

This Week's Citation Classic

Jarrett W F H, Martin W B, Crighton G W, Dalton R G & Stewart M F. Leukaemia in the cat: transmission experiments with leukaemia (lymphosarcoma). *Nature* 202:566-7, 1964; and Jarrett W F H, Crawford E M, Martin W B & Davie F. Leukaemia in the cat: a virus-like particle associated with leukaemia (lymphosarcoma). *Nature* 202:567-8, 1964.
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Feline leukaemia was shown to be transmissible experimentally in cats using cell-free extracts of lymphosarcoma tissue from a spontaneous field case. Type C virus particles were demonstrated in the experimentally induced tumour and in cells cultured from it. This was the first transmission of a spontaneous mammalian leukaemia. [The *SCI*[®] indicates that these papers have been cited in over 230 and 210 publications, respectively.]

Retroviral Leukemogenesis and Acquired Immunodeficiency Syndrome

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From the start of this century, it had been known that fowl leukaemia was transmissible and caused by a virus. Somehow this finding was not thought to be germane to mammals by those in veterinary or human medicine. In the 1950s Ludwig Gross had shown that a particular mouse leukaemia in inbred laboratory mice was associated with a virus but that the transmission of this agent was vertical, in the germ line. This gave

rise to several theories of leukaemogenesis, but unfortunately none of them met the facts of leukaemia as found in free-living and outbred species.

I had worked for some years in human pathology and had become particularly interested in haemopoietic tumours. When I returned to veterinary hospital work, I was surprised to find so many neoplasms of this type, and I was prompted to carry out a survey in Glasgow. Surprisingly, this showed that leukaemia appeared to be about five times more common in cats than in humans. I therefore cooperated closely with a local veterinarian, Harry Pfaff, and outlined to him the range of syndromes I was finding. We then started to find as many of these as possible in order to get fresh material for passage, electron microscopy, and culture. Here we had a stroke of luck. One of his clients was a dear, but slightly crazy, old lady who lived alone in a large house with 100 cats. She had taken these in, off the streets, as strays. Her feline philanthropy ran to bed and board, but not to sex. So she had my friend castrate them all, toms and tabbies alike. This was tough for the cats but excellent for us as it meant that all of these animals were outbred and unrelated.

In the course of a year or so, he submitted to me eight cases of different kinds of leukaemia from this household. This was very striking evidence for horizontal transmission of an infection, and so I decided to set up a transmission experiment from this source material.^{1,3}

I chose two cats with different tumours. The first was a thymic lymphosarcoma with leukaemia and the other was an alimentary lymphosarcoma. I now needed an isolation facility. What we used was extremely crude compared to our splendid experiment facilities of today. We had no grant and no other money. Mary F. Stewart, a veterinary surgeon from Cornell University, had recently settled in Scotland (because of a man and mountaineering) and had an isolated

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cottage and large garden in the country in the middle of a golf course. She was keen to look after them (for free), and I had a plentiful source of meat from the college PM room. We built two little sets of cat-proof pens and started off.

As the first year was drawing to a close, we wondered if we had failed, when suddenly a cat died at a weekend. At autopsy it looked like early lymphosarcoma, but the material was unsuitable for passage. Shortly afterwards, another cat became ill and this time we diagnosed leukaemia on a routine blood count. Material was taken from this animal and passed again. I was nailbiting for several days as I had recently been given access for the first time to an electron microscope. Instructed by Elizabeth M. Crawford, my technician and I prepared the cat material, cut sections, and popped it in the microscope. We found the virus almost at once, and it was one of the great moments of our lives. Despite the relative crudity of the techniques at that time, there it was, an incontrovertible leukaemia virus of perfect morphology, two virions in the first picture showing as much detail as they ever have since. It is one of my prized possessions still. Soon after that my colleague Bill Martin and I grew tumour cells in culture and isolated virus from that. The cats given the alimentary tumour later developed the disease, as did the second passage from the primary isolate.⁴

After this, I was joined by my brother Oswald, who has since become one of the main figures in this field. We set up a much larger isolation facility to study the pathogenesis of the disease, using about 60 cats plus controls, in individual isolation units of about 12 cats each.

Things started to go a little wrong. Cats were becoming ill with apparent infec-

tious diseases when they should not have, as they were bred on the premises and maintained in isolation. However, it was only in the pens of leukaemia virus-infected animals that diseases were occurring. At necropsy we found that these cats had grossly diminished thymuses and that their lymph nodes were failing to develop the normal cortical and paracortical histological features. We were looking at the first examples of the feline acquired immunodeficiency syndrome. Shortly after this Ed Hoover and his colleagues at Ohio State University showed that such cats failed to develop the normal graft rejection reaction, implicating the T-cell deficiency with which we are now all so familiar.

This series of experiments, soon to be confirmed by several groups, showed several salient facts: (1) Leukaemia in cats was caused by a virus identical to those already seen in fowl and mouse leukaemia. (2) This disease was being horizontally transmitted in a large household of unrelated cats and thus appeared to be exogenous. (3) In many infected cats, a lymphoid deficiency occurred that led to severe immunodepression.

The other finding that arose was that leukaemia induction in a large series of cats infected at one time occurred in a linear fashion over a long period of time with a median latent period of around four years, indicating a stochastic "strike event" much later shown to be due to promoter insertional mutagenesis and other related phenomena.^{5,6} The field study that we immediately carried out showed for the first time that feline leukaemia-virus infection was widespread in a large city and low on country farms and that the lower the socioeconomic group the cats were in, the higher the incidence. But that is another story....

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3. Mackey L J, Jarrett W F H, Jarrett O & Laird H M. An experimental study of virus leukemia in cats. *J. Nat. Cancer Inst.* 48:1663-70, 1972. (Cited 35 times.)
4. Jarrett W, Jarrett O, Mackey L, Laird H, Hardy W & Essex M. Horizontal transmission of leukemia virus and leukemia in the cat. *J. Nat. Cancer Inst.* 51:833-41, 1973. (Cited 200 times.)
5. Jarrett W, Jarrett O, Mackey L, Laird H, Hood C & Hay D. Vaccination against feline leukaemia virus using a cell membrane antigen system. *Int. J. Cancer* 16:134-41, 1975. (Cited 40 times.)
6. Jarrett W F H. Vaccination against and the epidemiology of feline leukaemia. *Proceedings of the Third International Symposium on Detection and Prevention of Cancer*, April 26-May 1, 1976, New York, NY.