Infections from animals to man

A conference on 'Infections from Animals to Man' was held at the Royal College of Physicians on 8 July 1992. The aim of the conference was to discuss the epidemiology and control of the zoonoses and the risks posed by zoonoses.

Infections, and in particular the zoonoses, are highly topical with frequent media fuss over the infective risks of eating chickens, beefburgers, and soft cheeses. Recognition of zoonoses depends on several groups of professionals: vets diagnosing infections in animals, microbiologists isolating and identifying zoonotic organisms, and doctors appreciating that their patients' infections may originate from animal contact, be it in the form of pet ownership, husbandry, or eating habits. There are important public health questions of how best to monitor zoonotic infections and what measures should be implemented to reduce or eradicate particular zoonoses. Finally there is the sensitive political issue of how much we are prepared to spend in controlling the zoonoses. The meeting reflected the interdisciplinary nature of zoonosis control with substantial contributions from vets, microbiologists, and physicians.

What is a zoonosis?

The meeting opened with a review of the definition of zoonoses by **C. E. D. Taylor**, president of the comparative medicine section of the Royal Society of Medicine. The World Health Organisation (WHO) defines zoonoses as 'diseases and infections which are naturally transmitted between vertebrate animals and man'. This definition has certain limitations: to specify both disease and infections seems unnecessary, and 'natural transmission' may exclude important animal-derived but food-borne zoonoses. The medical concept of zoonoses focuses on **infections** of animals transmissible to man, whereas the veterinarian regards zoonoses as **diseases** of animals transmissible to man. The second definition will exclude infections by animal commensals, such as *Pasteurella multocida* and *Salmonella,* that are non-pathogenic in their animal hosts. A simpler and equally useful definition of zoonoses might be 'infections of human beings acquired from animals'. Table 1 groups the zoonoses by route of acquisition.

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Epidemiology of zoonoses

S. R. Palmer (Communicable Disease Surveillance Centre, Cardiff) gave a wide-ranging review of the epidemiology of zoonoses in the UK. He divided the zoonoses into those which have been eradicated or are extremely rare, those which are controlled, and a large third group of presently uncontrolled zoonoses. **Bovine TB** and **brucellosis** are good examples of now rare zoonoses: in the three-years 1986–1989 there were only 20 cases of bovine TB in the UK. Other zoonoses may be controlled by intervention programmes such as vaccination of workers at risk of **anthrax** and vaccination of cattle against **leptospirosis.** Dosing farm dogs regularly with albendazole has been tried in South Powys as a way of breaking the transmission of **hydatid disease** to humans and no cases of hydatid have occurred in children in that area for the past seven years.

The most important uncontrolled zoonoses are the foodborne pathogens, *Salmonellae* and *Campylobacter.* Each year 14,000 cases of *S enteritidis* infection and 30,000 cases of *Campylobacter* occur in the UK. Both infections are associated with the consumption of chickens and are a major public health problem. **Cryptosporidial infections**, although usually spread by person-to-person contact, can be associated with an animal source in as many as 20% of cases. Other clinically important but unusual zoonoses include animal bite abscesses infected with *Pasteurella multocida* (250 cases/year), **Q fever** and **Lyme disease. Toxocariasis** presenting with visceral and ocular **larva migrans,** appears to be rare (20–40 cases/year) but is probably underdiagnosed.

Veterinary control of zoonoses

The elimination of brucellosis is undoubtedly the success story of veterinary control of zoonoses, eradication having been achieved within 11 years (Table 2). **W. J. Reilly** (Communicable Diseases (Scotland) Unit, Glasgow) described the services that are necessary to achieve such control: the State Veterinary Service which provides surveillance and research and organises and approves quarantine, the local authorities, and veterinary GPs. Zoonosis control raises important questions of both animal and public health, and it will be important to define who pays for zoonosis control.

Rabies

Rabies remains globally uncontrolled with an estimated 50,000 cases per year in India alone, and **D. A. Warrell** (Centre for Tropical Medicine, Oxford) warned that we should not be complacent about our island sanctuary. The rabies virus is widespread throughout

Table 1. A classification of the zoonoses

Type of zoonosis	Infections
Old	Bovine tuberculosis, brucellosis, rabies, anthrax
Food and waterborne	Salmonellosis, listeriosis, yersiniosis, giardiasis, cryptosporidiosis, haemorrhagic colitis and haemolytic uraemic syndrome caused by *E coli*
Occupational	Q fever, leptospirosis, *Streptococcus suis,* orf, cowpox, erysipeloid, Newcastle disease, louping ill
Pet associated	Toxoplasmosis, psittacosis, ringworm, *Pasteurella multocida,* toxocariasis, hydatid, *Mycobacterium marinum*
From wild and captive animals	Viral haemorrhagic fevers (Lassa, Marburg, Ebola and Hantaan), lymphocytic chroiomeningitis, rat-bite fever

the burgeoning fox population in Europe. The red fox is currently moving into new peri-urban habitats, so increasing the potential for spread of rabies. How can rabies be controlled? Muzzling dogs, and vaccinating both dogs and wild vectors, are two strategies being tried. Oral rabies vaccine can be droppd in baits for foxes and Switzerland has successfully eliminated fox rabies using this technique. Rabies encephalitis remains fatal and any patient with a suspected rabid bite should have the wound immediately cleaned, followed by passive and active immunisation. The rabies virus genome has now been cloned and sequenced. This allows for studies on the structural basis of pathology and the development of new vaccines.

Zoonoses and food

To have to speak after lunch is unfortunate but the misfortune is compounded when, after eating a chicken lunch, the speaker has to to tell the audience about the chicken-associated global pandemic of *S enteritidis.* **A. Fleetwood** (Animal Health Division, MAFF) reported that in the UK, the incidence of *S enteritidis* is rising while other **Salmonella** infections remain at a static level. *S enteritidis* infection is strongly associated with the consumption of chickens and eggs. Vertical transmission of *S enteritidis* may occur in hens and, if infection occurs in the elite grandparent hens which provide poultry for both breeding and laying flocks, infection is rapidly transmitted thoughout the hen population. The Department of Health has a statutory responsibility to implement the Salmonella legislation and the Zoonosis Order of 1989. Under this legislation all poultry-associated isolates of *Salmonellae* are reported to the Ministry of Agriculture, Farming and Fishery (MAFF). Both breeding and laying flocks are monitored with the aim of identifying and removing infected flocks. Infected flocks may be slaughtered and the carcases heat processed at slaughtering to reduce further transmission. In cases of *S enteritidis* food poisoning from eggs complex investigations are necessary to unravel the distribution and production of eggs in order to identify the infected flock. It is not clear what has produced the current pandemic; the contamination of foodstuffs of animal origin seems to be important and, perhaps, chickens have become more susceptible to *S enteritidis.*

Table 2. The eradication of brucellosis

1960	60% cow herds brucella + ve
1962	Free brucella vaccination introduced
1967	Voluntary accreditation of herds
1970	Incentives introduced for vaccination
1971	Compulsory eradication started
1980	Scotland attested brucella free
1981	UK attested brucella free
1984	Last brucella isolation in Scotland
1989	Sporadic breakthroughs with brucella

Zoonoses and farmers

It is surprising that there are virtually no data on zoonoses in farmers. **C. Ellis** (East Birmingham Hospital) reported a postal survey of farmers done in 1990 in which 36% respondents reported zoonotic illnesses, and 21% serious injuries. Ringworm and orf are the principal skin complaints; brucellosis, leptospirosis, and Lyme disease are diagnoses that should be considered in febrile farmers. Paradoxically, the first two diagnoses tend to be over-made, while Lyme disease is not considered at all or is misdiagnosed as chronic fatigue syndrome. The isolation and financial insecurity of many farmers may lead to depression which can masquerade as physical symptoms.

Zoonoses and pregnancy

The risks to the pregnant woman of contact with animals were presented by **S. M. Hall** (Communicable Disease Surveillance Centre, London). The most important of these is *Toxoplasma* infection during pregnancy because there are opportunities both for preventing infection of the pregnant woman and for antibiotic chemotherapy of infections acquired during pregnancy. Primary preventive measures include

avoiding contact with cat faeces, and offering health education about the dangers of eating undercooked meat. Secondary prevention depends on prenatal screening programmes to identify women who are susceptible to *Toxoplasma* infection. Media interest has been intense in the possibilities of screening programmes and in the government's perceived neglect of pregnant women by failing to implement such programmes. Unfortunately, screening for toxoplasmosis is no easy matter. No single lab test will identify all cases of congenital toxoplasmosis. Screening for *Toxoplasma*-specific IgM at booking even with a high test specificity would each year generate an estimated 35,000 abnormal first results among pregnant women in England and Wales. Positive results would have to be confirmed by a battery of confirmatory tests. Even then there would be no definitive answer as to whether or not the baby was infected. Although expectations for preventing fetal death and handicap have been raised by the debate, we do not yet have the epidemiological data nor the technology for designing appropriate algorithms for prenatal *Toxoplasma* testing.

Zoonoses and the compromised host

G. E. Griffin (Professor of Communicable Diseases, St George's Hospital, London) discussed the particular problem of *Toxoplasma* and *Salmonella* infection in the immunocompromised host. *Toxoplasma* infection is widespread in the UK, with 10% of 10-year-olds and 50% of 50-year-olds having anti-*Toxoplasma* antibodies. In the *Toxoplasma*-infected immunocompetent adult the parasite persists as bradyzoite cysts in brain, striated and cardiac muscle. In AIDS the immunological control keeping the parasite in its cystic state is lost, and 25% of *Toxoplasma* seropositive AIDS patients will develop *Toxoplasma* brain abscesses. Half the population being *Toxoplasma* naive has important implications for heart transplant surgery; if a heart bearing *Toxoplasma* cysts is transplanted into a *Toxoplasma*-naive recipient, severe primary *Toxoplasma* infection may develop. There are few, if any, *Toxoplasma* cysts in kidneys or liver.

While *Salmonella* infection is an irritating but usually self-limiting infection for the immunocompetent adult, in the AIDS patient it is a common invasive enteropathogen with a >80% incidence of bacteraemia. This pathogen is a major cause of morbidity in African AIDS. Little is known of the T cell or macrophage response to *Salmonella,* but AIDS patients fail to clear the infection.

Virus infection

M. McClure (St. Mary's Hospital, London) showed that animal models can provide useful insights into retroviral pathology. The simian immunodeficiency virus (SIV) provides the best model for the study of AIDS. It causes a disease characterised by a transient macular rash, chronic diarrhoea and lymphadenopathy, and a low CD4+ count. A group of SIV genes has been cloned and sequenced, and structural protein genes shared between SIVs and HIV2 have been identified. Finding viruses in primates may help to elucidate causes of other human pathologies: a foamy virus has been found in an orangutan dying of a neurological disease, and other orangutans have been found to have a high seroprevalence of antibodies to this virus. It is possibly sexually transmitted and may herald yet another sexually acquired disease.

Prion diseases

The last two talks concerned the prion protein which is postulated as the transmissible agent producing the spongiform encephalopathies. A wide variety of species is susceptible to spongiform encephalopathies which manifest in man as kuru, Creutzfeld-Jacob disease (CJD), and Gerstmann Straussle disease; in sheep and goats as scrapie and as bovine spongiform encephalopathy (BSE) in cattle. All these diseases share a common pathology, with histological evidence of spongiform neuronal degeneration and absent immune responses; their common clinical features are prolonged incubation times and progressive CNS deterioration. An important question is whether the unconventional transmissible agent that produces these encephalopathies can be transmitted from one species to another. The geographical distributions of scrapie and CJD do not correlate; in Australia and New Zealand there have been no new cases of scrapie for the past 40 years, but cases of CJD are still occurring. Case-controlled studies have shown no evidence for occupational risk, nor are dietary habits important; being vegetarian does not necessarily protect against CJD. Although scrapie does not appear to be transmissible, both kuru and CJD are transmissible to chimpanzees. The route of infection affects the likelihood of disease; oral infection is very inefficient by comparison with intracerebral inoculation from inadequately sterilised stereotactic electrodes or infected dura mater grafts. The infective agent has a restricted tissue distribution, muscle being non-infective. Medicines prepared from infected brain material may be infectious, and at least 21 cases of CJD are known to have been caused by contaminated human growth hormone. One should also be cautious about the injectable gangliosides that are much in vogue in Mediterranean countries for treating an ill-defined range of conditions. **R. G. Will** (Neuropathology Laboratory, Edinburgh) concluded that there was not yet enough evidence to incriminate transmission from animals to man, but prudent avoidance was perhaps the best policy for the moment.

J. Collinge (St. Mary's Hospital, London) discussed the mechanism of prion disease in humans. In early work it was assumed that the infectious agent was a virally encoded protein. Prion protein (PrP) is a cell

surface constituent of neurons and is encoded by a single gene. A modified form of prion protein, PrP^{Sc}, has been identified from scrapie-infected brains and is protease resistant. However, treatment of infected tissues with agents that destroy proteins caused a loss of infectivity. PrP^{Sc} is present in a monomeric form in scrapie-infected brain; in GSD a rare mutation of the human PrP gene leads to production of the pathogenic PrP^{Sc}. Thus this agent is both inherited and transmissible. Eighty-five per cent of CJD cases are sporadic, 15% are inherited, and there are occasional rare iatrogenic cases. An intriguing study of the PrP genes in iatrogenic cases of CJD shows that they have an unusual genotype that renders them susceptible to prion infection. The species barrier of prion disease which is perhaps vital to human protection from animal spongiform encephalopathies seems to be due to the inefficiency of different species in converting species specific PrP into pathogenic PrP^{Sc}.

The audience was disappointingly small, perhaps due to the meeting being held in July and the zoonoses being only a small part of most people's practice. Sadly, those who did come were not as questioning as one might have hoped. Although all the speakers spoke well a few took up more than their allotted span forcing others to shorten their talks, and restricting the time available for discussion. Some speakers should also look more closely at the title of the conference and make sure that their talks are relevant, rather than deliver their standard lecture-circuit seminar.

The meeting gave a wide perspective on the zoonoses. Animal health is important for all of us. There are many levels of interaction between animals, man, and the environment. As the environment changes different organisms will move into new niches and animals will alter their behaviour patterns. Changes in farming practices can have distant and unanticipated effects. As health care professionals we need to learn to recognise, understand, and respond to these changes.

The immunopathogenesis and immunotherapy of autoimmune disease

A conference entitled 'The Immunopathogenesis and Immunotherapy of Autoimmune Disease' was held at the Royal College of Physicians on 20 May 1992. Its aim was to consider advances in pathogenesis and their translation into therapeutic targets.

Current models of autoimmune disease are based on the concept that an autoantigenic peptide is presented by an appropriate human leucocyte antigen (HLA) to an autoantigen-specific T cell; these three components constitute the trimolecular complex. Activation of T cells specific for the autoantigen stimulates additional immune and non-immune effector mechanisms including antibodies, cytokines and other mediators which generate the pathology of the various diseases. It is still unclear whether the T cell response to autoantigens in humans is polyclonal or whether, as in some animal models, the T cell receptor (TCR) usage of the responder lymphocytes is restricted. The outcome of the trimolecular interaction is influenced by immunoregulatory processes and also by the hypothalamic-pituitary-adrenal axis.

Pathogenesis

The first three presentations concentrated on the HLA and non-HLA genes which contribute to autoimmune disease. **Dr J. Lanchbury** (United Medical and Dental Schools, London) reviewed the role of the major histocompatibility complex (MHC) in disease susceptibility using rheumatoid arthritis (RA) as a paradigm. He observed that only 30% of RA risk has a genetic basis, the rest being environmental, and that there were genetic influences outside the MHC: for example, chromosome 14. With regard to HLA associations, RA populations can be subdivided into three types: those like Northern Europeans who show the classical associations with DR4 and secondarily DR1; those like Jews, Indians, and Italians who have a primary association with DR1; and a group including Greeks without any

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