Review

Transgenesis in animal agriculture and zoonotic disease resistance

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Abstract

In 2009, the US Food and Drug Administration (FDA) released guidelines for the commercialization of genetically engineered (GE) farm animals. Numerous applications for approval of transgenic species are currently pending. Anthropocentric concerns raised to date have tended to neglect the impact of the physiological trade-off between production efficiency and immune function. Given animal agriculture's track record of prioritizing productivity – even at the expense of animal health – the incorporation of biotechnological tools to further stress production towards biological limits may continue to undermine immunocompetence. Regulatory schemata to avert adverse public health outcomes are discussed. Given the rising incidence of zoonotic disease associated with livestock industry intensification noted by the Food and Agriculture Organization of the United Nations, increased scrutiny should be given to any technology that may further erode farm animal disease resistance.

Keywords: Transgenesis, Biotechnology, Farm animals, Zoonoses, Immunocompetence

Review Methodology: A literature search was conducted using the following electronic databases: AGRICOLA, AGRIS, BIOSIS Previews, CAB Abstracts, EMBASE, PubMed, Scopus and Web of Science. The search strategy used for PubMed is representative: (("gene transfer techniques" [MeSH Terms] OR "biotechnology" [MeSH Terms]) AND ("livestock" [MeSH Terms] OR "animals, domestic" [MeSH Terms])) OR (("animal nutritional physiological phenomena" [MeSH Terms] OR (("livestock" [MeSH Terms] OR "animals, domestic" [MeSH Terms]) AND 'Stress, Physiological' [MeSH Terms])) AND ("zoonoses" [MeSH Terms] OR 'Public Health' [MeSH Terms])). No date or language restrictions were used for this narrative (non-systematic) review.

Genetically Engineered (GE) Farm Animals and Human Disease

In 2009, the US Food and Drug Administration (FDA) released industry guidelines for the commercialization of GE farm animals [1]. This has raised animal health and welfare concerns [2–4], given the epizootics of production diseases caused by extant breeding technologies [5], such as dystocia in double-muscled beef cattle [6], mastitis in dairy cattle [7], porcine stress syndrome in pigs [8], osteoporosis in egg-laying hens [9] and skeletal and cardiovascular disorders in turkeys and broiler chickens [10]. Human health concerns have typically been limited to porcine endogenous retroviruses in xenotransplantation [11] or the oncogenic potential of growth hormone (GH) constructs [12]. The physiological trade-off between production traits and immune function [13], however, may pose a broader public health risk.

Growth/productivity and disease susceptibility have been shown to be correlated in domestic fowl [14], pigs [15], beef cattle [16] and dairy cows [17]. The Resource Allocation Theory [13], used to describe the distribution of resources among traits in an evolutionary context, suggests that protein and energy diversion from host defence to breast muscle mass production in meat-type breeds of chickens, for example, may explain why chickens with accelerated growth are at risk for immune dysfunction [18–20] and increased disease morbidity and mortality [21]. Transgenic coho salmon expressing GH suffer diminished disease resistance to vibriosis [22] and preliminary data suggest AquAdvantage salmon,

a GH transgenic Atlantic salmon currently under consideration for FDA approval, appear to suffer an earlier peak in mortality to a furunculosis challenge [23]. Continued application with biotechnology of a productionist paradigm, in which yield is priced above all else [5], may only lead to further deterioration of disease resistance among the more than 56 billion animals annually raised for food, which could have global public health implications [24].

Woolhouse and Gowtage-Sequeria estimate that 73% of emerging and re-emerging human pathogens are zoonotic in origin [25]. The remainder come from within the human population or the external environment [26]. Agricultural animal zoonoses include avian and swine influenza, bovine spongiform encephalopathy (BSE), Nipah virus, *Streptococcus suis* and numerous poultry and aquaculture-related food-borne diseases. The unprecedented emergence and spread of both the highly pathogenic avian influenza virus A subtype H5N1 and pandemic swine-origin H1N1 underscores the human health importance of farm animal disease susceptibility. Excess disease losses resulting from selecting or engineering faster-growing breeds of chickens and pigs with immune impairment [13] can no longer merely be factored into the financial calculus. Should trait selection priorities contribute to the next influenza pandemic [27], the pork or poultry industry could find itself in the position of passing along a $1 trillion cost to the global economy and the loss of millions of lives [28].

The application of genetic engineering in animal agriculture may also diminish biodiversity, which can fuel zoonotic pathogen adaptation and hinder host evolution for disease resistance [29, 30]. Population diversity, especially at major histocompatibility (MHC) loci (the genomic region common to all vertebrates that codes an immune recognition mechanism) is a major factor limiting the spread of disease by providing a heterogeneity of host defence targets against rapidly evolving pathogens [31]. This was illustrated by the decimation of isolated 'New World' populations lacking adequate MHC diversity from diseases such as measles in the sixteenth century [32]. MHC uniformity increases the vulnerability of monocultures of animals in agriculture to zoonotic diseases that could cross over into human populations by reducing immune reactivity and the hosts' collective ability to control pathogens [33, 34].

According to the Food and Agriculture Organization of the United Nations, 1350 farm animal breeds are threatened by extinction or are already extinct: more than one-fifth of registered breeds [35]. An international analysis of commercial poultry breeds found that approximately half of the genetic diversity of chickens has already been lost [36]. Biotechnological innovation is subject to the same pressures that have already so narrowed the farm animal genetic base. This means that should an engineered line of animals gain a clear economic advantage, competitors may predictably replace varieties then viewed as obsolete, leading to further genetic bottlenecking [37].

Transgenic 'technofixes'

Breeding nearly exclusively for productivity, joins other controversial practices that have been used in animal agriculture to promote growth with theoretical or demonstrable public health consequences. These include the use of diethylstilboestrol [38], GH injections [39], oestrogenic implants [40], arsenic-containing compound feed supplements [41], meat, blood and bone meal [42], and the subtherapeutic dosing of clinically important antibiotics in feed [43], which itself may be exacerbated by trait selection priorities.

Increasing rates of mastitis [44] tied to selection for milk yield [45] has led to the extensive use of clinically relevant classes of antibiotics in the dairy industry, including aminoglycocides, β-lactams, macrolides and tetracyclines [46]. A survey of dairy herds in Pennsylvania, a top dairy state, found 18% of operations were injecting a third-generation cephalosporin (ceftiofur) off-label [47]. The dairy industry's reliance on pharmacological crutches to mediate the unfavourable effects of selective breeding for productivity may in turn breed antibiotic resistance to drugs necessary for human medicine [48].

Biotechnological fixes have been proposed to mediate some of these costs of industrial methods of production. Although early attempts to create transgenic farm animals resistant to influenza had failed [49], a recent breakthrough in developing transgenic chickens resistant to influenza transmission [50] likely offers the greatest potential for public health benefit. Resistance to prior diseases also appears to be an achievable goal [51]. Rather than engineer BSE-resistant cattle, though, it may be more cost-effective to stop the continued quasi-cannibalistic feeding of slaughterhouse waste [52], blood [53] and manure [54] to farm animals. Although the re-feeding of brains and spinal cords of older animals has been banned, the FDA reversed an earlier decision [55] to eliminate all bovine tissues from cattle feed such as blood products [56]. The innovative salivary phytase-expressing Enviropig™ produces manure with lower levels of phosphorus [57], but without improved manure lagoon management, the environmental and public health impacts of confined pig feeding operations may continue largely unabated [58]. To reduce mastitis rates, cows can be engineered to secrete glycyl–glycine endopeptidase lysostaphin in their milk to combat *Staphylococcus aureus* infection [59]. The dairy industry may be able to milk lysostaphin transgenic cows for additional tonne-years without further increasing somatic cell counts, but the metabolic and musculoskeletal problems associated with overproduction [60] may be further aggravated. Production-related diseases have become preferred

'technofix' targets, presumably because they represent barriers to even greater productivity [61].

Regulatory Solutions

The regulatory apparatus proposed in the USA to deal with GE farm animals, the application of the Federal Food, Drug, and Cosmetic Act (FFDCA) animal drugs provisions (21 U.S.C. §321 et seq.), has been criticized for lacking adequate transparency and oversight [62]. The use of statutory authority designed to oversee the pharmaceutical industry may introduce an unnecessary and counterproductive level of opacity to the process of GE animal approval. Regulating GE animals in the same way as drugs would mean that the scientific community may be unaware of the existence of the application until the day it was approved or denied. There would be virtually no opportunity to appeal or even gain access to safety and health data considered confidential business information under the FFDCA. In essence, the entire regulatory programme can be conducted covertly, closed to public participation [62].

Regulators may discount adverse health effects that do not differ substantially from those that arise from extant breeding technologies. US regulators disregarded animal health risks associated with both recombinant bovine somatotropin [63] and farm animal cloning by arguing that they did not differ qualitatively from traditional selection [64]. There are currently no legal constraints in the USA on what can be done in the quest for increased farm animal productivity [65]. The European Food Safety Authority Scientific Committee on Cloning's opinion concurred with the FDA [66], but the European Group on Ethics in Science and New Technologies (EGE), a multidisciplinary body of experts appointed by the European Commission, concluded farm animal cloning was unjustifiable given the resultant health problems, such as 'malformations and reduced viability at birth; respiratory problems; enlarged foetal liver; epidermal haemorrhages; kidney abnormalities, etc.' [67] The European Parliament subsequently voted to ban the practice [68].

There is no advisory body analogous to the EGE in the USA, but the Office of Science and Technology Policy's Coordinated Framework for Biotechnology (51 Fed. Reg. 23302-23393 (26 June 1986)) has been successful in regulating GE commodity crops and could be redirected to focus on GE animals. Other government bodies, private foundations and professional associations could also provide support for impartial forums tasked with the supplemental review of safety information [69].

Conclusion

The current trajectory of livestock industry practices has been considered unsustainable from a public health, environmental and animal welfare perspective by the Pew Commission on Industrial Farm Animal Production, formed to conduct a 'comprehensive, fact-based and balanced examination of key aspects of the farm animal industry' [70]. The joint project with the Johns Hopkins University School of Public Health was comprised of 15 commissioners, including former US Secretary of Agriculture Dan Glickman, former Assistant Surgeon General Michael Blackwell, James Merchant, then Dean of the University of Iowa College of Public Health and former Kansas Governor John Carlin as chair. After a 2.5-year examination, its 2008 report concluded: 'The present system of producing food animals in the United States is not sustainable and presents an unacceptable level of risk to public health and damage to the environment, as well as unnecessary harm to the animals we raise for food' [71]. The use of transgenics may prolong and intensify this harmful trend.

The US National Research Council's Committee on Defining Science-Based Concerns Associated with Products of Animal Biotechnology has expressed concern that 'we already have pushed some farm animals to the limits of productivity that are possible by using selective breeding, and that further increases only will exacerbate the welfare problems that have arisen during selection' [72]. These may translate into human welfare problems should a continued emphasis be placed on productivity at the expense of disease resistance.

The One Health vision of interdisciplinary collaboration linking human, animal and environmental health [73] can only be fully realized if conflicting commercial interests can be resolved [5, 74, 75]. The commercialization of transgenic farm animals could be the catalyst that triggers the critical reflection of trait selection priorities necessary to better align industry practices with societal expectations while bolstering defences against emerging zoonotic pathogens.

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