Causation in Medicine / Causalidad en Medicina

Jornadas sobre Revoluciones Conceptuales: De las Ciencias Cognitivas a la Medicina

Universidade da Coruña, Ferrol, Spain.

January 2010

Brendan Clarke
PhD Candidate
Department of Science and Technology Studies
University College London
Gower Street, London
UK

Introduction: Causation and conceptual change via cervical cancer

In this paper, I offer one example of conceptual change. Specifically, I contend that the discovery that viruses could cause cancer represents an excellent example of branch jumping, one of Thagard's[1] nine forms of conceptual change. Prior to about 1960, cancer was generally regarded as a degenerative, chronic, non-infectious disease. Cancer causation was therefore usually held to be a gradual process of accumulating cellular damage, caused by relatively non-specific component causes, acting over long periods of time. Viral infections, on the other hand, were generally understood to be acute processes, whereby single, specific and necessary causal agents acted alone to produce disease. However, during the 1960s and 1970s, a number of cancers were discovered to have an infectious aetiology. Of particular note were two—Burkitt's lymphoma and cervical cancer—which I will discuss in detail later in this piece. Together, these discoveries led, in the short term, to a tentative aetiological reclassification of some types of cancer as infectious diseases and, in the longer term, to a full-blown reclassification of cancer as an aetiological disease branch in its own right. This process of reclassification forms the empirical basis for my concluding remarks on the influence of classification upon causation in medicine. Through this, I aim to demonstrate that conceptual change, far from being a purely abstract concern of the philosopher of science, is of substantial import to scientific practitioners.

Burkitt's lymphoma (BL)

BL is an extranodal B-cell lymphoma[2] which occurs primarily in young children living in sub-Saharan Africa. It was first described in 1958 by Denis Burkitt in the following way. First, while malignant tumours of the jaw are generally rare in children, they appeared to be unusually common in parts of Uganda. In fact, they were by far the commonest malignant disease of childhood.[3] These jaw tumours appeared to be part of a wider clinical syndrome, with histologically similar material also found in other anatomical sites, including within the abdomen. This syndrome was strikingly unusual in three respects. First, despite the high incidence of the disease in Uganda, it was unknown in other parts of the world, suggesting the existence of some particular geographical distribution. Second, the disease appeared to affect only young children, in sharp contrast to most tumours. Third, the disease affected several sites of the body simultaneously, including multiple sites within the jaw and within the abdomen. For this pathogenic mechanism to be the case, a novel process of either simultaneous, multifocal oncogenesis occuring in both jaw and

1 Thagard, P. 1992. *Conceptual Revolutions*, Princeton, N.J: Princeton University Press.

2 Harris, N.L. et al., 1999. "World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting-Airlie House, Virginia, November 1997." *Journal of Clinical Oncology*. **17**(12): 3835—49.

3 Burkitt, D. 1958. "A Sarcoma Involving the Jaws in African Children." *The British Journal of Surgery*. **46**(197): 218—23.

abdomen, or a mechanism of sudden metastasis by unknown means, would be required. Together, these three anomalies suggested the action of an unusual causal mechanism underlying the disease.

The initial research direction was this. First, the clinical picture was developed through the investigation of further instances of the disease. While this led to numerous minor refinements, no substantial developments in understanding the aetiology of the disease were made. Second, the epidemiology of the tumour was systematically investigated. Importantly, the geographical limits of the disease were sought by conducted a postal survey of African hospitals, asking for sightings of the distinctive clinical features of the lymphoma.[4] This survey was sufficiently successful to allow the mapping of tumour cases across large parts of Africa. As a consequence of this mapping exercise, the lymphoma syndrome was seen to occur in a belt across the continent, spanning the equator, with a tail running down the east coast and sparing the northern and southern extremities.[5] The islands of Zanzibar and Pemba, lying off the coast of Tanganyika (now incorporated into Tanzania) were spared entirely. Furthermore, there appeared to be areas within this 'lymphoma belt' in which the tumour did not occur or, at least, occurred with greatly reduced frequency. This distribution led to enquiries into the unifying factors common to the regions of high tumour incidence. It was noted that this distribution could be mirrored by the consideration of certain climatic factors. For instance, eliminating all areas where the mean temperature fell below 15°C at any time of year, over 1500m altitude, and where mean annual rainfall was less than 750mm, gave a map which was "*almost identical with the map of tumour distribution*".[6]

This geographic distribution suggested the activity of some causally significant entity which depended on climatic factors, for instance flora or fauna. Two arthropods of known medical importance had distributions similar to that of BL. The first was the tsetse fly (*Glossina* spp.), the insect vector of African trypanosomiasis, while the second was the *Anopheles* mosquito, the vector of malaria. Certain recent outbreaks of viral disease in the region, in turn, suggested that these insects might act as vectors for unknown viruses. Could an insect-vectored virus be the cause of BL?

While the viral hypothesis was initially strengthened by the presence, under electron microscopy, of changes suggestive of viral activity in BL tumour cells, no virus itself was detectable, although a wide range of techniques were used, including cell cultures, infection of fertilized hens eggs and inoculation of material into newborn mice.[7] When the cells of BL were grown in cell culture, however, a different story developed. On the 24th of Feb 1964, samples of the first cell line derived from BL were examined using thin section electron microscopy. The findings were exciting– with "*...unequivocal virus particles in a cultured BL cell in the very first grid square to be searched*". These virus-like particles were subsequently rapidly detected in other BL cell lines.[8]

These virus-like particles seen on electron microscopy was the first detection of a new herpesvirus, which later became known as the Epstein-Barr virus (EBV) after its discoverers.[9] Immunofluorescence testing revealed that viral antigens were immunologically reactive against the serum of patients with Burkitt's lymphoma, and against BL cells. As might be expected, the extent of immunofluorescence correlated with virus particles as seen using electron microscopy.[10] Mystifyingly, though, despite the relatively specific immunological response obtained in cases of BL, it was also immunologically reactive against the sera of non-BL individuals, including leukaemia patients,[11] individuals with nasopharyngeal carcinomas[12] and, most confusingly of all, against many normal North American control

---

4 Burkitt, D. and Wright, D. 1963. "A Lymphoma Syndrome in Tropical Africa with a Note on Histology, Cytology, and Histochemistry." *International Review of Experimental Pathology*. **2**: 67—138.

5 Burkitt, D. 1961. "Observations on the Geography of Malignant Lymphoma." *East African Medical Journal.* **38**: 511—4.

6 *ibid*

7 Epstein, M.A. 2005. "The Origins of EBV Research: Discovery and Characterization of the Virus." In Robertson E.S., ed., *Epstein-Barr Virus.* Norfolk: Caister Academic Press, 1—14.

8 For example, Pulvertaft, J.V. 1964. "Cytology of Burkitt's Tumour (African Lymphoma)." *The Lancet*. **283**(7327): 238—40; Epstein, M.A., Barr, Y.M. and Achong, B.G. 1964. "A Second Virus-Carrying Tissue Culture Strain (EB2) of Lymphoblasts from Burkitt's Lymphoma." *Pathologie-Biologie*. **12**: 1233–4; Epstein, M.A., Barr, Y.M. and Achong, B.G. 1965. "Studies with Burkitt's Lymphoma." *The Wistar Institute Symposium Monograph*. **4**: 69—82 and Stewart, S.E., Lovelace, E., Whang, J.J. and Ngu, V.A. 1965. "Burkitt Tumor: Tissue Culture, Cytogenetic and Virus Studies." *Journal of the National Cancer Institute*. **34**: 319—27.

9 EBV is a B-lymphotropic γ-herpesvirus. It infects B-cells, and is capable of immortalising them. The virus is highly prevalent in adult human populations worldwide, with up to 90% of adults displaying evidence of infection.

10 Henle, G. and Henle, W. 1966. "Immunofluorescence in Cells Derived from Burkitt's Lymphoma." *Journal of Bacteriology*. **91**(3): 1248—56.

11 *ibid*

12 Henle, W., Henle, G., Ho, H.C., Burtin, P., Cachin, Y, Clifford, P et al. 1970. "Antibodies to Epstein-Barr Virus in Nasopharyngeal Carcinoma,

individuals.[13] This suggested that infections with EBV were far more common in non-BL populations than might be expected if EBV were really the causal agent of BL.

So if EBV was to be the cause of BL, an explanation for its presence in so many individuals without the disease was required. Could it be the case that, while EBV caused BL, it also caused a range of other diseases? Perhaps the most significant development in this field arose as following. While conducting a series of surveys for EBV antibodies using sera from a variety of paediatric illnesses of unknown, but presumptively viral, aetiology, one researcher by chance developed Infectious Mononucleosis (IM; glandular fever). It was discovered that, following this infection, her leukocytes became capable of growing in cell culture, a property they had not possessed when tested before the development of the disease. While she initially did not display antibodies to EBV, from the outset her cultured cells expressed EBV antigens, and contained the chromosomal abnormalities characteristic of BL.[14] When further sera from IM patients were examined, they were all found to be strongly positive for anti-EBV antibodies. This led to the conclusion that IM was causally related to EBV:

> *"Patients with infectious mononucleosis regularly develop antibodies to the herpes-type virus (EBV) found in cultures derived from Burkitt's tumors or other cells of the hematopoietic system. . . The epidemiology of IM and the seroepidemiology of EBV share many features. Thus, it appears that EBV, or a close relative of it, is the cause of IM. This conclusion does not preclude the possibility that EBV might also be involved, either directly or indirectly, in the etiology of Burkitt's lymphoma."*[15]

This probable aetiologic relationship could therefore explain the serological evidence of past EBV infection in otherwise healthy individuals. However, the causal mechanism linking BL and EBV was still rather incomplete by the early 1970s. There was, therefore, much resistance to it until the completion of various epidemiological studies demonstrating the increased risk of BL in populations with high levels of anti-EBV antibodies. One important example of these types of investigation was the large prospective seroepidemiological study in the lymphoma belt[16] that began in 1971. It followed 42 000 children from birth to 8 years old in the West Nile District of Uganda. Serum samples were taken at enrollment, and enrolled children were then monitored for the development of BL. In total, 14 of the 42 000 participants developed the disease during the lifetime of the trial. It was show that affected individuals had higher levels of anti-EBV antibodies than controls at baseline. When this finding was combined with earlier work that populations at high BL risk tended to acquire anti-EBV antibodies at a younger age than individuals in populations at low risk,[17] a mechanism of differential pathogenesis began to be developed. In broad terms, individuals who became infected with EBV young were at risk of developing BL,[18] while individuals becoming infected later in life tended to develop IM.

So BL is one example of human viral oncogensis that contributed significantly to the conceptual change occuring in cancer causation. The causal arguments above show modifications to, not only arguments regarding cancer causation, but also to those regarding the causation of viral illnesses more widely. However, the generalizability of these modifications appears doubtful. For one, Burkitt's lymphoma is a rather atypical tumour in several respects. It is rather uncommon, and occurs in a particular distribution – both geographically, restricted to a narrow band of sub-Saharan Africa, and in a narrow range of susceptible ages – really only between 5 and 8 years. For another, the causal relationship between EBV and its range of clinical manifestations remains highly complex. In detail, it is not at all clear what other factors predispose towards the different manifestations of the same virus in different populations. The case of BL and EBV therefore presented something akin to an oddity, rather than a revolution in cancer causation. It

---

Other Head and Neck Neoplasms, and Control Groups." *Journal of the National Cancer Institute*. **44**(1): 225–31.

13 About 30% of children and 90% of adults showed immunological evidence of past infection with EBV. Henle, G. and Henle, W. 1966. "Immunofluorescence in Cells Derived from Burkitt's Lymphoma." *Journal of Bacteriology*. **91**(3): 1248—56.

14 Henle, G., Henle, W. and Diehl, V. 1968. "Relation of Burkitt's Tumor-Associated Herpes-Type Virus to Infectious Mononucleosis." *Proceedings of the National Academy of Sciences of the United States of America*. **59**(1): 94—101.

15 *Ibid*

16 de-Thé, G., Geser, A., Day, N.E., Tukei, P.M., Williams, E.H., Beri, D.P. et al. 1978. "Epidemiological Evidence for Causal Relationship Between Epstein-Barr Virus and Burkitt's Lymphoma from Ugandan Prospective Study." *Nature*. **274**(5673): 756–61.

17 See, for example, Henle, G., Henle, W., Clifford, P., Diehl, V., Kafuko, G.W., Kirya, B.G. et al. 1969. "Antibodies to Epstein-Barr Virus in Burkitt's Lymphoma and Control Groups." *Journal of the National Cancer Institute*. **43**(5): 1147–57.

18 Although this branch of the mechanism remains incomplete, and the interactions of other risk factors with early-life EBV infection in the genesis of BL is poorly understood.

would take the discovery of viral oncogensis in a much more common setting before this conceptual change really took hold.

Cervical cancer

A much more surprising candidate for viral oncogenesis was cervical cancer. Unlike Burkitt's lymphoma, cervical cancer is a much more typical tumour: it occurs relatively commonly, has a worldwide distribution and (generally) increases in incidence with age. Before about 1960, cervical cancer was believed to have similar risk factors to other malignant diseases.

> *"Long-continued irritation and chronic inflammation are probably the conditions which pave the way for the development of the new growth."*[19]

These risk factors were thought typical for a disease of the degenerative-chronic type. However, it later emerged that the risk factors for cervical cancer were similar to those of an infectious disease. For instance, as one of the major reviews[20] of the epidemiology and aetiology of cervical cancer rather bluntly put it:

> *"The cancer patient is characterised by more marital misadventures, divorce and separation, more pre-marital coitus and deliveries and more sexual partners."*[21]

A great deal of sound epidemiologic data appeared to support this thesis, with a complex web of socioeconomic factors, particularly those indicating social class, marital and sexual habits and features of male sexual partners, modifying the risk of developing the disease.[22] However, no specific mechanism was developed to explain these phenomena. Instead, background plausibility assumptions played the major role in deciding which factors were causal, and which were confounders—that is, which factors were merely correlated markers of genuinely causal ones. So for instance, while investigating the correlation between marriage and the development of cervical cancer, Lombard and Potter noted that a direct causal link was implausible:

> *"...no one would consider the mere ceremony of marriage to have a bearing on the causation of the disease"*[23]

That is not to say there was no relevant investigation of the mechanism of oncogenesis. Some research—particularly into the mechanism of male factors in cervical cancer[24]—attempted to investigate questions raised by epidemiological research. But in general, epidemiological research was not coupled to a corresponding laboratory program of the mechanism of cancer causation.

That is until the discovery of human viral oncogenesis. A viral infection causing cervical cancer could provide a means of unifying and explaining these risk factors, and, by about 1970, cervical cancer commonly believed to be caused by a virus. The formerly known social factors were now generally explained as acting by modifying the chances of a

---

[19] Deaver, J.B. and Reimann, S.P. 1931. "Cancer of the Uterus: With General Remarks on the Pathologic Aspects of Cancer of the Uterus." *Annals of Surgery.* **94**(3): 381—8.

[20] Aitken-Swan, J. and Baird, D. 1966a. "Cancer of the Uterine Cervix in Aberdeenshire. Epidemiological Aspects." *British Journal of Cancer.* **20**(4): 624—41.

[21] Aitken-Swan, J. and Baird, D. 1966b. "Cancer of the Uterine Cervix in Aberdeenshire. Aetiological Aspects." *British Journal of Cancer.* **20**(4): 642—59

[22] In brief, these factors were:
Risk factors: low socioeconomic class, marriage, sexual intercourse, multiple sexual partners, employment as prostitutes, infection with syphilis.
Protective factors: Jewish or Muslim faith, abstinence from sex, circumcision of male partner, cleanliness of male partner, use of barrier contraception.
See, for instance, Elliott, R. 1964. "On the Prevention of Carcinoma of the Cervix," *The Lancet.* **1**(7327): 231—5, for a review.

[23] Lombard, H. and Potter, E. 1950. "Environmental Factors in the Etiology of Cancer," *Acta Unio Internationalis Contra Cancrum*. **6**: 1325—33.

[24] For example, both Plaut, A. and Kohn-Speyer, A. 1947. "The Carcinogenic Action of Smegma," *Science.* **105**(2728): 391—2 and Pratt-Thomas, H., Heins, H.C., Latham, E., Dennis, E.J. and McIver, F.A. 1955. "The Carcinogenic Effect of Human Smegma: An Experimental Study. I. Preliminary Report," *Cancer.* **9**(4): 671—80 showed experimentally that exposure to smegma could act as an initiation of carcinogenesis.

woman contracting it. Interestingly, though, this emergent research program was not a result of finding the correct causal virus. We now know that cervical cancer is caused by infection with certain strains of the human papillomavirus (HPV). However, this was not known until the 1980s. In fact, much of this earlier research suggested that herpes simplex virus (HSV), responsible for, amongst other things genital herpes infections, was responsible.[25] This seemed highly plausible: herpes viruses were known to be capable of causing cancers—for instance, the causal virus of Burkitt's lymphoma is a type of herpes virus; the epidemiology of the virus was consistent with the existing evidence and herpes infections and cervical cancer were rather well correlated on an individual case basis. In fact, the evidence linking HSV and cervical cancer was rather impressive.

To give a summary of this evidence,[26] HSV is a commensal organism, likely to grow in the female reproductive tract. In fact, it was known to be responsible for genital herpes infections. Thus, it was also known to be transmitted through sexual intercourse, offering a possible explanation for some cervical cancer risk factors. These included the role of first coitus, marriage or pregnancy, at an early age, the role of multiple sexual partners or promiscuity in increasing disease incidence, and the finding that women of low socioeconomic status were at higher risk of cervical cancer than wealthy. Second, herpesviruses were known to be implicated in other malignant diseases. Not only was the causal agent of BL a herpesvirus, but many non-human animals were known to suffer from herpes-associated malignant diseases. Third, there was an apparent serological association between the virus and the cancer. Antibodies against one type of HSV (HSV2) were present in prostitutes (who have a very high rate of cervical cancer) more than twice as often as in control populations and four times as often in women with cervical cancer than controls.[27] Fourth, HSV was known to be capable of causing chromosomal abnormalities *in vitro* in both animal and human cells,[28] similar to those known to be associated with many sorts of cancer. Fifth, it also became apparent that fragments of HSV DNA could be directly detected in cervical cancer cell, suggesting some specific role in pathogenesis.[29]

These supporting pieces of evidence were highly plausible, but did not constitute a causal mechanism for cervical cancer. Attempts to produce an experimental model of disease in animals were problematic. Early experimental attempts to induce tumours in animals by inoculation with various herpes simplex strains failed outright.[30] Later animal inoculation experiments too were equivocal, although some of them displayed a slight apparent effect of HSV2 inoculation on tumour development. In both cases this work was complicated by the very high subject mortality caused by the lytic effects of HSV. I might also speculate that a general unwillingness to publish negative findings makes it likely that there were even more unsuccessful attempts to induce cervical tumours using HSV than the literature reveals.

Similar experiments using *in vitro* cell cultures were more successful. For instance, cells *in vitro* could be transformed by incubation with UV-inactivated HSV2. These transformed cells displayed HSV antigens,[31] and were capable of inducing malignant tumour formation when inoculated into animal subjects. Fragments of HSV nucleic acids were also detectable in these cell lines.[32]

Thus the general oncogenic properties of the herpesviruses revealed, in part, by these experiments required some

---

[25] HSV as the causal agent of cervical cancer really began in earnest in 1966. See Naib, Z.M., Nahmias, A.J. and Josey, W.E. 1966. "Cytology and Histopathology of Cervical Herpes Simplex Infection," *Cancer*. **19**(7): 1026—31.

[26] Summary derived from Alexander, E. 1973. "Possible Etiologies of Cancer of the Cervix Other Than Herpesvirus," *Cancer Research.* **33**(6): 1485—90.

[27] Rawls, W.E., Tompkins, W.A., Figueroa, M.E., and Melnick J.L. 1968. "Herpesvirus Type 2: Association with Carcinoma of the Cervix." *Science.* **161**(847): 1255—6; Rawls, W., Tompkins, W. and Melnick, J. 1969. "Serological Association between Herpesvirus Type 2 and Cervical Cancer." *Bacteriological Proceedings.* **1969**: 178.

[28] Hampar, B. and Ellison, S.A. 1963. "Cellular Alterations in the MCH Line of Chinese Hamster Cells Following Infection with Herpes Simplex Virus." *Proceedings of the National Academy of Sciences of the United States of America* **49:** 474—80.

[29] HSV2 nucleic acids were recovered, in a single case, from cervical cancer tissue samples. However, this finding was not replicable, and it remained the case that HSV genetic material could generally only be detected from cells grown *in vitro* cell cultures. Frenkel, N., Roizman, B., Cassai, E. and Nahmias, A. 1972. "A DNA Fragment of Herpes Simplex 2 and Its Transcription in Human Cervical Cancer Tissue." *Proceedings of the National Academy of Sciences of the United States of America*. **69**(12): 3784—9.

[30] Rapp, F. and Falk, L. 1964. "Study of Virulence and Tumorigenicity of Variants of Herpes Simplex Virus." *Proceedings of the Society for Experimental Biology and Medicine*. **116**: 361—5.

[31] Duff, R. and Rapp, F. 1971. "Properties of Hamster Embryo Fibroblasts Transformed *in Vitro* After Exposure to Ultraviolet-Irradiated Herpes Simplex Virus Type 2." *Journal of Virology*. **8**(4): 469--77.

[32] Collard, W., Thornton, H. and Green, M. 1973. "Cells Transformed by Human Herpesvirus Type 2 Transcribe Virus-Specific RNA Sequences Shared by Herpesvirus Types 1 and 2." *Nature: New Biology*. **243**(130): 264—6.

specific demonstration in cervical cancer. However, no publications reporting such findings seem to be extant. It thus was the role of epidemiology to suggest that the herpesvirus hypothesis was mistaken. As with Burkitt's lymphoma, a large prospective seroepidemiological study was undertaken. This involved more that 10 000 women in Prague. While the results of this study showed general agreement between cervical cancer risk and the previously known risk factors,[33] no differences in HSV2 status appeared to exist between matched control subjects and cancer cases.[34] Thus this study did not seem to support a causal role for HSV in the development of the cancer. Thus, the role of HSV as a specific, necessary cause of cervical cancer seemed untenable. Instead, HSV was now thought to correlate with a second sexually transmitted agent. Various candidate agents were investigated, including human papillomavirus (HPV).

HPV initially seemed a most unpromising agent, for the simple reason that no detection of the virus had been made in cervical cancer tissue. However, it did seem at least plausible that HPV could have a pathogenic role. For example, various other diseases–including skin warts and the rare, heritable skin disease epidermodysplasia verruciformis–were known to be related to papillomavirus infection. Electron microscopy of material derived from several types of wart revealed strong morphological similarities between the various virus particles.[35] Similar too was the clinical course of disease seen during experimental or accidental wart transmission experiments. Together, these two features suggested that papillomaviruses could cause both benign and malignant diseases, and were transmissible. Yet the means by which this transmission could occur was unknown. For one, the different known papillomaviruses, despite having similar gross morphologies and genome lengths,[36] were antigenically distinct and their genomes showed a good deal of variance when analysed in terms of base composition.[37] Both immuno-EM and RNA-hybridisation experiments revealed a significant degree of difference between the papillomaviruses associated with different disease, with material derived from one type of disease appearing to share neither immunological nor genetic characteristics with material derived from others.[38] There were important epidemiological questions too. Different papillomavirus diseases in humans (warts, genital warts or laryngeal warts) characteristically occurred at different ages and in different populations. This finding too seemed to count against a strongly unified cause for these diseases.

Were HPV a group of related viruses? Could this explain the different clinical and experimental properties of the (visually identical) viruses? Part of the puzzle was resolved when researchers examined in detail the genomes of papillomaviruses from different types of wart material, when it rapidly became apparent that a number of diverse HPV strains were present. These strains were immunologically distinct, suggesting that, despite the previous lack of detection of the virus in cervical cancer cells, HPV could still be causally implicated:

> *"The condyloma agent has been entirely neglected thus far in all epidemiological and serological studies relating . . . to cervical . . . carcinomas. This is particularly unusual in view of the localization of genital warts, their mode of venereal transmission, the number of reports on malignant transition, and the presence of an agent belonging to a well-characterized group of oncogenic DNA viruses."*[39]

So the discovery that HPV did, in fact, cause cervical cancer required the development of a large number of strain-specific tests for HPV. In fact, it was not until the discovery and cloning of HPV–16 from a cervical cancer tissue

---

[33] Vonka, V., Kanka, J., Jelínek, J., Subrt, I., Suchnek, A., Havránková, A. et al 1984a. "Prospective Study on the Relationship Between Cervical Neoplasia and Herpes Simplex Type-2 Virus. I. Epidemiological Characteristics." *International Journal of Cancer.* **33**(1): 49—60.

[34] Vonka, V., Kanka, J., Hirsch, I., Závadová, H., Krcmár, M., Suchánková, A. et al 1984b. "Prospective Study on the Relationship Between Cervical Neoplasia and Herpes Simplex Type-2 Virus. II. Herpes Simplex Type-2 Antibody Presence in Sera Taken at Enrollment." *International Journal of Cancer*. **33**(1): 61—6; Krcmár, M., Suchánková, A., Kanka, J. and Vonka, V. 1986. "Prospective Study on the Relationship Between Cervical Neoplasia and Herpes Simplex Type 2 Virus. III. Presence of Herpes Simplex Type-2 Antibody in Sera of Subjects Who Developed Cervical Neoplasia Later in the Study." *International Journal of Cancer*. **38**(2): 161—5.

[35] Oriel, J.D. and Almeida, J.D. 1970. "Demonstration of Virus Particles in Human Genital Warts." *The British Journal of Venereal Diseases.* **46**(1): 37—42.

[36] Crawford, L. and Crawford, E. 1963. "A Comparative Study of Polyoma and Papilloma Viruses." *Virology*. **21**: 258—63.

[37] *ibid*; Le Bouvier, G.L., Sussman, M. and Crawford, L.V. 1966. "Antigenic Diversity of Mammalian Papillomaviruses." *Journal of General Microbiology.* **45**(3): 497—501.

[38] see, e.g. zur Hausen, H., Meinhof, W., Scheiber, W. and Bornkamm, G.W. 1974. "Attempts to Detect Virus-Specific DNA in Human Tumors. I. Nucleic Acid Hybridizations with Complementary RNA of Human Wart Virus." *International Journal of Cancer.* **13**(5): 650—6.

[39] zur Hausen, H. 1976. "Condylomata Acuminata and Human Genital Cancer." *Cancer Research.* **36**(2 pt 2): 794.

sample that HPV could be detected in most cases of cervical cancer.[40] This newly discovered strain of HPV was highly specific for cervical cancer, and generally could not be detected in other papillomavirus-related disease. A degree of strain variation by geographical region also seemed to be the case, with HPV-16 being detectable in at much higher rates in European cervical cancer samples than those from Africa or South America. A second novel strain, HPV–18, was soon detected in an African cervical cancer sample by similar means to that of HPV–16,[41] which also seemed relatively region-specific. Taken together, HPV–16 and –18 were present in most tested cervical cancer samples. This demonstration of strain-specificity was further support for the causal role of the virus. Unlike the earlier causal candidate HSV, a pathogenic mechanism was rapidly developed linking the virus with the disease. While I won't attempt a detailed review of it here, it seems worth giving an outline of a few of the major developments. First, it was found that cloned HPV DNA alone was capable of transforming cells *in vitro*.[42] This process of transformation involved incorporation of the HPV genome into the host genome.[43] RNA analysis revealed the expression of a number of non-structural viral proteins in these immortalised cells. These 'early' viral proteins appeared causally important in cellular transformation.[44] In particular, the E6 and E7 proteins appeared to be responsible for modifying cell cycle regulation through a number of specific mechanisms. Acting together, HPV–18 E6 and E7 proteins were found to be necessary and sufficient for cell transformation, *in vitro*, at least.[45] E6 is necessarily responsible for the maintenance of tumours.[46] However, acting alone, it also appeared capable of inducing immortalisation in some cell-types, causing cell-cycle deregulation by p53 degradation.[47] E7, though, acts through interactions with the retinoblastoma gene product pRp, leading to cell-cycle deregulation via disruption of the actions of transcription factor E2F.[48] Thus, E7 acts as the initiator of cell immortalization.[49] This process of HPV integration, early protein expression and disruption of cell-cycle regulation was suggested as the mechanism underlying the transformation of cells. These immortalised cells appeared capable too of malignant progression. *In vitro* studies of keratinocytes immortalised by HPV became malignant in a stochastic fashion upon prolonged passage.[50]

In summary, following prolonged investigation of HPV, particularly focusing on the technical difficulties of detecting the virus or growing it in culture, a strong statistical-mechanical link with cervical cancer was uncovered, with epidemiological investigations playing a subordinate role.[51] It is now thought that the evidence linking HSV and cancer of the uterine cervix can be explained on the grounds of similarity of risk factors: behaviours which place the individual at high risk for contracting HPV also place them at high risk of contracting HSV.

---

[40] Dürst, M., Gissmann, L., Ikenberg, H. and zur Hausen, H. 1983. "A Papillomavirus DNA from a Cervical Carcinoma and Its Prevalence in Cancer Biopsy Samples from Different Geographic Regions." *Proceedings of the National Academy of Sciences of the United States of America.* **80**(12): 3812—5.

[41] Boshart, M., Gissmann, L., Ikenberg, H., Kleineheinz, A. Scheurlen, W. and zur Hausen, H. 1984. "A New Type of Papillomavirus DNA, Its Presence in Genital Cancer Biopsies and in Cell Lines Derived from Cervical Cancer." *The EMBO Journal*. **3**(5): 1151—7.

[42] Chen, T.M., Pecoraro, G. and Defendi, V. 1993. "Genetic Analysis of *in Vitro* Progression of Human Papillomavirus-Transfected Human Cervical Cells." *Cancer Research.* **53**(5): 1167—71.

[43] Yee, C., Krishnan-Hewlett, I., Baker, C.C., Schlegel, R. and Howley, P.M. 1985. "Presence and Expression of Human Papillomavirus Sequences in Human Cervical Carcinoma Cell Lines." *The American Journal of Pathology.* **119**(3): 361—6.

[44] Kaur, P. and McDougall, J.K. 1988. "Characterization of Primary Human Keratinocytes Transformed by Human Papillomavirus Type 18." *Journal of Virology.* **62**(6): 1917—24.

[45] Münger, K., Phelps, W.C., Bubb, V., Howley, P.M. and Schlegel, R. 1989. "The E6 and E7 Genes of the Human Papillomavirus Type 16 Together Are Necessary and Sufficient for Transformation of Primary Human Keratinocytes." *Journal of Virology.* **63**(10): 4417—21.

[46] von Knebel Doeberitz, M., Rittmüller, C., Aengeneyndt, F., Jansen-Dürr, P. and Spitkovsky, D. 1994. "Reversible Repression of Papillomavirus Oncogene Expression in Cervical Carcinoma Cells: Consequences for the Phenotype and E6-p53 and E7-pRb Interactions." *Journal of Virology*. **68**(5): 2811—21.

[47] Scheffner, M., Werness, B.A., Huibregtse, J.M., Levine, A.J. and Howley, P.M. 1990. "The E6 Oncoprotein Encoded by Human Papillomavirus Types 16 and 18 Promotes the Degradation of p53." *Cell*. **63**(6): 1129—36.

[48] Chellappan, S., Kraus, V.B., Kroger, B., Münger, K., Howley, P.M., Phelps, W.C. et al. 1992. "Adenovirus EtA, Simian Virus 40 Tumor Antigen, Human Papillomavirus E7 Protein Share the Capacity to Disrupt the Interaction Between Transcription Factor E2F and the Retinoblastoma Gene Product." *Proceedings of the National Academy of Sciences of the United States of America*. **89**(10): 4549—53.

[49] Halbert, C.L., Demers, G.W. and Galloway, D.A. 1991. "The E7 Gene of Human Papillomavirus Type 16 Is Sufficient for Immortalization of Human Epithelial Cells." *Journal of Virology*. **65**(1): 473—8.

[50] Hurlin, P.J., Kaur, P., Smith, P.P., Perez-Reyes, N., Blanton, R.A. and McDougall. J.K. 1991. "Progression of Human Papillomavirus Type 18-Immortalized Human Keratinocytes to a Malignant Phenotype." *Proceedings of the National Academy of Sciences of the United States of America*. **88**(2): 570—4.

[51] zur Hausen, H. 1989. "Papillomavirus in Anogenital Cancer: The Dilemma of Epidemiologic Approaches," *Journal of the National Cancer Institute.* **81**(22): 1680—2.

Causal classification and conceptual change

At the outset of this piece I suggested that the discovery of the viral oncogenesis led to a revisionary, branch-jumping reclassification of cancer aetiology in general. While I hope I have demonstrated how this came about, what is the significance of such a reclassification? In order to answer this question, I need to discuss the ways by which disease are classified in clinical practice.

For instance, when making a diagnosis, the clinician may use classifications in order to understand the nature and cause of symptoms. Two sorts of classification are particularly important for physical illnesses. One way of classifying a disease process would be to begin by dividing possible causes of disease by their relevant anatomical site. To give an example, the symptom "pain in the abdomen" may arise as a result of disease occuring in a number of sites. These include:[52]

1. The stomach or duodenum (for instance, a perforated gastric or duodenal ulcer, perforated gastric carcinoma or acute gastritis)
2. The intestines (small bowel obstruction, Crohn's disease, intussusception)
3. The appendix (acute appendicitis)
4. The pancreas (acute pancreatitis, pancreatic trauma)
5. The gallbladder or bile-ducts (gall stone, acute cholecystitis, acute cholangitis)
6. The liver (trauma, acute hepatitis, malignancy, congestive heart failure); or
7. The spleen (trauma, spontaneous rupture, infarction)

and so on. But we could also classify these diseases in a second way, by their aetiology.[53] So the same symptom might be caused by:

1. Vascular diseases (congestive heart failure causing hepatic engorgement, splenic infarction...)
2. Infections (acute hepatitis, spontaneous splenic rupture[54])
3. Cancer (perforated gastric carcinoma, small bowel obstruction, hepatic malignancy)
4. Trauma (pancreatic trauma, hepatic trauma, splenic trauma)
5. Autoimmune diseases (Crohn's disease)
6. Metabolic diseases (gall stone)
7. Endocrine diseases
8. Degenerative diseases
9. Iatrogenic and idiopathic diseases
10. Congenital diseases

These causal classifications are useful, in a relatively superficial sense, for understanding patterns of disease. As an example, if we classify a set of diseases anatomically it may be difficult to detect their underlying aetiology. So while an individual might have symptoms compatible with pain arising in the pancreas, liver and spleen, an anatomical classification merely suggests an appropriate group of sites suitable for further investigation. If we were to attempt an aetiological classification, on the other hand, the same individual might be seen to have suffered trauma to the pancreas, liver and spleen, suggesting a coherent mechanism underlying all of their ailments. While in such a simple case any cognitive gain seems trivial, in more complex disease process aetiological classifications are likely to be rather more helpful. Take the case of an individual with an enlarged thryroid gland, an irregular heart rhythm (an arrhythmia) and acute abdominal pain. Here, an aetiological classification is likely to suggest an underlying mechanism in a way that an anatomical classification will not. In this instance, one possible explanation for these

[52] These causal categories are what I refer to when I suggest that viral oncogenesis caused a branch-jumping event. In this instance, both the disease causes and classificatory categories are derived from Bouchier, I.A.D, Ellis, H. and Fleming, P.R. (eds). 1996. *French's Index of Differential Diagnosis.* 13th ed. London: Arnold.

[53] Aetiological classifications (informally known as *surgical sieves*) such as this, are widely used in clinical practice. Sadly little is written about such classifications in the academic literature.

[54] Spontaneous splenic rupture is generally a consequence of infectious mononucleosis.

symptoms could be as follows. First, the enlarged thyroid gland could indicate that the patient is suffering from Graves' disease. One consequence of this is a predisposition towards atrial fibrillation, a type of cardiac arrhythmia. A consequence of this atrial fibrillation is an increased risk of unwanted blood clots. One of these clots may have caused a splenic infarction, leading to the abdominal pain. In this case, an anatomical classification will have been unhelpful in discovering this causal mechanism. Importantly for practice, discovering this underlying disease mechanism suggests therapeutic strategies in a manner that anatomical classification does not.

There is a more fundamental sense in which reclassifications are important. The further discovery of viral causes of cancer, such as has recently happened in the case of Merkel cell carcinoma,[55] or the discovery of new treatments for existing cancers requires the exploitation of causes in such a way as to be impossible in the absence of a correct classification. It would have been inconceivable for this to have occurred if the discovery of viral oncogenesis had constituted a conceptual change taking the form of simple addition to cancer as it existed within the degenerative disease hierarchy. These causal arguments would remain unintelligible without acceptance of such revisions in conceptual structure. In part, the reasons for the acceptance of this reclassification relate to the improvements offered in terms of causal explanatory coherence. Maximising coherence involves retaining much evidence that was developed at earlier stages of understanding cancer causation. For example, in order to maintain explanatory coherence, we should seek to retain the finding that cervical cancer incidence varies by number of sexual partners. This has occurred by fitting this observation into the broader framework of causation by HPV. Now promiscuity does not cause cervical cancer. Instead, it increases the risk of contracting HPV. Thus the discovery of viral oncogenesis does not involve replacing all that had been known about cancers. Rather, it was in part a matter of fitting existing evidence in to a new causal archetype.

This is reflected in the sorts of tools for causal inference applied to the case. For instance, within the paradigm of infectious disease, there were already well-used tools for interpreting epidemiologic and laboratory data, such as the Koch-Henle postulates[56] which could be used to interpret existing data when making new causal claims. So when an infectious cause was suspected for cervical cancer, researchers began to use tools originating in infectious disease research, such as seroepidemiological surveys, electron microscopy and animal transfection experiements in their search for causes. This—ideally—allowed the interpretation of risk factors and other pieces of causal knowledge identified at an earlier stage of cancer classification. Thus the risk of developing the disease under certain conditions of marital status, sexual habits, social class and so on were examined in terms of a particular underlying causes, namely a virus. While it was the discovery of viral oncogenesis that finally made the case for cancer reclassification, it was the suspicion that a conceptual reclassification could be made that allowed these questions to be formulated in the first instance.

---

[55] Kassem, A., Schopflin, A., Diaz, C., Weyers, W., Stickeler, E., Werner, M. et al. 2008. "Frequent Detection of Merkel Cell Polyomavirus in Human Merkel Cell Carcinomas and Identification of a Unique Deletion in the VP1 Gene." *Cancer Reseach.* **68**(13): 5009—13.

[56] Carter, K.C. 2003. *The Rise of Causal Concepts of Disease: Case Histories*. Hants: Ashgate.

Bibliography

Aitken-Swan, J. and Baird, D. 1966a. "Cancer of the Uterine Cervix in Aberdeenshire. Epidemiological Aspects." *British Journal of Cancer.* **20**(4): 624—41.

Aitken-Swan, J. and Baird, D. 1966b. "Cancer of the Uterine Cervix in Aberdeenshire. Aetiological Aspects." *British Journal of Cancer.* **20**(4): 642—59.

Alexander, E. 1973. "Possible Etiologies of Cancer of the Cervix Other Than Herpesvirus," *Cancer Research.* **33**(6): 1485—90.

Boshart, M., Gissmann, L., Ikenberg, H., Kleineheinz, A. Scheurlen, W. and zur Hausen, H. 1984. "A New Type of Papillomavirus DNA, Its Presence in Genital Cancer Biopsies and in Cell Lines Derived from Cervical Cancer." *The EMBO Journal*. **3**(5): 1151—7.

Bouchier, I.A.D, Ellis, H. and Fleming, P.R. (eds). 1996. *French's Index of Differential Diagnosis.* 13th ed. London: Arnold.

Le Bouvier, G.L., Sussman, M. and Crawford, L.V. 1966. "Antigenic Diversity of Mammalian Papillomaviruses." *Journal of General Microbiology.* **45**(3): 497—501.

Burkitt, D. 1958. A Sarcoma Involving the Jaws in African Children. *The British Journal of Surgery*, **46**(197): 218—23.

Burkitt, D. 1961. Observations on the Geography of Malignant Lymphoma. *East African Medical Journal.* **38**: 511—4.

Burkitt, D. and Wright, D. 1963. A Lymphoma Syndrome in Tropical Africa with a Note on Histology, Cytology, and Histochemistry. *International Review of Experimental Pathology.* **2**: 67—138.

Carter, K.C. 2003. *The Rise of Causal Concepts of Disease: Case Histories*. Hants: Ashgate.

Chellappan, S., Kraus, V.B., Kroger, B., Münger, K., Howley, P.M., Phelps, W.C. et al. 1992. "Adenovirus EtA, Simian Virus 40 Tumor Antigen, Human Papillomavirus E7 Protein Share the Capacity to Disrupt the Interaction Between Transcription Factor E2F and the Retinoblastoma Gene Product." *Proceedings of the National Academy of Sciences of the United States of America*. **89**(10): 4549—53.

Chen, T.M., Pecoraro, G. and Defendi, V. 1993. "Genetic Analysis of *in Vitro* Progression of Human Papillomavirus-Transfected Human Cervical Cells." *Cancer Research.* **53**(5): 1167—71.

Collard, W., Thornton, H. and Green, M. 1973. "Cells Transformed by Human Herpesvirus Type 2 Transcribe Virus-Specific RNA Sequences Shared by Herpesvirus Types 1 and 2." *Nature: New Biology*. **243**(130): 264—6.

Crawford, L. and Crawford, E. 1963. "A Comparative Study of Polyoma and Papilloma Viruses." *Virology*. **21**: 258—63.

de-Thé, G., Geser, A., Day, N.E., Tukei, P.M., Williams, E.H., Beri, D.P. et al. 1978. "Epidemiological Evidence for Causal Relationship Between Epstein-Barr Virus and Burkitt's Lymphoma from Ugandan Prospective Study." *Nature*. **274**(5673): 756–61.

Deaver, J.B. and Reimann, S.P. 1931. "Cancer of the Uterus: With General Remarks on the Pathologic Aspects of Cancer of the Uterus." *Annals of Surgery*. **94**(3): 381—8.

Duff, R. and Rapp, F. 1971. "Properties of Hamster Embryo Fibroblasts Transformed *in Vitro* After Exposure to Ultraviolet-Irradiated Herpes Simplex Virus Type 2." *Journal of Virology*. **8**(4): 469--77.

Dürst, M., Gissmann, L., Ikenberg, H. and zur Hausen, H. 1983. "A Papillomavirus DNA from a Cervical Carcinoma and Its Prevalence in Cancer Biopsy Samples from Different Geographic Regions." *Proceedings of the National Academy of Sciences of the United States of America.* **80**(12): 3812—5.

Elliott, R. 1964. "On the Prevention of Carcinoma of the Cervix," *The Lancet.* **1**(7327): 231—5.

Epstein, M.A. 2005. "The Origins of EBV Research: Discovery and Characterization of the Virus." In Robertson E.S., ed., *Epstein-Barr Virus*. Norfolk: Caister Academic Press, 1—14.

Epstein, M.A., Barr, Y.M. and Achong, B.G. 1964. "A Second Virus-Carrying Tissue Culture Strain (EB2) of Lymphoblasts from Burkitt's Lymphoma." *Pathologie-Biologie*. **12**: 1233–4.

Epstein, M.A., Barr, Y.M. and Achong, B.G. 1965. "Studies with Burkitt's Lymphoma." *The Wistar Institute Symposium Monograph.* **4**: 69—82.

Frenkel, N., Roizman, B., Cassai, E. and Nahmias, A. 1972. "A DNA Fragment of Herpes Simplex 2 and Its Transcription in Human Cervical Cancer Tissue." *Proceedings of the National Academy of Sciences of the United States of America*. **69**(12): 3784—9.

Halbert, C.L., Demers, G.W. and Galloway, D.A. 1991. "The E7 Gene of Human Papillomavirus Type 16 Is Sufficient for Immortalization of Human Epithelial Cells." *Journal of Virology*. **65**(1): 473—8.

Hampar, B. and Ellison, S.A. 1963. "Cellular Alterations in the MCH Line of Chinese Hamster Cells Following Infection with Herpes Simplex Virus." *Proceedings of the National Academy of Sciences of the United States of America* **49:** 474—80.

Harris, N.L. et al., 1999. World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting-Airlie House, Virginia, November 1997. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. **17**(12): 3835—49.

Henle, G. and Henle, W. 1966. "Immunofluorescence in Cells Derived from Burkitt's Lymphoma." *Journal of Bacteriology*. **91**(3): 1248—56.

Henle, G., Henle, W. and Diehl, V. 1968. "Relation of Burkitt's Tumor-Associated Herpes-Type Virus to Infectious Mononucleosis." *Proceedings of the National Academy of Sciences of the United States of America.* **59**(1): 94—101.

Henle, G., Henle, W., Clifford, P., Diehl, V., Kafuko, G.W., Kirya, B.G. et al. 1969. "Antibodies to Epstein-Barr Virus in Burkitt's Lymphoma and Control Groups." *Journal of the National Cancer*

Institute. **43**(5): 1147–57.

Henle, W., Henle, G., Ho, H.C., Burtin, P., Cachin, Y, Clifford, P et al. 1970. "Antibodies to Epstein-Barr Virus in Nasopharyngeal Carcinoma, Other Head and Neck Neoplasms, and Control Groups." *Journal of the National Cancer Institute.* **44**(1): 225–31.

Hurlin, P.J., Kaur, P., Smith, P.P., Perez-Reyes, N., Blanton, R.A. and McDougall. J.K. 1991. "Progression of Human Papillomavirus Type 18-Immortalized Human Keratinocytes to a Malignant Phenotype." *Proceedings of the National Academy of Sciences of the United States of America*. **88**(2): 570—4.

Kassem, A., Schopflin, A., Diaz, C., Weyers, W., Stickeler, E., Werner, M. et al. 2008. "Frequent Detection of Merkel Cell Polyomavirus in Human Merkel Cell Carcinomas and Identification of a Unique Deletion in the VP1 Gene." *Cancer Reseach.* **68**(13): 5009—13.

Kaur, P. and McDougall, J.K. 1988. "Characterization of Primary Human Keratinocytes Transformed by Human Papillomavirus Type 18." *Journal of Virology.* **62**(6): 1917—24.

Krcmár, M., Suchánková, A., Kanka, J. and Vonka, V. 1986. "Prospective Study on the Relationship Between Cervical Neoplasia and Herpes Simplex Type 2 Virus. III. Presence of Herpes Simplex Type-2 Antibody in Sera of Subjects Who Developed Cervical Neoplasia Later in the Study." *International Journal of Cancer*. **38**(2): 161—5.

Lombard, H. and Potter, E. 1950. "Environmental Factors in the Etiology of Cancer," *Acta Unio Internationalis Contra Cancrum*. **6**: 1325—33.

Münger, K., Phelps, W.C., Bubb, V., Howley, P.M. and Schlegel, R. 1989. "The E6 and E7 Genes of the Human Papillomavirus Type 16 Together Are Necessary and Sufficient for Transformation of Primary Human Keratinocytes." *Journal of Virology.* **63**(10): 4417—21.

Naib, Z.M., Nahmias, A.J. and Josey, W.E. 1966. "Cytology and Histopathology of Cervical Herpes Simplex Infection," *Cancer*. **19**(7): 1026—31.

Oriel, J.D. and Almeida, J.D. 1970. "Demonstration of Virus Particles in Human Genital Warts." *The British Journal of Venereal Diseases.* **46**(1): 37—42.

Plaut, A. and Kohn-Speyer, A. 1947. "The Carcinogenic Action of Smegma," *Science.* **105**(2728): 391—2.

Pratt-Thomas, H., Heins, H.C., Latham, E., Dennis, E.J. and McIver, F.A. 1955. "The Carcinogenic Effect of Human Smegma: An Experimental Study. I. Preliminary Report," *Cancer.* **9**(4): 671—80.

Pulvertaft J.V. 1964. "Cytology of Burkitt's Tumour (African Lymphoma)." *The Lancet.* **283**(7327): 238—40.

Rapp, F. and Falk, L. 1964. "Study of Virulence and Tumorigenicity of Variants of Herpes Simplex Virus." *Proceedings of the Society for Experimental Biology and Medicine*. **116**: 361—5.

Rawls, W.E., Tompkins, W.A., Figueroa, M.E., and Melnick J.L. 1968. "Herpesvirus Type 2: Association with Carcinoma of the Cervix." *Science.* **161**(847): 1255—6.

Rawls, W., Tompkins, W. and Melnick, J. 1969. "Serological Association between Herpesvirus Type 2 and Cervical Cancer." *Bacteriological Proceedings.* **1969**: 178.

Scheffner, M., Werness, B.A., Huibregtse, J.M., Levine, A.J. and Howley, P.M. 1990. "The E6 Oncoprotein Encoded by Human Papillomavirus Types 16 and 18 Promotes the Degradation of p53." *Cell*. **63**(6): 1129—36.

Stewart S.E., Lovelace E., Whang J.J. and Ngu V.A. 1965. "Burkitt Tumor: Tissue Culture, Cytogenetic and Virus Studies." *Journal of the National Cancer Institute.* **34**: 319—27.

Thagard, P. 1992. *Conceptual Revolutions*, Princeton, N.J: Princeton University Press.

von Knebel Doeberitz, M., Rittmüller, C., Aengeneyndt, F., Jansen-Dürr, P. and Spitkovsky, D. 1994. "Reversible Repression of Papillomavirus Oncogene Expression in Cervical Carcinoma Cells: Consequences for the Phenotype and E6-p53 and E7-pRb Interactions." *Journal of Virology*. **68**(5): 2811—21.

Vonka, V., Kanka, J., Jelínek, J., Subrt, I., Suchnek, A., Havránková, A. et al 1984a. "Prospective Study on the Relationship Between Cervical Neoplasia and Herpes Simplex Type-2 Virus. I. Epidemiological Characteristics." *International Journal of Cancer.* **33**(1): 49—60.

Vonka, V., Kanka, J., Hirsch, I., Závadová, H., Krcmár, M., Suchánková, A. et al 1984b. "Prospective Study on the Relationship Between Cervical Neoplasia and Herpes Simplex Type-2 Virus. II. Herpes Simplex Type-2 Antibody Presence in Sera Taken at Enrollment." *International Journal of Cancer*. **33**(1): 61—6.

Yee, C., Krishnan-Hewlett, I., Baker, C.C., Schlegel, R. and Howley, P.M. 1985. "Presence and Expression of Human Papillomavirus Sequences in Human Cervical Carcinoma Cell Lines." *The American Journal of Pathology.* **119**(3): 361—6.

zur Hausen, H. 1976. "Condylomata Acuminata and Human Genital Cancer." *Cancer Research.* **36**(2 pt 2): 794.

zur Hausen, H. 1989. "Papillomavirus in Anogenital Cancer: The Dilemma of Epidemiologic Approaches," *Journal of the National Cancer Institute.* **81**(22): 1680—2.

zur Hausen, H., Meinhof, W., Scheiber, W. and Bornkamm, G.W. 1974. "Attempts to Detect Virus-Specific DNA in Human Tumors. I. Nucleic Acid Hybridizations with Complementary RNA of Human Wart Virus." *International Journal of Cancer.* **13**(5): 650—6.