Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Treatment of SARS with human interferons

Sir—We agree with J Cinatl and colleagues (July 26, p 293) that effective antiviral agents are urgently needed to treat severe acute respiratory syndrome (SARS). On the basis of their results, the authors state that interferons inhibit replication of SARS-associated coronavirus (SARS-CoV) in vitro, with interferon beta being the most potent of those interferons tested. However, we are concerned that shortcomings in the methods used to calculate and interpret their results could have led to misleading conclusions.

First, when comparing the antiviral action of different preparations of interferons, the use of antiviral units of measurement, including international units (IU), might be inappropriate. Different preparations can have different specific activities—ie, IU/mg protein—as in the case of interferon beta (32·108 IU/mg protein) and interferon alfa (2·0–2·4·108 IU/mg protein). Therefore, for instance, the inhibitor concentration (EC50) value in Vero cells of interferon beta is not 62–ie, 6500/105 IU—times higher than the EC50 of interferon alfa, as stated,1 but only nine times—ie, 29·5/3·2 ng; this difference could be clinically relevant in pharmacokinetic and pharmacodynamic terms.

Second, Cinatl and colleagues calculated the selectivity index, a parameter of fundamental importance from a therapeutic viewpoint, without knowing the cytotoxic concentration (CC50) values of the interferons used. In their calculation, a value of more than 10 000 was assumed. However, when the therapeutic efficacy of different drugs is compared, this assumption might be incorrect: higher than 10 000 might mean 10 001 IU, for example, for interferon beta and 100 000 IU, for example, for interferon alfa. Although such wide variations in the values are highly unlikely, they would imply indirectly that interferon alfa, which has a lower antiviral activity, is more interesting from a therapeutic viewpoint than interferon beta because the selectivity index for interferon alfa is higher.

Finally, the antiviral action of interferons against a specific virus is usually, historically, measured by back titration of the viral yields when the interferon is added some 18–24 h before virus adsorption. The addition of interferon before and after virus infection does not allow a direct comparison of the sensitivity of SARS-CoV with that of other animal viruses, including human coronaviruses. Cinatl and colleagues have undoubted merit in having addressed promptly the issue of antiviral action of interferons against SARS-CoV. We consider, however, that their calculations could have been made and their general conclusion—that only interferon beta can be used as an antiviral agent after infection—might have been drawn with undue haste, which has led to errors.

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1 Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. Lancet 2003; 362; 293–94.

Authors’ reply

Sir—Guido Antonelli and colleagues are right to point out that different interferon preparations, including those we used, can have different specific activities (IU/mg protein). In clinical practice this difference can be important in pharmacokinetic and pharmacodynamic terms, since interferons with high specific activity can be used at low protein concentrations relative to interferons with low specific activity. However, our data based on the use of IU/mL suggest that even in the case of application of same protein concentrations interferon beta (specific activity 3·2·108 IU/mg) would be better than interferon alfa (2·4·108 IU/mg) in terms of antiviral activity.

To directly address this point we tested different preparations of interferon alfa and interferon beta in Vero cells infected with SARS-CoV. The results (not presented in our research letter) showed higher antiviral potency for interferon beta than for interferon alfa independent of specific activity—ie, interferon beta-1a has a specific activity (2·108 IU/mg) similar to interferon alfa-2b, but its antiviral activity was about 40 times higher.

The differences in antiviral activity of both type 1 interferons could result from their ability to differentially influence expression of cellular genes important for antiviral activity. For example, when the human fibrosarcoma cell line HT1080 is treated with 10 000 IU/mL of type 1 interferons, more than 20 genes, including double-stranded RNA-activated protein kinase, are induced by interferon beta but not by interferon alfa.

Antonelli and colleagues also argue that selectivity index as a parameter for therapeutic efficacy cannot be ascertained without knowing cytotoxic concentrations (CC50) of the interferon used. 10 000 IU/mL was the maximum concentration we tested, since higher concentrations of interferons are probably not achievable in the infected cells of patients. CC50 value higher than 10 000 simply means that antiviral effects in our culture system are not due to non-specific toxic effects. Our initial experiments were undertaken with a range of concentrations that are commonly used in in-vitro investigations. In additional experiments done by us, interferon concentrations up to 100 IU/mL were used without increased toxicity of interferon beta versus interferon alfa in confluent layers of Vero cells.

In conclusion, these results do not lend support to the notion that increased antiviral activity of interferon beta is associated with increased toxicity and thus decreasing of therapeutic index relative to interferon alfa as suggested by Antonelli and colleagues. Treatment of patients with SARS with interferon alfa and restricted use of steroids did not improve clinical symptoms and signs. This finding could be explained at least partly by our observations, indicating an inability of interferon alfa to inhibit SARS-CoV replication when added to cultured cells after virus infection. Therefore, the selective antiviral activity of interferon beta...
justifies its clinical testing in patients with SARS.

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1 Der SD, Zhou A, Williams BR, Silverman RH. Identification of genes differentially regulated by interferon α, β or γ using oligonucleotide arrays. *Proc natl acad Sci USA* 1998; 95: 15623–28

2 Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003; 52: 715–20.

Sir—The results of J Cinatl and colleagues\(^1\) show that interferon beta is effective against SARS-CoV—a membrane-enclosed RNA virus\(^2\)—in vitro, when used either alone or in combination with other antiviral drugs. Their results concur with our beliefs that interferon, with its broad-spectrum antiviral activity against RNA viruses, might be useful in the treatment of SARS, either as a monotherapy or plus ribavirin.

However, the findings of Ozes and co-workers\(^3\) show that the specific activity (antiviral units/mg) of recombinant human interferon-consensus 1 (IFN-Con1) was ten-fold higher than that of interferon alfa-2a and interferon alfa-2b in vitro. Furthermore, IFN-Con1 increases the ability of or induces natural killer cells to kill target cells to a greater extent than does interferon alfa.\(^4\)

Therefore, we suggest that IFN-Con1 and IFN-Con1 plus ribavirin are assessed as potential antiviral drugs for the treatment of SARS with the method used by Cinatl and colleagues.

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**Politics and science**

Sir—In his Correspondence letter (Aug 2, p 404),\(^1\) Mark Robson criticises our incursion into politics in the pages of a scientific journal, castigating our “litany of complaints about US political decisions”.\(^2\) We offer no apology for doing so, modestly continuing what we view as a virtuous tradition in public health that ranges from Virchow’s advocacy\(^3\) for social reform after the typhus epidemic in upper Silesia in the 19th century to, more recently, the activities recognised by the award of Nobel Peace prizes to the International Physicians against Nuclear War and Médecins Sans Frontières.

We wrote our Commentary for two related reasons. First, the policies of the US administration, in many different areas, are having profound and damaging consequences for the health of people worldwide, including that of many Americans. Second, this administration is engaged in a wide-ranging series of activities that will prevent these health effects being documented adequately. Any lingering doubt that we might have been mistaken about its attitude to independent scientific research has been dispelled since we wrote our Commentary by the publication of an important report from the US House of Representatives.\(^4\) The report reveals that what we described was only the tip of the iceberg, cataloguing more than 20 areas in which the administration has sought to interfere with the scientific agenda. It also makes clear that these efforts are not unconnected; each has the effect of advancing the interests of one of two groups. For some, such as abstinence or abortion, religious right-wing constituencies support President Bush. For others, such as global warming or environmental protection, there are important economic consequences for his corporate supporters.

We believe that a core element of public health involves making the often invisible causes of population ill-health visible. That we would remain silent in the face of such threats to population health and academic freedom would, therefore, be inconceivable. History has repeatedly shown the dangers of not speaking out until it is too late.

And should our views be published in *The Lancet*? We believe that a serious medical journal should examine not only the immediate, but also the underlying, causes of disease and premature death, which inevitably involve political issues. However, we also agree with the web editor of the *British Medical Journal*,\(^5\) who has eloquently described how many apparently apolitical decisions such as how much coverage to give to issues like bioterrorism, that are being talked up by politicians for their own reasons, are unknowingly advancing a political agenda. To concentrate on the immediate causes, while ignoring the social and political factors underlying ill health, is itself a political decision. Virchow was right when he said that “politics is nothing but medicine on a grand scale”.\(^5\)

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**Power shutdown and biological standards**

Sir—The August, 2003, power shutdown in vast areas of the northern parts of the USA and in Canada lasted several days. An inadvertent casualty during the shutdown might well have been the biological standards maintained in these areas.

The potency of various biological products for human and veterinary use is expressed in international units rather than in conventional units of weight. Biological activity of these products is standardised against their biological activity when stored under temperature fluctuation. Contents of such ampoules maintain their biological activity when stored without temperature fluctuation. There is every probability that the August, 2003, power shutdown involved electrical appliances used to store such preparations. If so, the...