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Ecologies of cancer: constructing the "environment" in oncobiology*

Abstract

The influence of environmental factors on the initiation of cancers seems to have been pushed into the background with the trend towards the "molecularization" of explanations of the deregulation of cell growth. If cancer is a "disease of the genes", and if its "logic" is to be looked for at the molecular scale, the environment becomes little more than a "triggering" factor linked to exposure to chemicals, radiations, food additives, bacteria, electro-magnetic fields or other agents. In spite of the widespread recognition that most of the human cancers are linked in one way or another to these "environmental factors", it is often difficult to find out just what the "environment" means in oncobiological research. In recent years, however, new research orientations in the biology of cancer have been trying to develop a more complex, "contextual" understanding of the initiation and progression of cancers, exploring the links and interaction between genetic and "environmental" processes, and articulating approaches drawing on molecular biology, immunology and epidemiology which meet on a "trading zone" where biologists, biochemists, pathologists, nutritionists and public health specialists meet. The "environment" is still an ill-defined object,

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however, whose fuzzy definition and identification contrasts with the more "standardized" views of molecular genetics.

Drawing on ethnographic research on oncobiology, this paper focuses on the way researchers construct the "environment" and "environmental factors", as part of emerging ecologies of cancer - that is, of representations of cancer as the emerging result of sets of heterogeneous processes. This, in turn, is the outcome of a range of ecologies of practices in oncobiology, which "accomplish" the ecologies of cancer through the use of particular techniques and approaches.

> ... the majority of human cancers is traceable to environmental exposures and therefore potentially preventable (WHO, 1964)
>
> It has been estimated that about 75% to 80% of all cancer in the United States is due to environmental factors (Fraumeni, *et al.*, 1993).
>
> By making country-to-country comparisons, epidemiologists could conclude that 70 to 90 percent of American cancer is environmentally caused (Varmus and Weinberg, 1993)
>
> The overwhelming majority of human cancers are of environmental origin (Manuel Sobrinho-Simões, 1994).

The assertion that the vast majority of human cancers have environmental causes has become almost a commonplace for those who are involved, in any capacity, with cancer prevention, treatment or research. Even those who are most vocal in expressing their belief that, ultimately, our understanding of cancer and our capacity to act upon it depend on the understanding of its molecular mechanisms seem to share this idea[1]. More recent approaches in the biology of cancer have tried to articulate in an explicit way cell- or molecular-centered views of cancer with the environment, as is clear in this definition given by a researcher: "Cancer is a

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[1] Harold Varmus and Robert A. Weinberg, *Genes and the Biology of Cancer*, New York, Scientific American Library,1993, especially p. 50. More than 90 percent of human cancers occur in epithelial cells - including those of organs like the breast, lung, stomach, liver, mouth, uterus, colon, bladder, cervix or skin -, which is presumably linked to their "exposed locations" putting them "in direct contact with many carcinogenic agents" (*ibid.*, p. 36). On the "geneticization" and "molecularization" of cancer, see Joan H. Fujimura, *Craftng Science: A Sociohistory of the Quest for the Genetics of Cancer*, Cambridge, Massachusetts, Harvard University Press, 1996, and, for an account by a core participant, Robert A. Weinberg, *Racing to the Beginning of the Road: The Search for the Origin of Cancer*, London, Bantam Press, 1997.

deregulation of the proliferation and differentiation of cells which makes them less dependent on environmental regulatory mechanisms"[2].

According to historian Robert Proctor, the causes of cancer are "largely known - and have been for some time"; they include "chemicals in the air we breathe, the water we drink, and the food we eat..., bad habits, bad working conditions, bad government and bad luck - including the luck of your genetic draw and the culture into which you're born"[3]. He documented in great detail the long history of the association of cancer with environmental causes, an idea which gained a secure foothold in the 1960's. But Proctor also showed that definitions of the "environment" in this respect are all but precise or homogeneous, and that defining what the "environment" is for the purpose of identifying causes of cancer is a highly charged and politically sensitive operation.

The "environment" may range from precisely identified agents - as in Wilhelm C. Hueper's focus, in the 1940's, on exposure to "carcinogenic chemical, physical and parasitic agents"[4] - to a range of heterogeneous entities, from "naturally" occurring carcinogens to human-made substances, from place-related agents to life-style practices. In 1969, responding to what he considered to be an excessive and unwarranted focus on industrially produced carcinogens and on workplace exposures, John Higginson stated that "the environment" included much more than industry - diet, sexual behaviour, hormonal influences, social pressures, etc[5]. In a 1979 interview, he expanded his thoughts on what "the environment" meant:

> Environment is what surrounds people and impinges on them. The air we breathe, the culture you live in, the agricultural habits of your community, the social cultural habits, the social pressure, the physical chemicals with which you come in contact, the diet, and so on. A lot of confusion has arisen in later days because most

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[2] Manuel Sobrinho-Simões, interview, 27.12.94. More recently, the same researcher redefined "deregulation" in terms of an imbalance between cell proliferation and differentiation and cell death (interview, 23.02.98).

[3] Robert N. Proctor, *Cancer Wars: How Politics Shapes What We Know and Don't Know About Cancer*, New York, Basic Books, 1995, p. 1.

[4] Quoted in *ibid.*, p.44.

[5] Quoted in *ibid.*, p.56.

people have not gone back to the early literature, but have used the word environment purely to mean chemicals[6].

The business of defining the environment involves assigning responsibilities, and thus is a highly conflicting field. Different definitions of what is and is not "environmental" were often used to dilute or minimize the alleged impact of industrial carcinogens on human health, or to assign some carcinogenic effects to "lifestyle" choices, and thus to individual behaviour (as in the case of smoking or diet). This has been a common line of argument of conservative opponents of environmental and workplace regulation, which reached its most effective political expression in the efforts of Reagan's administrations, in the United States, to dismantle or coopt the regulatory apparatus that had been built during the 1970's. The effects of these initiatives on the prevention of cancer and on the regulation of carcinogens led Proctor to state that "Ronald Reagan may have been the most powerful new carcinogen of the 1980's"[7].

The recent development of "genetic" approaches to cancer has raised additional questions on the modes in which environmental "triggers" act upon cellular and molecular mechanisms which, in turn, are taken to be the "proximate" causes of cancer. These developments have confirmed a trend towards centering the study of carcinogenesis - the cancer-generating action of certain "environmental" factors - on the processes of mutagenesis - the genetic mutations associated with cancer following exposure to carcinogens[8]. The study of mutagenesis brought with it a more complex understanding of the process of carcinogenesis, particularly of its "multistage" nature and of the differences between carcinogens acting as initiators or as promoters of cancerous growth[9]. It should not be forgotten, however, that the focus on mutagenesis requires in vitro procedures which do not subsume all the processes and conditions associated with

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[6] Quoted in *ibid.*, p. 57.

[7] *Ibid.*, p. 100.

[8] For a detailed, reader-friendly discussion of mutagenicity, see Varmus and Weinberg, *op. cit.* in note 1, supra. pp. 61-65.

[9] Ibid., pp. 160 ff.; for detailed discussions of viral, chemical and physical carcinogenesis, see Chapters 10-12 of Vincent T. DeVita, Jr., Samuel Hellman and Steven A. Rosenberg (eds.), *Cancer: Principles and Practice of Oncology*, Fourth Edition, Philadelphia, J.B. Lippincott Co., 1993.

carcinogenesis affecting organisms *in vivo*. Both epidemiological and laboratory studies are still required for a "complete" or "complementary" (in the Bohrian sense) description of cancer and of carcinogenesis[10]. Recently developed hybrid procedures (like molecular epidemiology) have not made more conventional approaches redundant, as we shall see, just as they have not made the identification and definition of the "environment" easier or more precise.

The growing emphasis of research programs and of research funding on the understanding of biological mechanisms underlying cancer, on its early diagnosis and on effective therapies has tended to weaken the effort to develop effective interventions for prevention, which are invariably linked to the identification of environmental conditions as the ultimate "causes" of cancer. Among these, smoking is a particularly relevant contributor. It is highly significant that, as far as the tobacco-lung cancer link is concerned[11] - which has been demonstrated for decades, to the satisfaction of most scientists, regardless of their political leanings or disciplinary affiliations by scores of epidemiological studies (indeed, it is probably the only consensual result attained by research on cancer) - the tactics, widely used by the tobacco manufacturers, of "nourishing doubt" by invoking the uncertainty of the conclusions of epidemiological studies as to the proximate causal link between smoking and lung cancer suffered a severe blow only when the "proof" of the molecular mechanisms underlying the link was established and published. I shall return to this point later.

The consensus of scientists, clinicians, regulators and politicians of different leanings and persuasions around smoking as a cause of cancer probably rests upon the ambiguous status of smoking as an "environmental" factor. Whereas it is possible to put the blame for its harm on the tobacco

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[10] A "complementary" description of a phenomenon as it is generated in experimental or observational practice requires that different procedures - which cannot be integrated - be used in order to provide a "complete" description of the phenomenon of interest for the practical purposes of the research. This seems to be a routine requirement of work in the biomedical sciences. For a detailed treatment of the origins of the notion of complementarity in association with Niels Bohr's work, and for some suggestive insights on how it can be used in cultural and science studies, see Arkady Plotnitsky, *Complementarity: Anti-Epistemology after Bohr and Derrida*, Durham, North Carolina, Duke University Press, 1994.

[11] See Proctor, *Cancer Wars*, *op. cit.*, chapter 5, especially pp. 105-110.

industry or on the non-existent or shallow regulation of exposure to tobacco smoke by non-smokers, conservative antitobacco activists and spokespersons have rather included it in the class of "life-style" factors, together with habits related to eating, drinking, exercise or sex, which ultimately displace the responsibility for the harm to the individual and to his choices. Smoking is, in fact, the most striking example of the difficulties of defining the "environment" and how it relates to cancer.

This difficulty is easy to identify in the practice of research on cancer, including cancer biology. Since the authority for defining causes and attributing responsibilities as far as cancer is related rests upon the routine invocation of scientific research, it is important to inspect more closely the ways in which the "environment" is defined and specified as a set of "do-able" concepts and procedures in scientific practice. In other words, how is the environment constructed in and through research practices in cancer biology? This raises another intriguing question: is there any explicit link between the way the environment is constructed and performed in cancer biology and approaches to the environment as developed in ecology? This question will not be dealt with here, since it would require an extended and detailed discussion of the languages and imageries of medicine and of biomedical research - and, in particular, of the concepts of "system" and "specificity" -, which is beyond the scope of this paper[12]. I shall briefly return to this point in the conclusion, to suggest that the idea of ecologies of cancer may be particularly suited for dealing with the complex of practices

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[12] It would be interesting, in this light, to explore the history and current practices of immunology. As Anne-Marie Moulin showed, in its early stages, in the 19th century, research and clinical practice focusing on immune mechanisms and immune responses routinely drew on the notion of "milieu". The later definition of immunology as the science of self-other distinction suggests a further analogy with the language of environment-organism relations. The difficulty in developing and "ecological" approach in medicine and the biomedical sciences, including immunology, may well be linked to the centrality of the concept of specificity and to the way it came to dominate research and medical practice. See Anne-Marie Moulin, *Le Dernier Langage de la Médecine: Histoire de l'Immunologie de Pasteur au SIDA*, Paris, Presses Universitaires de France,1991; Alfred I. Tauber, *The Immune Self: Theory or Metaphor?*, Cambridge, Cambridge University Press,1994; Scott H. Podolsky and Alfred I. Tauber, *The Generation of Diversity: Clonal Selection Theory and the Rise of Molecular Immunology*, Cambridge, Massachusetts, Harvard University Press, 1998.

associated with the modes of construction of cancer as an object of research, medical practice and prevention. Stengers's concept of *ecologies of practices*[13] and the "ecological" approach championed by symbolic interactionist/pragmatist sociology[14] are particularly relevant, here. They suggest that the construction of the environment should be dealt with as part of these ecologies of practices[15], and that ecologies of cancer and ecologies of practices dealing with cancer should be treated as coterminous for all practical purposes.

An ethnographic study of oncobiological research in a Portuguese cancer research institution provided a first-hand involvement with the modes of construction of the environment in research practice. The institution is the Centre for Research in Biopathology and Oncobiology/Institute for Pathology and Molecular Immunology of the University of Oporto (CIBO/IPATIMUP). It is an independent, non-profit research centre affiliated with the University of Oporto, funded by a diversity of public and private sources. The senior generation of scientists working at the Centre are in their 40's. They include a signficant proportion of physicians with PhD's in pathology, who have played a prominent role in shaping complex, multi-scale and multifactorial approaches to cancer. The younger researchers, most of them graduate students or postdocs, have backgrounds in biology, for the most part. The pivotal unit of the centre, the tumour pathology laboratory, which receives tissue samples and identifies cases of cancer, is staffed by technicians trained in a set of techniques for the diagnosis of cancer pathologies. The approaches used in the various units of the centre range from histomorphological analysis of tissues to immunochemistry, static and flow cytometry, immunophenotyping and molecular biology. The centre has

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[13] Isabelle Stengers, *Cosmopolitiques, Tome1: La Guerre des Sciences*, Paris/Le Plessis-Robinson, La Découverte/Les Empêcheurs de Penser en Rond, 1997.

[14] See the contributions to Susan Leigh Star (ed.), *Ecologies of Knowledge: Work and Politics in Science and Technology*, Albany, New York, State University of New York Press, 1995.

[15] See Lisa M. Mitchell and Alberto Cambrosio, "The invisible topography of power: electromagnetic fields, bodies and the environment", *Social Studies of Science*, vol. 27, 1997, pp. 221-271, for an exemplary study of how environmental exposures and risks are constructed and circulate across different settings, through the work of identifying, mesuring and monitoring the effects of electromagnetic fields.

strong collaborative links with other institutions in Europe (especially Scandinavia, the Netherlands, Britain and France), Africa (Mozambique), Latin America (Brazil, Mexico, Chili), the United States and China. Collaborations include visiting professorships, participation in scientific meetings and editorial boards of scientific journals, refereeing, joint research projects, training courses, exchange of graduate students and consultancy in cancer diagnosis. Both the range of activities and orientations and the heterogenous background of researchers and students require the use of devices for establishing a common language, shared theoretical orientations and common technical skills. This is achieved both through teaching and training programs with a heavy "hands-on" component and the use of common textbooks, which are routinely drawn upon as teaching and reference material[16].

Two of these textbooks were particularly useful in identifying the set of concepts and approaches more widely used in oncobiological research and routine diagnosis of cancer. The environment appears, in these textbooks, either as part of epidemiological approaches or of "environmental pathology". As we shall see, the latter is more resonant with the kind of work currently done in oncobiology whenever there is an interface between "basic" research and clinical problems and where different approaches meet in a "trading zone"[17], as is the case in the centre. After a discussion of how

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[16] For more detailed descriptions of the centre, of its members and of its work, see João Arriscado Nunes, "A política do trabalho científico: articulação local, conversão reguladora e acção à distância", in Maria Eduarda Gonçalves (ed.), *Ciência e Democracia*, Venda Nova, Bertrand Editora, 1996, pp. 251-276; *id.*, "Entre comunidades de prática e comunidades virtuais: os mundos da ciência e as suas mediações", *Oficina do CES*, 70, 1996; *id.*, "Ecologias do julgamento na actividade científica: a construção do viável entre o ajustamento e a justificação", *Oficina do CES*, 89, 1996; *id.*, "Escala, heterogeneidade e representação: para uma cartografia da investigação sobre o cancro", *Revista Crítica de Ciências Sociais*, 46, 1996, pp. 9-46; *id.*, "The transcultural lab: articulating cultural difference in/through scientific work", *Oficina do CES*, 84, 1996; *id.*, "Shifting scales, articulating cancer: towards a cartography of oncobiological research", *Oficina do CES*, 98, 1997; *id.*, "Publics, mediations and situated constructions of science: the case of microscopy", *Oficina do CES*, 103, 1997.

[17] The expression was originally used by Peter Galison in the context of the history of physics. For a detailed discussion, see Galison, *Image and Logic: A Material Culture of Microphysics*, Chicago, University of Chicago Press, 1997, Chapter 9. Ilana Löwy has proposed specific

the "environment" is defined and turned into concepts and "do-able" research objects in these two texts, I shall focus on the practical accomplishment of a study carried out at the centre, which provides an interesting example of a multifactorial and multiscale approach sensitive to environmental conditions and to the relationship between "ultimate" and "proximate" causes of gastrointestinal pathologies and, in particular, of stomach cancer. The materials used range from ethnographic materials and interviews with researchers to research proposals, reports and publications. In the conclusion, the question of an ecological approach to cancer and cancer research will be taken up again.

Cancer epidemiology: exposures and causes

Epidemiology is defined as "the study of variations in disease frequency among population groups and the factors that influence these variations"[18]. Unlike clinical approaches and other modes of doing biomedical research, epidemiology deals with populations rather than individual cases, with the frequency of the occurrence of diseases and with the quantification of risks associated with different causes, and with the distribution and determinants of disease. In the case of cancer, epidemiological studies allow the "detection and quantification of the risks associated with specific environmental exposures and host factors"[19]. Unlike laboratory studies, epidemiology deals with human populations, and not with

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extensions of its use to the biomedical sciences and medicine and to their articulations and forms of cooperation; see Löwy, "The strength of loose concepts: boundary concepts, federative experimental strategies and disciplinary growth: the case of immunology", *History of Science*, Vol. xxx, 1992, pp. 371-396; *id.*, *From Bench to Bedside: Science, Healing, and Interleukin-2 in a Cancer Ward*, Cambridge, Massachusetts, Harvard University Press, 1996, especially pp. 247 ff.

[18] Joseph F. Fraumeni, Jr., Susan S. Devesa, Robert N. Hoover and Leo J. Kinlen, "Epidemiology of Cancer", in DeVita *et al.*, *Cancer, op. cit.* (see note 9, supra), pp. 150-181, quote on p. 150.

[19] *Ibid.*, p. 151.

animal models or experimental systems involving the manipulation of biological materials.

The notion of "environmental exposure" is at the centre of cancer epidemiology, and its definition and operationalization is a crucial step in any study. But it is also highly contested and a frequent object of controversy. Proctor showed in considerable detail the inextricability of the scientific and the political in defining what the environment is, and what environmental exposure means.[20] A further difficulty relates to the very distinction of "environmental exposures" and "host factors". A textbook in environmental pathology provides an instance of this problem. In a section on "host factors" related to lung diseases, the former are said to include "genetic, acquired, and environmental factors"[21]. Environmental factors may be turned into "host" factors - that is, into incorporated factors which have an environmental origin - such as those resulting from prolonged exposure to pathogenic agents in the workplace, for instance. Racial and ethnic characteristics, usually assigned to individuals, are also known to be strongly related to influences which would best be described as environmental. Some diseases associated with racial or ethnic background are often related to cooking practices or eating habits, for instance, and their incidence may be reduced or eliminated following migration to a place where practices and habits are different - as is the case with the different incidence of stomach cancer among Japanese residing in Japan and Japanese migrants to the United States.

An assertion repeatedly found in epidemiology textbooks is that epidemiological studies do not allow direct identification of causes of cancer, but only of associations between the presence of the disease in a given population and the risks of developing certain types of cancer. Relating associations to causes requires making causal inferences. These, in turn, are particularly important when it comes to establishing preventive measures. The case of the association between smoking and lung cancer is a classical illustration of this process, to which I shall return later. Beyond its role in both providing information relevant to prevention and the means to

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[20] Proctor, *op. cit.*

[21] A. R. Gibbs and J.C. Wagner, "Dust diseases", in James O'D. McGee, Peter G. Isaacson and Nicholas A. Wright (eds.), *Oxford Textbook of Pathology, Volume 1: Principles of Pathology*, Oxford, Oxford University Press, 1992, p. 722.

assess prevention measures and programs, epidemiological studies play two additional roles. On the one hand, they provide leads to the understanding of the etiology of different forms of cancer, namely through the identification of "peculiarities in the distribution of the disease"[22]. These, in turn, often offer useful insights for further studies on the mechanisms of carcinogenesis, using laboratory approaches and animal models. On the other hand, epidemiology allows risks associated with different exposures (carcinogenic and protective) to be quantified, either by resorting to the computation of different rates - like incidence, mortality or prevalence rates - or through the controversial method of drawing dose-response curves[23].

It should be clear, by now, that two crucial terms in cancer epidemiology are "exposure" and "risk". How they are defined and turned into observable and manipulable entities is a central problem for cancer epidemiologists. In fact, the mode of existence of the "environment" in epidemiology is dependent on the definition of exposure: who is exposed to what, where, when and how? Exposure, in turn, is the starting point for the quantitative assessment of the risks attributable to each specific type of exposure[24].

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[22] Fraumeni *et al.*, *op cit.*, p. 151.

[23] Proctor, op. cit., pp. 153-173. The measurement of exposure and its centrality to both "expert" and "lay" assessments of the effects of electro-magnetic fields is analysed and discussed in great detail in Mitchell and Cambrosio, *op. cit.* in note 15, supra.

[24] Strictly speaking, the term "risk" should be used to refer to those situations where the number of events associated with a given type of exposure can be related to a population at risk. It is common, however, to see it used in epidemiological studies in a more "qualitative" way, conveying a "strong" sense of likelihood of an association of exposure and occurrence of an event. The literature in the social sciences dealing with risk is extensive and growing. Risk has become a highly popular subject in the wake of Ulrich Beck's *Risikogesellschaft* thesis and of the ensuing debates (see U. Beck, *The Risk Society: Towards a New Modernity*, London, Sage,1992). Some of the most interesting recent work on this theme focuses not only on the assessment and regulation of risks - environmental risks in particular -, but, more generally, on the way different actors, "lay" or "expert", construct and define notions of risk; see Sheila Jasanoff, *The Fifth Branch: Science Advisers as Policymakers*, Cambridge, Massachusetts, Harvard University Press, 1990; Alan Irwin, *Citizen Science: A Study of People, Expertise and Sustainable Development*, London, Routledge,1995; Alan Irwin and Brian Wynne (eds.), *Misunderstanding Science: The Public Reconstruction of Science and*

One of the most widely used textbooks in oncology[25] subsumes the main causes of cancer under the rubrics "tobacco", "alcohol", occupational hazards", "environmental pollution", "ionizing radiation", "solar radiation", "medication", "viruses" (and other infectious agents), "diet and nutrition" and, finally, "genetic susceptibility". The latter is usually excluded from the range of factors labeled as "environmental", but gene-environment interactions are an important focus of attention in research in cancer biology, particularly in molecular epidemiological approaches, as we shall see later. Table 1 provides a more detailed specification of the elements involved in the notion of "environmental causes" of human cancer.

The table is constructed as a series of horizontal relations between the site of occurrence of a particular form of cancer, the type of exposure generating a risk of cancer on that site and the carcinogenic agent (usually a chemical substance, a physical process or a biological agent) involved. A table like this is both the outcome of epidemiological and laboratory studies of cancer and the basis for launching and interpreting new epidemiological studies. Notice that "type of exposure" usually involves a complex of factors, including, social, economic, cultural and political ones, which often are edited out when exposure is translated into "agent". Although the table is organized around an alphabetical ordering of agents, it is possible to use any column and any "cell" in the column as the entry point for identifying relevant relationships between exposure, agent and site. This means that a previous definition of a type of exposure may guide the search for populations at risk, and the inverse is also true. Identifying patterns of distribution of cancer within given populations and across populations, in space - as is the case when spatial clusters of given kinds of cancers - and over time, may point towards the identification of the types of exposure

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Technology, Cambridge, Cambridge University Press, 1995; Scott Lash, Bronislaw Szerszynski and Brian Wynne (eds.), *Risk, Environment and Modernity: Towards a New Ecology*, London, Sage, 1996. For recent work dealing with health risks, see the contributions to Bob Heyman (ed.), *Risk, Health and Health Care: A Qualitative Approach*, London, Arnold, 1998. The Introduction by the editor (pp. 1-23) offers an useful review of definitions and uses of the concept, and Chapters 1-5 deal with different issues related to the meanings and uses of "risk" and related concepts - like "probability" - in the health sciences and health care.

[25] De Vita *et al.*, *op. cit.* pp. 170-179.

deemed relevant, and of the agents involved. In these instances, exposure is deduced or assumed from patterns of distribution of the different types of cancer.

Other possibilities are suggested for how to read this table. The same site may be subject to different types of exposures and to the action of different carcinogenic agents. Conversely, the same type of exposure or the same agent may affect a variety of sites. Some readings, however, are precluded by the mode in which the table is constructed. Some published studies suggest that a given type of exposure or a given agent may have a carcinogenic effect on a given site and a protective effect on another; interactions and synergies between agents or types of exposure may arise; and other pathogenic states and agents may be involved in exposure to given types of cancer. I shall return to these issues later. For the moment, it is important to stress that how a table is constructed, or how an inscription is crafted, allow certain readings to be performed and preclude some others.

Epidemiology can be divided into two major types of approaches: *descriptive* and *analytical*. Descriptive approaches include studies of the distribution of disease frequency, expressed in the form of rates (of incidence, prevalence, mortality or case-fatality), referring to a given population at a given time. Exposure is often assumed or taken-for-granted for all practical purposes, on the basis of previous knowledge of the population under study or of populations with characteristics defined as similar to the ones of the population of interest; or of the presence, in the area of residence of the population, of "factors" assumed to constitute a carcinogenic risk or, inversely, to provide protection against certain forms of cancer. Descriptive studies generally use aggregate data obtained from cancer registries, often based on special surveys, hospital-based registries of cancer patients or death certificates. These sources provide different kinds of information and refer to populations constructed on the basis of different principles of inclusion and selection. It is often the case that descriptive studies resort to what is commonly referred to as the *correlational* or *ecologic* approach (interestingly, this is one of the rare uses of the word *ecologic* in studies dealing with the environmental causes of cancer...), in which "the rates of disease in populations are compared with the geographic or temporal distribution of suspected risk factors"[26]. The problems with this

[26] Fraumeni *et al.*, *op. cit.*, p. 153.

approach are well known, particularly in relation to the dangers of the *ecologic fallacy*, that is, jumping from conclusions derived from data for populations to conclusions pertaining to individuals or to specific sub-groups within the population, particularly if one takes into account the possible existence of "confounding factors", which tend either to obscure or to give unwarranted visibility to the factor of interest. This problem generated a lot of controversy on the relationships between lung cancer and exposure to occupational hazards among asbestos workers or miners when the latter were smokers. The reference, in the passage just quoted, to "suspected" risk factors, rather than to precisely defined and quantified ones, is symptomatic of these problems.

Analytical studies are used to test etiologic hypotheses. For that purpose, individuals within populations are selected, and information on suspected risk factors is collected. Individuals are divided in groups according to exposure to the risk factor(s) and/or occurrence of the disease of interest. Other risk factors or potentially confounding variables are controlled, so that "the risk of disease associated with exposure can be estimated". The groups should be large enough and "the time intervals between initial exposure and tumor onset sufficiently long to identify the lowest excess risk considered important to detect"[27]. There are three types of analytical studies: cohort studies, case-control studies and experimental studies. The first two types are based on the constitution of two groups, one with and the other without a particular exposure. Cohort studies follow individuals in both groups over time, comparing incidence and mortality rates. "The cohort approach is used mainly when it is possible to evaluate high exposures in clearly defined subgroups of the population", particularly those subject to an easily identified exposure, like smoking, medically administered drugs or radiation or occupational hazards[28]. Case-control studies are based on the constitution of two groups, one with the disease of interest, the other one without. Individuals in both groups should be matched for relevant characteristics, so that they can be compared across groups. Information on past exposures is then collected, so that differential

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[27] *Ibid.* , p. 165.

[28] *Ibid.*

exposures can be associated with the presence or absence of the disease[29].

A third type of analytical studies includes so-called intervention or experimental studies. They are often used for confirming associations suggested by studies of the other two types, for instance, in assessing the effects of diet or nutrition. In this type of study, exposures are manipulated, which may raise thorny ethical issues.

Exposure itself is often based on reporting by the subjects included in the study. A problem arising in case-control studies in particular - which rely on the reporting of past exposures - is that of biases leading to under-or over-reporting of exposures. This, in turn, may be closely linked to social or cultural characteristics associated with the particular populations, groups or settings the subjects are part of. In a recent editorial published in the *Journal of the National Cancer Institute*, two senior members of the NCI, Douglas Weed and Barnett Kramer, discussed this problem in relation to the contradictory results of case-control studies of the possible links between induced abortion and breast cancer. A study of women from two areas of the Netherlands - the more "liberal" western regions and the more "conservative" southeastern regions - enrolled in a study of the use of oral contraceptives and of breast cancer came up with some disturbing results. The association between induced abortion and breast cancer was very weak in the liberal regions, whereas it was very strong in the conservative regions. The adjusted relative risk was 1.3 for the former and 14.6 for the latter. As Weed and Kramer suggest, this and other work on the subject

> give credence to the idea that the modest relationship reported in studies stretching back four decades can be explained, at least in part and perhaps even in large measure, by reporting (recall) bias. The bias arises when women are asked whether they have ever had an abortion. For very personal and perhaps even subconscious reasons, women - especially healthy women - underreport this emotionally laden decision[30].

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[29] Fraumeni *et al.*, *op. cit.*, p. 165.

[30] Douglas L. Weed, Barnett S. Kramer, "Induced abortion, bias, and breast cancer: why epidemiology hasn't reached its limit", *Journal of the National Cancer Institute*, Vol. 88, No. 23, 1996, pp. 1698-1700, quote on p. 1698. See also, for a more general debate on

This is part of the more general problem of how to define exposure, of how to specifiy it in terms of quantifiable variables and of how to evaluate the reliability of that kind of data. The problem can be rephrased in terms of how to define the mode of existence of the environment in these studies. Since they deal with individuals and not with populations, many of the environmental exposures or factors invoked in descriptive studies often appear as incorporated in individuals, as the result of past exposures. The already mentioned difficulty of drawing a clear boundary between environmental factors and host factors is particularly conspicuous here.

Epidemiological studies generate three main kinds of inscriptions[31]: tables, maps and graphs plotting time trends or frequency distributions. In descriptive studies, each of these types of inscriptions includes explicit information on place, time or variables related to age, sex, race and ethnicity, socio-economic status (usually based on income and educational level), as well as measures of incidence, prevalence or mortality from different types of cancer. Variables related to exposure are usually absent from this kind of studies. Instead, patterns or trends for incidence, prevalence or mortality may be used as "surrogates" for environmental conditions or exposures[32]. The "environmental" component of cancer causes is often estimated by subtracting rates for the population known to have the lowest recorded risk from the rates for the population under study. "The lowest risk is considered the baseline level for so-called spontaneous tumors that in theory cannot be prevented"[33]. In these cases, the environment is treated as the sum of the "factors" associated with cancer beyond the common baseline level of tumors occurring "spontaneously".

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epidemiology, Gary Tauber, "Epidemiology faces its limits", *Science*, Vol. 269, 1995, pp. 165-169 and the ensuing dscussion in the following issue of the same journal, pp. 1325-1328.

[31] Bruno Latour and Steve Woolgar, *Laboratory Life: The Construction of Scientific Facts*, Princeton, Princeton University Press, 1986 (2nd revised edition); B. Latour, "Drawing things together", in Michael Lynch and Steve Woolgar (eds.), *Representation in Scientific Practice*, Cambridge, Massachusetts, MIT Press, 1990, pp. 19-68; Michael Lynch, *Art and Artifact in Laboratory Science: A Study of Shop Work and Shop Talk in a Research Laboratory*, London: Routledge and Kegan Paul, 1985.

[32] Fraumeni *et al.*, *op. cit.*, p. 168.

[33] *Ibid.*, p. 154.

It is noteworthy that exposure and risk are usually not specified in a quantitative mode in most descriptive studies, and that in spite of all the qualifications concerning the need to separate "statistical association from spurious coincidence" and "causal associations from noncausal"[34], causal inferences are often advanced as highly plausible, if not inescapable, in many epidemiological studies, both descriptive and analytic. Attempts were made, in the course of debates over the smoking-lung cancer link, to establish guidelines to serve as criteria for assessing the plausibility and credibility of causal inferences. These included the assessment of the strength and specificity of associations, the presence of dose-response gradients, the consistency and reproducibility of results, the biological plausibility and coherence of the results, and the appropriateness of the temporal sequence observed[35]. But, as this enumeration reveals, these criteria not only include allegedly "objective" and measurable procedures, but also others based on a sort of pragmatic "reasonableness". Indeed, as Fraumeni and his co-authors point out,

> [c]ausal inferences from epidemiology usually develop gradually after taking into account all relevant biologic information, including laboratory studies. Although epidemiologic observations can accumulate to the point at which causation is virtually inescapable, strictly speaking it is not possible to prove causality by these means alone. Nevertheless, causation can often be shown to be sufficiently probable to provide a compelling basis for prevention and public health action and certainly so in the case of cigarette smoking and lung cancer[36].

Causal inferences may thus develop gradually through the accumulation of epidemiologic observations, to a point when it becomes virtually inescapable to identify causal links, although this does not mean that strictly speaking causation can be proved. The mutual reference between epidemiologic and laboratory studies allows interpretations based on all relevant biological information to become compelling assertions of a causal link which, if it is insufficient as a scientific proof is, however, sufficient to warrant preventive measures and interventions. In the absence of what

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[34] Weed and Kramer, *op. cit.*, p.1698.

[35] *Ibid.*, p. 169.

[36] *Ibid.*, p. 170; the emphases are added.

the authors take to be strict standards of proof, causal inferences gain their compelling quality from a consensus among researchers and clinicians on how to interpret mutually supporting information from different sources, produced using a variety of procedures[37]. Rigour and precision are linked, as in other kinds of scientific practice, to the possibility of quantifying results. The number of subjects or the size of the populations included in epidemiological studies are seen as a crucial criterium for evaluating etiologic hypotheses and assessing levels of risk. In fact, however, judgments on exposure and risks associated with exposure are usually put together using a version of what Garfinkel named the "documentary method of interpretation"[38]. A remarkable discussion of the problems related to judgment and inference in epidemiological studies is provided by Weed and Kramer, which is worth quoting at length:

> Making these judgments in the face of considerable uncertainty and complexity is a serious matter, requiring prudence and the superimposition of qualitative methods on quantitative... Typically, inferential judgments appear in reviews, editorials, textbook chapters, and reports of organizations. The judgments in these publications reflect the scientific values of the author, which may differ as a result of training, professional development, and other factors. Put another way, the evidence does not "stand alone", not in medical science and not in journals that report its results. There is no proof akin to that found in theoretical mathematics. Evidentiary assessments, even when expressed in quantitative terms, are more qualitative than most lay persons appreciate. Although quantitative concepts are undeniably relevant, in the end our judgments are qualitative. Even strength of association, a very quantitative idea, enters into judgments in terms of the very qualitative consideration of the extent to which unknown (and therefore unmeasurable) confounders exist[39].

Apart from the reference to an epistemological ideal of precision - theoretical mathematics -, the authors' comments are very much in line with

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[37] Fraumeni *et al.*, *op. cit.*, p. 169.

[38] Harold Garfinkel, *Studies in Ethnomethodology*, Englewood Cliffs, New Jersey, Prentice-Hall,1967.

[39] Weed and Kramer, *op. cit.*, p. 1698.

some of the arguments of constructionist approaches in science and medicine studies. They fail to identify, however, how some accounts become more compelling than others, and for whom they are compelling.

The smoking-cancer link

The work on the smoking-lung cancer link is an interesting instance of consensus among scientists and clinicians but also of the failure to provide compelling evidence for the link both for the tobacco industry and for the legal system.

The smoking-lung cancer link has been identified both in descriptive and in analytical epidemiological studies. The risk of cancer associated with smoking or with exposure to tobacco smoke was established directly through analytical studies, where both exposure and the degree of exposure could be determined through the individual identification of smokers and non-smokers, and the quantities and duration of smoking for the former, as well as a range of indirect clues to exposure by non-smokers (such as being married to a smoker, or living together with one or more smokers, or working in an environment exposed to tobacco smoke). Indirectly, the same association was suggested through descriptive studies of age-patterns and differences between the sexes and their evolution over time as far as incidence of lung cancer is concerned. The recent "flattening" of the curves of incidence of lung cancer among men and the concurrent rise in curves for women, for instance, can be plausibly interpreted as being linked to changes of exposure associated, in turn, with changes in the habit of smoking.

Ever since these associations were established through epidemiological studies, most researchers and medical practitioners accepted the results of these studies as compelling evidence of the existence of a link. This was largely due to a widely held consensus on the value of epidemiological information and on its reliability, based on the shared professional and scientific cultures of medical practitioners and biomedical researchers. The tobacco industry, however, refused to

recognize that the association had been proved, invoking the inexistence of evidence based on biochemical and molecular biological research on the mechanisms enacting the link. Only after the publication in *Science*, in 1996, of a paper by Mikhail Denissenko and his co-authors demonstrating the molecular mechanisms through which benzo[*a*]pyrene - a carcinogenic compound present in cigarette smoke - induced mutations in the *p53* tumor suppressor gene, did tobacco companies start agreeing on settlements for compensation of lung cancer patients whose condition was related to smoking. The opening and closing sentences of the abstract of the paper are affirmative and straightforward: "Cigarette smoke carcinogens such as benzo[*a*]pyrene are implicated in the development of lung cancer... These results provide a direct etiological link between a defined chemical carcinogen and human cancer"[40]. The ultimate authority of science does not rest upon a - no matter how compelling for scientists as for "lay" people or policy makers - causal inference based on epidemiological studies and on their convergence with laboratory studies, but on the demonstration of a proximate - in this case, molecular - causal link. This obviously raises many questions concerning both the status of epidemiological studies and of explanations of the causes of cancer as environmental when confronted with the authority of a style of scientific work and of scientific explanation such as that of molecular biology.

More recently, the tobacco-cancer link raised other interesting questions. Clinicians and researchers by now agree that smoking is associated with lung cancer, but also with cancers of the larynx, mouth, pharynx, esophagus, bladder and pancreas, and it is also linked to increased risks of cancers of the kidney parenchyma and pelvis, of the cervix, of nasal passages, of the stomach and of leukemyas. Tobacco is thus dealt with for its carcinogenic effects. But a recent case-control study of women who were carriers of mutations of the BRCA1 and BRCA2 genes, and thus at risk of developing a form of hereditary breast cancer, showed that women who were smokers were less at risk of developing a cancer than non-smokers, and raised "the possibility that smoking reduces the risk of

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[40] M. F. Denissenko, A. Pao, M. Tang and G.F. Pfeifer, "Preferential formation of benzo[*a*]pyrene adducts at lung cancer muatational hotspots in *p53*", *Science*, Vol. 274, 1996, pp. 430-432.

breast cancer in carriers of BRCA1 or BRCA2 gene mutations"[41]. The explanation, once again, is biochemical: "Cigarette smoke has been found to have antiestrogenic effects, and smoking is associated with an early menopause, with an increased risk of osteoporosis, and with a decreased risk of endometrial cancer"[42]. The point, here, is not that of tobacco not being a carcinogen, or being less dangerous as a carcinogen, but that some carcinogenic agents may, in different circumstances, have a protective effect on certain sites. In fact, this possibility had already been advanced in an earlier study, which stated that tobacco may have opposed carcinogenic and antiestrogenic effects. These effects will have different consequences for different groups of people, depending on the kind of risks they are exposed to[43]. The site-specificity of cancer studies often makes it difficult to take into account the more complex ecology of carcinogenesis and of protection against carcinogenesis, and how different environmental "factors" may act differently on different sites.

Environmental pathology: diagnosing the effects of carcinogenesis

Pathology can be defined as "the scientific study of the causes and effects of disease", the latter, in turn being specified as "an abnormal variation in the structure and function of any part of the body"[44]. Over the last century, pathology evolved from the "gross morphological description of diseased organs" to a heterogeneous field of practices ranging from

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[41] J.B. Brunet et al, "Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes", *Journal of the National Cancer Institute*, Vol. 90, 1998, pp. 761-766; quote on p. 761.

[42] *Ibid.*

[43] *Ibid.*

[44] R.J. Anderson (ed.), *Muir's Textbook of Pathology* (Twelfth Edition), London, Edward Arnold, 1985, p. 1.1.

morphological diagnostic descriptions of tissues to a range of techniques in molecular and cell biology and immunology[45].

Tumour pathology is a central component of research and clinical practice involving the diagnosis and description of different types of cancer. Pathologists analyse the features of samples of tissues which have been processed and fixed on slides, stained and subject to reactions with specific antibodies. These samples are inspected for the presence of "abnormal variations", by drawing on a range of laboratory techniques. The first aim of routine work in tumour pathology is the identification of "positive" cases of cancer pathologies, by excluding those cases recognized as "negatives" or "false positives". Tumour pathology is adequately described as a problem-solving activity articulating a heterogeneous set of practices related to, among others, histology (the study of structural changes of tissues), cytology (the study of changes in cells), biochemistry or chemical pathology (the investigation of the metabolic disturbances of diseases using assays), immunology (the identification of abnormal conditions in the immune system through specific antigen-antibody reactions) or molecular biology (the study of the molecular processes involved in the imbalance of cell proliferation and programmed cell-death)[46]. Pathological work is carried out against a background of detailed anatomical and physiological knowledge of human organisms[47]. Pathologists draw upon relevant competences across this range of approaches to carry out systematic comparisons of new cases with previous cases and with a body of shared knowledge, treating each new case as an instance of a more general category of cases and, at the same time, revising the prevailing categories, when needed, in order to

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[45] James O'D. McGee et al (editors), "Preface", in *Oxford Textbook of Pathology, op. cit.*, Volume 1, p. v.

[46] For detailed treatments of the ways in which these approaches are articulated or made to coexist in the case of lymphomas and leukemyas, see Peter Keating and Alberto Cambrosio, "Diseases and platforms: on the transformation of lymphoproliferative disorders", paper delivered to the EASST'98 General Conference, Lisbon, 30 September - 3 October 1998, and id., "`Real compared to what?´: diagnosing leukemyas and lymphomas", forthcoming in M. Lock, A. Young and A. Cambrosio (eds.), *Intersections: Living and Working With the New Medical Technologies*, Cambridge, Cambridge University Press. I am grateful to Alberto Cambrosio for making these materials available before publication.

[47] This section draws partially on Nunes, "Publics, mediations...", *op. cit.*,, pp. 11-12.

accomodate the new cases. The reference to protocols, reference works or textbooks is frequent in the course of this work. Although it is generally described as "routine", the pathological description of neoplasias is a necessary step in the location of relevant material for cancer research.

Researchers, research assistants, technicians and graduate students at CIBO/IPATIMUP, regardless of their academic background - in biology, biochemistry, medicine or pharmacy - are all required to develop some skills in pathological work and to master a common vocabulary. This is accomplished through the use of a common textbook, the *Oxford Textbook of Pathology*[48], routinely drawn upon for both teaching and reference. The textbook is a massive three-volume work, organized around "Principles of Pathology" and "Pathology of Systems". Most of the work is based on a site- or system-specific representation of pathology, even if it tries to bring together different approaches and techniques around each system. Table 2 presents an enumeration of the systems specified (to which a separate treatment of the pathology of tropical infections is added).

The detailed discussion of these systems, of their "normal" functions and pathologies, is completed with a chapter on techniques for diagnosis and investigation. These include the preparation of diagnostic biopsies, immunocytochemical analysis of human tissues, nucleic acid analysis of tissues (*in situ* hybridization, viral detection, *in situ* RNA analysis, DNA and RNA extraction, Northern and Southern blotting, and PCR), exfoliative cytopathology (including the Papanicolaou smear), fine-needle aspiration, flow cytometry, and a brief discussion of some of recent developments in molecular biology. Each of these techniques, as will be discussed in the next section, has a role to play in studies bridging epidemiology - molecular epidemiology in particular - and environmental pathology, and they all raise different questions as to what is defined as "environmental" and how its is made part of specific sets of practices.

The "Principles" volume, in turn, is based on a detailed examination of cells, of their structure and function, and of the molecular processes underlying them. A set of chapters deal with the specific subject matter of pathology, under headings like "cell injury and death", "defence mechanisms", "response to injury", pathophysiology of infection" and

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[48] McGee et al, *Oxford Textbook of Pathology*, *op. cit.*

"circulatory disorders". Cancer is the object of two chapters, on "cell growth, size and differentiation" and "neoplasia". The final chapters focus on "environmental pathology" and "principles of developmental pathology". The long chapter on environmental pathology provides the focus for this section. Although no definition of this particular subfield of pathology is given, it is clear that it deals with the relationship between causes attributable to environmental factors and to their effects on the structure and function of specific sites (organs or systems). This requires a detailed description of the physical, chemical or biological characteristics of the causal agent, of its effects on the site of interest and of the specific mechanisms through which the agent generates these effects. Rather than looking for associations between exposure to an agent and occurrence of the disease - as in epidemiological studies -, the purpose of environmental pathology is thus to determine the paths and mechanisms followed by pathogenic agents acting on specific sites. This usually takes the form of detailed descriptions of the properties of causal agents and of the particular reactions of the sites affected by them.

Different sections, with different authorship, deal with a particular agent of type of agents or with diseases associated with those agents, including:

• dust diseases (associated with silica, coal and abestos);

• environmental pollution (associated with natural and synthetic molecules, and "pollution of the general environment" through the action of agro-chemicals, pesticides or DDT, including low-level contamination by carcinogens);

• nutritional disorders (including those related to satiety and nutrition selection; nutrients; assessment of nutrition, food availability; gastrointestinal tract and disorders associated with excesses or lacks related to nutrition);

• adverse reactions to drugs (both dose-related and non-dose-related);

• photopathology (including reactions to UV Radiation);

• ionizing radiation;

• damage to normal tissues due to radiotherapy.

The relationships between pathogenic agents and the reactions to their effects may, of course, vary depending on the site and on the type of agent and of effect involved. But the pathologic agents described as "environmental" all have one thing in common: they are identifiable in terms of their physical, chemical or biochemical properties and of the reactions they trigger from specific sites. Constructing "do-able" entities that can be identified, and eventually quantified, with specifiable properties and traceable to their effects on particular organs or systems is a *sine qua non* condition for the appropriate use of common procedures in pathology. The focus on specificity - or, rather, on specifiable relations or processes - is crucial. Environmental pathology has to rely on objects which are recognizable as appropriate to the modes and scales of the procedures it uses.

From environmental exposures to ecologies of cancer

The convergence of research, prevention and clinical intervention occasionally emerges within programs involving public health authorities, clinical institutions and research units, focused on the screening and treatment of certain conditions. Some kinds of cancer lend themselves to this type of initiative, thus providing interesting occasions for the articulation of a range of practices, procedures and actors dealing with different facets of the relationship between the "ultimate" or environmental causes of cancer and its "proximate" mechanisms. In this section, I shall deal with one such initiative, which sheds some light on the limits and potentials of current approaches to the environment-cancer link.

Unlike other countries of Europe and the United States, Portugal still displays a high prevalence of stomach cancer. It will thus not be surprising to find it among the priorities of research, public health initiatives and cancer prevention. Over the last decade, research on gastric carcinoma searched both for those causes of the disease that could be attributed to

"environmental" factors - such as diet - and to the mechanisms of carcinogenesis and mutagenesis, particularly genetic ones. In 1995, two research projects were initiated at CIBO/IPATIMUP with the aim of identifying new genes in gastric cells, the possible role of genetic factors in the variable susceptibility to gastric disorders in general and to gastric carcinoma in particular, and its interplay with environmental factors. Findings on the extent of endemic infection (over 80%) of the Portuguese population by *Helicobacter pylori*, a bacteria associated with disorders of the gastrointestinal tract, hinted at an important environmental condition likely to contribute to the high prevalence of stomach cancer. Research in molecular biology showed that "during carcinogenesis in general and gastric carcinogenesis in particular" mucin glycoproteins, which have a significant role in protection against environmental aggressions, underwent "systematic alterations", and that these were linked, in turn, to the high polymorphism of mucin genes. Individuals with MUC1 and MUC6 genotypes containing a low number of tandem repeats coding for "small" mucins were more susceptible to gastric cancer[49]. In 1997, an article based on a molecular epidemiological study of patients with gastric carcinoma and blood donors in Northern Portugal examined evidence for the association between genetic susceptibility to gastric carcinoma and environmental aggressions, particularly infection by *Helicobacter pylori*. It was possible to establish a significant association between having "small" mucins and being diagnosed with gastric carcinoma, thus confirming the crucial protective role of mucins and the variations in susceptibility to gastric disorders correlated to the polymorphism of the genes coding for mucins[50].

In 1998, researchers at CIBO/IPATIMUP joined the Northern division of the state agency for public health (Administração Regional de Saúde do Norte) and the departments of surgery, gastroenterology and immunohemotherapy of one of the University Hospitals of Oporto (Hospital

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[49] CIBO/IPATIMUP, *Identificação de novos genes em células gástricas utilizando `expressed sequence tags´*, research proposal, 1995, mimeo.

[50] F. Carvalho, R. Seruca, L. David, A. Amorim, M. Seixas, E. Bennett, H. Clausen, M. Sobrinho-Simões, "MUC1 gene polymorphism and gastric cancer - an epidemiological study", *Glycoconjugate Journal*, 14, 1997, pp. 107-111. For a more detailed dicussion of this article and of the research underlying it, see Nunes, "Escala...", "Ecologias...", and "Shifting scales..." (cf. note 16, supra).

de S. João) to launch a program aimed at the screening and research of gastric pathologies associated with infection by *Helicobacter pylori*. The target population included the workers of a shipyard in Viana do Castelo, a town in Northwestern Portugal. The choice of the population was due to its location - in one of the areas of highest incidence of gastric disorders and, in particular, of gastric carcinoma -, but also to conditions of access granted by the administration of the shipyard, who became the fourth partner sponsoring the program.

The main interest of this program, as far as the subject of this paper is concerned, lies in its explicit concern with what is generally described as gene-environment interactions related to exposure to cancer, and in the possibility of examining in detail the emergence of a "trading zone" where an "environmental factor" - infection by *Helicobacter pylori* - appears as a very central boundary object. It also offers a privileged setting for examining the different ecologies of practices involved in constructing the environment in cancer research and in defining the particular ecologies of cancer that are co-extensive with them.

The stated aim of the program is the "study of risk factors involved in the development of a diversity of types of gastric pathologies associated with infection by *Helicobacter pylori*" in the target population[51]. It starts from the following core hypothesis:

> The genetic constitution of individuals (genotypes of mucins and [phenotypes related to] blood groups in the ABO/Lewis systems) and the virulence of strains of *H. pylori* are determining factors (in isolation or jointly) of the consequences of the infection by *H. pylori* in the gastric mucosa, namely of the lesions of atrophic chronic gastritis (ACG), considered as a precursor condition of gastric carcinoma. It is also postulated that the same factors related to host and microorganism determine the evolution of

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[51] *Rastreio/Estudo Piloto de Patologia Gástrica associada à Infecção por Helicobacter pylori na População Constituída por Trabalhadores dos Estaleiros Navais de Viana do Castelo - Resultados Intercalares*, October 1998, Edição da Administração Regional de Saúde do Norte, 1998, p. 3. I am grateful to Professor Leonor David for making available this document. In the remainder of this section, I draw freely on this document and on my ethnographic materials on the performance of the different laboratory procedures involved.

ACG, through intestinal metaplasia (MI), towards gastric carcinoma (GC)[52].

The project is clearly based on a site-specific orientation: it focuses on gastric pathologies. Several interesting features, however, qualify this site-orientation.

• The project does not deal exclusively with one type of pathology, as is often the case with screening as well as research programs. Rather, it takes up a range of pathologies whose interrelations are examined.

• It is based on an explicit focus on the interaction between genetic susceptibility and environmental factors. The "environment" is enacted, in this project, through the central roles played by two actants: *H. pylori*, explicitly referred to as an "environmental factor", and mucins, "the most important component of the layer of mucus which covers the gastric mucosa and protects it against environmental aggressions", which appears as the crucial interface between genes and environment. Mucins are where the action is expected to be.

• Although there is a clear site-specific orientation towards gastric pathologies, the "site" is itself constructed in different ways, depending on the kind of work performed by the different participants in the project and on the scale-specific modes of intervention of the researchers and clinicians.

The consequences of these three sets of features are best examined by having a closer look at how the project is enacted and what kinds of practices are involved in it.

As of September 1998, 352 subjects were participating in the project. Most of them were men (328), with ages ranging from 19 to 62 (median age 43 years). This age-sex composition is obviously related to the fact that this is a population of shipyard workers. Clinical histories identified the majority of them (72.7 %) as asymptomatic for most of the pathologies of interest. Less than one third had complaints of dispepsia, and only three suffered from peptic ulcers.

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[52] *Ibid.*

This population was subject to the collection of detailed clinical histories using forms detailing personal information, personal and familial antecedents of gastric pathologies, and current state related to the presence of symptoms of the pathologies of interest. Following this, blood samples were collected from all participants. These provided the materials for a range of procedures aimed, in a first moment, at determining the ABO, Rh and Lewis blood groups for all individuals, and the polymorphism of the MUC1 gene, coding for mucins. A serologic study was also performed to identify infection by *H. pylori*. In the following stage, all the subjects with dispepsia or asymptomatic with positive serology for *H. pylori* were advised to undergo an endoscopy to locate gastric lesions. These subjects were then biopsed (except one). It is important to underline the fact that these interventions are not targeted at a specific type of pathology, like gastric carcinoma, but are based on an understanding of what may well be appropriately called an ecology of interrelated conditions and lesions which, under certain circumstances, may evolve towards cancer. This understanding is crucial for interventions aiming at prevention, since it allows an identification of lesions which increase the risk of cancer, while being themselves the source of a diversity of site-specific pathologies.

The materials obtained from these different interventions were processed and analysed, and the results compared. Three types of comparisons were performed:

- clinical/endoscopic diagnosis versus serological and histological study

- infection by *Helicobacter pylori* versus polymorphism of MUC1 gene

- serology versus histology concerning infection by *Helicobacter pylori*.

This work involves the active participation of clinicians, patients and researchers. The collection of clinical histories is performed jointly by clinicians and patients, as are the collection of blood samples, the endoscopies and the biopsies. The interpretation and diagnosis based on both the clinical histories and the endoscopies are the task of clinicians,who resort to their specialized skills. These two stages of the project shape ecologies of practices which include a range of activities involving *in vivo* observation and intervention. The presence of the patients and the need for their compliance to the clinical procedures is a fundamental stage in

granting access to the materials needed for the *in vitro* procedures performed by the researchers. At this stage, a body/environment boundary is still recognizable, although the use of invasive procedures redefine these boundaries, to set them within the patients' bodies and to relocate them on the "internal surface" of the gastric system. The removal of tissues through blood sampling and biopsies relocates the boundary again. Those tissues, which were within the body, become themselves the "bodies" which are to be subject to laboratory procedures, a sort of synedochical version of the patient, to whom it is still linked through the recording devices (forms and labels) that allow the chain of operations involved to be tracked. Once these tissues get into the laboratory, they are subject to manipulations and transformations that turn the synedochical body into an environment for the infectious agent, but also for the protective protein which emerges as the agent of establishing a new boundary, between the tissues and cells that are to be protected, and the bacteria.

The sequence of procedures used by the researchers on the biological materials collected are associated with successive redefinitions of the body/environment or organism/environment boundary under in vitro conditions. For each procedure, an appropriate environment is created through the use of instruments, biological and chemical materials and human interventions, in order to avoid the untimely decay, contamination or uncontrolled modification of the samples, and to maximize their compliance to the requirements of the procedure. The use of the "right tools" is crucial, in order to generate the ecologies which allow specific materials to perform as they should[53]. This is why the detailed specification of materials and procedures is so important.

- Biopsies are thus included in paraffin blocks, sliced and stained using different methods (HE, Alcian Blue/PAS and Steiner coloration). The morphological inspection and histological evaluation is performed using the modified Sidney system, with additional evaluation of the following parameters: lesion of the surface epithelium, inflammatory infliltrate, glandular atrophy, intestinal metaplasia (complete and incomplete), displasia and infection by *H. pylori.*

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[53] See Adele C. Clarke and Joan H. Fujumura (eds.), *The Right Tools for the Job: At Work in the Twentieth-Century Life Sciences,* Princeton, Princeton University Press, 1992.

- The study of the polymorphism of MUC1 is performed through Southern blotting. DNA is first extracted from peripheral blood (due to its high molecular weight). After digestion with an appropriate restriction enzyme (EcoRI), samples are separated through electrophoresis in an agarose gel, transfered to nylon membranes and hybridized with a specific probe for MUC1.

- Routine methods for assessing the ABO and Lewis phenotypes of blood groups are drawn upon; infection by *H. pylori* is determined using a serological method, drawing on the detection of IgC anti-*H. pylori* antibodies with a diagnostic kit.

- The strains of *H. pylori* are characterized form frozen biopsies, using PCR and reverse hybridization, with specific probes for different alleles, and focusing on the vac A and cag A genes.

This range of procedures generates a mass of information which is brought together in the form of tables, allowing the results of different procedures to be compared. Although each procedure constructs its own objects and constitutes an irreducible ecology of practices[54], it is able to

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[54] See Michael Lynch, "The idylls of the Academy", *Social Studies of Science*, Vol. 25, 1995, pp. 582-600, and *id.*, "A practice under construction", paper for the conference "The Meaning of Practice", Manchester, 14 November 1997, for the need to identify the specificity of practices and of their situated features. For a different kind of argument, but pointing in the same direction, see Stengers, *Cosmopolitiques*, *op. cit.* The notion of "ecology" is used by Galison as a base for his distinction between the "inner laboratory" and the "outer laboratory", as, respectively, the micro- and macro-environments of the scientific work of physicists; see Galison, *Image and Logic*, *op. cit.*, Chapter 1, esp. pp. 3-4.
Keating and Cambrosio, "Diseases and platforms...", op. cit., argue that the different procedures drawn upon in a particular domain of medical practice co-exist in the form of platforms A platform is defined as "a way of arranging things in both a material and discursive sense... the basis for the organization of activities". And they add that, unlike a Kuhnian paradigm, "in order to operate, a platform does not need shared understandings. The order created by a platform, in the simplest sense, results from consistency between the various parts, be it consistency of purpose or consistently measurable distances". I would argue that boundary concepts are drawn upon whenever the requirements of consistency call for shared - even if situated, provisional, partial and unstable - understandings, as is the case of documents reporting on a project or research program.

relate to other procedures drawing on boundary concepts - "loosely defined concepts which, precisely because of their vagueness, are adaptable to local sites and may facilitate communication and cooperation" - and on two-dimensional inscriptions which "flatten" the potentially incommensurable materialities that emerge from the different ecologies of practices and allow them to be recombined and made compatible for the purposes at hand[55].

Conclusion

As a senior researcher in oncobiology stated in an interview, defining the environment in cancer research is dependent on the specific experimental or observational assemblages involving an intervention by the researcher. If the research procedures change and, in particular, if there is a change in the scale at which the procedure defines its object, what is "object" at a given scale may become part of the "environment" at another scale, and vice-versa. The cell may thus be the object of procedures focused on cells (like immunocytochemistry or static or flow cytometry) and tissues located at specific sites may be defined as their environment, as far as these particular procedures are concerned. But the cell may become in turn the environment for approaches based on molecular biology. If the scale is changed, and with it the research procedures, there will be a concurrent change in the definition of what the "environment" is. Another intriguing idea, advanced by the same researcher, is that of the "epi" in epigenesis referring to something we call "the environment" for lack of a more precise definition. He gives the striking example of how the same nucleus of a mammarian cell, if the environment in

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[55] Löwy, "The strength...", *op. cit.*, pp. 374-375. The properties and uses of two-dimensional inscriptions are discussed in Latour, "Drawing...", *cit.* On boundary objects, see also Susan Leigh Star and James R. Griesemer, "Institutional ecologies, `translations´, and boundary objects: amateurs and professionals in Berkeley's -museum of Vertebrate Zoology, 1907-39", *Social Studies of Science*, Vol. 19, 1989, pp. 387-420, and Joan H. Fujimura, "Crafting Science: standardized packages, boundary objects, and `translation´, in Andrew Pickering (ed.), *Science as Practice and Culture*, Chicago, University of Chicago Press, 1992, pp. 168-211.

which it is manipulated is that of a mammarian cell, is linked to the generation of mammarian tissue, whereas in the case of cloning the same nucleus, when transferred to a denucleated egg cell, gives rise to a whole animal. In cancer research, the ultimate aim has been the opposite: to manipulate the environment in order to stop cell proliferation. These manipulations may involve either changing the environment while keeping the object stable (as in the transference of cells or DNA material across different animal models) or manipulating the object while keeping the environment stable through controlled experimental conditions. The increasing recognition of the heterogeneous quality of cancer tissues — and for some researchers, of their polyclonality — makes it even more urgent to pay more attention to the environments in which the imbalance of cell proliferation and cell death (apoptosis) that defines cancer takes place[56].

It makes sense, thus, to speak of a diversity of ecologies of cancer which do not refer solely to the complex and interacting conditions associated with a given setting and with the exposures and carcinogenic risks arising from it. They include the whole range of observational and experimental asssemblages and procedures through which cancer research, clinical intervention or preventive measures are enacted. According to Susan Leigh Star, speaking of ecologies in science studies means "trying to understand the systemic properties of science by analogy with an ecosystem, and equally important, all the components that constitute the system", while rejecting a functionalist, closed-system organic perspective. It involves the refusal of "social/natural or social/technical dichotomies" and the invention of "systematic and dialectical units of analysis"[57]. John Law and Annemarie Mol have proposed approaches to a range of diseases and to the different ways these are defined and managed in a variety of settings, involving heterogeneous practices, actors and resources, which point in the same direction[58]. Cancer research may itself be

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[56] The arguments in this paragraph follow very closely those advanced by Manuel Sobrinho-Simões in an interview, 21.08.98.

[57] Susan Leigh Star, "Introduction", in Star (ed.), *Ecologies...*, *op. cit.*, pp. 1-35; the quotes are from p. 2.

[58] Annemarie Mol and John Law, "Situated bodies and distributed selves: on doing hypoglycaemia, paper for WTMC/CSI workshop "Theorizing the Body in Medical Practice", Centre de Sociologie de l'Innovation, École nationale Supérieure des Mines de Paris, 9-11

conceived of as a set of ecologies, of practices involving moving between scales and procedures, constructing objects whose properties as "natural" or "biological" and "social" or "technical" are inextricably interwoven. This view has important implications for the politics of research - and, in particular, for the modes of defining or transgressing boundaries, including, excluding and ordering actors, materials, resources and activities.

The previously mentioned studies documenting opposite effects of smoking on exposure to lung cancer and protection from hereditary breast cancer can be reinterpreted in the light of these considerations. The choice of site and of type of cancer and the specific assemblage of actants - in Latour's sense, including human actors, biological materials and instruments[59] - related to each of the chosen procedures configure different ecologies of practices[60] which, at the same time, are ecologies of cancer-as-an-object-of-research. For all practical purposes, cancer ecologies are thus indistinguishable from the ecologies of practices through which cancer becomes an object for research, diagnosis, treatment and prevention.

September 1998. See also A. Mol, "Missing links, making links: the performance of some atherosclerosis", in Marc Berg and Annemarie Mol (eds.), *Differences in Medicine: Unravelling Practices, Techniques and Bodies*, Durham, North Carolina, Duke University Press, 1998, pp. 144-165.

[59] Bruno Latour, *Science in Action: How to Follow Scientists and Engineers Through Society*, Milton Keynes, Open University Press, 1987.

[60] Stengers, *op. cit.*

Table 1
Environmental Causes of Human Cancer

Agent	Type of Exposure	Site of Cancer
Aflatoxin	Contaminated foodstuffs	Liver
Alcoholic beverages	Drinking	Mouth, pharynx, esophagus,larynx, liver
Alkylating agents (melphalan, cyclophosphamide, chlorambucil, semustine)	Medication	Leukemia
Androgen-anabolic steroids	Medication	Liver
Aromatic amines (benzidine, 2- naphthylamine, 4-aminobiphenyl)	Manufacturing of dyes and other chemicals	Bladder
Arsenic (inorganic)	Mining and smelting of certain ores, pesticide manufacturing and use, medication, drinking water	Lung, skin, liver (angiosarcoma)
Asbestos	Manufacturing and use	Lung, pleura, peritoneum
Benzene	Leather, petroleum, and other industries	Leukemia
Bis(chloromethyl)ether	Manufacturing	Lung (small cell)
Chlornaphazine	Medication	Bladder
Chromium compounds	Manufacturing	Lung
Estrogens Synthetic (diethylstilbestrol) Conjugated (Premarin) Steroid contraceptives	Medication	Vagina, cervix (adenocarcinoma) Endometrium Liver, cervix
Immuoosuppressants (azathioprine, cyclosporine)	Medication	Non-Hodgkin's lymphoma, skin (squamous carcinoma and melanoma), soft-tissue tumors (including Kaposi's sarcoma)
Ionizing radiation	Atomic bomb explosions, treatment and diagnosis, radium dial painting, uranium and metal mining	Most sites
Isopropyl alcohol production	Manufacturing by strong acid process	Nasal sinuses
Leather industry	Manufacturing and repair (boot and shoe)	Nasal sinuses, bladder
Mustard gas	Manufacturing	Lung, larynx, nasal sinuses
Nickel dust	Refining	Lung, nasal sinuses
Parasites *Schistosoma haematobium* *Clonorchis sinensis*	Infection	Bladder (squamous carcinoma) Liver (cholangiocarcinoma)
Pesticides	Application	Non-Hodgkin's lymphoma, lung
Phenacetin-containing analgesics	Medication	Renal pelvis
Polycyclic hydrocarbons	Coal carbonization products and some mineral oils	Lung, skin (squamous carcinoma)
Tobacco chews, including betel nut	Snuff dipping and chewing of tobacco, betel, lime	Mouth
Tobacco smoke	Smoking, especially cigarettes	Lung, larynx, mouth, pharynx, esophagus, bladder, pancreas, kidney
Ultraviolet Radiation	Sunlight	Skin (including melanoma) lip
Viruses Epstein-Barr virus Hepatitis B and C virus Human immunodeficiency virus Human papillomavirus Human T-lymphotropic virus type I	Infection	Burkitt's lymphoma, nasopharyngeal carcinoma Hepatocellular carcinoma Kaposi's sarcoma, non-Hodgkin's lymphoma Cervix, other anogenital tumors T-cell leukemia/lymphoma
Vinyl chloride	Manufacturing of polyvinyl chloride	Liver (angiosarcoma)
Wood dusts	Furniture manufacturing (hardwood)	Nasal sinuses (adenocarcinoma)

Source: Joseph F. Fraumeni, Jr. *et al*, "Epidemiology of Cancer", in V.T. DeVita *et al* (eds), *Cancer: Principles and Practice of Oncology, Fourth Edition*, Philadelphia, J.B. Lippincott, 1993, Table 9-17

Table 2

Classification of systems in pathology

Circulatory system
Respiratory system
Mouth, salivary glands, jaws and teeth
Ear, nose and throat
Alimentary system
Liver and biliary system
Exocrine pancreas
Kidney
Male Generative System
Female genital tract and ovaries
Breast
Blood and bone marrow
Lymphoreticular tissues
Nervous system
Endocrine system
Locomotor system
Skin

Source: James O'D. McGee et al (editors), Oxford Textbook of Pathology, Oxford, Oxford University Press, 1992, Volumes 2a and 2b