemical Cancer

Characterization, Modified Nucleosides, Management of Human Leukemias, Patient Surveillance, Receptors and Hormones, Enzymes and Isoenzymes. The papers are in the form of either original studies or overview articles containing data pertaining to both experimental and clinical oncology. It is of particular interest that besides articles reporting recent studies on the conventional tumor markers, there are numerous contributions on the "new" tumor markers, such as the oncogenes, and their diagnostic use either to reveal restriction polymorphisms associated with high-risk populations or to determine the prognosis of certain types of cancer.

Credit for the quality of the volume goes, of course, to the individual authors, who must also be applauded for having promptly delivered their papers.

Sincere thanks and gratitude are due to Jean Gilder and Mariarosaria Calabria for the excellent editing of the manuscripts and for the careful preparation of the subject index. The helpful cooperation of the staff of Walter de Gruyter is also acknowledged.

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WHAT DOES "MARKER" MEAN?

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Introduction

Generally, when we speak of a "tumor marker" we mean a condition related to a tumor, i.e., the presence of the marker equals the presence of a tumor. The marker allows us to find the tumor when it is still asymptomatic (by mass screening), or we can follow its natural history, its relapse, or the appearance of metastases. The same concept applies to preneoplastic lesions. In fact, the marker can be useful in determining the risk, and hence in individuating groups that should be studied in greater detail.

A marker, therefore, is a sign, a state that stands for something else under some aspect or quality, to use an expression coined by Peirce.

As any clinical symptom or laboratory finding, a tumor marker can be considered under three aspects. The first is the semeiotic aspect, whereby a sign is meaningful within the framework of a code. The second aspect is according to the informational theory whereby such a sign is viewed in the light of the information that it provides with regard to the implication sought, and thus it is associated to other signs and distinct from them. The third aspect is that of communication theory, where the sign is a material condition emanating from a source and brought by a channel to a receiver. These three aspects are closely related because communication and information are intrinsic to the nature of the sign and code.

Semeiotic Prospectives

In semeiotics, a condition that stands for another in purely material terms (like smoke for fire, as smoke comes from fire, therefore it is associated to it) is distinguished from a condition that stands for another in

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conventional and discursive terms (like a word in relation to its reference -- object). The former is called "signal" and the second "sign". They are distinct from each other because one is a material implication, the other a codified relationship. However, I believe there is a misunderstanding in this distinction. In physics, things are as they are, and we have to admit that fire produces smoke, at least on some occasions. All material events are chains of implications and also our neurologic ability to understand them cognitively is formed by chains of implications, albeit very complex and obscure. But in terms of cognitive understanding, the signal is not at all distinguishable from the sign: smoke equals fire only when there is a connection verified empirically that establishes a cognitive fact. Thus, within the framework of a theory, a signal is also a sign. The only difference is that smoke and fire are apparently so closely related that the underlying theory is, at first sight, almost invisible. Therefore, they are often confused with the objective reality that forms their reference. For other aspects of knowledge, the connection is more complex, because their theory is wider and sometimes more uncertain.

When we speak of smoke as a signal of fire, we refer to a relationship among words. This connection is conventional, as is easily demonstrated by citing cases in which fire does not produce smoke or smoke is without fire. In turn, words are connected to reality by way of an empiric habitual framework, which is codified and made fluent. Thus, also words are material operations.

A clinical symptom, in our case a tumor marker, is a sign that is meaningful only within a previously established theory. The relationship with the objective reference "for which it stands" (in this case, the tumor) is not direct and biunivocal, but it is mediated and certified by a wider and empirically established theory. This demonstrates that the sign "stands for" something else. As any sign, a clinical symptom is significant in a system that we can call theory, code, language, or science, i.e., a coherent whole of organized knowledge, working <u>a priori</u> like a system of reference and decodification. The interpretative problem arises when the relationship between a signal or sign and its theory is equivocal or not univocally established, either because the theory is still weak or because the sign is indistinct. Now we shall consider the first case and leave the question of distinction and clarity of signal to the next two points.

We can establish a very strong theory and include in it all the signs that are such because of the theory itself. The theory can be pure fantasy. The history of medicine provides numerous examples of such theories: the connection of humour and stars, and fluxes and horoscopes. In this context, even the hour of birth, even the most irrelevant facts become precise signs. The theory is incorrect because the system of empiric connection of it with the referent (with the field of reality, in particular with disease and the body) is inappropriate or inexistant: but the interpretation of the sign may be univocal and precise.

Since science has placed as limit to the construction of any theorey the continuous compatibility with facts, by way of experimentation, things have become more difficult. Facts have not eliminated the need for the theoretical framework, which is always the indispensable mediator for all human interpretations. But the adherence to reality is linked to the fact that the framework, in any scientific sector, is in continual movement, that it is always transformed because it is always imperfect in relation to the data found, and only in well consolidated sectors does a sign find an adequate theory, that is a linguistic framework of satisfying and unambiguous correspondence with reality. The situation is different in in ordinary language, where daily use necessarily produces a satisfactory relationship between the signs that we continuously use and their interpretation in the terms of ordinary language.

In the field we are now considering, a marker would be an unambiguous sign of cancer in the framework of a theory that was previouly defined: A) the specificity of the tumor condition with respect to any other condition in, or occurrence of the organism; B) the link between the considered marker and that specificity. Only in this way would the data observed "stand for" the tumor -- would it assume the character of the sign.

Unfortunately, such a theory does not yet exist. Cancer research may be defined as an uninterrupted search to define qualitatively distint and specific traits of the tumor cell. What has been defined as "qualitative" (by Warburg up to the recent immunological studies, and the still more recent oncogene theory) has always been interpreted as "quantitative", that is, as "more or less". The tumor cell is highly mimetic, and it is relatively invulnerable for the same reason as it has such ambiguous