DEFINITION AND CLASSIFICATION OF CANCER: MONOTHETIC OR POLYTHETIC?

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ABSTRACT. Since the microbiological revolution, most infectious diseases have been defined and classified according to an etiologic criterion, i.e. the identification of single, external "necessary" causes (for example, Mycobacterium for tuberculosis). This is not the case with cancer. Not only external "necessary" causes of cancer have not been identified, but also the morphological classification cannot be based on univocal criteria. Although "neoplasia" and "anaplasia" appear to be universal attributes of cancer, these events are only quantitative. Neoplastic growth can be fast or slow (development may take weeks or years), and tissue pathologies are difficult to detect from normal tissue in some cancers but are obvious in others. Common special properties of anaplasia appear to be concealed in the wide range of morphologies. In the absence of a coherent morphological definition, and of external necessary causes (such as bacteria for infectious diseases), a mechanistic definition could be adopted. However, unless molecular biology discovers specific mechanistic steps in carcinogenesis, which indicate the existence of "necessary" events in carcinogenesis, we cannot adopt a univocal (monothetic) definition of cancer. The alternative is to use a polythetic definition, according to Wittgenstein's model of a "long rope twisted together out of many shorter fibres."

Key words: cancer, carcinogenesis, disease definition, classification, family resemblances

The purpose of this paper is to examine the criteria for definition and classification of cancer, making a comparison with other diseases, in particular infectious diseases. The basic question is whether a univocal, "monothetic" definition and classification is possible, as in the case of infectious diseases, or "polythetic" criteria are unavoidable.

1. INTRODUCTION

The definition and classification of diseases can be based on three different criteria: *manifestational* (i.e. according to similarities in the signs and symptoms which the patients manifest), *etiologic* (i.e. according to exposure to causal agents), and *mechanistic* (i.e. according to pathogenesis). Diabetes or hypertension are examples of diseases which are defined and classified on a manifestational basis; infectious diseases are classified on an etiological basis; and toxic injuries of the liver are classified according to their mechanism of induction.

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During the 19th century, the discoveries of microbiology led to a shift from a manifestational towards an etiologic classification. For example, before Mycobacterium was identified, there were four entities which overlapped with what was later called tuberculosis: pyrexiae, locales, neuroses and cachexiae. Of the patients affected by these four manifestational entities, only a small part were subsequently included into tuberculosis [1]. So, the identification of the causal agent entailed two radical changes: (1) a subset of patients, affected by four different manifestational entities, was delimited and their manifestations were recognized as belonging to a single disease; (2) the classification of infectious diseases was reconducted to a simpler and more rational etiologic frame. Such a change corresponded, somehow, to a "paradigmatic shift" in disease classification [2].

In the late 19th century, the possibility of redefining infectious nosologic entities on an etiologic basis was offered by two basic concepts: (1) the etiologic agent is a necessary cause of the disease, i.e. all the patients affected by the disease have been exposed to it or vehicle it in their bodies; (2) for most diseases, the definition and classification can be based on unequivocal criteria, with clearcut boundaries between different entities. As far as point 1 is concerned, in fact the cause of many infectious diseases is necessary *by definition*, since tuberculosis or syphilis are diagnosed only after Mycobacterium or Treponema have been isolated in the patient, or their presence has been indirectly demonstrated (for example through a diagnosis *ex juvantibus*, i.e. based on the effectiveness of specific therapy). This, however, does not mean that the correspondence between Mycobacterium and tuberculosis is purely artificial.

What is curious about infectious diseases is that, although the "necessary" cause was identified in the last century for many of them, effective prevention came almost entirely from measures which involved "contributory" causes, like nutritional status, and the levels of hygiene.

Also the second point mentioned above deserves a comment, since the concept of an unequivocal definition of disease, based on a *single common property* (i.e. the etiologic agent) among a range of different manifestational entities has a long history in philosophy and is obviously appealing. The British empiricists in particular, as well as Frege and Russell, cultivated the idea that the *explanation* of a concept (e.g. "infectious disease") corresponds to its definition, which in turn is made possible by the identification of a single common property among all the objects included in that concept. This interpretation of how to define a concept is what philosophers call a *Merkmal*-definition (Merkmal is a German word which means "label", "flag") [3]. In practice, a series of events are classified according to a *Merkmal*-definition when they share a single common property (a label), which is the "monothetic" criterion for a correct classification.

2. DEFINITION AND CLASSIFICATION OF CANCER

Cancer has been classified, up until now, according to a manifestational criterion. The ICD-O Classification makes use of 1089 codes for morphology (i.e. histologic types) and 312 for the topography (sites) [4]. So many categories, particularly as far as the microscopic aspect is concerned, clearly express the failure of any simpler and meaningful classification. Inconsistencies within the existing classifications still remain, and not always the classification has a clearly rational basis. For example, it has been noted that poorly differentiated lymphomas of the stomach would not be grouped with poorly differentiated lymphomas of other organs and nodes, but instead grouped with the well-differentiated lymphomas of the stomach; this is suggested because lymphomas of an organ tend to have in common the pathologic process that introduced lymphoid tissue into the organ [5]. On the contrary, the epidemiology of squamous cell carcinoma of a particular site would be expected to differ more from adenocarcinoma at that site than for the adenocarcinomas to differ from one another. These "epidemiological" recommendations, are sometimes exactly the contrary of the coding instructions within ICD. Pathology and epidemiology should be strictly linked, since morphology is a reflection of pathogenesis, but this is not usually reflected in the existing classifications [5]. In fact, classifications are a mixture of criteria which may serve different purposes. Such purposes may even conflict: for example, the classification of gastric cancer that emphasizes clinical behaviour is in conflict with the important epidemiological separation between "intestinal" and "diffuse" carcinomas, which does not carry enough clinical information [5].

Indeed, even a definition of cancer is not easy. If we consider some recent definitions [6], they usually include "neoplasia" (i.e. proliferation) and "anaplasia" (i.e. loss of normal properties of the cell) as key concepts. According to Ewing, "A neoplasm is a relatively autonomous growth of tissue". According to Ponten, "The functional abnormalities of neoplastic cells may be divided into those which concern the control of position, proliferation, or differentiation". Although "neoplasia" and "anaplasia" appear to be universal attributes of cancer, these events are only *quantitative*. Neoplastic growth can be fast or slow: tumors may take weeks to develop at one extreme, and years at the other. Tissue pathologies are minimal and difficult to detect from normal tissue in some cancers but are obvious in others. "Common special properties of anaplasia appear to be concealed in the profusion of forms that cancer takes. Discovery of some basic anaplastic property, common to even a subclass of neoplastic cells, would seem to require more guided insight or more sophisticated methods than we possess at present" [6].

Invasiveness is a property which is certainly common to many cancers, but

not to all of them. Conversely, normal connective tissue cells like fibroblasts or cells of the lympho-reticular system are able to invade the surrounding tissues. Similarly, *lethality* is not a necessary property of cancer: one person with a malignant neoplasm of the prostate may survive, whereas another with benign hyperplasia might die from urinary obstruction. Also a definition based on molecular changes is not univocal; DNA alterations are found in diseases other than cancer, not all malignant tumours clearly express DNA mutations, and not all carcinogens are mutagens. Therefore, it is only presumed that the unifying, necessary mechanism of cancer induction is some type of damage to DNA.

The idea that cancer cannot be defined on the basis of any single property was clearly expressed already in 1840, by the pathologist Johannes Muller ("On the nature and structural characteristics of cancer"):

> The principles in accordance with which morbid structures must be classified cannot be exclusively derived either from their minute structure, or from their chemical composition. For growths widely differing in their physiological characters and in their susceptibility to cure may present a perfect identity in their minute structure: similarity of structure may coexist with differences in their chemical constituents, or the same chemical characters may be found in growths, between which the greatest diversity exists with regard to their structure, physiological characters, or curableness [7].

The fact that no simple definition of cancer, based on a single common property, can be found is reflected by the persistence of a complex manifestational classification and the inability to overcome a curious phenomenological denomination (cancer = crab).

Could an *etiologic* classification of cancer be developed? Given the present status of knowledge, such a possibility is not offered, partly because no *necessary external cause* of cancer is known, but also because the correspondence between external causes and morphology is rather weak. In other words, whereas the types of manifestations associated with Mycobacterium infection are fairly characteristic – at least from the microscopic point of view – lung cancers due to asbestos seem to be identical to those due to smoking, and chronic myeloid leukemia due to benzene is identical to that caused by ionizing radiation. Even if we could attempt to classify cancer according to its etiology, such a classification would be largely incomplete and would satisfy only some purposes, and not others. In fact, it would not help much to classify separately cancers due to smoking, those due to exposure to aromatic amines, those due to viruses, and so on; and at least 50% of cancers would not fit into such a categorization. Unless a more evident association between specific morphologic aspects of cancer and specific etiologic agents emerges, an etiologic classification would be of little use for medical practice, although it may make sense for practical preventive purposes.

A third alternative to either a manifestational or an etiologic classification is a *mechanistic* classification. For example, cancers could be classified according to

the presence of point mutations, chromosome rearrangement, or an "epigenetic" mechanism. More specifically, they could be distinguished according to the presence or absence of well-defined structural lesions in *ras* or *myc* or other oncogenes, or to the presence of gene amplification, or to mutations in tumor suppressor genes.

Unfortunately, at the present time none of the known mechanisms of cancer induction seems to be specific enough as to be associated with well-recognizable forms of cancer. The activation of single specific oncogenes has been found in different histologic types of tumours and at different sites. Oncogene activation itself has been demonstrated in only about 15% of human cancers; although this proportion might increase with increasing sensitivity of the techniques, it is not a certainty that it could reach 100%. Therefore, lack of specificity in the association with cancer type, and a proportion lower than 100% of cancers in which oncogenes are activated, mean that we are far from the recognition of a single mechanism as a *necessary* cause. Also in the case of chromosomal abnormalities, not all Chronic Myeloid Leukemias present the Ph chromosome, nor all Burkitt's lymphomas the typical 8–14 translocation.

The situation might improve if we were to consider not only the association between disease and oncogene activation, but also the inclusion of chemical exposure. There is some experimental evidence suggesting that ras oncogenes are activated in 100% of liver angiosarcomas induced with vinyl chloride [8]. To reach sufficient specificity, we would therefore have to construct complex entities formed by a cause, a mechanism, and a cancer type. A very recent epidemiological example concerns the mutational spectrum of the p53 tumor suppressor gene; in a study on 19 patients with lung cancer having past exposure to radon in uranium mining, a spectrum of mutations in the p53 gene was found which did not correspond to mutations usually found in lung cancers due to cigarette smoke [9]. However, even in this case only 7 out of 19 patients had some type of p53 mutation.

Therefore, it seems justifiable to state that

> Common special properties of anaplasia appear to be concealed in the profusion of forms that cancer takes. Discovery of some basic anaplastic property, common to even a subclass of neoplastic cells, would seem to require more guided insight or more sophisticated methods than we possess at present [6].

Also it seems justifiable to extend such concepts from morphology to etiology and mechanisms. In fact, an even more radical view has been recently proposed, according to which cancer should be interpreted not as a disease but as a process [10]. Time is a critical dimension in the process of carcinogenesis: whereas classical pathology and clinical oncology have dealt with cancer in the three dimensions of space, a more realistic view would be to consider it as a "four-dimensional process of dysregulation of gene function, leading first to clonal

expansion and clonal heterogeneity of initiated and promoted cells, second to local tissue invasion, and finally to metastasis" [10]. This new perspective, which does not include any reference to a necessary cause or mechanism, emphasizes that carcinogenesis is fundamentally an evolutionary process of aberrant cell differentiation.

3. PERSPECTIVES: "FAMILY RESEMBLANCES"

Problems with the definition and classification of cancer do not seem to find an easy and quick solution. Definition and classification are linked: in the case of infectious diseases, in fact, they have been dealt with successfully by introducing the concept of a *necessary* external cause, i.e. the specific etiologic agent. Since all the existing epidemiological and laboratory evidence is against the possibility of a single cause (either external or internal) for cancer, the following alternatives remain open:

1. The development of molecular biology will make it possible to recognize sufficiently specific mechanisms (corresponding to "necessary" causes), perhaps in association with specific etiologic factors, so as to permit unequivocal definition and classification of cancer. An example might be the mutational spectra of the p53 tumor suppressor gene, with specific mutations corresponding to specific environmental exposures.

2. A second possibility is that already put forward by epidemiologists decades ago, according to which cancer is inevitably a stochastic process which does not require single necessary causes. According to the multistage model, cancer arises as a consequence of the activation of a series of changes (some of which can be represented by oncogene activation, others by chromosomal rearrangements), the sequence of which may or may not be fixed (as suggested by Vogelstein and others [11]). According to this model, therefore, there is a common pathway (or even different pathways without a fixed sequence) upon which different exposures exert their action. No specificity in the association between exposure, mechanism and cancer type is required, nor a single necessary mechanism. For example, exposure to smoking might induce squamous-cell lung cancer through the activation of a certain sequence (ras oncogene activation plus clonal selection of initiated cells), but the same sequence might be activated by UV radiation in inducing melanoma, while benzene would induce leukemia through chromosomal translocations, and dietary carcinogens might induce colon cancer *via* ras mutation plus allelic deletions in different chromosomes (as in Vogelstein's model).

If we accept the second alternative as realistic, it might entail an important consequence, i.e. that even in the future cancer will not be defined and classified

unequivocally. Such a consequence falls within the concept of definition which Wittgenstein proposed, based on the idea of "family resemblances." Wittgenstein noticed that the concept, for example, of "game" could not be explained with a "*Merkmal*"-definition, i.e. finding a single common property (a necessary property) for all games: neither competition, nor the absence of retribution, etc. Also the distinction between some games, wars and jobs is not clearcut, i.e. their boundaries are blurred or clearly overlapping. The *concept* of game (but also formal concepts such as "name", "number" ...) resembles a long rope twisted together out of many shorter fibres [3]. In practical terms, "no property is sufficient for membership in the group, nor is any one necessary" [3], exactly as in the case of cancer. To define a game you need a multiplicity of examples, i.e. the explanation is by "paradigms."

Therefore, if the project of molecular biology, to find the key for an unequivocal definition and classification of cancer, fails, we have to admit that the concept of "family resemblance" must substitute the search for a "*Merkmal*"-definition. From a manifestational point of view, there is very little in common among Chronic Lymphatic Leukemia, a malignant meningioma or breast cancer. From an etiologic point of view, such different things as chemicals, UV radiation, viruses, parasites, vitamines and hormones have been implicated in cancer causation. Finally, I have already described the overlapping of different mechanisms of causation and their apparent lack of specificity.

If the definition and classification of cancer are to be conceived according to the model of a "long rope", we do not need a crucial experiment which reveals a single, ultimate mechanism, but a series of coherent observations confirming each other.

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