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Risk, uncertainty and innovation in biomedicine: tumour pathology and translational research*

"Risk" has become a common word in the field of biomedicine, allegedly as a central feature of the "scientifization" of the field. According to a document from the Royal Society (1992, quoted in Heyman, 1998), risk would be defined as "the probability that a particular adverse event occurs during a stated period of time, or results from a particular challenge. As a probability in the sense of statistical theory risk obeys all the formal laws of combining probabilities". This "expert" definition of risk and of its assessment has often been contrasted to "lay" definitions of risk, either as a confrontation between scientific rigour and perceptions resting upon ignorance or, as in most of the STS (Science, Technology and Society studies) literature, as an often conflicting coexistence of different definitions of risk and risk assessment, held by "experts" and "lay" citizens respectively (Wynne, 1996; Heyman, 1998).

* Research for this paper was carried out as part of the project "The Mediations of Science: Managing Uncertainty in the Biomedical and Health Sciences", funded by a grant from the Portuguese Ministry of Science and Technology. I am grateful to the researchers, graduate students, technicians and remaining staff of CIBO/IPATIMUP for their invaluable help and generosity. An earlier version of this paper was delivered to a seminar at the Institute of Environment, Philosophy and Public Policy, Lancaster University. I am grateful to Brian Wynne, Ruth Chadwick, Carmen Diego and other participants in the seminar for their comments. Parts of the argument were presented at the joint meeting of the Society for Social Studies of Science and European Association for the Study of Science and Technology, Vienna, 27-30 September 2000.

If we take a closer look at how "risk" inhabits the discourses and practices of biomedicine, we come to realize that fields like epidemiology, environmental pathology or genetics have taken up the concept (and associated practices of quantitative risk assessment) in much the same way the Royal Society defines it. "Risk", however, seems to relate rather awkwardly to an area of biomedicine which has been hailed, for the last two centuries, as the cornerstone of scientific medicine, based on the "marriage" of the clinical "art of healing" to the rigour of the laboratory and resting upon an anatomopathological model of disease (Foucault, 1963).[1] This area ispathology. According to a major textbook, pathology can be defined as "the scientific study of the causes and effects of disease", that is, of any "abnormal variation in the structure and function of any part of the body" (Anderson, 1985: 1.1). Whereas in its beginnings in the early 19th century pathology included the "gross morphological description of diseased organs", it gradually incorporated a heterogeneous set of practices which ranged from morphological and topological descriptions of tissues to molecular and cell biology and immunological techniques (McGee *et al.*, 1992: v). A core feature of pathology is its handling of individual cases in order to produce accurate diagnoses and prognostic evaluations. It is easy to understand why a concept like risk, which deals with populations and with the probability of the occurrence of certain specified events affecting that population, seems ill-suited to a field dealing with individual cases. Risk, however, enters pathology through other pathways, namely through its association with the issue of uncertainty.

As several commentators have been careful to point out, dealing with risk and dealing with uncertainty have considerably different implications in so far as they point towards different ways of acting in the world. This, however, does not mean that it will be easy to distinguish between a situation where risk can be assessed as the probability of occurrence of an adverse event in a given population, allowing preventive action to be carried out, and a situation characterized by uncertainty, when neither a definition of risks nor their probabilistic assessment are possible, thus calling for precautionary action.[2] Many of the situations pathologists have to deal with stand uneasily on the borderline between "risk" and

[1] On the uses of the concept of risk in epidemiology and environmental pathology, see Nunes (1998). A short but illuminating discussion of genetic risk may be found in Prior (2000).
[2] On this distinction, see the illuminating discussion by Callon *et al*., (2001). Herbert Simon and his collaborators had already drawn that distinction in their work on "bounded rationality".

"uncertainty" so defined. They draw upon different kinds of "formal" and "informal" probability assessment on the basis of previous experience, but also on the need for judgment in the face of singular expressions of heterogeneous, intersecting processes.[3] The predicament of pathologists thus suggests interesting continuities between "lay" constructions of risk and uncertainty and ways of dealing with uncertainty within this central domain of biomedicine.

I shall explore, here, some of the features of the conventions and practices of pathology and, in particular, of how pathologists handle uncertainty and how they use the concept of risk. Tumour pathology is particularly interesting for my purpose, since the stakes of accurate diagnosis and prognostic evaluation are particularly high, and they may affect the chances of survival of a patient in a way which is far more significant than when the disorder he or she suffers from is benign. This also helps in highlighting the centrality of the management of uncertainty in cases where the issue is no longer whether a pathology is present, but whether the pathology is benign or malignant. The issue of risk has been raised, lately, in connection with the increasing focus on early diagnosis and the associated problems of how to define precursor lesions of cancer, how to assess their potential for malignancy and how to deal with the gap between early diagnosis and the clinical manifestations of cancer. This has been the focus of much of research and of innovation in tumour pathology, with far reaching consequences for conceptions of prevention and early treatment, as we shall see.

The elusive gold standard

In an article with the provocative title "Do pathologists play dice? Uncertainty and early histopathological diagnosis of common malignancies", published in 1997 in *Histopathology*, one of the leading journals in the field, E Foucar, an American pathologist, outlined the history of the centrality of pathological diagnosis in 20th century medicine, as the "gold standard" for the determination of the presence of tumours in patients and for their classification. Foucar concurs with Kassirer and Kopelman's definition of a gold standard in medicine as a "relatively irrefutable standard that constitutes recognized and accepted evidence that a certain disease

[3] I take this formulation from Peter Taylor (2001).

exists" (Foucar, 1997: 495). According to Foucar, the relevance ot that "gold standard" is expressed in two ways:

> At an individual case level, the pathological diagnosis plays a pivotal role in the patient's and physician's choice of therapy for neoplastic disease. At a societal level, pathological diagnoses determine the apparent frequency of malignancy, guide public policy decisions about the allocation of health care and research funding, and supply data to decide whether massive screening programmes are effective or ineffective (Foucar, 1997: 495).

If "confounding factors" like the complexity of biological systems and variations in pathologists' skills may lead (and have indeed led), in some cases, to "some diagnoses that either falsely predict behavior characteristic of malignant disease or falsely predict behavior characteristic of benign lesions", it is no less true that histopathological techniques "are remarkably successful at identifying patients who either are or not at greatly increased risk for near or intermediate-term morbidity or mortality from neoplasia" (Foucar, 1997: 495).

These passages of Foucar's article are exemplary of the way different sources of uncertainty in pathology are identified and how risk is brought into pathologists' discourse. One first source of uncertainty lies in the "confounding factors" originating either in the "complexity of biological systems" (complexity breeds uncertainty) and the variable skills of practitioners. These two factors would account for two common types of errors in pathological diagnosis and prognostic evaluation: false positives and false negatives. Vicky Singleton (1998) has discussed at length the problems raised by these two types of error, and how they affect not only the credibility of screening programs for some types of cancer, but also, and above all, the situation of patients. Although consequences (particularly for patients) of the two types of error are different, the sources of these errors are seen to be common.[4]

Whereas biological complexity is irremediable and will always be present as a potential source of mistakes - despite hopes that more knowledge will reduce uncertainty (I shall get back to this later) -, pathologists' skills can, in principle, be improved, and the setting up of

[4] See Casper and Clarke (1998), for a detailed discussion of the sources of error and the ways of managing them in the case of the "Pap smear", a central tool in the screening and diagnosis of cervical cancer.

procedures of quality control of pathological diagnosis may reduce the consequences of that variability. But uncertainty is also a feature of the pathologies themselves and of their manifestations in individual patients. This uncertainty is captured by the use of the word "risk". A patient diagnosed for a given benign condition may be more or less at risk of developing malignity, and a patient diagnosed for malignancy may be at more or less risk of mortality from cancer. "Risk" stands, here, for the uncertainties associated with prognostic evaluation. Although retrospectively a series of cases may be dealt with in probabilistic terms, the predicament of the pathologist (and of the clinician) is to diagnose and evaluate specific cases by drawing both on epidemiological information and on the particulars of the case at hand.

Let us look in more detail, still using Foucar's article as a guide, to the terms of this predicament. Tumour pathology rests upon a "paradigm" centered on the benign/malignant distinction. This paradigm had the considerable advantage of being "congruent with the available therapeutic options" (Foucar, 1997: 495). In the presence of a lesion of the breast with features suggesting neoplasia, current pathological procedures would allow a clear definition of its malignancy or benignity and, on the basis of that definition, propose appropriate courses of treatment, for instance, radical surgery of discontinuation of treatment, respectively. This "paradigm" thus was hailed as the gold standard of tumour pathology. But as less clear-cut cases appeared, its limitations became evident, with some problematic consequences for pathologists and clinicians:

> Occasionally, pathologists encountered examples of lesions that appeared to be early steps in the development of carcinoma. Some of these lesions resembled advanced cancers in every way except for size and the absence of metastatic disease at diagnosis, while other lesions had only a few histopathological features in common with traditional cancers. Because pathologists had experienced such remarkable success in the evaluation of advanced neoplastic disease, it was to be expected that they could apply their proven techniques and their benign/malignant paradigm to the diagnostic labeling of these early lesions. Furthermore, pathologists were under considerable pressure from patients and medical colleagues to classify these lesions as either benign or malignant, and the answer `in between´ or `I don't know´ was met only with the demand to show the case to someone who did know. Thus, acknowledgement of uncertainty was

> confused with incompetence, and, conversely, exuding confidence when evaluating equivocal lesions was held to be an important diagnostic skill (Foucar, 1997: 495).

The problem of "borderline cases", which display features of both benignity and malignancy (for instance, morphologically similar to carcinomas but with "no clinical manifestations of malignancy") is a central concern of the current procedures for the training and updating of the skills of pathologists. Consultations or "slide seminars"[5] are common ways of trying to define specimens on the basis of their describable features and allocate them to each side of the bening/malignant divide. This is accompanied by attempts at defining more precise and detailed conventions for the description of pathologies.

An interesting example of this is the so-called "Updated Sidney System" for the classification and grading of gastritis (Dixon *et al*., 1996). Although the system aims more generally at the diagnosis and prognosis of gastritis, the recommendations made in the article provide important guidelines for the assessment of the potential for malignancy in certain types of benign gastric lesions. The recommendations are based, first of all, on descriptions of the topological, morphological and etiological features of the lesions, described using an agreed upon vocabulary and drawing on "visual analogue scales". Individual practitioners are advised, however, to "decide to what extent they want to adhere to [the] recommendations and how they want to adapt them to the social, economic, and medical realities of the populations they serve" (Dixon *et al.*, 1996: 1162). The limitations of the system are thus openly recognized. They are of two kinds. First, there are the cases "categorized as *unclassifiable* or *type indeterminate*", as a consequence, for instance, of the impossibility of establishing the etiopathogenesis of the pathology in specific cases (ibid.). Secondly, the uncertainties arising from the variable settings in which the pathology occurs may advise, for example, the choice and taking of biopsy specimens according to "local epidemiologic conditions with respect to the types of gastritis and the incidence of gastric carcinoma" (Dixon *et al.*, 1996: 1163). Epidemiological information is used, in such instances, very much in the way Garfinkel described as the "documentary method of interpretation" (Garfinkel, 1967). It is interesting to notice that, in

[5] In slide seminars, participating pathologists engage in diagnostic evaluations of specific cases on the basis of the histomorphological evidence provided by slides and discuss and confront these evaluations with the detailed information on the cases made available by the convenor of the seminar.

their conclusions, the authors of the article remind readers that "[c]lassifications are not right or wrong: they cannot even be said to be good or bad except in relation to a purpose. The most that can be said about them is that they are useful or not useful" (Dixon et *al*., 1996: 1175).[6]

But, as Foucar notes, the issue of uncertainty in dealing with "borderline cases" extends beyond the professional and scientific world of pathologists and clinicians, since it "involves the complex interaction between deeply held diagnostic beliefs, and a changing external environment that includes both increasingly sensitive screening programmes and a harsh legal system that is particularly intolerant of `missed cancer´ (Foucar, 1997: 495). Concerns with the latter problem are also voiced by Dixon *et al.* (1996: 1175), in the context of the diagnosis of gastritis:

> … the prognostic implications of a diagnosis of multifocal atrophic gastritis in areas with high gastric cancer risk (e.g.), certain regions of South America or Eastern Asia [or Portugal, for that matter, JAN] may differ substantially from those in an area where gastric cancer is uncommon (e.g., North America). Such facts should always be kept in mind to help avoid exaggerated responses from clinicians and to minimize the possibility of inappropriate interpretations in countries where medical litigation is commonplace.

Sources of uncertainty

Calls for reconsidering uncertainty as part and parcel of pathological diagnosis is closely linked to the perceived difficulty in dealing with the concept both in the routine handling of benign pathologies and in the diagnosis and classification of neoplasias. The sources of that difficulty are linked to some of the issues described above, but also to the emergence of new objects such as the "in situ carcinoma" - non-invasive proliferations of

[6] The pragmatic mood of this statement converges with work in STS on the classification of cases in pathology. See, for instance, Keating and Cambrosio (2000), and Nunes (1999).

malignant cells - and of new methods for the early diagnosis of some types of cancer. These sources include:

a) the need to deal with a "morphological continuum", which does not fit into the benign/malignant dichotomy. Drawing on the language of computer science, Foucar (1997: 496) uses the expression "combinatory explosion" to refer to the complexity and multifactorial features ot tumours;

b) the resistance to deal with uncertainty, trying to replace it with peremptory conclusions based on experts with a "star" status and on their authority;

c) the confusion of risk and disease - well-known in genetics, and giving rise to the new category of the "healthy ill", of non-symptomatic carriers of a given genetic trait or polymorphism who will be treated, for a range of purposes, as carrying the condition they are at risk of (Hubbard, 1995) -, or of the probability of a given anomaly evolving towards malignancy;

d) following from the previous topic, the propensity towards overtreatment, to recommend aggressive therapies even when no evidence is available of the progression of an anomaly to malignancy. This may be compounded, in countries like the United States, by the features of health care systems and of the liability of physicians;

e) the tendency to ignore the natural history of carcinomas, namely due to the failure to draw on epidemiological studies providing information on a large number of cases - and not just on a small number, as seems to be a widespread practice;

f) the difficulties in evaluating *in situ* carcinomas in terms of their relationships to further development of malignant pathologies. The problem here, according to Foucar, is very similar to the one of, after identifying microorganisms, defining their links to pathologies. He suggests that a set of rules similar to Koch's postulates would be needed here (Foucar, 1997: 498);

g) the transformation of criteria for pathological diagnosis and their relationship to what Foucar describes as the "cascade of intervention", i.e., the generalization of

> aggressive treatments based on the identification of early stages of tumours. This has significant political and social consequences, namely through increased pressure for "broader application of ever more sensitive screening tests, producing more examples of patients caught in a cascade of intervention leading to aggressive treatment" (Foucar, 1997: 498).

This set of problems brings us back to the question of risk. The latter is never precisely defined throughout Foucar's argument. It is clear, however, that, according to him, dealing with uncertainty in pathology requires some notion of risk, in order to make pathological practice less subject to unacknowledged and uncontrolled sources of uncertainty. But can the latter be reduced? Assessing probabilities on the basis of past experience is certainly considered as a precious resource for more accurate diagnosis and prognosis. But it does not solve the problem of how to deal with present and future individual cases and with the built-in and constitutive uncertainties of pathological practice. This much seems to be acknowledged by Foucar. In an interesting analogy with environmental pathology and with the assessment of risks of exposure to toxics and carcinogens, he suggests that pathology should focus on how to specify links between risk assessment and early diagnosis of cancer and, in particular on how to determine levels of risk and how to deal with risks assessed as low. His summary of the dilemmas of early diagnosis is worth quoting at length:

> Like the environmentalists who saw only benefits when increased sensitivity allowed detection of lower and lower quantities of pesticide, we pathologists have welcomed screening efforts that brought us more and more cases of 'atypia', 'dysplasia' and early cancer. This enthusiasm for early diagnosis has placed the pathologist closer to the `evangelist´ camp (advocates of screening unless shown to be harmful), as opposed to the `snail´ camp (advocates of screening only when proven to do more good than harm).
>
> Enthusiasm for early diagnosis is reasonable, but must be accompanied by an appreciation of the multidimensional nature of risk and the numerous value judgments associated with treatment decisions prompted by elevated risk. The histopathological study of early steps in the development of malignancy cannot today and probably will not in the future provide the terminology consumer with a definite answer to every reasonable question. However, our clearly stated goal can be to provide a diagnosis that is always based on scientifc assessment of

> outcomes. Diagnostic uncertainty will persist, but it should not be viewed as a `manifestation of ignorance, weakness, or failure´, and it should not be hidden from view (Foucar, 1997: 500).

Foucar goes on to propose that pathologists enroll the help of experts of other areas familiar with the problems of risk, in order to develop a "diagnostic infrastructure for which risk, with all its uncertainty and complexity, is not the tail of the dog, but is in fact the dog" (Foucar, 1997: 500-501). This would entail a reformulation of the question which, according to Virchow, launched Morgagni, two centuries ago, to found pathological anatomy as a scientific approach. Morgagni's question, "ubi est morbus?" (where is the disease?) was taken up by tumour pathologists in the 20th century as "is it benign or malignant?". The next century should be asking a different question: "what is the risk of malignant behavior established by this finding, how should this risk and the associated uncertainty be communicated to the individual patient, and how should this risk influence the choice of available treatments?" (Foucar, 1997: 501).

An interesting implication of Foucar's discussion is that, as early diagnosis is at a premium in current approaches to tumour pathology, the link seems to have been severed between the diagnosis of cancer and the clinical manifestations of cancer. Risk seems to provide a new link, but at the cost of an increase in uncertainty. Risk assessment for tumour pathology is explicitly based, here, on the models of environmental pathology, epidemiology and molecular biology. It is based on the retrospective assessment of probabilities based on populations of cases, but it does not necessarily solve the problems of decision-making on current cases. The earlier the detection of a pathology, the more uncertain is the prognostic evaluation, and the more problematic is the decision on how to treat it. As we shall see, this apparent paradox is increased when diagnosis and prognostic evaluation try to enlist approaches which, at some point, promised to deliver more precise diagnostic instruments, such as immunology or molecular biology. But it also raises the interesting question of how to deal with uncertainty arising from increased and more detailed knowledge of cases.

Morphological anchors and translational research

These problems were taken up in a paper authored by a team of Portuguese pathologists and cancer researchers, delivered to a meeting of the Pathological Society of Great Britain and Ireland in 1998 (Sobrinho-Simões *et al*., 1998). The title, once again, is provocative: "The proeminence of morphology and the quasi-futility of genetics and molecular biology in tumoural pathology". The focus of the paper is not so much uncertainty but a defense of the centrality of morphological approaches in pathology, an identification of the problems and shortcomings involved in the use of other approaches, such as those based on molecular biology, and the possible articulations of morphological, molecular and other approaches to generate innovative resources for diagnosis, prognosis and the design of therapies for different types of cancers. As the argument goes, diagnosis and prognostic evaluation in tumour pathology should be based on a configuration of approaches "anchored" in morphology, aiming at the production of more dense and detailed "natural histories" of neoplasias. Elsewhere, I have described the overall approach as "cartographic", in that it identifies pathological phenomena at different scales or levels. This configuration is explicitly anti-reductionist and deals with interactions within and among the different scales or levels: organism/environment, organs or systems, tissues, cells, subcellular levels (membrane, cytoplasm, nucleus) and molecules. Each scale has a privileged link with a specific biomedical platform (Keating and Cambrosio, 1999). These appear as loci of articulation of diagnosis and prognosis, on the one hand, and of research activities, on the other.[7] Biomedical platforms are "material and discursive arrangements or sets of instruments and programs that, as timely constructs, coordinate practices and act as the bench upon which conventions concerning the biological or normal are connected with conventions concerning the medical or pathological" (Keating and Cambrosio, 1999: 53-54).

Two features of biomedical platforms highlighted by Keating and Cambrosio are particularly interesting here. The first relates to the way "[t]hinking in terms of platforms allows one to see and analyze the continuities between (...) apparently distinct activities", such as "mundane or routine medical activities and the more exceptional work of biomedical discovery and innovation". The second feature focuses on the way the notion of platform "draws together actors - physicians, researchers, industrialists, patients - as well as objects -

[7] See Nunes (1999: 165-175) for a detailed discussion.

research materials, specimens, standards, contracts, high-tech and low-tech equipment - that were previously thought to inhabit separate social worlds although, empirically speaking, they are often found in the same rooms" and, I would add, sometimes in the same persons (Keating and Cambrosio, 1999: 54-55).

I shall summarize the crucial arguments of the paper and go on to illustrate the enactment of the approach for the diagnosis and prognostic evaluation of cancer:

a) the crisis of the benign/malignancy paradigm is openly acknowledged;

b) cancer is defined as a multifactorial, multilevel process, with each level displaying a privileged association with a given "method" (or biomedical platform);

c) different biomedical platforms will be more or less useful for diagnosis and research depending on the type of neoplasias dealt with: molecular biological approaches seem to be more effective for tumours of the blood, bone and soft parts, whereas tumours of epithelial or epitheliform tissues (carcinomas) are likely to be more effectively dealt with through histopathological procedures, due to the centrality of supra-cellular lesions and tissue disorganization;

d) the use of a range of biomedical platforms often generates heterogeneous flows of information which, in turn, give rise to more uncertainty or, at least, do not reduce the latter;

e) for carcinomas, an approach combining different platforms by "anchoring" them in histopathology is likely to generate a configuration of different kinds of information which have to be interpreted as part of the "natural history approach" of specific cases;

f) the same approach can be used for the development of procedures for defining these configurations at earlier stages, by identifying precursor lesions - and not just through early diagnosis of already existing tumours - and by trying to find "markers" of different kinds (immunological or molecular, for instance), allowing anomalies

identified through morphological inspection to be more thoroughly inspected for possible evolution towards malignancy;

g) although "anchoring" procedures are proposed, attempts at finding a successor "gold standard" to the histopathological platform - the most likely candidate being molecular biology - is explicitly refused as incompatible with this "multilevel" or "cartographic" approach;

h) finally, this approach would allow certain types of cancer, particularly those characterized by a slow progression linked to older ages, to be dealt with as chronic diseases, rather than as conditions to be cured through radical and aggressive treatments.

The authors of this paper are all members of a biomedical research institute in Porto, Portugal, which I studied over several years (Nunes, 1999). In their daily activity, they combine routine diagnosis of cancer with research in cancer biology. Drawing on my ethnographic study of the Institute, I shall explore an instance of how uncertainty is redefined and reconstructed within the frame of "translational research", that is, a way of articulating the priorities and concerns of clinical work with practices and schedules usually associated with "basic" research, without the constraint of delivering "applicable" results to be tested in clinical trials. The "use" of these results, as we shall see, is always closely linked to what might be described as an "experimental" approach coupled with the "natural history" of specific cases - or, alternatively, as a "weight of evidence" approach.[8] It explores uncertainty and how to manage it as part of the contingencies associated with diagnosis and prognostic evaluation, and instead of aiming at the reduction of uncertainty as something which could be achieved it tries to identify markers and indicators which allow knowledge of precursor lesions and identification of specific molecular and immunological markers to be mobilized as clues to malignancy or to the potential for malignancy.

[8] This approach is based on the acknowledgement that there is no single best source of evidence for the problem under study. It is thus required that evidence based on different approaches related to a variety of "levels of organization" and biomedical platforms - epidemiological, morphological, immunophenotypical, immunochemical, molecular - be carefully considered and the whole set of evidential materials be "weighed" in order to produce the most adequate interpretation given the problem and the circumstances.

Much of what these researchers do looks strikingly like "basic" research; some of the things they do look like clinical research, but without some of the features usually associated with the latter, like randomized trials, and the previous, clear-cut definition of what is being put to the test (diagnostic tools or therapies, for instance). It would be possible, of course, to define this particular configuration of procedures in "neither/nor" fashion: translational science would thus be defined in a negative way, as neither "basic" nor "applied" or clinical research. As practiced by this team of researchers, however, it appears as a specific, identifiable "style" of research (Nunes, 1999: 139-186).

The topics to be investigated are initially framed in terms of their significance for clinical activity or public health. Biological processes associated with the initiation and promotion of neoplasias are not dealt with as particular instances of "normal" phenomena of interest to biologists - such as cell growth and differentiation, programmed cell death or genetic mutations -, but as processes which are identified as candidates for, or confirmed significant factors in pathological phenomena. This is enabled by the meeting of research and clinical issues in biomedical platforms. Morphological, immunohistological, immunophenotypical, molecular and epidemiological platforms, among others, provide the basis upon which translational research becomes "do-able".

Research is conducted on small numbers of cases, studied in detail, with a focus on their "natural histories", drawing on a range of procedures "anchored" in histopathology either as a central set of approaches or as framework for conceptualizing the phenomena of interest. Comparisons are made between "normal" and "pathological" cases and between malignant and benign cases, and different "levels of organization" of the phenomena under study are considered - environment/organism interactions, organism, organ or system, tissue, cell, subcellular levels and molecules.

The phenomena under study are explicitly - even if tentatively - linked to their possible significance for the development of tools for diagnosis, including early diagnosis and detection of precursor lesions, prognostic evaluation and therapies "adjusted" to specific cases. These, however, do not entail the development of massive trials of new procedures resorting to

standardized tools. The latter are to be taken up by teams or institutions with the appropriate resources - which is rarely the case in countries like Portugal. It will come as no surprise, then, to find out that this strategy is an ingenious way of taking advantage of limited resources coupled with high-level scientific skills.

Let us look at one instance of the practice of translational research which is closely linked to the general topic of this paper. The starting point is the recognition that the initiation of different types of cancer is often linked to the presence of non-malignant lesions, of which some types may be premalignant, that is, they have a potential for malignant transformation. Identification of these premalignant lesions and of the features associated to their malignant transformation may thus be a crucial step towards the development of appropriate strategies of prevention and early diagnosis of malignancy, of prognostic evaluation and of adequate therapies. In this particular instance, researchers were looking for molecular markers of the evolution towards malignity of specific gastric pathologies, in this case two different types of polyps - adenomatous and hyperplastic. Whereas hyperplastic polyps are usually considered to have low malignant potential, adenomatous polyps are regarded as premalignant lesions which become malignant in up to 75% of the cases (Nogueira *et al*., 1999: 1649). Although it is possible to describe the morphological features of adenomas which have transformed into malignant lesions, effective tools for prognostic evaluation, which would allow intervention at a stage preceding malignant transformation, are not available. Published studies suggested that molecular markers could fulfill that role, particularly through studies of the immunoexpression of p53, or of p53 gene mutations.

The results of studies focusing on these factors were inconclusive, as well as those based on other molecular markers, like APC or K-ras, and on microsatellite instability (MSI), that is, the instability due to replication errors of non-coding regions of DNA characterized by tandem repeats of two, three or four nucleotides. The inconclusive and conflicting results found in the literature led the research team to engage in an analysis of a range of molecular alterations occurring in different types of gastric polyps, through identification of MSI using two different kinds of markers, and of immunoexpression of p53 and ERBB-2. In all, 20 cases were analyzed, including 6 hyperplastic polips, 10 adenomatous polyps and 4 adenomatous

polyps with foci of malignant transformation. Three platforms were mobilized to carry out the study: morphological, immunohistochemical and molecular. Different scales or "levels of organization" were inspected, namely the tissue, cellular and molecular levels.

The results suggest the relevance of these approaches to the development of diagnostic and prognostic tools to deal with premalignant types of gastric polyps, in spite of these results being largely tentative and far from conclusive, as only a small number of cases were examined in minute detail and in terms of the pattern of occurrence of several molecular transformations. This explains the cautious tone of the researchers, in interviews and conversations and in the publications which grew out of this project, as well as their call for work with a much larger series of cases[9].

Redefining prevention?

This kind of approach redefines the meaning of uncertainty by recognizing its unavoidability, and also redefines prevention and early diagnosis through a focus on precursor diseases, markers (molecular or immunological) and prognostic evaluation based on "extended" natural histories of cases. As a matter of fact, there seems to be considerable overlap between the prognosis of precursor lesions and the early diagnosis of cancer. The stabilization of procedures associated with different biomedical platforms allows reliable markers or indicators of specific biological and biochemical processes to be developed. It does not, however, exonerate pathologists from the need to engage in the uncertainty-fraught task of interpreting the emerging configurations of markers and indicators. This also has consequences for decisions concerning therapeutic interventions. Depending on how "risk" - understood here as an assessment, quantitative or "narrative", of the probability of evolution of a lesion towards malignancy - enters the process of decision-making, even in the absence of clinical signs of a malignant pathology, clinicians may advise either radical or aggressive forms of treatment - surgery, chemotherapy and radiotherapy -, or a follow up of the patient, with close surveillance

[9] The place of publication of the paper reporting on the results is also significant: *The Journal Cancer*, read by a heterogeneous public of "basic" and "clinical" researchers.

of signs of an evolution towards malignancy ending up, eventually, in aggressive therapies. But some types of cancer, particularly those more frequent in aging patients and with a slow evolution may be treated as chronic diseases, controlled through appropriate medical surveillance, changes in life-style and medication.

We are far, here, from the assumption that uncertainty is inherently reducible through the increase in knowledge of the initiation and promotion of cancers. More detailed knowledge of multiscale and contingent processes does not mean that they become more predictable, but that the analytical and interpretive work required to deal with these processes will involve a more rich and dense use of the "natural history" or "weight of evidence" approaches to pathology and to the study of and intervention in cases of cancer. Translational research appears, in this context, as a specific mode of articulating routine pathological diagnosis and innovation. In the process, the boundaries between uncertainty and risk, precaution and prevention are increasingly difficult to define in any stable way.

This brings us, at last, to a dilemma that researchers/pathologists and translational researchers have to face: how to stabilize these approaches, which are certainly innovative, but also charged with uncertainty, in order to achieve the aim of developing "fast, cheap and accurate" (Casper and Clarke, 1998: 255) tools for diagnosis and prognosis?

The answer brings us back to a path already explored by STS studies. Any extension of this work into effective intervention in diagnosis and treatment requires the building of a network, or rather an actor-network (Latour, 1987, 1999; Law and Hassard, 1999), and a process of translation,[10] namely through the setting-up of screening programs for gastric pathologies, with a focus on lesions defined as premalignant. Some limited initiatives in this area have so far allowed researchers to enroll public health authorities, clinicians and local populations in screening and treatment of gastric pathologies based on the use of the tools

[10] As it is used in actor network approaches, translation "refers to all the displacements through other actors whose mediation is indispensable for any action to occur. In place of a rigid opposition between context and content, chains of translation refer to the work through which actors modify, displace, and translate their various and contradictory interests" (Latour, 1999: 311).

developed through this particular style of research.[11] This is where translational research would be closest to "translation" as it is understood and used in STS studies.

References

Anderson, R.J. (1985), *Muir's Textbook of Pathology*. London: Edward Arnold (12th edition).

Callon, Michel; Lascoumes, Pierre; Barthes, Yannick (2001), *Agir dans un monde incertain: essai sur la démocratie technique.* Paris: Éditions du Seuil.

Casper, Monica J.; Clarke, Adele E. (1998), "Making the Pap Smear into the `Right Tool´ for the Job: Cervical Cancer Screening in the USA, Circa 1940-95", *Social Studies of Science*, 28: 255-90.

Dixon, Michael F., *et al*. (1996), "Classification and Grading of Gastritis: The Updated Sydney System", *The American Journal of Surgical Pathology*, 20 (10): 1161-1181.

Foucar, E. (1997), "Do Pathologists Play Dice? Uncertainty and Early Histopathological Diagnosis of Common Malignancies", *Histopathology*, 31: 495-502.

Foucault, Michel (1963), *La naissance de la clinique*. Paris: Presses Universitaires de France.

Garfinkel, Harold (1967), *Studies in Ethnomethodology*. Englewood Cliffs, New Jersey: Prentice-Hall.

Heyman, Bob (ed.) (1998), *Risk, Health and Health Care: A Qualitative Approach*. London: Arnold.

Hubbard, Rute (1995), *Profitable Promises: Essays on Women, Science and Health.* Monroe: Common Courage Press.

Keating, Peter; Cambrosio, Alberto (1999), "Biomedical Platforms", *mimeo*.

[11] For the detailed discussion of such an initiative, see Nunes (1999: 351-361).

Keating, Peter; Cambrosio, Alberto (2000), "`Real Compared to What?´: Diagnosing Leukemias and Lymphomas", *in* Margaret Lock *et al*. (eds.), *Living and Working with the New Medical Technologies: Intersections of Inquiry*. Cambridge: Cambridge University Press, 103-134.

Latour, Bruno (1987), *Science in Action; How to Follow Scientists and Engineers Through Society.* Milton Keynes: Open University Press.

Latour, Bruno (1999), *Pandora's Hope: Essays on the Reality of Science Studies*. Cambridge, Massachusetts: Harvard University Press.

Law, John; Hassard, John (eds.) (1999), *Actor Network Theory and After*. Oxford: Blackwell Publishers/The Sociological Review.

McGee, James O'D., *et al*. (eds.) (1992), *Oxford Textbook of Pathology, Volume 1: Principles of Pathology*. Oxford: Oxford University Press.

Nogueira, Ana M.M.F., *et al.* (1999), "Microsatellite Instability in Hyperplastic and Adenomatous Polyps of the Stomach", *Cance*r, 86: 1649-1656.

Nunes, João Arriscado (1998), *Ecologies of Cancer: Constructing the "Environment" in Uncobiology*. *Oficina do CES*, 133.

Nunes, João Arriscado (1999), *Os Mundos Sociais da Ciência e Tecnologia em Portugal: O Caso da Oncobiologia e as Novas Tecnologias da Informação*. Research Report, Coimbra: Centro de Estudos Sociais.

Prior, Lindsay (2000), "Mathematics, Risk and Genetics", *in* Barbara Adam *et al*. (eds.), *The Risk Society and Beyond: Critical Issues for Social Theory*. London: Sage, 106-109.

Singleton, Vicky (1998), "Stabilizing Instabilities: The Role of the Laboratory in the United Kingdom Cervical Screening Programme", *in* Marc Berg and Annemarie Mol (eds.), *Differences in Medicine: Unravelling Practices, Techniques, and Bodies.* Durham, North Carolina: Duke University Press, 86-104.

Sobrinho-Simões, Manuel, *et al*. (1998), "A proeminência da morfologia e a quasi-futilidade das análises genéticas e moleculares no dia-a-dia da patologia oncológica", *mimeo.*

Taylor, Peter J. (2001), "Distributed Agency Within Intersecting Ecological, Social and Sscientific Processes", *in* Susan Oyama, Paul E. Griffiths and Russell E. Gray (eds.), *Cycles of Contingency: Developmental Systems and Evolution*. Cambridge: Massachusetts: MIT Press, 313-332.

Wynne, Brian (1996), "May the Sheep Safely Graze? A Reflexive View of the Expert-lay Knowledge Divide", *in* Scott Lash *et al*. (eds.), *Risk, Environment and Modernity: Towards a New Ecology*. London: Sage, 44-83.