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SPECIAL ARTICLE

The origin of major human infections and the crucial role of person-to-person spread

INTRODUCTION

In discussions of the origin of new infectious diseases, prominence is usually given to dramatic infections acquired from animals (Lassa fever, Marburg and Ebola viruses) or from the environment (legionellosis). But these infections do not spread from human to human, and their impact on mankind can never be catastrophic. If a new infectious agent is to pose a major threat to the human species, it will need to kill tens or hundreds of millions of people over a short period of time (a few years), before vaccines and antimicrobial agents can be developed or effective blocks to transmission established. The 1918 influenza pandemic (total deaths about 20 million) almost came into this world-shaking category, but many of the deaths were presumably due to secondary bacterial pneumonia and this was the pre-antibiotic era. A similar airborne pandemic occurring today could spread globally within weeks by air transport and would have a greater impact. Smallpox arose long before the world became one from an infectious disease point of view, and although it caused devastating epidemics it did not have the opportunity to develop into the 'major threat' category. A significant proportion of people recovered, less virulent strains of virus (variola minor) appeared, and an effective vaccine not only kept it under control in many continents but finally eliminated it from the world. The plague (*Yersinia pestis*) influenced the course of history in Asia and Europe [1] but even in its respiratory form could not in those days be transferred rapidly from continent to continent.

Human immunodeficiency virus (HIV), at least in its present form, is not destined to be in this 'major threat' category. The incubation period is lengthy and spread is slow, antivirals and vaccines are being developed, and effective blocks to transmission are already available. Its human impact, especially in subsaharan Africa, will continue to be massive, but it will eventually settle down in our species as a notable infection but (like plague or syphilis) one that can be controlled and prevented. However, HIV differs from earlier pestilences because of the influence of modern human society as well as science on the course of the epidemic. Communications and the media have made people aware of the method of transfer and the steps they themselves can take to avoid infection. Also, our scientists, after unravelling the virological phenomena with unprecedented rapidity, are discovering useful antiviral agents and vaccines.

This article is prompted by a belief that any new infections that post a major threat to the human species may well come from animals, and will need to have acquired the capacity for efficient and direct spread from human to human. This capacity for transmission is crucial and deserves careful consideration. In focusing on transmission we first have to distinguish it from virulence, then we must ask

Table 1. *The origin of new human infectious agents*

Source	Mechanisms	Examples
Pre-existing human microbes	Genetic changes in microbe	New strains, species of: enteroviruses, rhinoviruses, influenza viruses, papillomaviruses, streptococci, chlamydiae
Mammal, bird	Direct contact with human	Psittacosis, rabies.
	Indirect contact via milk, water, food, etc.	Brucellosis, tuberculosis, Lassa fever, leptospirosis, etc.
	Transfer to humans via biting arthropod	Bubonic plague, trypanosomiasis
	Genetic recombination between virus strains infecting birds and humans	Pandemic influenza [2]
Arthropod	Primary tyransovarial cycle in arthropod, transfer to various mammals via blood feeding	Certain rickettsial infections? Colorado tick fever virus?
Environmental microbes	New opportunity to infect humans	Legionella (air conditioning); environmental mycobacteria (immunodeficient patients); cholera (possible origin fresh water bacteria); listeriosis
Lower vertebrates, invertebrates, plants	Transfer via direct contact (turtle, fish) or bite (lizard, spider, etc.) or ingestion (plants)	Turtle or other reptilian source of salmonella, fish source of *Erysipelothrix rhusiopathiae* (erysipeloid)
		No examples known from lizards, spiders, etc.
		No examples known from plants
Laboratory manufacture	Accidental or (more likely) genetic engineering	Recent H1N1 influenza (accidental)?
Outer space	Comet brings microbe to earth; infectious mist descends to human level	Influenza? [3]

questions about pathogenesis, with emphasis on actual quantities of microorganisms shed from the body. We need to know about genetic factors in the microorganism that determine pathogenesis. We must also consider the transmission of infectious agents from other vertebrates and from invertebrates to humans, and this is something that comes more naturally to parasitologists than to microbiologists

THE ORIGINS OF HUMAN INFECTIONS (TABLE 1)

Origin from pre-existing human microbes

Existing human infectious agents, as they evolve, are constantly giving rise to new types or strains. This is especially true for microbes infecting the surface epithelia of the body, where under the pressure of antibody, antigenic variants are

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continually emerging. New varieties of *Streptococcus pyogenes*, new types of *Chlamydia trachomatis*, new enteroviruses, new rhinoviruses, new papillomaviruses and influenza viruses arise under these circumstances. It is a general rule that microbes whose pathogenesis requires them to spread systemically through the body, invading different tissues, overcoming different host defences, show less dramatic variation. Presumably their ability to traverse a complex pathogenic pathway is readily affected by small genetic changes and in a given host this acts as a restraining force on the production of genetic variants. Variants are seen but these are often based on geographic separation rather than on diversification within a given host population. Thus, it is possible to distinguish different geographical strains of rabies virus by monoclonal antibodies [4], strains of *Mycobacterium tuberculosis* by phage typing [5], and strains of herpesviruses by restriction enzyme analysis [6, 7]. Apart from this, systemic infectious agents such as measles, rubella, mumps, typhoid, syphilis, hepatitis A and B, may show minor variations but tend to be monotypic in the sense that infection with a given strain confers resistance to other strains.

Origin from mammals, birds, arthropods

Infectious agents of all types come to humans from infected mammals and birds, either directly or via biting arthropods. Many of them are from domestic animals, for instance toxoplasmosis from cats; rabies, leptospirosis and leishmaniasis from dogs; brucellosis and Q fever from cattle; Rift Valley Fever from sheep, cattle, camels. Some are from animals that are not domesticated but share human living quarters, such as lymphocytic choriomeningitis and rickettsialpox from mice, and murine typhus and bubonic plague from rats. Others, however, are from less frequently encountered animals whose infectious agents are given occasional opportunities to infect humans, either directly or via biting arthropods. These include the various haemorrhagic and encephalitic fevers (e.g. Japanese encephalitis) acquired from ticks and mosquitoes that have previously fed on infected mammals or birds. Also included are infections such as Lassa fever (African bush rat), Bolivian hemorrhagic fever (Bolivian bush mouse), tularaemia (rabbits, muskrats), Lyme disease (deer), Colorado tick fever and hantaan virus infections (rodents), yellow fever and monkeypox (monkeys), rabies (wolves, vampire bats), and Chaga's disease (armadillos, opossums).

A few infectious agents possibly evolved primarily in certain species of biting arthropods in which they were maintained by vertical (transovarial) transmission. If excreted in the arthropods saliva (or faeces) such agents are regularly given the opportunity to infect the vertebrate host. Some of the rickettsial infections of humans were perhaps derived from gut commensals of arthropods in this way. It is often difficult to assess the importance for the infectious agent of the transovarial cycle in the arthropod in relation to the cycle in the vertebrate host. But the transovarial cycle, although often invoked to explain 'overwintering', presumably arose as a basic adaptation for microbial survival.

It is a striking feature of all these infections derived from animals that under natural circumstances they are *not transmitted from human to human*, or transmitted with low efficiency. The infection cannot be maintained in the human species. Pandemic strains of influenza A virus are an exception, but this is not

surprising because many influenza A viruses are already human and adapted to transmission between humans.

Origin from environmental microbes

There is no doubt that new infections can come from environmental microbes. The causative organism of Legionnaires' disease had its origin in the various species of legionella bacteria that inhabit fresh water. Their close association with free-living amoebae has provided an evolutionary training ground for resistance to intracellular killing following phagocytosis. When present in water used in air-conditioning systems they are suspended in droplets and are given the opportunity to reach the human lung by inhalation. Here, after phagocytosis by alveolar macrophages, they survive and multiply and cause pneumonia. Legionnaires' disease, however, like the infections derived from animals, fails to spread from human to human.

The list of environmental microbes that can at times act as infectious agents for humans has been extended as a result of the survival of patients with major deficiencies in antimicrobial defences. Certain normally innocuous microbes (e.g. *Serratia marcescens*, *Acinetobacter* species, *Mycobacterium kansasii*) can act as 'opportunist' pathogens under these abnormal circumstances.

Listeria are environmental bacteria, carried in the gastrointestinal tract of a wide variety of animals because they are often eaten with food. They are perhaps in the process of establishing more regular infections in the human species. It seems likely that *Vibrio cholerae* also arose from an environmental source. Many closely related bacteria inhabit fresh and sea waters.

Origin from lower vertebrates, invertebrates, plants

I have listed possible origins from lower vertebrates, invertebrates and plants because this has always been a possibility. Certain arthropod-borne viruses in the USA are known to infect snakes [8] and there are several viruses (Ebola, Marburg) whose natural origin is unknown and might well be in this category. Certain groups of viruses can infect a wide variety of species; for instance different Birnaviruses infect insects, molluscs, fish and chickens.

Even plants should be considered. There are viruses (arboviruses) that infect both vertebrates and invertebrates. There are also viruses that infect both invertebrates (leaf hoppers, aphids) and plants. The fact that so far none have been found to infect both vertebrates and plants may be because there have been no thorough checks or because it is a possible but unusual occurrence. Could delta hepatitis virus, with a genome smaller than any known animal virus, and a structure and replication cycle similar to the plant satellite viruses [9] have arisen in this way?

Origin from laboratory

New human infections could theoretically arrive from microbes engineered in laboratories. This has been a constant cause for concern since the development of genetic engineering. Although a new human pathogen could conceivably arise in this way accidentally, it would take a well thought out programme of research and development to deliberately engineer a successful pathogen. It could be done, but

in view of the probably greater opportunities for human destruction by the agents of chemical warfare the forces of evil would be unlikely to undertake the more daunting task of constructing a new infectious pathogen, which would, moreover, remain as a permanent threat to human beings after its release.

Origin from outer space

To complete the list I have included Hoyle's idea about the origin of viruses from outer space. It seems a fantasy, but it has been seriously proposed by a professional scientist [3].

RESPIRATORY INFECTIONS AS THE PRINCIPAL THREAT TO THE HUMAN SPECIES

If the microbe is to spread rapidly and infect most human beings the exact route of transmission is of key importance. Of all the routes of transmission the respiratory and salivary routes are the ones that seem least amenable to effective control. Faecal or oral infections can be reduced to acceptable levels by safe sewage disposal and water supplies, sexually transmitted infections by mechanical prophylaxis (condoms) and reduction in promiscuity, blood-borne infections by attention to needles, blood transfusions, intravenous drug abuse, and the zoonoses by control of infection in animals. Continued spread of respiratory infections in contrast, seems inevitable in crowded human communities. Acute respiratory infections as a group stand at the top of the world list as causes of death [10]. Respiratory spread is unique. Material from one person's respiratory tract can straight away be taken up fresh and unchanged into the respiratory tract of other individuals, in striking contrast to material expelled from the gastrointestinal tract. Given a few minutes in a crowded room, the infected individual can readily transmit microorganisms to a dozen others, a feat that is out of the question for the sexual or faecal–oral routes.

Control of air circulation is possible, for instance by laminar flow systems in high risk areas in hospitals, but this is expensive and 'air sanitation' seems an impossible dream under most circumstances.

Acute respiratory infections also pose major obstacles for control because of the great diversity of causative agents involved. New types are constantly appearing in the evolutionary hothouse provided by dense human populations and these agents are likely to remain a step ahead of traditional vaccines or antimicrobial agents.

It is true that in developed countries respiratory tuberculosis has been brought under control. This was initially because of improved housing and nutrition which decreased transmission and increased individual resistance, and later because of effective antitubercular agents and a vaccine. But respiratory tuberculosis is a rather slowly evolving disease with strong genetic determinants in host susceptibility. Over the centuries genetically susceptible individuals have been weeded out and the impact on humanity, while severe, has never been catastrophic.

Infections acquired only by direct or indirect contact with animals can never be a major threat to humanity. Without the capacity for transmission between

humans, they will remain episodic or localized. Although serious and sometimes lethal outbreaks are possible as with Ebola virus in Zaire and South Sudan in 1976 [11], or yellow fever outbreaks in Central America, the bulk of mankind stays unaffected. But such infections have at times caused major epidemics, especially in the days when lice (typhus) and rats (plague), were almost universal human associates. And in mosquito-ridden lands, plasmodia, in particular, continue to take a heavy toll of human life and health. This burden, surely, will slowly be reduced by relentless pressure applied at all stages of the parasite life-cycle. *Yersinia pestis* provides an interesting example, because its explosive spread in the form of pneumonic plague was associated with development of direct respiratory transmission between individuals.

Therefore, when a new human infection arises its chance of rapidly colonizing the entire species are greatest if it spreads by the respiratory route. Of course, it may or may not be pathogenic. The highly successful rhinoviruses, like most of the enteroviruses, spread effectively without posing major disease threats, and most human encounters with bacteria such as *Neisseria meningitidis* and *Mycoplasma pneumoniae* are without serious consequences.

POSSIBLE FUTURE DEVELOPMENTS

The story of myxomatosis in European rabbits in Australia after its successful introduction in 1950 gives a classic picture of the evolution of a novel and lethal infection in a susceptible host [12]. In this case the virus came from a different continent and from a different species of rabbit, in which it caused a harmless infection. Myxomatosis was acutely lethal (> 99% mortality) and, to the delight of Australian farmers, posed a 'major threat' to the rabbit in Australia. However, during the next 10–15 years both rabbit and virus underwent important changes. Not all infected rabbits died, and a genetically resistant population was gradually selected out. Also, strains of virus that were less lethal were selected for and replaced the original ones because they gave greater opportunities for transmission from rabbit to rabbit. If a new human pestilence behaved like myxomatosis it would undoubtedly pose a major threat and kill most humans before settling down to a less pathogenic role as a result of genetic changes in both virus and host.

It is instructive to consider alterations in known infectious agents that could conceivably prove disastrous for the human species. By asking existing infectious agents to do unlikely things one can focus on blocks to transmission between humans. Each infection with Lassa fever virus, Rift Valley Fever virus [13], *Chlamydia psittaci*, or *Rickettsia prowazeki* results from an encounter with an infected animal or arthropod. The disease in humans is sometimes severe, and with Lassa fever [14] (as with Ebola virus infection) there can be limited spread to hospital staff following contact with infected blood or tissue fluids. Yet if any of these microorganisms produced extensive infection of respiratory epithelium, then effective human-to-human transmission and rapid global spread could occur, as with rhinoviruses or measles virus.

Another possibility is that an existing, slightly pathogenic but well-transmitted virus acquires a virulence factor that makes it into a catastrophic infection. For instance, a new pandemic strain of influenza virus that localized and replicated in

cardiac muscle (a rare event at present) could have a devastating effect on the human species.

In these theoretical examples, transmission is greatly enhanced if the individual becomes infectious and then behaves more or less normally for days or weeks, rather than becoming seriously ill at an early stage of the infection. This gives more opportunity for the infection to spread through the community during the individuals normal movement and activities. Obviously a new respiratory infection that became infectious for others only after the infected individual had been admitted to hospital would be less serious than one in which the patient coughed and sneezed in the community for several days before becoming ill. In the same way a sexually transmitted infection would be a complete failure if the infected individual felt ill just when the microorganism was being shed from the sites of infection.

THE NATURE OF THE HUMAN-TO-HUMAN BLOCK

The striking inability of the human infections derived from animals (mammals, birds, arthropods) to spread effectively from human to human has been referred to. There is also an inability of infections recently derived from an environmental source (legionellosis, listeriosis) to spread from human to human. What is the nature of the block? This is of fundamental importance in considering the possible source of new infections that could conceivably arise and be a serious challenge to human survival.

The block in terms of pathogenesis

The key factor is the ability to reach and replicate in the respiratory tract. In the case of Lassa fever, for instance, the virus does replicate in the pharynx, but presumably the titres are too low for effective transmission. Actual amounts of a microorganism shed are prime determinants for transmission, as argued elsewhere [15]. For instance, the release of a few hundred infectious units per microlitre of respiratory secretions may mean a failure in transmission, whereas the release of more than 10^4 infectious units per microlitre could ensure transmission.

Infectious agents that are effectively transmitted by the respiratory route must either infect by this route and then spread locally (rhinoviruses, influenza virus) or alternatively invade the respiratory tract after first causing a systemic infection, as with measles. In the latter case initial respiratory infection takes place without local multiplication and damage, the virus reappearing in the respiratory tract at a later stage after multiplying elsewhere in the body, and then being seeded out from the blood onto respiratory surfaces.

Primary infection in the respiratory tract, with local spread and replication is not difficult to understand. We know much less about the mechanisms, or indeed the events, that take place when respiratory infection occurs as a sequel to systemic infection. The microorganism has a formidable series of tasks. It must gain entrance into the blood, localize and multiply in distant target organs or tissues, reappear in the blood in large enough amounts and for long enough to localize in the naso-pulmonary vascular bed, then reach and finally replicate in respiratory epithelium. All the time, host defences must be evaded or avoided.

The pathogenetic factors determining localization in target organs and tissues

have been discussed recently [16]. Microorganisms may have tropisms that are not normally expressed. Rotaviruses, for instance, although generally restricted to enterocytes are evidently capable of growth in hepatocytes to cause hepatitis [17]. It is perhaps asking too much for an established microorganism such as yellow fever virus, malaria or typhus to undergo a complete change in nature and invade respiratory epithelium. But for microorganisms such as *Chlamydia psittaci*, *Coxiella burnetii*, or *Legionella pneumophila* the prospect seems less remote. Instead of infecting interstitial tissues or alveoli in the lung the infectious agent would need to spread locally and replicate extensively in respiratory epithelium, and there would be rapid selection of microbial variants that were effectively transmitted in this way. It has long been known that *Chlamydia psittaci* is occasionally transmitted from patients to nurses, presumably by the respiratory route, and some strains cause ocular infections in humans. *Chlamydia trachomatis*, on the other hand, focuses on urethral and conjunctival epithelium, although sometimes invading the respiratory tract of neonates. One of the chlamydia, *Chlamydia pneumoniae* strain TWAR, has already achieved regular transmission from human to human and occurs throughout the world as a common cause of pneumonia [18].

There is always the possibility that transmission between humans is determined not merely by the tropism of the microorganism or by the titres reached in infected tissues, but by unrelated factors. For instance, it seems highly probably that HIV arose from a similar virus infecting primates in Central Africa. Various HIV-like retroviruses have been described, including chimpanzee viruses [19]. Initial infection of an occasional human following direct contact with an infected primate may have caused sporadic AIDS, which would have passed unnoticed, the virus not being transmitted from human to human, as is usual in infections derived directly from animals. However, the spread of sexually transmitted disease in these Central African communities, perhaps as a result of socio-economic upheavals and migrations, meant that genital ulcers and discharges became common. Until then, the virus, present in infected leucocytes, had not been present on the genital tract in adequate titres for transmission. Now it appeared in larger amounts and was effectively transferred as a new sexually transmitted disease, especially if the partner, also, had genital lesions. No change in the virus was needed for this to take place but once it had established itself as a human-to-human infection, it could undergo further genetic changes as it adapted to the new host. Perhaps the heterosexual transmission of hepatitis B is promoted in a similar way by genital lesion [20].

FINAL COMMENTS

When a microorganism from an arthropod or from another vertebrate infects man and then has the ability to be transmitted between humans, a new evolutionary future unfolds. It can now adapt to humans, undergoing genetic alterations, becoming more efficient in spreading and maintaining itself in the human species, losing the multiple genetic features that had enabled it to infect, spread, and multiply in the original vertebrate or arthropod.

For most of this discussion I have referred to respiratory infections and

respiratory transmission. Important, although less catastrophic infections could arise if, for instance, microorganisms that already appear in the blood in large enough amounts and in suitable form for them to be transmitted between humans, began to behave like hepatitis B, hepatitis C or HIV. Yellow fever virus, malaria, and many other arthropod-borne infections could theoretically be transmitted in this way. The block here is that the infected individual would not only have relatively short periods of viraemia or parasitaemia, but would rarely feel well enough to engage in the necessary activities (intravenous drug abuse, sexual intercourse) for transmission to others. In other words, the infectious agent would need to persist in the blood after recovery from the acute illness. It is not out of the question that hepatitis C is descended from an arthropod-transmitted flavivirus.

A final example is provided by the recent appearance in England of the disease bovine spongiform encephalopathy (BSE) [21]. In animals, the atypical infectious agents of the scrapie group appear to be primarily infections of sheep and goats, in which species they are transmitted from individual to individual by infected placentas or infected pastures. So far nearly all infections seen in other non-human species (mink, cows, cats, zoo antelopes) have been derived from infected sheep. Also in these 'unnatural' species there is a failure of transmission from individual to individual, although the disease in mink, like Kuru, can be transmitted by cannibalism. The origin of the almost identical agents causing Creutzfeld–Jakob disease and Kuru in man, however, is unknown. So far the evidence is against an origin in sheep or goats, and transmission from human to human, other than as a result of certain iatrogenic procedures (corneal grafts, use of stereotactic electrodes in brain surgery, injection of contaminated growth hormone), has not been demonstrated. Kuru, possibly originating from Creutzfeld–Jakob disease, was transmitted among the Fore tribe in Papua, New Guinea in association with cannibalistic practices. No one born since the cessation of cannibalism in 1957 has developed Kuru, and none of the hundreds of affected females transmitted the condition to their children.

Much of our thinking about the scrapie group of infectious agents comes from observations on experimentally infected mice and hamsters. After extraneural infection there is a stage of replication of the agent in lymphoreticular tissues, followed by invasion of the central nervous system, probably via peripheral nerves. It is conceivable, as suggested elsewhere [22], that the infectious agent causes a common but extraneural and asymptomatic infection, and is spread readily between humans, perhaps via saliva, faeces or urine, with neural invasion and disease as a very uncommon sequel. This would be a picture similar to that seen with poliomyelitis. Unfortunately, the agent is very difficult to isolate and no immune response to infection have been detected, so that the incidence of infection in human beings has never been established. If spread between humans did occur in this way, and was similar to the spread between naturally infected sheep, it might depend on replication of the agent in gut-associated lymphoid tissues. The block to the spread of scrapie itself between mink, cows, cats, etc. after infecting these species could be a failure of adequate replication in gut-associated lymphoid tissue or other extraneural tissues.

The best strategy for avoiding and combating a major infectious threat to

mankind is to maintain continued epidemiological alertness at a global level, to provide early warning of possible threats. This must be coupled to continuing intensive study at the basic level of infectious agents of humans, of other mammals (especially primates) and of birds. Scientists should focus on the molecular and genetic basis of that neglected property, transmission, as well as on pathogenicity.

Heightened surveillance, and increased basic understanding of infectious agents (especially viruses) will lay the foundations for rapid scientific and social responses to any new pestilence that arises and threatens our species.

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