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Research Article

Researching new diseases: assumptions and trajectories

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Abstract

New diseases in humans and animals have been the subject of considerable research as well as policy development and popular attention. Researchers commonly proceed on the basis of plausible assumptions about mechanisms, pathways, and dangers but seldom question the assumptions themselves. Studies in the history and sociology of science show that research trajectories are conditioned by social, political, and economic arrangements. The assumptions underlying research into three new diseases—devil facial tumor disease in Tasmanian devils, AIDS in humans, and leukemia in soft-shell clams—are examined, and dominant and alternative research programs compared. In each case, most research has assumed the disease is spread through “natural processes”, while research about possible human influences has been left undone.

Keywords

new diseases, research trajectories, Tasmanian devil facial tumour disease, AIDS, soft-shell clam leukemia

Introduction

New diseases pose both dangers and opportunities. The dangers are obvious: possible devastation to humans and animals, possible precisely because the diseases are new, so there is less biologically acquired resistance and less knowledge about how to combat them. The danger is shown most dramatically in AIDS, which has caused tens of millions of deaths and continues to infect and kill millions more.

New diseases also offer an opportunity to learn. Because they are new, it is often possible to determine the cause of the disease. This potentially can offer many benefits: lessons on how to prevent related diseases, ideas for treatment, and clues about resistance. Understanding the origin of the numerous variants of HIV might inspire measures to prevent new transfers of simian or other viruses to humans, for example through xenotransplantation.

There is a huge amount of research on many new diseases. AIDS in particular has received intensive study including immunology, epidemiology, and treatment, and there has been considerable research into the origin of the disease. However, there has been little study into how this research proceeds, including assumptions, priorities, and outcomes, in what might be called the metastudy of new diseases: research into how research is conducted, how knowledge is created and validated, and how policy is formulated. Metastudy is the domain of the field called science and technology studies (STS), which examines the history, philosophy, psychology, sociology, politics, and economics of science, technology, and medicine (Hackett et al. 2008, Jasanoff et al. 1995).

As proposed by historian-of-science Thomas Kuhn (1962), most scientific research proceeds on the basis of paradigms, which are sets of assumptions and practices that shape the choice of hypotheses and investigations. Though Kuhn's original ideas have been subject to considerable discussion (Barnes 1982), within STS it is generally accepted that the assumptions that guide research are affected by social factors, including prevailing ideas and vested interests.

Some research topics could readily be undertaken but are not because groups with sufficient funding might find the results unwelcome. The result is what has been called "undone science," referring to research that could be carried out but is not, while other sorts of research are amply funded and results widely disseminated (Frickel et al. 2010, Hess 2016). For example, research on the health effects of lead was neglected or suppressed for decades (Markowitz and Rosner 2002).

To refer to paradigms, undone science, and the potential influence of vested interests does not imply that individual scientists are themselves biased. The shaping of research trajectories operates through systems of power and ideas that influence the way scientists think about research problems and priorities.

Our aim here is to highlight the importance of assumptions, possibly shaped by vested interests, in the trajectories of research into new human and animal diseases. In particular,

we are interested in research pathways that may be neglected even though they have promise. To probe this topic, we present case studies of three new diseases said to be contagious: devil facial tumor disease in Tasmania devils (carnivorous marsupials), AIDS in humans, and soft-shell clam leukemia. Although they occur in widely disparate species, there are striking parallels in the assumptions underlying research about them. We look, among other things, at the dominant hypothesis concerning the cause of each disease, how it is spread, pathology, genetics, and also look at alternative hypotheses and vested interests.

In the next three sections, we briefly discuss each of these three diseases, giving background about the disease, its origins, spread, and impact, describing the main trajectories of research into the disease and the assumptions underlying the research trajectories. In the discussion we compare the three cases, noting avenues not pursued and the response to alternative theories. In the conclusion we outline some implications for research and policy.

Tasmanian Devil (*Sarcophilus harrisii*) Facial Tumor Disease

The Tasmanian devil is the last surviving carnivorous marsupial, found in the wild only in Tasmania, an Australian island state. In the mid-1990s a facial cancer, not previously seen in devils, was discovered. Termed devil facial tumor disease (DFTD), it now threatens the survival of the species. DFTD has been described as a neuro-endocrine tumor of unknown origin (Loh 2006). A viral cause was initially suspected but remains unconfirmed (TDPIWE 2005). Research has investigated hematology, blood biochemistry, immunology, endocrinology, and identification of the etiology of the disease, including a trial to test for a range of environmental toxins (TDPIWE 2005). In 2006 the novel hypothesis that DFTD was an allograft—an infectious cell line passed between individuals through biting—was proposed (Pearse and Swift 2006).

The dominant research trajectory has been built on the assumption that the cancer is a natural phenomenon originating in and spread by Tasmanian devils (for example, as presented by Ujvari et al. 2017). An early finding contrary to this assumption was reported in an abstract by Steve Marvanek, a Commonwealth Scientific and Industrial Research Organisation (CSIRO) expert in applying geographic information systems (GIS). He stated DFTD appears to “have broken out spontaneously” in three separate locations “rather than moved in from nearby” as might have been expected if the disease was contagious (Marvanek 2007). This finding by Marvanek appears to have been ignored. Also in 2007, a further claim supporting the allograft theory was made that DFTD was transmissible because of a lack of histocompatibility barriers (Siddle et al. 2007); this claim was later disproved (Carbonell 2012). Another supporting claim was also made, following genetic studies, that DFTD originated in a female devil (Deakin et al. 2012). However, this claim has been challenged by two recent findings that some DFTD cancers in male devils originate in these same male devils (Cui et al. 2016, Pye et al. 2016). Why the host devil does not reject the transplanted cancerous cells is still not known. Meanwhile, DFTD is not

the only cancer afflicting devils; there are also a lymphosarcoma, a skin lymphoma, and a mammary cancer in female devils (Warren 2013).

The allograft research trajectory ignores a possible alternative, that an environmental toxin may have initiated or progressed the cancer. In 1994 a study found herbicides used in plantation forestry had contaminated many waterways in Tasmania (Davies et al. 1994). In 2004 a correlation in time and space was made between the increase in forestry plantations, the use of chemicals, oyster abnormalities and the Tasmanian devil cancer (Scammell 2004). Pearse and Swift (2006) also acknowledged that "a carcinogen may have been the initial cause." By 2007 many of the waterways in Tasmania were polluted by pesticides used in forestry plantations (Bleaney 2007). A preliminary study of toxins used in Tasmania (Vetter et al. 2008), which found evidence of flame retardants, has not been followed up. Tasmania's economic development has relied heavily on an expansion in forestry plantations (Parsons et al. 2006). Despite this evidence and numerous expert opinions and articles raising the need for further toxicology studies (Warren 2015), no further investigations have been undertaken into the role of human activities in the development of DFTD.

The assumption that the devil cancer is a natural occurrence has meant that alternative ideas about the possible cause of the cancers, such as the role of pesticides used in plantation forestry, have not been vigorously pursued. This is despite the lack of conclusive evidence from either the laboratory or the field that DFTD is transmissible. Stindl (2016) recently questioned the transmissibility of DFTD; however, in proposing the unorthodox theory that the cancer may be caused by excessive UV radiation, he attributes the disease to a different natural process.

AIDS

The disease today called AIDS—acquired immunodeficiency syndrome—was first diagnosed in the US in 1981 based on symptoms observed in gay men. Epidemiological studies soon showed that AIDS was contagious and a search was undertaken to detect an infectious agent. In 1983, HIV—human immunodeficiency virus—was discovered and widely considered to be the causative agent. In 1985, SIVs—simian immunodeficiency viruses—were discovered, and many scientists then assumed that AIDS originated from one or more SIVs from monkeys entering the human species and becoming transmissible.

AIDS typically had a very slow incubation period, which made it especially dangerous because numerous infections could occur before anyone was aware of the danger. Today, most scientists believe that AIDS has been responsible for over 35 million deaths, primarily in Africa, with millions more HIV-positive, making AIDS the most deadly new human disease in recent history.

Numerous explanations for the origin of AIDS have been proposed. Some say HIV is harmless and AIDS is a label applied to a variety of other diseases (Duesberg 1996). The dominant scientific view has been that AIDS resulted from SIVs in Central African

chimpanzees getting into humans and becoming HIV-1, the variant of HIV responsible for most cases of AIDS worldwide (Worobey et al. 2008). One particular SIV, found in chimps, is most similar to HIV-1. The transfer from chimps to humans is assumed to have occurred by a hunter butchering a chimp and getting chimp blood into a cut, or perhaps by a human being bitten by a chimp, or some other such example of so-called "natural transfer."

In the late 1980s, another method was proposed for SIVs to enter humans and become transmissible: that a polio vaccine given to nearly a million Africans in the late 1950s was contaminated by SIVs (Martin 1993). Polio vaccines at the time were cultured on monkey kidneys and there was a documented precedent for contamination of polio vaccines by monkey viruses (Shah and Nathanson 1976). Furthermore, the timing and location of the 1950s vaccination campaign fitted with the evidence of the earliest known samples of HIV-positive blood, obtained from Kinshasa (formerly Leopoldville) in 1959 and 1960. The polio-vaccine theory for the origin of AIDS was dismissed by mainstream scientists until the publication of Edward Hooper's book *The River* (Hooper 1999), which triggered enormous interest and led the Royal Society of London to hold a conference the next year to address the origin of AIDS, with the focus on the natural transfer and polio-vaccine theories. Afterwards, the polio-vaccine theory was dismissed, though Hooper continues to contest the claims by cut-hunter theory proponents (Hooper 2003, Hooper 2017).

Most mainstream scientists, who have carried out nearly all the research, have assumed that AIDS originated by a "natural" process—such as the infection of a chimp hunter through cuts in his skin—that occurred routinely rather than one implicating potentially risky human activities. The burden of proof has been placed on the proponents of the polio-vaccine theory (Martin 2001), which has been repeatedly claimed to have been disproven though later evidence overturned these alleged refutations (Martin 2010). Nearly all the research effort relating to the origin of AIDS has assumed some form of a natural transfer, while Hooper and others have been given little support to pursue research on the polio-vaccine theory, so therefore much remains to be investigated.

Soft-shell Clam (*Mya arenaria*) Leukemia

Since the 1800s the soft-shelled clam has been an important commercial resource along the east coast of the USA but in the 1980s there was a dramatic decline in annual harvests (Böttger et al. 2013). In Chesapeake Bay, soft-shell clams were discovered to be suffering from a suspected sarcoma, a new and fatal neoplasm not previously observed in the population (Farley et al. 1986). It has since been described as a disseminated neoplasia (a leukemia-like cancer). Soft-shell clams in the US state of Maine have also been found to have a gonadal neoplasia (Barber 2004). An infectious etiology, through the introduction of clams from New England, was initially suspected to be spreading the cancer. Meanwhile, the sudden appearance of isolated occurrences in widespread areas of Chesapeake Bay further suggested an infectious etiology rather than a point source of pollution (Farley et al. 1986, 855).

Little is known about the onset and distribution of fatal outbreaks of the leukemia-like cancer in populations of soft-shelled clams (Böttger et al. 2013). In an early study, Farley et al. noted the cancer cells had identical characteristics and stated, an “[a]ntigenic similarity between neoplastic clams in NE and Maryland suggests that target cells in the disease are the same in both areas” (Farley et al. 1986, 856). Oprandy et al. (1981)reported evidence for a viral etiology in a Rhode Island study. Other studies support the potential of viral involvement in the disease process (Barber 2004). Meanwhile, Stindl refers to the soft-shell clam cancer as “a warning example of the implications that a false theory [transmissible cancer] can have on modern biology” (Stindl 2016, 6).

Böttger et al. (2013) found a correlation between the frequency of the cancer in soft-shelled clams in New England and contaminated sites. These sites had elevated levels of heavy metals, PCBs, and PAHs. In a study undertaken by the Mussel Watch Project it was found that 18 sites where neoplasia occurred had significantly higher concentrations of PAH, chlordane, pesticides and cadmium (Barber 2004). Muttray et al. (2012) found evidence of an association between potato farming, which relies on widespread application of fertilizers and pesticides, and the prevalence of clam leukemia in the Prince Edward Island area of Canada. The role of contaminants, as well as toxic algae, in the development or progression of the cancers in bivalves has not been thoroughly investigated.

In 2015, Metzger et al. published in *Cell* the results of their study of leukemia in soft-shell clams which they suggested because of “nearly identical genotypes that differ from those of the host,” similar to the claim made by DFTD researchers, the cancer is a clonal transmissible cell derived from a single original clam (Metzger et al. 2015, 255). They assert “these neoplasms did not arise independently but are descendants of a primordial leukemic cell” (Metzger et al. 2015, 256). In 2016 Metzger et al. made a further claim that the disseminated neoplasia in mussels, cockles and golden carpet shell clams are all “attributable to independent transmissible cancer lineages” (Metzger et al. 2016, 705). This assumption also points to a natural cause, filter feeding (Ujvari et al. 2017), which is supported by Murchison et al. (2010) when describing “shellfish beds around the world that are awash with microscopic cancer cells.” In 2016 Mateo et al. published the findings of their laboratory and field studies on the transmission of haemic neoplasia (HN) in soft-shell clams. They concluded from their field experiment: "The change from HN negative to HN positive might have occurred due to transmission of HN-infected cells through the water into naive clams from the surrounding HN-positive clams on site. It is also possible that an environmental change (climatic or anthropogenic) facilitated this transformation, debilitating the host in the process." (Mateo et al. 2016, 924).

Whilst there is evidence that the cancer is transmissible (Elston et al. 1988) and strong evidence that a virus is involved, the cause and mechanism of transmission are uncertain. Meanwhile, the alternative theory that marine contamination may be involved in the development of the cancer has not been pursued.

Discussion

The three new diseases examined here occur in very different species and circumstances. Yet there are several striking commonalities in the research programs into the origin of the diseases (see Table 1). In each case, a key assumption in the dominant research program has been that the disease originated “naturally” through a mutation or infection involving a single individual; this assumption then underpinned most of the subsequent research. In each case, there is a subordinate or marginalized assumption and associated research program: that the disease’s origin and/or transmission was triggered or facilitated by human activity, namely a polio vaccination campaign for AIDS and environmental chemicals for DFTD and the clam leukemia. In fact, with regard to wildlife cancers, Giraudeau et al. (2018) claim "scientists have never considered how interactions between pollutants might influence cancer prevalence in wild populations".

Table 1.

Comparisons relevant to the research programs for three new diseases: devil facial tumor disease (DFTD), AIDS and soft-shell clam leukemia.

	Devil facial tumor disease	**AIDS**	**Soft-shell clam leukemia**
Origin query	Why did a transmissible cancer appear in devils in the 1990s?	Why did SIVs become transmissible in humans (as HIV) so recently?	Why did a transmissible cancer appear in clams in the 1980s?
Origin assumption	DFTD is a naturally occurring transmissible cancer passed from devil to devil via biting when eating or mating.	HIV is a naturally occurring transmissible virus initially passed from a chimp (as SIV) to a human (becoming HIV-1) or from a sooty mangabey to a human (becoming HIV-2).	Clam leukemia is a naturally occurring transmissible cancer in the marine environment.
Dominant hypothesis as to cause	Single female infectee (“index case”) surviving long enough to allow transmission via biting	Single human infectee (“index case”) from cut or bite surviving long enough to allow transmission	Single clonal leukemic cell surviving in marine environment long enough to allow transmission
Dominant research hypothesis	The allograft theory	The cut-hunter (bushmeat) hypothesis	Natural spread through bivalve filtration of seawater contaminated with cancer cells
Alternative hypothesis as to cause	Environmental toxins	SIV-contaminated oral polio vaccine used in Africa in late 1950s	Virus or environmental toxins
Relevant precedents	Cancers caused by environmental toxins	SV40 (virus) from Asian monkeys contaminated polio vaccines	Cancers caused by viruses or environmental toxins
Research not undertaken (“undone science”) or not published	Transmission studies; toxicology studies	Oral polio vaccine testing; epidemiology of early AIDS cases in Africa; testing of chimp stool samples	Transmission studies of viruses; toxicology studies

Commercial or reputational consequences	Chemical hypothesis could undermine the use of pesticides in plantation forestry in Tasmania.	Polio-vaccine hypothesis could (unfairly) discredit vaccination.	Chemical hypothesis could impact industrial and agricultural industries via compensation and remediation costs.
Groups with vested interests	The forestry industry in Tasmania and the agrichemical industry worldwide	Vaccination researchers; the medical profession; vaccine manufacturers	Industrial and agricultural industries, e.g. petrochemical industry.

It is also striking that in each case, there are vested interests that would be threatened should the alternative hypothesis be considered credible. The pattern of research in each case, in which a less threatening hypothesis receives most of the research attention while crucial studies concerning the alternative hypothesis are neglected, suggests that the category called “undone science” applies: some studies are not undertaken because the findings might be unwelcome to influential groups.

Hess describes several processes by which areas of ignorance can be maintained or produced, two of which are relevant to the new diseases we have addressed (Hess 2016, 30-33). One is a policy decision not to undertake certain types of research because the results might be unwelcome, sometimes influenced by campaigning by opponents of the research (Dreger 2015, Hunt 1999, Kempner 2015, Kempner et al. 2011). This is highly relevant to three new diseases addressed here: policy makers or individual scientists have decided not to undertake studies into ways that human activities might have contributed to the origin or transmission of the disease.

Also relevant, to a lesser extent, is what Frickel (2014) calls “knowledge sequestration,” in which research findings are prevented from being distributed, as in the case of the tobacco industry’s research on the health effects of smoking (Oreskes and Conway 2010, Proctor 1995). The few studies following the neglected research trajectories into the new diseases have been denigrated (AIDS) or given scant acknowledgement (DFTD).

The category of “undone science” most commonly refers to areas where research is not carried out despite calls from civil society groups, such as environmentalists, to undertake it (Hess 2015, 142). The case of the three new diseases differs somewhat from this usual pattern in that there are no social movements calling for research on the role of human activities in these diseases. Instead, implicit advocacy has occurred by the researchers doing research on neglected trajectories, such as Marvanek (2007) on DFTD and Hooper (2017) on the origin of AIDS, and more explicit advocacy by social scientists studying these issues, in particular the co-authors of this paper (Warren 2013, Warren 2015, Martin 1993, Martin 2010).

To talk of undone science is to refer to factors that shape judgments about what research is worth doing, what studies are funded, and what findings are worth publishing. This process is usually unconscious: most scientists are sincere in their investigations and judgments.

There are several limitations to this analysis of research trajectories. Only three new diseases have been examined, so assumptions underlying research undertaken may not

be representative of those for other new diseases. Other analysts might contest our assessment of commonalities. Furthermore, we have not highlighted differences between the research trajectories for the three diseases, of which there are several. For example, there has been a bitter dispute between advocates of the dominant and alternative hypotheses concerning the origin of AIDS, whereas for DFTD and the clam leukemia there has been little exposition of alternative hypotheses.

It might be argued that the dominant hypotheses will eventually be vindicated, in which case the research choices made were well chosen. However, this is after-the-fact reasoning, reflective of a storybook history of science in which investigators inevitably proceed towards better understandings, the view contested by Kuhn's idea of paradigms and its successors. Beforehand, there is no way of definitively determining the best research pathway, and hence it can be argued that considering a multiplicity of hypotheses is more likely to avoid putting all effort into a dead end (Feyerabend 1978). In other words, exploring various possible origin hypotheses is a type of insurance against wasting large amounts of effort on what seems, at the time, to be the most promising option.

Conclusion

The emergence of new diseases including novel cancers is a growing problem worldwide. The reasons for these problems are complex; habitat destruction, pollution, and climate change are all possible contributing factors. But in each of the case studies described here, it has been assumed that these diseases are the consequence of natural causes. In the Tasmanian devil cancer the focus is on the fact that devils bite each other causing the spread of the disease. In HIV/AIDS the focus is placed on a "natural" event, a human hunter being infected with an SIV, which it is assumed subsequently transformed into an HIV transmissible to other humans. In the clam cancer, the bivalves naturally absorb the cancer cells as they filter feed.

These assumptions that the causes are natural leave alternative theories under-investigated. In each case the cause of the disease has a plausible alternative, that human activities are implicated. In the case of the Tasmanian devil the role of pesticides and poisons used in forestry plantations is yet to be investigated. In the case of HIV/AIDS, medical programs designed to eliminate polio may have inadvertently provided a pathway for SIVs to become transmissible HIVs. Likewise, in the case of the clam cancer the role of contaminants in the environment or a viral cause have not been thoroughly investigated. Alternative theories involving human activities have been abandoned, dismissed, and avoided.

When investigating the origins of a new disease, it is scientifically and socially risky to put nearly all research effort into a single pathway, even when it seems the most likely one. This is especially the case when vested interests can influence research trajectories. Comparing the research programs for a number of new diseases can reveal assumptions and patterns not evident when studying a single disease. This shows the importance of scrutinizing not only disease origins but also the research programs into these origins.

Hosting institution

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Conflicts of interest

The authors declare no conflicts of interest

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