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Shaping the norms that regulate international commerce of embryos

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ABSTRACT

As various embryo technologies in livestock were developed and evolved to a state of usefulness over the past 40 years, scientists with a specific interest in infectious diseases sought to determine the epidemiologic consequences of movement, especially international movement, of increasing numbers of embryos. Many of the foundational studies in this area were reported in *Theriogenology*, beginning in the 1970s and especially throughout the 1980s and 1990s. Unquestionably, *Theriogenology* has been a widely used venue for dissemination of basic information on this subject, which ultimately led to the development of the now universally accepted techniques for certification of embryo health. Today it is well-recognized that movement in commerce of embryos, especially *in vivo*–derived embryos, is a very low-risk method for exchange of animal germ plasm. This paper chronicles the evolution of strategies for health certification of embryos. An overview is provided of the calculated efforts of practitioners, scientists, and regulators to organize, forge necessary partnerships, stimulate needed research, provide purposeful analysis of the results, and, through these processes, guarantee the universal acceptance of efficient protocols for certifying the health of embryos intended for movement in international commerce.

1. Introduction

A recent report by the International Embryo Transfer Society's (IETS) Statistics and Data Retrieval Committee revealed that annual global transfers of *in vivo*–derived (IVD) bovine embryos remained stable while transfers of *in vitro*–produced (IVP) bovine embryos increased for the sixth straight year [1]. For the reported year (2011), 732,862 transferrable IVD bovine embryos were collected, and 453,471 transferrable IVP bovine embryos were produced. Production of lesser but significant numbers of transferrable IVD embryos from horses, goats, sheep, and deer were also reported. Today, we have well-defined sanitary precautions that provide a high degree of confidence that infectious diseases are unlikely to be transmitted as large numbers of embryos move in commerce. However, that was not the situation when the first reports on this subject began to appear in *Theriogenology* during the 1970s.

In this paper, we reflect on the hypotheses, research strategies, distribution of information, and evolution of embryo health–certifying schemes, as well as the decades of disease-free embryo transfers that have led to the current conventional wisdom that movement of livestock embryos is a very low-risk method for exchange of animal germ plasm. In-depth descriptions of the procedures are not provided.

However, we do briefly outline current recommendations and identify continually updated, detailed sources of information and protocols for health certification of embryos intended for international commerce.

2. Hypotheses and research strategies

2.1. In vivo–derived embryos

By the late 1970s, it was clear that techniques for nonsurgical recovery, cryopreservation, and nonsurgical

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transfer of IVD bovine embryos were rapidly evolving to a state of usefulness. Further, it was equally clear that increased numbers of these embryos would be available for international commerce, prompting concerns that infectious diseases might be transmitted if their movement was not properly regulated. A philosophic tug-of-war ensued between those who believed that embryo transfer was innately safe and embryo movement in commerce should not be hampered by burdensome regulations and those inclined to implement strict and somewhat cumbersome controls to ensure that infectious diseases were not spread between nations.

Early formal suggestions for regulation included requirements that the herds and/or nations in which donors resided were free of all diseases of potential concern to importing countries [2]. Alternative approaches were that either embryo donors were assembled in isolation facilities for a sufficient period of time to be tested and certified to be free from a variety of infectious diseases or embryo recipient herds be isolated throughout pregnancy in the country of destination and that they and their offspring similarly be tested to confirm absence of a variety of diseases. Although many knowledgeable persons on both sides of the issue believed that embryo recovery and processing procedures could be applied in such a way as to serve as "broad spectrum" health certifying procedures, there was little specific experimental evidence to confirm their beliefs [3].

Thus, potential importing countries developed expensive, cumbersome, and at times arbitrary or illogical embryo health–certifying procedures to protect their national herds. This regulatory burden threatened to seriously undermine, if not prevent, the movement of embryos in international commerce. The problems were compounded by the fact that there was no uniformity of import requirements. The frustration by well-meaning people on both sides was profound and provided the impetus for the funding and conduct of research that was needed to test the belief that zona pellucida-intact (ZP-I), IVD, bovine embryos were not likely to transmit infectious diseases if properly handled and processed, even if some donors resided in "infected" countries.

Some of the earliest reports on such research began to appear in *Theriogenology* in the late 1970s [4,5]. From these and additional reports in the 1980s, a somewhat universal strategy emerged among research teams that allowed a comprehensive assessment of the risks and simultaneous development of health-certifying protocols. This comprehensive approach to conduct and assessment of critical research was summarized in a paper in *Theriogenology* by W.C.D. Hare, one of the earliest and strongest advocates for uniform sanitary precautions and embryo processing procedures for certification of embryo health (Fig. 1) [6].

Even at this early stage, embryo transfer practitioners and researchers recognized that full implementation of their technologies would require cooperation of the international regulatory community. And so, the beginning of their relationship in the form of a "Roundtable Meeting on Sanitary Problems Related to Embryo Transfers" was jointly organized by the IETS and the Office International des Epizooties (OIE; later renamed the World Organization for Animal Health). This ground laying meeting occurred on December 9, 1985, at the headquarters on the OIE in Paris.

Fig. 1. W.C.D. Hare (behind) and E.L. Singh (front) in a laboratory at the Animal Disease Research Institute, Nepean/Ottawa, Canada (1977).

Six informative papers, encompassing critical issues of the time, were presented and published as an individual proceedings in an official scientific publication of the OIE (Fig. 2) [7].

The experimental hypotheses of that time were that an intact zona pellucida would protect the early conceptus from infectious agents, and proper handling of embryos would decrease the likelihood of pathogen transmission [8,9]. Of course, the null hypothesis was that diseases might be transmitted by transfer of embryos. In the interest of achieving the consistency that would result in comprehensive and complementary data from multiple research teams, Dr. Hare detailed his strategic views on design and analysis in which he described four main approaches to the needed research [6]. In the first approach, ZP-I embryos from disease-free donors were artificially exposed (*in vitro*) to a variety of pathogens that were domestic or international regulatory concerns. Then the embryos were subjected to cleaning protocols (a.k.a. embryo processing,

Fig. 2. Four of those presenting papers at the Roundtable Meeting on Sanitary Problems Related to Embryo Transfers which was jointly organized by the International Embryo Transfer Society (IETS) and the Office International des Epizooties (OIE) pictured here in front of the OIE headquarters in Paris, France (1985). From left: E.L. Singh, G.D. Mahon, D.A. Stringfellow, and R.J. Mapletoft.