Fighting the Ebola virus

Dennis R. Burton and Paul W. H. I. Parren

A vaccine that protects monkeys against a lethal dose of Ebola virus has been developed. But there is still a lot to learn about how this vaccine works before a version that can protect humans is available.

Perhaps no infectious agent is more associated in the modern consciousness with rapid and terrifying consequences than the Ebola virus. Regular outbreaks in Africa, together with appearances in literature and the cinema, have kept the virus in the public eye. Frequently, news reports heighten apprehension, speaking of a disease with no cure and no vaccine. Effective measures to prevent or control infection with this virus are sorely needed. On page 605 of this issue[1], Sullivan and colleagues describe a vaccine that protects monkeys against a lethal dose of Ebola virus. There's still some way to go before a human vaccine is available, but this is a step in the right direction.

Ebola virus and its lesser known cousin, Marburg virus, belong to a family called the filoviruses[2,3]. These viruses cause haemorrhages and fevers, and are characterized by very high mortality rates, causing death in 80–90% of cases in some outbreaks. Ebola virus is transmitted through direct physical contact with infected individuals. High concentrations of virus particles are found in bodily fluids and in the skin, and the virus can be passed on through a handshake and possibly as an aerosol, through coughing and sneezing. About a week after exposure to the virus, patients become ill with influenza-like symptoms accompanied by vomiting and diarrhoea. The second phase of the illness is characterized by haemorrhages, with blood oozing from mucosal surfaces such as the gums and nose. Death usually results from shock, typically about ten days after the start of symptoms. The 'liquefaction' of internal organs sometimes attributed to the virus is fictional.

Ebola virus emerged in the African rainforest in 1976 from an unknown natural reservoir, presumed to be an animal. It caused two outbreaks at the time (Fig. 1), one in Sudan and one in the northern part of the Democratic Republic of Congo (DRC, then Zaire). The strain involved in the latter outbreak re-emerged, with an almost identical genetic make-up, nearly 20 years later some 600 miles away in the southern part of the DRC[4]. And, as we write, the Sudan strain has re-emerged to cause an outbreak in the north of Uganda[5]. Ebola virus has also caused outbreaks in Gabon and has been identified in monkeys in the Philippines.

Typically, these outbreaks flared up suddenly, probably as a result of a single transmission event from the natural reservoir to a human, and were rapidly contained. Early detection of infection and isolation of patients, as well as community education, were particularly effective in halting the spread of the virus in such outbreaks[6]. But an outbreak of Marburg virus with high mortality (more than 80% of infected patients have died) has been ongoing in the Durba area in the north of the DRC for several years now, apparently involving repeated transmission of the virus from its natural reservoir to humans (S. T. Nichol and R. Swanepoel, personal communication). Such repeated transmission may represent a disturbing development in the relationship between humans and filoviruses.

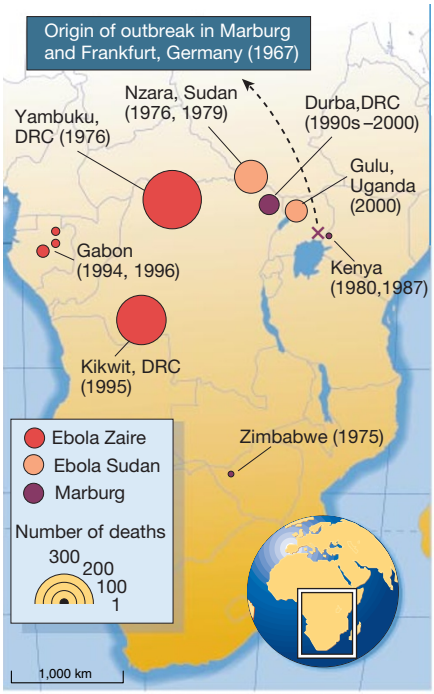

Figure 1 **Lethal outbreaks of filovirus infection. The first outbreak of haemorrhagic fever caused by a filovirus (Marburg virus) originated in Uganda (marked by a cross) but occurred in 1967 in Germany, with fatalities in Marburg and Frankfurt. A few isolated cases of haemorrhagic fever caused by Marburg virus were recognized in the 1970s and 1980s in Zimbabwe and Kenya. An outbreak with a high per-case fatality rate is ongoing in the area surrounding Durba, Democratic Republic of Congo (DRC). Haemorrhagic fever caused by the other filovirus, Ebola virus, was first recognized in 1976 in two simultaneous epidemics in the DRC and Sudan. Two different subtypes, Ebola Zaire and Ebola Sudan, were involved. A second large epidemic of Ebola Zaire occurred in the south of the DRC in 1995. There is currently an Ebola Sudan epidemic in the Gulu district of Uganda. As of late November 2000, over 300 cases and 100 deaths had been reported there[5]. A total of about 1,100 people are known to have died from filovirus infection.**

Vaccination has been our most powerful antiviral strategy to date. But anyone hoping to develop a vaccine against Ebola virus has some substantial obstacles to negotiate. A vaccine that consists of a killed or attenuated (weakened) virus is unlikely, for safety reasons, to be accepted by health bodies or the public. Moreover, any vaccine must be tested under rigorous Biosafety Level 4 conditions, which require special facilities and are expensive.

Sullivan *et al.*[1] have tackled the problem by developing a new vaccine strategy. First, they vaccinated animals with DNA encoding Ebola virus proteins (DNA immunization) — according to dogma, this type of vaccination most effectively elicits protection based on cellular immunity. Then, the immune response to these proteins was boosted with an attenuated form of a virus that normally causes colds but had been engineered to express Ebola virus proteins (adenoviral-vector immunization). Adenoviral-vector immunization is effective in inducing protective molecules called antibodies, as well as cellular immunity. Many vaccinologists think that a vaccine that elicits both types of immune response is likely to give the best results.

Having shown that their strategy was effective in protecting guinea-pigs against challenge with a rodent version of Ebola virus, the authors turned to monkeys, which can be infected directly with human strains of Ebola virus and show a clinical course similar to that seen in humans. Dramatically, whereas control animals succumbed in a matter of days following infection, vaccinated monkeys were protected and did not get sick. Moreover, three out of four of the vaccinated animals did not show any evidence of virus replication.

Does this mean that we now have in hand

a human vaccine for Ebola virus? The short answer is no, not yet. For example, Sullivan *et al.* infected the monkeys with relatively small amounts of virus, equivalent in human terms to only a few nanolitres of blood from an infected person[7,8]. True, this amount of virus did lead to the deaths of the unvaccinated monkeys, but previous studies have shown that antibody preparations that protect against low doses of virus may be ineffective against higher doses[9,10]. It will be crucial to know whether the vaccine strategy can protect against more substantial challenge. Also, Sullivan *et al.* did not identify the immune mechanism of protection (antibody, cellular or both), and this may be important in guiding further vaccine development. Nevertheless, coupled with earlier findings that monkeys can be protected against high doses of Marburg virus by a vaccine based on a modified alphavirus construct[11], it seems hopeful that human vaccination against filoviruses will be achieved.

Who will benefit from a vaccine for Ebola or Marburg viruses? The obvious answer is the local population in an outbreak area, and the medical and support personnel travelling there. In reality, however, funds are likely in the first instance to be directed towards surveillance, hygiene and barrier-nursing methods, which can be highly effective in containing an outbreak[6]. An immediate benefit of a vaccine will be to increase the margin of safety for those studying the viruses, permitting more research into the control of infection. One such aspect of research is the search for the natural reservoirs of the filoviruses.

Finally, some have rightly raised concerns about the amount of effort spent studying Ebola and Marburg viruses, given that they affect relatively few people compared with the major pathogens in Africa, such as HIV and malaria. But our ability to predict developments in our struggle with microbes is limited. We may yet encounter more dangerous versions of the existing filoviruses, or even new ones. To be prepared, by learning how to control those viruses that are here now, is only prudent. ■

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Superconductivity

C_{60} — the hole story

Olle Gunnarsson

Superconductivity has been demonstrated at a surprisingly high temperature in a C_{60} solid, raising questions about its electronic properties and hopes of even higher temperatures to come.

The sudden drop in electrical resistivity at low temperatures that characterizes superconductivity was first seen in fullerenes such as C_{60} nearly a decade ago. By introducing electrons into the carbon lattice, fullerenes can become superconducting at temperatures up to 40 K. As reported by Schön *et al.* on page 549 of this issue[1], it turns out that superconductivity can be achieved at even higher temperatures if positively charged 'holes' are introduced instead of electrons.

Almost a century has passed since Kamerlingh Onnes unexpectedly discovered superconductivity when he noticed that mercury's resistivity abruptly dropped to zero at 4 K. Ever since then, this field has been an active area of research, resulting in two Nobel prizes in 1972 and 1987. Early ideas about conventional superconductivity culminated in a theory put forward by Bardeen, Cooper and Schrieffer (BCS) in 1957. In the BCS theory, the interaction of conduction electrons with tiny vibrations of the crystal lattice (phonons) leads to an attraction between the normally repulsive electrons so that they can pair up and flow without resistance.

Over the same period, experimentalists were searching for superconducting materials with higher transition temperatures, T_c, below which a material is superconducting. But progress was slow, and after a T_c of 23 K was reached in 1973, no further increase was achieved for 13 years (Fig. 1). This led to a lively discussion[2,3] about whether 23 K was close to some theoretical upper limit to T_c.

This all changed in 1986, when superconducting copper-oxide materials were discovered[4]. The maximum T_c was quickly pushed up to well over 100 K. Unlike most earlier superconductors, the copper oxides are normally insulators rather than conductors, and charge carriers have to be introduced into the material by chemical doping before they can become superconducting. It was soon accepted that superconductivity in the copper oxides is not primarily due to a phonon mechanism, as in conventional superconductors, but to an electronic mechanism, the nature of which is still under debate. So the high transition temperatures found for the copper oxides do not rule out the possibility of a maximum T_c for phonon-driven superconductors.

Coincidentally, in 1985, chemists discovered a new form of carbon[5] — known today as buckyballs or fullerenes. Like the copper oxides, crystalline C_{60} is normally an insulator, but can be made metallic by chemical doping. In normal C_{60} there are no charge carriers because the energy bands in its electronic structure are either completely filled or completely empty. To create a metal, the conduction band has to be partly filled with electrons (electron doping) or the valence band has to be partly emptied (hole doping). In 1991 it was found that adding alkali atoms to C_{60} crystals leads to charge transfer from the alkali atoms to C_{60} — that is, electron doping. Such alkali-doped compounds (A_3C_{60}) can become 'metallic'[6] and, at low temperatures, superconducting[7,8].

The superconductivity in A_3C_{60} is thought to be due to an interaction between electrons and phonons. The strength of this interaction is one of the factors that determine the value of T_c. Modifying the crystal

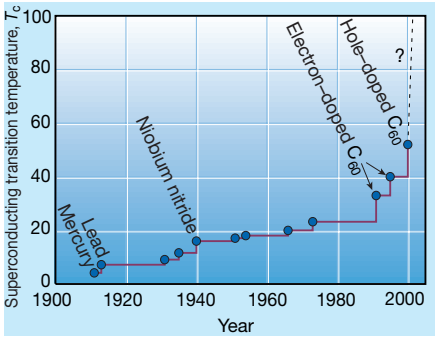

Figure 1 **The maximum transition temperature, T_c, for which superconductivity has been found in conventional superconductors over the past century. It is assumed that C_{60} superconductivity conforms to this standard phonon-driven mechanism, in which tiny lattice vibrations (phonons) provide the glue that binds electrons into superconducting pairs. Electron doping of C_{60} crystals, and now hole doping of C_{60} by Schön *et al.*[1], have allowed phonon-driven superconductors to reach much higher transition temperatures.**