THE IMPORTANCE OF THE SPECIES BARRIER IN INFECTIOUS OR PARASITIC DISEASES

by Jean Blancou, Director General of the Office international des epizooties
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The concept of the species barrier has become important in light of the discover of bovine spongiform encephalopathy and of the possibility of transmission to other animal species and to human beings.

This concept is, in fact, quite old and includes not only the phenomenon of natural genetic resistance to pathogens, but also the influence of various other factors, which explains why certain species of animals are not affected by a given infectious agent or parasite. The purpose of this paper is to evaluate the different constituents of the species barrier[1] that make animals capable of resisting[2] major infections or parasitic diseases. This paper is confined to vertebrate species.

This study is based on historical data and on epidemiological and genetic knowledge currently available. The conclusion provides some suggestions in regard to currently emerging diseases of animals or humans.

HISTORICAL BACKGROUND

Even in ancient times, writers were impressed by epidemics that crossed the species barrier, affecting man and animals indiscriminately. Therefore, it is not surprising that this particular type of epidemic received much attention, no doubt confusing it with other different episodes, and painting a blacker picture than was justified in order to impress readers. For example, no species barrier seemed capable of stopping the panzoonosis described by Ovid in *Metamorphoses* – a 'plague' that affected nearly all of the inhabitants of Egine Isalnd, and numerous animals in 129 BC:

Strage canum primo volcrumque, aviumque, boumque
Inque feris subite deprehensa potential morbis est [3]

Many other authors of the same period described similar events where mammals, birds,

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[1] In this account, the term 'species barrier' is used in the broad sense; barriers between subspecies, or even lines of vertebrates will be considered in addition to barriers between species defined stricto sensu

[2] In this article, the word resistance is also to be used in the broad sense, bearing in mind that there could be different levels of resistance (from weak to complete) and several types of disease in resistant animals, such as subclinical cases, latent infections, carrier state, etc.

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fish and reptiles were equally affected by various *pestilencia.*

It was not until much later that the first veterinarians reported their observations on the natural or experimental resistance of certain species of animals to infectious or parasitic diseases, such as rinderpest, contagious bovine pleuropneumonia, sheep pox and glanders. Such observations were often based on the inoculation of virulent material, whereas, the actual nature of the pathogens remained unknown. It was not until the discovery of micro-organisms by Louis Pasteur that it became possible to quantify with precision the virulence of different strains of bacteria or viruses. Pasteur was the first to demonstrate that different species of animals were not equally receptive to the inoculation of a micro-organism, and that this receptivity could be modified by serial passages of the micro-organism. Other workers showed the same phenomenon with most of the infectious diseases, to the extent that the causal agents were known, and nowadays the occurrence of species barriers is well recognized.

Once the basis and mechanisms of the barriers were established, the information gathered was exploited by humans. For example, when a species barrier was absent or weak, this fact has contributed to the development of pathogens for bacteriological warfare (e.g. anthrax), and when a barrier existed and seemed wrong, it was used in the biological control of certain vertebrate pests (e.g. the virus of viral haemorrhagic disease of rabbits).

COMPONENTS OF THE SPECIES BARRIER

As a general rule, a pathogen may encounter three successive lines of defense in attempts to infect or parasitise a potential host (Table 1.):

- first, the pathogen has to encounter the host animal;
- next, the pathogen has to penetrate the body, overcoming mechanisms of nonspecific, natural, constitutional or innate resistance;
- the pathogen may also face specific, adaptive or acquired resistance.

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Table 1: The species barrier to certain infectious diseases

	Vertebrate species				
Disease	**Birds**	**Carnivores**	**Ruminants**	**Pigs**	**Humans**
Pox virus infections, Tuberculosis, etc.	-	-	-	-	-
Anthrax, rabies, etc.	+	-	-	-	-
Foot and mouth disease, etc.	+	+	-	-	-(*)
Erysipelas, etc.	+	+	+	-	-
Human acquired immumo-deficiency syndrome, Leprosy, etc	+	+	+	+	-

+ : resistance to the natural disease
- : lack of resistance to the natural disease
(*): exceptional cases

In every case, these three lines of defence form part of genetic determinism, and may also be considered to be a way in which prey evades its predator. For example, a gazelle that is unable to avoid an encounter with a lion, can outrun it by natural speed, or escape its grip by zigzagging.

These three main constituents of the species barrier will be examined in greater detail here, in the widest sense. This subject, which has been the object of much research, does not provide an exhaustive review, but rather, is confined to some important examples, according to the general plan given in Fig. 1.

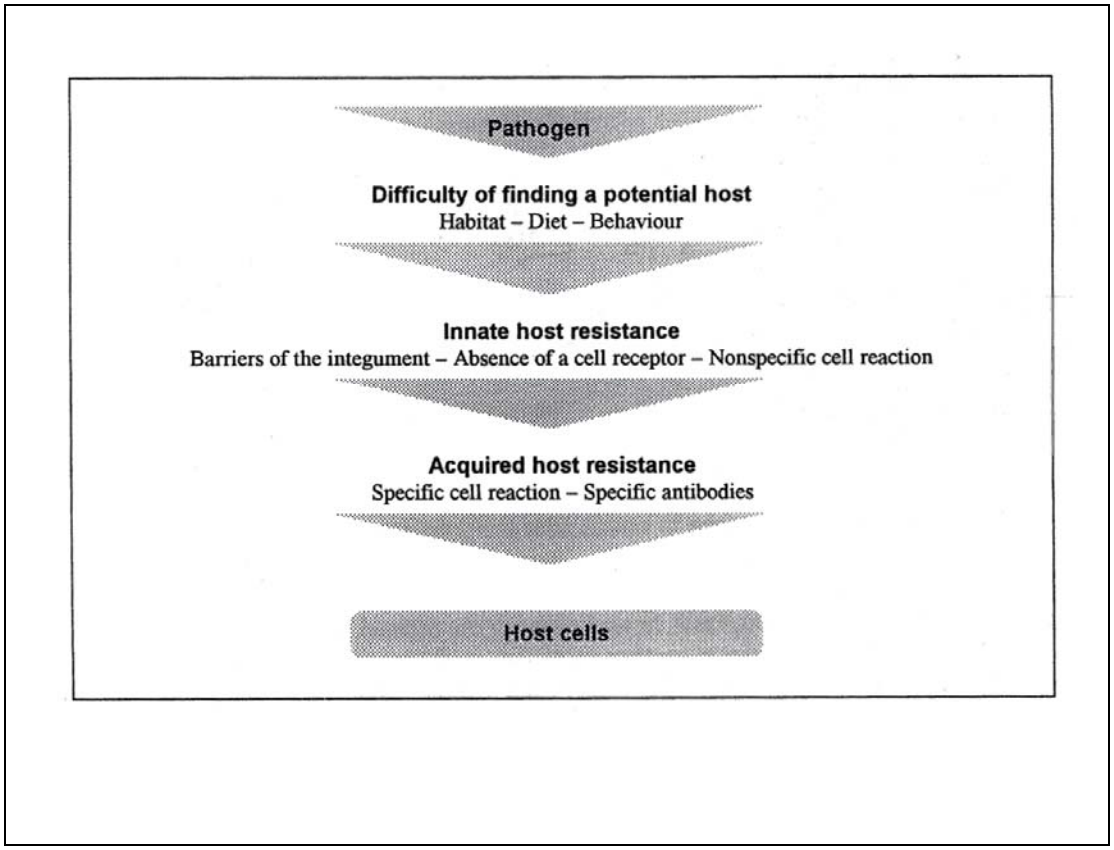

Figure 1: Successive barriers in a potential host to infection with an intracellular pathogen

1. First defence: the difficulty for a pathogen to find a vertebrate host

Numerous circumstances may make it difficult for a pathogen to find its vertebrate host, and this is the first natural specific barrier to infection [review in Pastoret, 1984].

Thus the *characteristics specific to* aquatic or flying animals makes it improbable that they will encounter a pathogen if its habitual host is a terrestrial species, and *vice versa.* Nevertheless, this is not always an insurmountable obstacle, as explained below.

The *rhythm of biological activity* of a species (i.e., diurnal, nocturnal, etc.) may also create an obstacle to encountering a pathogen. The best example of this influence is the chronobiological adaptation of a parasite to match the activity rhythms of its potential host. Such adaptations results in a type of parasitism that is confined to a given species [Combes, 1995, p. 196] and, as it can also be discouragement to parasitism of other species; it may be regarded as a specific barrier. The best-documented example of this type of barrier is *Schistosoma mansoni* infestation in human beings or rodents (Fig.2)

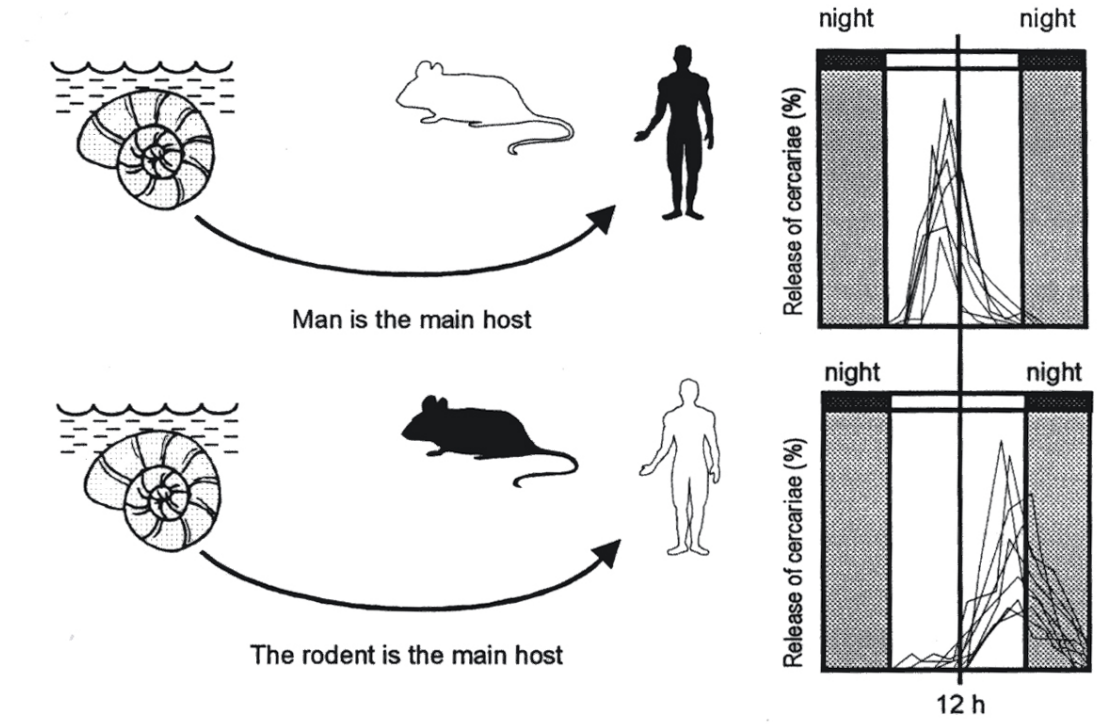

Figure 2: Chronobiological adaptation of parasite transmission

At transmission sites where humans are the main host of *Schistosoma mansoni*, the aquatic larvae (cercariae) of the parasite emerge from molluscan vectors at midday. At sites where rodents are the main hosts, the larvae emerge at the end of the afternoon. This 'hour of release' character is genetically determined [*in* Combes, 1995, p. 196].

The *diet* of an animal species may preclude, or seriously hinder, an encounter with the pathogen. The best examples are, or course, parasitic life cycles which rely on an animal, itself an intermediate host of the parasite, being ingested by a predator. The same barrier may exist *vis-à-vis* the agents of infectious foodborne diseases, which multiply in an inert medium (soil, water, etc.) or within the body of a given mammal, bird, fish or invertebrate. There are many examples, but the best known to the general public is that of the bovine spongiform encephalopathy agent, which was capable of crossing the species barrier only when cattle were fed with meat and bone meal, as described below.

The *behaviour* of various animal species may also constitute a more or less effective species brier to infection. Natural aversion to, or distrust of, one species by another (prey/predators, domestic/wild species, cats/dogs, etc.) reduce the chances of contact and the exchange of common pathogens while, on the other hand, overpopulation or gregariousness favour such an exchange as discussed below. Some animal species instinctively remove the ectoparasites that attack them: African antelopes detach their ticks, primates their fleas, birds their lice, etc. Of course, humans are a special case, because they can voluntarily avoid contact with pathogens or

their reservoirs (mainly ectoparasites, but also sick animals, biting animals, etc.), even if such behaviour is instinctive rather than an attempt to avert transmission.

2. Second defence: innate resistance of the host

If an encounter with a pathogen cannot be avoided, other mechanisms of genetic resistance intervene, whether nonspecific, constitutional, natural or innate. The latter is the most characteristic, because it exists before any contact with the pathogen occurs. This form of resistance usually relies on many different genes, but the outcome is the same: precluding penetration and invasion of the body by a pathogen. The mechanism of resistance is still under investigation for some important animal diseases, such as dermatophilosis [Dumas et al., 1971], foot and mouth disease [Dunn & Donaldson, 1997], rabies [Blancou *et al*., 1986], etc. In several other cases the different components of innate resistance are known and, are sometime well documented the first of which is resistance to penetration by the pathogen.

Resistance to penetration by the pathogen

Penetration by a pathogen into the body of a vertebrate may be averted or retarded by multiple mechanisms, the most important of which are listed below.

Resistance of skin or mucous membranes to penetration by the pathogen: the nature, structure or thickness of the epidermis enables many species (notably batrachians and reptiles) to raise an effective initial barrier to attack by ectoparasites, larvae of endoparasites, and even certain micro-organisms.

The existence of *various antimicrobial substances* (lysozyme, antibiotics, etc.), on the surface of the skin or mucous membranes of certain species, or the presence of an acidic pH, is a second effective barrier to penetration by bacteria (e.g.,*Straphylococcus* sp., *Esterichia coli,* etc.), and viruses (e.g., Sendai virus). On the other hand, the absence of certain factors indispensable to the development of a micro-organism, in some species can preclude infection. For example, erythritol is the preferred nutrient for *Brucella* sp.: its absence in the genital tract of some species (guinea-pigs and humans) is a major factor in their resistance to abortion [Smith, 1991].

The body temperature of a given species may be an obstacle to multiplication of particularly heat-sensitive or cold-sensitive micro-organisms. Thus, retiles and batrachians (homoeothermic) are less sensitive than mammals and birds to tetanus and botulism toxins, which require relatively high temperatures in order to act [Rumyantsev, 1992]. On the contrary certain reptiles (e.g., *Dipsosaurus dorsalis)* use this mechanism to eliminate heat-sensitive bacteria (*Aeromonas hydrophila)* by staying in warm places [Kluger *et al.* 1975].

Resistance by absence of cell receptors

Intracellular pathogens that can overcome the first defences of the body might fail to become established because they first have to enter cells.

Cell penetration can occur only if there is mutual recognition between cells and the pathogen. Such recognition, which is a vital step in multiplication of an intracellular pathogen, depends on the existence of appropriate complementary molecules (and ligands) within the host. The adhesion of micro-organisms to the cells of a potential host depends on the existence of highly specific microbial adhesions (e.g., enterobacteria) or glycoprotein spikes (e.g., Sendai virus). There must match a certain receptor on the host cells before the micro-organism can penetrate

and multiply. The lack of cellular receptors in the lungs or intestines explains the natural resistance of human beings to *Bordetella bronchiseptica* infection (pathogenic for many animals), and of animal's to *Bordetella pertussis* infection (whopping cough) or *Neisseria gonorrhoeae* (human gonorrhea) [Koransky *et al.,* 1975; Tuomanen *et al.,* 1983]. Similarly, human beings and most rodents are not susceptible to infection with *Escherichia coli* type 1, responsible for diarrhoea in rabbits, because only rabbit intestinal cells possess the specific receptor for this bacterium [Cheney *et al.,* 1980]. By the same mechanism, certain breeds of piglets are resistant to infection with *Escherichia coli* K88, which can infect most pigs, because they lack the specific cellular receptor for this strain of bacterium [Selwood *et al.,* 1975].

There are numerous other examples of genetic resistance in animals [4] resulting form the lack of appropriate cellular receptors: resistance of rodents to the action of diphtheria toxin, and resistance of many species to cytolysis by salmonellas [Rumyantsev, 1992]. In virology, two different properties of the cells are needed for the infection to succeed: susceptibility (the virus can multiply in the cell). There are several examples of this complex resistance in veterinary medicine: certain lines of fowl are resistant to avian leucosis viruses A and B, and some cattle to bovine leucosis virus, both instances are due to the lack of receptors to the virus [Young *et al.,* 1993]. In human virology, it has been demonstrated that the natural resistance of mice (and other species) to the HIV [5] is due to the absence of cellular receptors which correspond to human CD4 and CCR5 for this virus and that the natural resistance of chicken to infection by the human poliovirus is also due to the absence of a cell receptor [Pastoret, 1990].

Resistance due to a nonspecific cell reaction

A third mechanism of innate resistance to pathogens whether or not this is intracellular, is based on the response of certain polynuclear cells.

Without ever having been in contact with a pathogen, an organism can defend itself by the response of macrophages, the activity of which varies with animal species. It has been demonstrated that the resistance of mice to intracellular parasitism with certain mycobacteria Salmonella or Leishmania, depends on the *Nramp*[6] gene [Blackwell, 1996; Skamene *et al.,* 1982]. Similar genes have been identified in many domestic species, particularly cattle. These are apparently linked to a natural resistance to brucellosis or tuberculosis [Templeton *et al.,* 1988]. In this way, the resistance of certain lines of cattle to *Brucella abortus* infection depends on genetically controlled macrophage activity [Adams & Templeton, 1995]. For virologists, the resistance of certain breeds of fowl to Marek's disease appears to be linked to genes that control the activity of NK[7] cells [Lanier & Phillips, 1996].

It is interesting to note that an innate resistance may become combined with an existing acquired resistance: in mice infected with BCG[8], the *Nramp* gene controls the infection, and then genes of group H2 take over [Nadeau *et al.,* 1995].

[4] The genetic resistance of some human beings (SH heterozygotes) to malaria can be added to this type of resistance. This resistance is due to the possession of a special haemoglobin (S instead of h) incompatible with the intracellular development of *Plasmodium* (Allison, 1954)

[5] Human Immunodeficiency Virus

[6] Natural resistance association macrophage protein 1

[7] Natural Killer

[8] Bacillus Bilié-Calmette –Guérin

3. Third defence: acquired host resistance

Acquired resistance, which develops only after an initial contact with a pathogen, depends on molecular recognition of the antigenic determinants of that agent. This recognition leads to the development of specific adaptive resistance governed by the experience (*Nurture*) versus innate resistance (*Nature*). There are two types of acquired resistance:

Cell-mediated resistance

In this type of resistance, the infected cell is destroyed by the direct action of immune cells (usually T lymphocytes) with which it comes into contact. For the pathogen to become vulnerable, its antigens must first be 'presented' to T lymphocytes by other intermediary cells, notably macrophages and B lymphocytes. This presentation occurs if the organism under attack possesses the necessary molecules. The existence of such molecules depends in turn on genes, located in part of the genome coding for the presentation of the antigen, called MHC II[9], or on genes coding for T lymphocyte receptors (T cell receptors).

Numerous experiments on mice have shown that the difference in resistance of various lines of these rodents to certain nematodes, particularly *Trichinella spiralis,* is determined genetically at the MHC level [Wasson *et al.*, 1984]. Subsequently, other experiments demonstrated that the MHC (classes I and II) genes, or related genes, are responsible for acquired resistance to nematodes in other species of animals[10] [Stear & Murray, 1994].

Resistance mediated by humoral mechanisms

This type of resistance is usually linked to the existence of specific immunoglobulins (antibodies) produced by B lymphocytes following initial contact with a pathogen. The specificity and amount of antibodies produced in this way is itself dependent on many genes, and this was demonstrated for the first time in pigs where certain breeds were resistant to *Brucella suis* infection [Cameron *et al.*, 1943]. Experiments have also demonstrated that the amount of antibody produced by certain lines of mice (high responder and low responder) was genetically controlled [Biozzi *et al.*, 1984]; the same findings in pigs have been applied to the selection of animals resistant to mycoplasmas [Mallard *et al.*, 1993]. The absence (or inactivity) of B lymphocytes responsible for antibody production, which may result from a mutation, brings about the suppression of any existing species barrier. Such a spontaneous or induced failure renders animals susceptible to various infections, as described above.

FAILURE OF THE SPECIES BARRIER

The different lines of defence against a pathogen available to a species, subspecies or line of vertebrates may fail, and some examples are given below.

1. Facilitating the encounter between host and pathogen

The encounter between host and pathogen depends, as noted above, on numerous factors.

[9] Major histocompatibility complex class II.

[10] A similar mechanism has been demonstrated in certain human lines, which are more or less resistant to leprosy, depending on their human leukocyte antigen type [Van Eden *et al*., 1985].

The *biological characteristics* of a species, which form an effective barrier against diseases, which affect other species in different biotopes, might change. Thus, diseases that are unknown (or very rare) among wild species which live alone or in small groups can spread much more readily when the animals are confined to artificial enclosures, or when their domestic equivalents are managed intensively. Such animals can become infected by contact with other species, including human beings. Examples of this are the infection of the European cervids by malignant catarrhal fever or tuberculosis (acquired from domestic ruminants) or of carnivores by pseudorabies (acquired from domestic pigs) [Brown, 1997, Pastoret, personal communication;].

Displacement of wild or domestic animals by humans (for farming, hunting or leisure) has certainly been important during the course of history, and has facilitated the infection of animals hitherto protected by a sedentary mode of living. There are numerous examples of this with respect to infectious and parasitic diseases (review by Moutou, 1994)

A change in *activity rhythms* can also facilitate an encounter with a pathogen. When the pressure of human activities (such as hunting and tourism) forces a wild animal to change from diurnal to nocturnal living, it may encounter the pathogens of nocturnal animals.

A change in *diet* may weaken (or suppress) the first line of defence against pathogens. Such a change may by accidental, when an animal east an unusual prey harboring the parasite of another species, even though this animal acts as a dead-end host and the parasite cannot complete its development [Euzéby, 1997]. This can also happen when certain predators are forced by famine or lack of experience (in young animals) to alter their feeding preferences. This type of accident can be observed readily in human beings, by reason of their selective diet: many people have died recently after eating African monkeys infected with Ebola virus. Human activity can also infect domesticated herbivores, such as by feeding them with meat products. Cattle in the United Kingdom probably contracted bovine spongiform encephalopathy by being fed protein supplements prepared from the carcasses of sheep infected with the scrapie agent, or from other cattle not known to have been infected at the time [review in Bradley, 1997]. Similarly, horses have contracted trichinellosis from accidental incorporation of parasitised rat carcasses into their cereal meal [Magras *et al.,* 1997].

Changes in the *behaviour* of a species may facilitate contact with an infectious or parasitic agent that it would not otherwise have encountered[11]. Animal behaviour can be altered by environmental changes (Climatic variation, etc.), movement of populations (including migration) and accidental promiscuity, placing them in contact with species, which normally live separately. In human beings, such changes may arise from inhibition of natural instincts or from abolition of ancestral taboos. This can lead to people handling animals normally regarded as repugnant (bats, reptiles, batrachians, spiders, etc.), and contracting diseases harbored by such animals (rabies, enterobacterial infections, mycobacterial infections, etc.). Human beings may also contract diseases of animals during ritual practices or sexually deviant behaviour.

2. By-passing innate host resistance

As mentioned above, **penetration by a pathogen** into the body of a vertebrate can occur if the defence mechanisms of the potential host have been destroyed or weakened.

[11] In some cases, the species barrier is overcome by a change in the behaviour of an animal acting as the reservoir of a pathogen: rabid bats only transmit rabies to terrestrial mammals (including humans) because they have lost their instinct for preservation which normally keeps them away form mammals.

Any disruption of the *cutaneous or mucosal barriers*, or failure of neutralization by antimicrobial protective substances, can facilitate the infection of a normally resistant species. This occurs when barriers are damaged by accidents such as burns, attack by chemical products, or radiation, allergy, inflammation, etc.

Similarly, a change in *body temperature* may render a species susceptible to a pathogen that it normally resists. Louis Pasteur was the first to succeed in infecting fowl with the agent causing anthrax after cooling them by immersing their feet in iced water, and Gibier succeeded in infecting frogs with the same pathogen by warming their bodies [in Galtier, 1897, p. 1005]. Such variation in external temperature might occur accidentally in nature.

Experimentally, it is possible to transfer the **cellular receptors** (needed to confer sensitivity to a pathogen) to a species naturally resistant to infection by that pathogen. Such genetic manipulation consists of introducing genes that code for the expression of a specific cellular receptor into the host genome. It has modified mice susceptibility to certain pathogens, such as the agents of transmissible encephalopathies [Collinge *et al.*, 1995]. In the case of AIDS, it has been possible to render mice susceptible to this disease after 'humanising' their genotype, and introducing the cellular receptors CD4 and CCR5, normally absent from mice [Browning, 1997].

In nature, such a transfer is highly unlikely but, on the other hand, mutations or genetic recombinations of the pathogen can change the target cells of the host, rendering the host susceptible to the mutant or recombinant, s is often the case with the influenza virus. Emergence of new strains of virus could also be explained by the existence of 'quasi-species' (variable particles within a single host) that facilitate selection for ability to replicate among the genomes [review in Domingo, 1988].

However, the **nonspecific cell reactions** that protect a species from a pathogen can be neutralized, leading to a breakdown in the first line of cellular defence. The causes of such a breakdown are practically the same as those of specific defences (see below), and may be due to the action of various factors:

> *Physical factors:* adverse environmental conditions (extreme temperatures, abnormal humidity), enhanced irradiation (natural or accidental), etc.
>
> *Chemical factors:* action of any product that changes the rhythm or quality of cells produced by the body, particularly immunocompetent cells (immunodepressive agents).
>
> *Biological factors:* infections by immunodepressive pathogens (e.g., retroviruses), physiological stress (malnutrition, overcrowding), psychological stress, autoimmune diseases, etc. [review in Morris & Potter, 1997]

3. Neutralising the acquired resistance of the host

Cell-mediated resistance can be diminished by the factors listed above. The species barrier against certain intracellular parasites (protozoa, bacteria or viruses) is then impaired or abolished. When cellular immunity breaks down, species normally resistant to diseases such as

trypanosomosis, coccidiosis and tuberculosis can become infected after contact with a reservoir host.

Resistance mediated by humoral mechanisms can be overcome in exactly the same way, and the resultant depression of antibody production can result in suppression of the species barrier. This can be studied experimentally in various ways, after inducing immunodepression by physical, chemical or biological means, by using natural mutants (nude athymic mice, mice with SCID[12]), by inducing artificial mutations, or by suppressing resistance genes.

Such procedures are currently being used in the laboratory to obtain animals receptive to diseases to which they are naturally resistant. They range from quite simple procedures, such as those used for testing certain vaccines (inoculating calcium chloride at the same time as *Clostridium chauvei*, in order to render guinea-pigs susceptible to bovine blackleg) to more elaborate systems for creating animal models of human diseases: inserting human genes into mice or using 'knock out' germ line mice to study tuberculosis, leishmaniosis, transmissible spongiform encephalopathies, etc.

Of course, there is very little chance of such events occurring in nature, but they may explain why certain individuals have contracted diseases normally harboured by other species. Recent examples are the infection of African lions with canine distemper virus, of dogs with wildlife parvovirus infection [Parrish, 1992], and of human beings with AIDS or smallpox from African monkeys [review in Brown, 1997]. Centuries ago, malaria was probably acquired by humans from contact with birds, measles from contact with cattle infected with rinderpest, schistosomosis and leprosy from contact with rodents, etc. [Combes, 1995]. Such pathogens become progressively adapted to their new host after successive passages, so that the new host then becomes infected readily, the species barrier having been abolished s seems to be the case for the rabies virus [review in Blancou & Aubert, 1997], or for the 'porcinophilic' strain of foot and mouth disease recently described in south-East Asia [Dunn & Donaldson, 1997].

This unexpected crossing of the species barrier may be explained by conditions which are unfavourable for the operation of the immune system, linked particularly to a deterioration in living standards: overcrowding leads to malnutrition, which results in deficiencies and hypogammaglobulinaemia[13.]

CONCLUSION

The concept of a species barrier is becoming more important in the view of biologists and physicians.

In human medicine, the study of the species barrier has become a vital part of investigation real or potential zoonoses, and is used to justify the implementation of special surveillance and control measures.

In veterinary medicine, most attention has been paid to the positive aspect of disease resistance. An entire discipline is devoted to the identification of subjects naturally resistant to diseases (genetic markers), in order to promote breeding (genetic selection), and to transfer resistance to other species (genetic manipulation). The object of such research is often to overcome the lack of vaccine or treatment, or to reduce the use or cost of such preventive measures.

[12] Severe combined immunodeficiency

[13] There may also be exceptional circumstances, due to human intervention, under which species normally resistant to certain pathogens become susceptible after inoculation of live vaccines. This applies to two viruses of sheep (bluetongue and Border disease), which have infected pregnant bitches and pigs, respectively, inoculated with vaccines containing these viruses [Brown, 1997]. Another example is the infection of dogs with 'attenuated' parvovirus (used as feline leukopenia vaccine) after contact with vaccinated cats [Tratschin *et al*., 1982].

When referring to a species barrier, the three following important points must always be borne in mind:

- The robustness of the species barrier can only be evaluated if the breed of vertebrate species to be confronted by the pathogen, the strain and the titer of that pathogen, as well as the penetration route of that strain has all been determined.

- It is rare for a species barrier to be definitively insurmountable.

  There could be a breakdown, one day, under the influence of multiple natural factors and above all, and more often, under the direct or indirect influence of human interventions.

- The barrier possessed by a species against a pathogen is always under threat of mutation of that pathogen.

  The battle between host resistance and a pathogen, aimed at ensuring optimum fitness, leads to an 'arms race' [Dawkins & Krebs, 1979] that could destabilize one or the other. This race is based on a capacity for rapid genetic mutations (which change the target cells), and the pathogen has the best chance of winning because of its faster replication rate. There are many examples of such unexpected destabilization of a potential host confronted with a pathogen regarded as harmless. The most recent is a diminution of human resistance to avian influenza virus. The disease killed several people in Hong Kong during 1997 when a chicken virus (type H5N1), usually harmless for human beings, breached the species barrier.

All these considerations mean that a biologist should avoid claiming that a species barrier can never be overcome. One must also avoid complete confidence in barrier when using a pathogen to control the population of a vertebrate species regarded as a pest.

REFERENCES

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REFERENCES

ADAMS, L. C. & TEMPLETON, J.W. (1995)- Identifying candidate genes for natural resistance brucellosis. *Proc. Ann. Meet. US Anim. Health Assoc.*, 111-115.

ALLISON, A. C. (1954)- Protection afforded by sickle-cell trait against subtertian malarial infection. *Brit. Med. J.*, **1**: 290-294.

BIOZZI, G., MOUTON, D., STIFFEL, G. & BOUTHILLIER, Y. (1984)- A major role of the macrophage in qualitative genetic regulation of immunoresponsiveness and anti-infectious immunity. *Adv. Immunol.,* **36:** 189-234.

BLACKWELL, J. M. (1996)- Genetic susceptibility to leishmanial infections: studies in mice and man. *Parasitology,* **112:** 567-574.

BLANCOU, J. & AUBERT M.F.A. (1997)- Transmission du virus de la range: importance de la barrière d' espèce. *Bull. Acad. Natle. Méd.,* **181** (2): 301-312.

BLANCOU, J., AUBERT, M.F.A., BARRAT, M.J., CAIN, E. & SELVE, M. (1986) – Résistance génétique à l'infection rabique. Essai de mise en évidence de l'héritabilité d'une résistance à l'infection (bilan préliminaire sur un modèle murin). C.R. *Soc. Biol*., **180**: 364-371.

BRADLEY, R. (1997)-Bovine spongiform encephalopathy as an emerging disease: measures, ways and means to protect animals and consequently humans from the possible risk of disease. *In* Comprehensive Reports on Technical items presented to the International Committee or to Regional Commissions, 1996, 131-149.

BROWN, C. (1997)- emerging diseases –What veterinarians need to know. *J. Vet. Diag. Invest.,* **9:** 113-117.

BROWNING, G. (1997)- Mice transgenic for human CD4 and CCR5 are susceptible to HIV infection *Proc. Natl. Acad. Sci.* USA, **94**: 14637-14641.

CAMERON, H.S., GREGORY, P.W. & HUGHES, E.H. (1943)- Inherited resistance to brucellosis in inbred Berkshire swine. *Am. J. Vet Res.,* **3**: 387-389.

CHENEY, C.P., SCHAD, P.A. & FORMAL, S.B. (1980)- Species specificity of *in vitro Escherichia coli* adherence to host intestinal cell membranes and its correlation with *in vivo* colonization and infectivity. *Infect Immun.,* **28**: 1019-1027.

COLLINGE, J., PALMER, M.S., SIDLE, K.C.L., HILL, A.F., GOWLAND, I., MEADS, S.J., ASANTE, E., BRADLEY, R., DOEY, L.J. & LANTOS, P.L. (1995)- Unaltered susceptibility to BSE in transgenic mice expressing human prion protein. *Nature,* **378**: 779-783.

COMBES, C. (1995)- Interactions durables. Écologie et évolution du parasitisme. Mason (ed.), Paris, 524 pp.

DAWKINS, R. & KREBS, J.R. (1979)- Arms races between within species. *Proc. R. Soc. Lond.,* (B) **205:**489-511.

DOMINGO, E. & HOLLAND, J.J. (1988)- High error rates, population's equilibrium and evolution of RNA replication systems. *In:* (E. Domingo, J.J. Holland & P. Ahlquist, eds.) RNA Genetics. Vol. III. Variability of RNA genomes. CRC Press, Boca Raton: 3-36.

DUMAS, R. LHOSTE, P., CHABEUF, N. & BLANCOU, J. (1971)- Note sur la sensibilité héréditaire des bovines à la streptothricose. *Rev. Élev. Méd. Vét.,* **24:** 349-353.

DUNN, C.S. & DONALDSON, A.I. (1997)- Natural adaptation to pigs of a Taiwanese isolate of foot-and –mouth disease. *Vet. Rec.,* **141**: 174-175.

EUZÉBY, J. (1997)- Devenir des parasites d'origine animale trasmis à l'homme. *Méd. Trop.,* **57**: 165-225.

GALTIRE, M.V. (1897)- Traité des maladies contagieuses et de la police sanitaire des animaux domestiques, 3rd. Ed. Asselin & Houzeau. Paris, 1,280 pp.

KLUGER, M.J., RINGLER, D.H., & ANVER, M.R. (1975)-Fever and survival. *Science,* **188**: 166-168.

KORANSKY, J.R., SCALES, R.W. & KRAUS, S.J. (1975)- bacterial hemoagglutination by *Neisseria gonorrhoea. Infect. Immune.,* **123**: 495-496.

LANIER, L.L. & PHILLIPS, J.H. (1996)- Inhibitory MHC class I receptors on NK cells and T cells. *Immonol. Today,* **17**: 86-91.

MAGRAS, C., FREDERIGHI, M. & SOULÉ C. (1997) –Les dangers pour la santé publique liés à la consommation de viande de cheval. *Rev. sci. tech. Off. Int. Epiz.,* **16** (2): 554-563.

MILLARD, B.A., WILKIE, B.N. KENNEDY, B.W. & MAGNUSSON, U. (1993)- Use of estimated breeding value in a selection index to bread Yorkshire pigs for high and low immune and innate resistance factor. *Vet. Immunol Immunopath.* ,**38**: 392-393.

MORRIS, J.G. & POTTER, M. (1997)- Emergence of new pathogens as a function of changes in host susceptibility. *Emerg. Infect. Dis.,* **3**(4): 435-441.

MOUTOU, F. (1994)- Déplacements d'espèces animals par l'homme: conséquences écologiques et sanitaries. *Bull. info. path. anim. sauvages,* **10:**83-90.

NADEAU, J.H., ARBUCKLE, L.D. & SKAMENE, E. (1995)- Genetic dissection of inflammatory response. *J. Inflamm.,* **45**: 27-48.

PARRISH, C.R. (1992)- Emergence, natural history and variation of canine parvovirus type 2, feline panleukopenia virus, and mink enteritis virus. *Virology,* **72**: 267-278.

PASTORET, P.-P. (1984)-La question de anthropozoonoses d'origine virale. *Bulletin et Mémoires de l' Acad. R. de Méd. De Belgique,* **139**: 205-217.

PASTORET, P.-P. (1990)- La réceptivité aux infections d'origine virale. *Ann. Méd. vét.,* **134**: 291-299.

RUMYANTSEV, S.N. (1992)- Observations of constitutional resistance to infection. *Immunol. Today,* **13**: 184-187.

SHELWOOD, R., GIBBONS, R.A. & JONES, G.W. (1975) – Adhesion of enteropathogenic *Escherichia coli* to pig intestinal brush borders: the existence of two phenotypes. *J. Med. Microbiol.,* **8**: 405-411.

SKAMENE, E., GROS, P., FORGET, A., KONGSHAVN, P.A.L., ST CHARLES, C. & TAYLOR, B.A. (1982)- Genetic regulation of resistance to intracellular pathogen, *Nature*, **297**: 506-509.

SMITH, H. (1991)- The influence of the host on microbes that cause disease. *Proc. R. Soc. Lond.,* **246**: 97-105.

STEAR, M.J. & MURRAY, M. (1994)- Genetic resistance to parasitic disease: especially of resistance in ruminants to gastrointestinal nematodes. *Vet. Parasitol.,* **54**: 161-176.

TEMPLETON, J.W., SMITH, R. III, & ADAMS, L.G. (1988)- Natural disease resistance in domestic animals. *J. Am. Vet. Med. Assoc.,* **192**: 1306-1315.

TRATSCHIN, J.P., MCMASTER, K., KRONAUER, G., & SIEGL, G. (1982)- Canine parvovirus relationship to wild-type and vaccine strains of feline panleukopenia virus and mink enteritis virus. *J. gen. Virol.,* **61**: 33-41.

TUOMANEN, E.I., NEDELMAN, J. HENDLEY, J.O., & HEWLETT, E.C. (1983)-Species specificity of Bordetella adherence to human and ciliated respiratory epithelial cells. *Infect. Immun.,* **42**: 692-695.

VAN EDEN, W., GONZÁLEZ, N.M., DEVRIES, R.R.P., CONVIT, J. & VAN ROOD, J.J. (1985)- HLA-linked control of predisposition to lepromatous leprosy. *J. Infect. Dis.,* **151**: 9.

WASSON, D.L., WAKELIN, D., BROOKS, B.O., KRCO, C.J. & DAVIS, C.S. (1984)- Genetic control of immunity to *trichinella spiralis* infections in mice. Hypothesis to explain the role of H-2 genes in primary and challenge infections. *Immunology,* **51**: 625-631.

YOUNG, A.T., BATES, P. & VARMUS, H.E. (1993)- Isolation of a gene that confers susceptibility to infection by subgroup A avian leucosis and sarcoma viruses. *J. Virol.,* **67**: 1811-1816.