Cervical cancer: a tale of two viruses

Institute of Cancer Research
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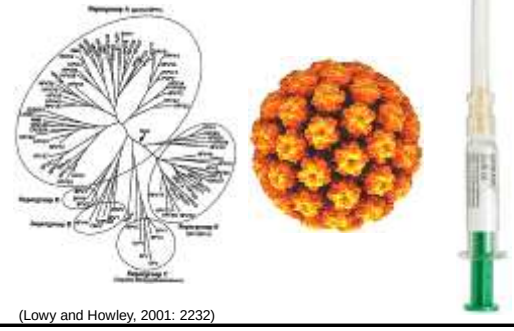
HPV and cervical cancer



(Lowy and Howley, 2001: 2232)

"This new mandatory STD vaccine shouldn't hurt a bit."

http://philotheaonphire.blogspot.co.uk/2012/02/guard-against-gardasil.html

The discovery of the cause of cervical cancer

1. The infectious tumour
2. Mechanisms of cancer causation
3. HSV research and the herpes heuristic
4. From HSV to HPV

Characterising the infectious tumour

Cervical cancer was found to behave like a sexually transmitted disease

- Nuns have a very low risk (Rigoni-Stern 1842; English translation Stavola 1987)
- High rates in commercial sex workers (Martin 1967)
- Correlates with marriage, parity (ibid), age-at-first-sex, syphilis… (Aitken-Swan and Baird 1966b)

…mere frequency of intercourse is unlikely to account for the differences found. Intercourse must be further analysed for special features which conduce to cancer.

(Elliott, 1964, 232)

The cancer patient is characterised by more marital misadventures, divorce and separation, more pre-marital coitus and deliveries and more sexual partners.

(Aitken-Swan and Baird, 1966a, 656)

Two big questions

1: how does cancer of the cervix compare to other tumours in its pathology and aetiology?

2: mechanisms of cancer causation

Mechanisms of cancer

Three causal mechanisms of oncogenesis (Oberling 1944)

- cellular irritation
- microbial
- embryonic

Background: *Omnis cellula e cellula,* germ theory

Cellular irritation and cancer

Long-continued irritation and chronic inflammation are probably the conditions which pave the way for the development of the new growth.

(Deaver and Reimann, 1931, 383)

The uterine cervix is rendered vulnerable in the parous woman, where it is stellate with the fissures of parturition, and both in her case and in that of the nulliparous or unmarried woman the cervix is frequently eroded by acrid discharges. From the uterus to the ovary, scarred all over by the rupture of numberless follicles, the transition is easy and the way open.

(Brand 1902, 240)

No doubt the loose and open arrangement of the nether garments of the majority of women would naturally favour access to the generative organs of the infective micro-organism, especially if its habitat is the soil.

(Brand 1902, 240)

Microbial infection and cancer

Cancer a deux

Transmissible tumours

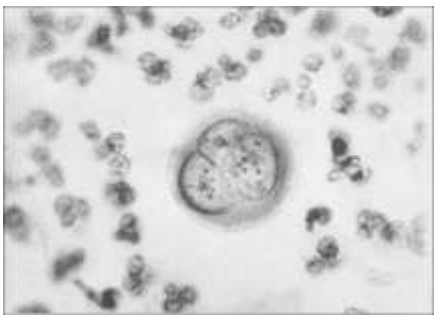
http://blogs.nature.com/amch/2011/08/18/contagious-cancer-beyond-the-devils

Cervical cancer and HSV

Risk factors suggested an infectious aetiology of cervical cancer

How did this general mechanism become specifically about HSV infection?

Naib et al. 1966



Evidence for herpes simplex virus as cause of cervical cancer

(Alexander, 1973: 1486)

1. HSV is a commensal organism
2. HSV is transmitted venerally
3. HSV is compatible with known risk factors, including:
   1. First coitus at early age
   2. Multiple sexual partners or promiscuity
   3. Low socioeconomic status
4. **Herpes viruses are implicated in similar disease states**
5. HSV is recoverable from some tumour cells

Herpes viruses cause many tumours

Name	Disease
Epstein-Barr virus (HHV-4)	Burkitt's lymphoma
	Nasopharyngeal carcinoma
	Various leukaemias and lymphomas
Kaposi's sarcoma virus (HHV-8)	Kaposi's sarcoma
	Abdominal cavity B-cell lymphoma / Primary effusion lymphoma
	Multicentric Castleman's disease
Gallid herpesvirus 2 (GaHV-2)	Marek's disease (chickens)
Saimiriine herpesvirus type 2 (HVS-2)	Transmissible tumours in new world monkeys
Herpesvirus ateles type 1 (HVA-1)	T-cell lymphomas in new world monkeys
Ranid herpesvirus 1 (RaHV-1)	Lucké renal adenocarcinoma (Northern leopard frog)

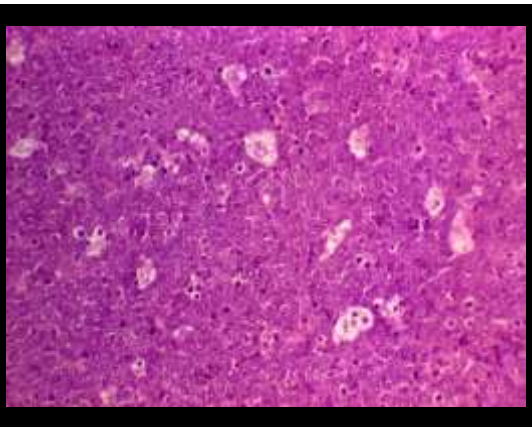
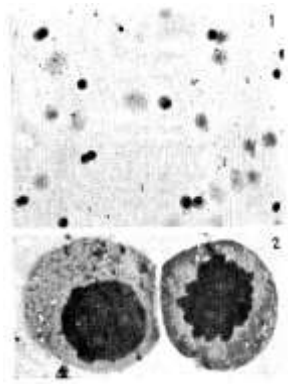
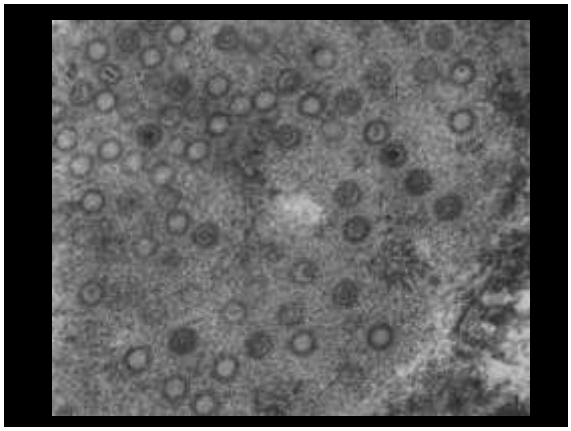


FIG. 1.—The safari route.





Not the only disease…

- Evidence of EBV infection in nearly all adults (Henle and Henle 1966)
- Leukaemia (Henle and Henle, 1966)
- Infectious mononucleosis (Henle et al 1968)
- Nasopharyngeal carcinomas (Henle et al. 1970)

Herpes heuristic

Scope of HSV research programme

HSV not found in cervical tumour cells

But the virus could be detected in *in vitro* cultures of various kinds. HSV NA were also not detectable in cervical cancer tissue.

Detection failure?

Details of causal mechanism – the 'hit and run' hypothesis

Prague study

Prospective studies demonstrated no link (Vonka et al., 1984a; 1984b; Krcmár et al., 1986)

If not HSV, what?

Another virus – human papillomavirus (HPV) had been suggested to be a possible cause of cervical cancer since the early 1970s

A promising cause?

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.

(zur Hausen, 1976, 794)

HPV by analogy

Warts

Epidermodysplasia Verruciformis

BPV

CRPV

But…

As with HSV, HPV was not actually to be found in cervical cancer cells

It was not until the discovery of distinct types of HPV that this began to be resolved

HPV-16 detected in most cervical cancer tissue samples (Durst et al. 1983)

Epidemiological surveys

Greatly increased risk of cervical cancer in those with evidence of HPV infections (Munoz et al. 1992: 747)

Vaccination against HPV

Sublata causa, tollitur effectus

‘it is seldom at the frontier that discoveries are made but more often in the dustbin.’

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