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Causality, Complexity, and Carcinogenesis

Much There is no doubt that cancer causation is characterised by a very high degree of complexity. The following are some of the most important features that describe the carcinogenesis of typical cancers:

(1) *No necessary cause*. With the possible exception of human papilloma virus, which seems to be responsible for all or almost all cervical cancers, cancers do not have necessary causes.[1] Rather, different instances of the same disease are caused by a variety of environmental and genetic factors. Lung cancer, for example, is caused by smoking, radon gas, asbestos air pollution and genetic factors.

(2) *No sufficient cause*. Few causes bring about their effects all on their own. More specifically, there are at least three senses in which causes fail to determine their effects in cancer ontogeny:

> (2a) Cancer susceptibility. In order to be at risk for cancer individuals must be genetically predisposed. CYP1A1 gene polymorphisms for instance interact with tobacco smoking in a way that dramatically increases lung cancer risk.[2] In addition to genetic susceptibility there are several acquired forms of susceptibility. Asbestos interacts with cigarette smoke to modify the risk of lung cancer.[3]
>
> (2b) Lack of determination. At the individual level, there is no way to predict whether the disease will develop given the measurement of all known risk factors. Though molecular biology has made a lot of progress in this area in recent years, the implications of this progress for cancer causation are limited. It is known for instance that transfection of MIH 3T3 cells which already underwent partial transformation with a mutated

[1]Walboomers, Jan et al. 1999, 'Human papillomavirus is a necessary cause of invasive cervical cancer worldwide', *Journal of Pathology* **189** (1): 12–19

[2] San José, Carmen et al. 2010, 'CYP1A1 gene polymorphisms increase lung cancer risk in a high-incidence region of Spain: a case control study', *BMC Cancer* **10**: 463

[3] Tomatis, Lorenzo (ed.) 1990, *Cancer: causes, occurrence and control*. Lyon: IARC (IARC Scie. Publ.; no. 100).

oncogene is sufficient for the development of cancer.[4] Transfection of MIH 3T3 cells is, however, hardly an interesting risk factor from an epidemiological or public health point of view because (among other things) it occurs far too late in the pathological chain.

(2c) Plurality of effects. Many cancers have no unique morphology or prognosis. Gastric lymphomas are non-Hodgkin's lymphomas, an extremely heterogeneous category. Some of them have a mild, others a rapid clinical course, they have a wide range of manifestations and disparate cells of origin.[5] Helicobacter pylori is an important risk factor. Even if infection with H. pylori was, together with susceptibility and other risk factors, sufficient for developing gastric lymphomas knowledge of all risk factors would not determine the type of lymphoma or prognosis.

(3) *Feedback mechanisms*. Feedback mechanisms and homeostasis are a frequently occurring phenomenon in carcinogenesis. So-called 'hedgehog signalling', a signalling mechanism that transmits information to embryonic cells required for proper development, is activated in numerous cancers including gastric cancer, pancreatic cancer, breast cancer and other tumours. Hedgehog signals are fine-tuned based on positive and negative feedback loops. Excessive positive or collapsed negative feedback due to epigenetic or genetic alterations leads to carcinogenesis.[6]

(4) *Multiple and overlapping pathways*. Multiple pathways are dysfunctional in most cancers, and cancers accumulate new oncogenic mutations as they progress. The concept that cancer development is the result of defects in multiple biological processes is well accepted.[7] It is also well-known that the pathway to a tumour includes several stages, and that some exposures to risk factors can lead to cancer by completing the chain initiated by previous exposures.

The aim of this paper is to draw conclusions from these observations about complex cancer causation for the concept of cause. The paper will show (a) that traditional accounts of causation

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[4] Vineis, Paolo 2003, 'Causality in Epidemiology', *Soz.- Präventivmed.* **48**: 80–87

[5] Koch, Peter et al. 2001, 'Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL 01/92', Journal of Clinical Oncology **19**(18): 3861–73

[6] Katoh, Y. and M. Katoh 2009, 'Hedgehog target genes: mechanisms of carcinogenesis induced by aberrant hedgehog signaling activation', *Current Molecular Medicine* **9**(7): 873-86

[7] Hanahan, Douglas and Robert Weinberg 2011, 'Hallmarks of Cancer: The Next Generation', *Cell* **144**(5): 646-674

all fail to make sense of carcinogenesis; and (b) that the inferentialist theory[8] has no difficulty accommodating the mentioned features. It is easy to see that, for instance, Codell Carter's account of cause as 'necessary universal condition' (which goes back to work by Louis Pasteur, Jakob Henle and Robert Koch) conflicts with (1) and (2). Mackie's INUS account conflicts with (2b) and (2c) because even complete sets of INUS conditions (or causal 'pies' in Rothman's sense[9]) are not invariably followed by an event-type. Probabilistic causation, especially in the Bayes' net variety, assumes acyclicity and therefore does not allow (3). Finally, Woodward's interventionist account struggles with (4) because interventions tend to have multiple effects (causal relations are non-modular) and because a number of intervention is normally needed for bringing about a desired result (for prevention, therapy etc.). The inferentialist theory, by contrast, according to which causal relations are inferential relations between evidential statements, causal statements and predictive/explanatory statements, deals will all these cases with ease, which this paper will show in some detail.

[8] Reiss, Julian 2012, 'Causation in the Sciences: An Inferentialist Account", *Studies in the History and Philosophy of Biological and Biomedical Sciences* **43**(4): 769-77

[9] Rothman, Kenneth et al. 2013, *Modern Epidemiology*, Philadelphia (PA): Lippincott, Williams & Wilkins