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Responsibility for truth in research

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For over half a century, cell cultures derived from animals and humans have served researchers in various fields. To this day, cross-contamination of cultures has plagued many researchers, often leading to mistaken results, retractions of results, cover-ups and some out-and-out falsification of data and results following inadvertent use of the wrong cells. Also, during years of examining cultures for purity we learned that many virologists were not too concerned about the specificity of the cultures they used to propagate the particular virus under study as long as the substrate (whatever it might have been) gave optimal virus yield. Polio virus propagates in primate cells, and much research has involved cells from man and various species of primates. In the 1950s a large number of chimpanzees were held in captivity in Africa for extensive studies of the efficacy of polio vaccine in production at the Wistar Institute in Philadelphia and elsewhere. Chimpanzee tissues, particularly kidneys, were thus readily available and could have also provided substrates for polio virus production, since little was known about the purity of substrates and little attention was paid to their specificity at that time.

Keywords: cross-contamination of cell cultures; erroneous results; inattention to cell specificity; polio virus; primate cells

From the early 1960s until 1981 the Cell Culture Laboratory at the School of Public Health, University of California, Berkeley, sponsored by the National Cancer Institute (NCI), strove to establish and characterize cell cultures from domestic and wild animals and man. Its goal was to provide scientists with pure cell cultures about which as much was known as possible. Of all disciplines, it is surely virology that has used and benefited the most from the success in growing mammalian cells *in vitro*.

We were to realize as time went on that for many virologists, the eagerness to grow viruses often resulted in ignoring (or not caring about) the precise substrates used, as long as virus yield was optimal. In fact, it was the quest for the most productive substrate for the given virus that drove the need for cultures of many different species, and which was one of the main reasons for creating the laboratory.

During the last ten years of our contract, emphasis was guided by the NCI's viral oncology programme, under which primarily human cell cultures were sought, derived from many tissues, cancerous and normal, from different ethnic and age groups and from both sexes. Thousands of cell cultures were distributed worldwide. The laboratory was shut down in the early 1980s and all remaining frozen cell seed stocks were turned over to the American Type Culture Collection, then in Rockville, Maryland (present address: American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, USA).

Our expertise in working with many cell cultures became a resource for identification of cells used by numerous laboratories in the USA and abroad. While we were soon popularized for uncovering HeLa-cell contaminations in other researchers' work, and I was referred to as 'the Ralph Nader of cell culture', we also discovered many cases of varying kinds of contamination involving species other than man, and in some cases revealed cells from different species flourishing simultaneously in the same culture (Nelson-Rees 1978*a*, 1984).

Most researchers appreciated the results of our analyses of their cultures and, I believe, corrected their mistakes. Some ignored our results and continued using the wrong cells while defending their purity (Chang 1978; Nelson-Rees 1978*b*).[1]

One notable exception to this folly was the forthright withdrawal of the wrong cells, and public admission of error by NCI's Robert Bassin, regarding his human breast carcinoma-derived culture (Gold 1986, p. 68). Another honest admission of a mishap was that of Harvard's Essex and Kanki, on viral contamination of their African green monkey and Senegalese human cells with SIVmac (Essex & Kanki 1988). Carel Mulder, writing in *Nature* (18 February 1988), commented that 'too seldom do researchers in *this* field retract data found to be erroneous' and then warned virologists to be more careful in laboratory work to avoid contamination (Mulder 1988).

Criticism of our *modus operandi* and our spreading the word on a morass of contamination problems did not endear us to many colleagues. Not too-well-kept secret attempts to cancel our contract by powerful colleagues at the source surfaced. My ethics were questioned. Rumours of 'let's get him' were heard. An unsigned telegram offering me a position in Uganda, including a one-way ticket there, was perhaps the least friendly response.

On the other hand, our long 1976 list of HeLa contaminants published in *Science* (Nelson-Rees & Flandermeyer 1976), and revised and expanded in 1981 (Nelson-Rees *et al.* 1981), was prominently posted in a large New York research laboratory as a welcome warning. Incidentally, it

took a lot of prodding to finally get *Science* to publish the brief original list in 1974 (Nelson-Rees *et al*. 1974).

That *publishing* details about contamination is not easy is noted, however, from a published note in *Science* indicating that editors or anonymous reviewers of reputable publications sometimes themselves muddy the waters. In the late 1970s, Todd and Furcinitti at Pennsylvania State University were using cells, presumably of normal human kidney origin, derived from a little Dutch boy, in radiation sensitivity studies (Todd & Furcinitti 1979). In August 1980 we revealed that these cells were in fact HeLa (Nelson-Rees *et al*. 1980), and William Broad, concerned about this problem, wrote in *Science* that an anonymous reviewer for the *International Journal of Radiation: Oncology Biology–Physics* had written that 'if you [the researcher Todd] really want the punch line to reach the therapist, the manuscript needs to be simplified and detail omitted'. Although Todd had himself already suspected HeLa contamination, the reviewer suggested that the paragraph concerning possible HeLa descent be cut, and Todd subsequently struck it. Furthermore, Broad went on to write that in the journal *Photochemistry and Photobiology*, a full page of speculation by Todd of possible HeLa contamination was deleted. Todd was frustrated and said 'not all attempts by scientists to be honest and thorough are accommodated by journal editorial policies' (Broad 1980).

In 1978, we studied samples of cells that Jonas Salk had used in his polio vaccine production during the 1950s (Salk & Ward 1957). Although his protocol specified the use of cynomolgus heart cells, and although he had some time earlier suspected that he might be working with HeLa cells instead of monkey cells, it was not until the famous 1978 Lake Placid conference on the use of cells in making vaccines that he broadcast from the podium that 'in retrospect he believed those cells may not have been his harmless monkey heart cells at all but HeLa cells' (Gold 1986, p. 126). At this meeting I offered to study his cells and subsequently revealed that, indeed, he had been working with HeLa cells. Strangely, this *faux pas* was so unsettling to the organizers of the meeting (and to the editors of the ensuing publication) that they advised him to skip it in the written version to be submitted for publication (Gold 1986, p. 127). And so it was (Salk 1979).

In a different case, in January 1981, in collaboration with three other laboratories, we revealed that three out of four presumably human cultures assumed to be of neoplastic Hodgkin's disease origin were in fact from Colombian brown-footed owl monkey (Harris *et al*. 1981). The fourth cell culture was human, but not Hodgkin's derived. What followed was 'yet another corruption of the scientific literature' (Dickson 1981).

Editors of scientific journals do have to strike a balance between undue scepticism of people's ethics and motives and uncritical acceptance of their results. For example, John Maddox, then Editor of *Nature*, in a lengthy article praising responsibility for research, assured the reader that 'there is no reason to suppose that the few cases of dishonesty that have come to light are in any sense the top of the iceberg.' He then ended his argument with the following admonishment to the likes of me: 'It would be tragic if these civilized habits [namely, responsible research] were to be corrupted by the activities of self-appointed vigilantes' (Maddox 1981). An interesting comment.

Believe it or not, however, a *Nature* article in January 2000, headlined 'Cell contamination leads to inaccurate data: we must take action now', signed by British, American and German researchers, bemoaned the fact that 'despite the [1981] warning, the number of published cases of cross-contamination is still increasing' (Stacey *et al*. 2000).

As they relate to the current and on-going conflict involving the OPV/AIDS theory, I would like to quote two scientists who to my knowledge are not vigilantes. The great Max Planck reportedly once said: 'A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents finally die, and a new generation grows up that is familiar with it'. And, finally, one of the many startling items revealed by Ed Hooper in his book *The river* is the following comment by Dr Simon Wain-Hobson: 'Only people who have got something to hide don't want to discuss it' (Hooper 1999, p. 363).

I have one final comment to make. The question has arisen as to whether chimpanzee kidney cells might have been used at the Wistar Institute or elsewhere, in the production of the polio vaccine used in Africa. In my opinion there is no logical reason why this could not have been the case, given the availability of these normal non-human cells and the prevailing custom in the 1950s of using cells about which little or nothing was known, except that they could optimally support the growth of a given virus.

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ENDNOTE

[1]For refutations of HeLa contamination of WISH and MAI60 cells, see the BBC documentary 'The way of all flesh', transmitted in the series 'Modern times' on 19 March 1997. For Chang liver cells, see Chang (1978) and Nelson-Rees's reply (Nelson-Rees 1978*b*).

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