REVIEW ARTICLE

Drugs & Aging 1999; 15 Suppl. 1: 1-10
1170-229X/99/0001-0001/$05.00/0

A Brief History of Pneumococcal Vaccines

Robert Austrian

Department of Molecular and Cellular Engineering, The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Abstract

Attempts to control pneumococcal infection by vaccination, undertaken initially in 1911, have gone through 3 phases during the subsequent 8 decades. Initially, vaccines of killed pneumococcal cells prepared in a variety of ways were used in epidemic settings with inconclusive results, although administered to approximately 1 million recipients. The discovery that adults injected with small amounts of purified capsular polysaccharide developed antibodies to the homologous capsular type led to the trial of a tetravalent vaccine that showed conclusively its ability to prevent infection by the types represented in it. With the advent of penicillin and other effective antipneumococcal drugs, interest in prophylaxis waned. Interest in vaccination was revived only after demonstration that some segments of the population remained at high risk of death if infected and after the emergence of multidrug-resistant pneumococci. Infants and young children, among whom the incidence of pneumococcal infection is high, respond poorly to purified bacterial polysaccharides but develop satisfactory responses to bacterial polysaccharides when these are linked chemically to a protein. The early results of trials with such polysaccharide protein conjugate vaccines give promise that control of a significant portion of pneumococcal infection in the paediatric population will soon be feasible.

Pneumococcal infections are endemic in all societies throughout the world in which their presence has been sought. Epidemics of pneumococcal infection are less common; they occur most often during outbreaks of viral influenza or as a manifestation of recruit disease in military and industrial populations, or in institutions for the sick and elderly. Among adults, the attack rate of pneumococcal pneumonia in the USA is in the vicinity of 1 to 5 cases per 1000 persons per annum. The case fatality rate of untreated pneumococcal pneumonia was in the range of 30 to 35% before the advent of specific antipneumococcal therapy;[1] and, even since its introduction, identifiable segments of the population in developed countries are at significant risk of a fatal outcome.[2] In addition, pneumococcus is the leading cause of bacterial otitis media and bacterial meningitis in infancy and early childhood, responsible both for significant morbidity and for expenditures for medical care.[3] The foregoing observations, together with the rapid increase during the past 3 decades in the number of pneumococcal strains resistant to antimicrobial drugs, provide strong impetus to the utilisation of prophylaxis as a means of dealing with these significant problems.

The pneumococcus was isolated first by George Miller Sternberg, later Surgeon General of the US Army, from his own saliva in 1880.[4] A year after the publication in 1881 of his initial findings,

Sternberg, who was then working on antiseptics, wrote, 'I can no longer say (that injection of my saliva) infallibly produces death, as in several instances death has not occurred in rabbits which have been previously injected with saliva mixed with certain substances – alcohol, quinine – which when added to it in a certain proportion, prevent the usual fatal results, but do not prevent an impression being made by the mixed injection which seems subsequently to protect the animal from the lethal effects of injection of saliva alone'.[5]

What Sternberg had done, without intent, was to demonstrate that injecting killed pneumococci into a laboratory animal would protect it against subsequent infection with live organisms of the same kind, i.e. he had immunised the animal against pneumococcal infection 4 years before Weichselbaum published his classical report in 1886 showing pneumococcus to be the principal cause of community-acquired bacterial pneumonia.[6]

Several decades were to elapse before any serious effort was made to prevent pneumococcal infection; and, after more than a century, work towards this goal continues. In reviewing the record of the past, it may be useful to look sequentially at 3 generations of pneumococcal vaccines: (i) those composed of whole killed bacteria; (ii) those consisting of purified pneumococcal capsular polysaccharides; and (iii) those made up of capsular polysaccharide-protein conjugates still undergoing development, primarily to prevent pneumococcal infection in the paediatric population.

1. Vaccines of Whole Killed Pneumococci

The first major attempt to control pneumococcal infection by vaccination took place in South Africa early in this century.[7] Gold had been discovered near the site of Johannesburg in 1886, the year that Weichselbaum had established pneumococcus as the major cause of bacterial pneumonia. As the mining industry expanded, large numbers of native Africans were recruited from rural environments and housed in barracks to work in the mines. In this population, the attack rate of pneumonia approximated 100 per 1000 persons per annum and the case fatality rate 25%. The morbidity and mortality of pneumonia were so high as to threaten the continued existence of the mining industry. This circumstance led to the enlistment of the services of Sir Almroth Wright, knighted for his work in the development of typhoid vaccine, in the hope that he might develop an effective vaccine against pneumonia. Wright and three colleagues arrived in South Africa in the autumn of 1911 and initiated a series of experiments involving more than 50 000 miners, half of whom received one or another of several vaccines of heat-killed pneumococci. Wright, who had a marked antipathy to biostatistics, left South Africa before the completion of the trials, leaving them in the hands of a colleague, W. Parry Morgan. In his 1914 publication in the *Lancet*, Wright concluded, '...the comparative statistics which have been set forth above testify...in every case to a reduction in the incidence-rate and death-rate of pneumonia in the inoculated...Where in comparative statistics we find the difference between the inoculated and the uninoculated is after a certain time effaced, this does not necessarily indicate that the immunity of the inoculated is diminishing. We may be witnessing, instead of a descent of the level of the inoculated to the level of the uninoculated, an ascent of the uninoculated to the level of the inoculated. ...We recommend that prophylactic inoculation should...be applied as a routine measure to every native on recruitment'.[8]

The studies of Wright and his associates were analysed by Maynard, statistician of the newly founded South African Institute for Medical Research.[9] He concluded that, although there had been some diminution of the attack rate of pneumonia in the 4 months subsequent to vaccination, there had been no reduction in the death rate associated with that disease.

Maynard's conclusions are, in retrospect, not surprising. Much had been learned about the pneumococcus in the 3 decades since its initial isolations by Sternberg[4] and by Pasteur.[10] In addition to the establishment of the pneumococcus as the commonest cause of community-acquired bacterial

pneumonia in 1886, the protective properties of the sera of animals that had recovered from infection against reinfection with pneumococci of the homologous strain had been shown by the Klemperers,[11] and both the bile solubility of pneumococci and the Quellung reaction had been reported by Fred Neufeld[12,13] at the turn of the century. Intimations of the serological diversity of pneumococcal strains were described by Bezançon and Griffon[14] in 1897, and pneumococcal types 1 and 2 were delineated clearly by Neufeld and Haendel in 1910.[15] No awareness of the heterogeneity of pneumococcal strains (capsular types) is evident in the accounts of Wright's studies; and, as shown in subsequent investigations, the number of pneumococci included in the vaccines employed was marginal at best, in terms of their ability to stimulate an effective antibody response.

Wright left a protégé in South Africa, however, an English-born physician, F. Spencer Lister, who had arrived in that country in 1907. In his studies of pneumonia in collaboration with Wright and independently of others, he recognised the serological heterogeneity of pneumococci causing pneumonia in miners and classified them into several groups the same year that Dochez and Gillespie at the Rockefeller Institute described pneumococcal types 1, 2 and 3.[16] By 1916, Lister had identified 8 pneumococcal serotypes and had shown both the immunogenicity and lack of toxicity of vaccines of killed pneumococcal cells injected into rabbits or into humans. As many as 40 billion heat-killed pneumococci could be given to the latter intravenously without significant untoward effect.[17] Lister's studies suggested also that the numbers of pneumococci included in Wright's vaccines were too small regularly to have stimulated adequate levels of specific anticapsular antibodies.

With the knowledge acquired from his laboratory studies, Lister moved next to field trials of tri- or tetravalent vaccines in mining populations. In planning his trials, Lister had two options as stated in one of his writings: 'In the system hitherto employed on the Rand for assaying the results of prophylactic inoculation against the pneumococcus, a certain advantage conferred upon the uninoculated has, I think, been overlooked. If pneumonia is spread, as I believe it to be, either directly from case to case or through the agency of carriers it follows that the inoculation of half of the inhabitants of a Native compound may interrupt the chain, not only of actual pneumonic patients but also of carriers; if the inoculation achieves this it is obvious that the uninoculated half of the population will achieve an advantage which is not allowed for in the calculations.'[17] For the foregoing reason, Lister chose to vaccinate all the members of one mining compound and to use those of another compound as controls. Because the attack rates of pneumonia differed in different compounds, the results of Lister's trials were questioned. The second ground that gave rise to uncertainty in assessing these trials was the paucity of bacteriological studies of pulmonary secretions and blood, which were necessary to establish whether or not protection against infection with the pneumococcal serotypes represented in the vaccine was demonstrable. Lister was knighted, later, nonetheless, for his fundamental contributions.

Lister's chief sceptic at the time was Alexander Jeremiah Orenstein. Two years after Sir Almroth Wright had been approached to solve the major medical problem of the mining industry, the views of General William C. Gorgas, the sanitarian who had made possible the building of the Panama Canal, were sought; and Gorgas went to South Africa to survey the situation in the mines. He recommended changes in the housing of the miners, the establishment of medical services for their care and the appointment of a physician to serve as sanitarian for the industry, a post for which he recommended Orenstein. Although the Chamber of Mines rejected Gorgas' recommendation, Orenstein was employed by one of the mining companies and introduced a number of changes to which he attributed declines in the morbidity and mortality of pneumonia. Although pneumococcal vaccines continued to be used, the differences held by Lister and Orenstein were never resolved completely; and, following the introduction of sulphona-

mide therapy for pneumococcal pneumonia in the late 1930s, the issue became moot.[7]

Several additional trials of vaccines of killed pneumococcal cells were carried out in the US, Europe and India before the introduction of sulphonamides, the results of which, while suggestive of some protective efficacy, were never conclusive, despite the fact that Heffron estimated that such vaccines had been given to approximately 1 million recipients.[1] Advances in the knowledge of the pneumococcus were to make them obsolete.

2. Vaccines of Pneumococcal Capsular Polysaccharides

In 1917, Dochez and Avery at the Rockefeller Institute published two landmark papers describing an immunologically active soluble substance of pneumococcus, elaborated during growth in culture and found in the urine and blood of infected patients.[18,19] So widely held at the time was the association of immunological activity with protein that they wrote in the first of these two reports, 'The determination of total nitrogen and nitrogen partition on the active substance, obtained by repeated precipitation with acetone and alcohol, shows this substance to be of protein nature or associated with protein', even though it was not inactivated by trypsin. Six years later, Heidelberger and Avery were to show that the specific soluble substances of which the capsules of pneumococci are composed are polysaccharides.[20,21]

In 1927, Schiemann and Casper in Germany reported the immunogenicity of type 3 pneumococcal capsular polysaccharide in the mouse,[22] an observation confirmed in 1929 with a purified preparation of the capsular polysaccharide of pneumococcus type 2.[23] Working independently at the Rockefeller Institute in New York, Francis and Tillett reported that humans injected intradermally with 0.01mg amounts of capsular polysaccharides of pneumococcal types 1, 2, and 3 developed antibodies to one or more of the same pneumococcal types,[24] an observation confirmed by Finland and his co-workers.[25,26] These findings led to a field trial of a bivalent vaccine containing 1mg each of the capsular polysaccharides of pneumococcal types 1 and 2, administered to approximately 29 000 young adult males in the American Civilian Conservation Corps in the 1930s.[27] As was true of the earlier trials of whole bacterial vaccine in South Africa, the results of this trial, while suggestive of some beneficial effect of vaccination, were rendered uncertain by the paucity of bacteriological data and, in some instances, by the incompleteness of follow-up.

The advent of World War II led once again to the enlistment of large numbers of military recruits. In a US Air Force pilot training centre, pneumococcal pneumonia became a significant military medical problem, one addressed by the trial of a vaccine of pneumococcal capsular polysaccharides to determine whether or not the disease could be controlled by prophylaxis.[28] Six pneumococcal capsular types (types 1, 2, 4, 5, 7 and 12) accounted for the majority of disease. A tetravalent vaccine containing 50μg each of the polysaccharides of types 1, 2, 5 and 7 was administered to 8586 recruits, and 8449 men who served as controls were injected with saline. There were 4 cases of pneumonia caused by types in the vaccine among its recipients, all occurring in the 2 weeks following its receipt and in the period required for the development of antibodies. Thereafter, there were no illnesses associated with types in the vaccine among its recipients, in contrast with 23 such illnesses among the controls. There was no difference in the incidence of illness associated with types excluded from the vaccine between the vaccinated and control populations; in other words, protection was type specific.

Two additional observations of note emerged from this study. By studying the incidence of disease in the vaccinated and control populations caused by the two epidemic pneumococcal types excluded from the vaccine (types 4 and 12), and calculating the expected incidence of disease in the control population caused by the 4 types included in the vaccine, the correctness of Lister's perception of the effect upon the spread of disease in a closed population of interposing a large number of

immune individuals was established. One way to deal with this problem is to vaccinate only 20% of such a closed population, as was done in trials of Group C meningococcal vaccine in the US Army.[29] The second finding of note was the impact of vaccination on the pneumococcal carrier state. It was found that, if one were the carrier of a pneumococcal type represented in the vaccine prior to vaccination, vaccination would not eliminate the carrier state. If, however, one were not a carrier of a type included in the vaccine prior to its receipt, the likelihood of becoming one after vaccination was reduced by approximately half, an observation that has been confirmed in subsequent studies.

The foregoing results led to the licensing in the 1940s of two hexavalent vaccines, one formulated for administration to adults, the other containing types known to be more frequent causes of illness in the paediatric population. The timing of their release, however, was unpropitious. In 1944, Tillett and his co-workers reported that both non-bacteraemic and bacteraemic pneumococcal pneumonia could be cured by the daily parenteral administration of 40 000 to 100 000 units of benzylpenicillin (penicillin G),[30] and additional effective antibiotics were introduced soon thereafter. The decline in the mortality of pneumococcal pneumonia was sufficiently dramatic that what had been viewed previously as a dread disease came to be regarded almost casually. Concomitantly, the increasing unavailability to hospital laboratories of pneumococcal typing serum, which had been a by-product of therapeutic antiserum, led to declining recognition of pneumococci. The combination of these two circumstances resulted in the view that, with the advent of effective antipneumococcal therapy, pneumococcal disease had been largely eliminated and that what remained need no longer be considered serious. Little, if any, need for pneumococcal vaccine was perceived; and, after several years, the licences for the two formulations cited were withdrawn without prejudice by the manufacturer, for lack of their use.

A re-evaluation of bacteraemic pneumococcal infection in the 1950s suggested, however, that despite the marked advances in antipneumococcal therapy, significant and identifiable problems remained.[2] Among adults with bacteraemic pneumococcal pneumonia uncomplicated by an extrapulmonary focus of infection treated with penicillin, at a time when penicillin-resistant pneumococci had not yet emerged, the case fatality rate was 17%. Among those 50 years of age or older and/or those who had one of several underlying systemic illnesses, the case fatality rate exceeded 25%. What was evident also was the absence of any reduction in mortality among those treated with antimicrobials and dying within 5 days of the onset of illness when contrasted with the survival of those receiving only symptomatic treatment in an earlier era. In the absence of knowledge to reverse the early physiological derangements of infection, the only alternative for those identifiably at high risk appeared to be prophylaxis.

To redevelop a polyvalent vaccine of pneumococcal capsular polysaccharides, several requirements had to be met. To determine the formulation of the vaccine, the distribution of capsular serotypes of more than 3000 isolates from blood cultures was ascertained. Six types were responsible for half the bacteraemic infections, an additional 6 types for a quarter and 6 more for an eighth – 18 types accounting for 87.5% of the total. Although the rank order of the more invasive types may change over time, it appears unlikely that there will be a need to alter frequently the formulation of a vaccine containing more than 18 polysaccharides. Next, volunteers were injected with individual polysaccharides in doses ranging from 5 to 1000μg, and then with combinations thereof, and their immunological responses assayed. Both the safety and the immunogenicity of the antigens having been ascertained in this fashion, it remained to demonstrate the efficacy of the vaccine.[31]

Pneumococcal vaccines are unique in their degree of polyvalency, the currently licensed formulation being designed to prevent 23 immunologically distinct infections; and, accordingly, it is

unlikely to equal in its aggregate efficacy that of vaccines designed to prevent 1 to 3 infections. If the efficacy of each antigen in pneumococcal vaccine were 90% and if one were exposed over time to 4 of the pneumococcal types represented in the vaccine, the likelihood of being infected with none would be 0.9^4 or 64%. In evaluations of polyvalent pneumococcal vaccines, it is important that these considerations be borne in mind.

Of several randomised double-blind trials of pneumococcal vaccines conducted in the 1970s, two in South Africa were the most revealing. At a gold mine near Johannesburg where the attack rate of pneumococcal pneumonia among African miners approximated 100 per 1000 persons per annum, over a period of 4 years 12 000 men were enrolled.[31] From a table of random numbers, participants were administered either a polyvalent pneumococcal vaccine, a meningococcal vaccine or a saline placebo. Analysis of the trial yielded the following results:

- A 78.5% reduction in putative and proven pneumococcal infection caused by types represented in the pneumococcal vaccine among its recipients, when contrasted with similar illnesses in the two control populations.
- An 82.3% reduction in bacteraemic infection caused by the same pneumococcal types in recipients of the pneumococcal vaccine, when contrasted with that in controls.
- A 50% reduction in radiologically confirmed pneumonia, irrespective of cause, among recipients of pneumococcal vaccine, when contrasted with that in the control populations, demonstrating the ability of the vaccine to prevent pneumonia as well as bacteraemia.

As determined by statistical analysis, the likelihood of each of the foregoing results having occurred by chance is less than 1 in 10 000. On the basis of these findings and those in a similar trial in South Africa,[32] a 14-valent pneumococcal vaccine was licensed in the US in 1977, and its valency increased to 23 polysaccharides in 1983.

To obtain comparable data in the US, where attack rates are approximately 100-fold less than those among South African miners, would be logistically unfeasible because of the very large populations that would need to be enrolled, the difficulty in ensuring that appropriate cultures were obtained prior to initiation of antimicrobial therapy, and the large expenditures such a trial would entail. For the foregoing reasons, post-licensing assessments of pneumococcal vaccine have been carried out using two retrospective methods of analysis: case-control studies and indirect cohort studies.[33] The former method contrasts the incidence of pneumococcal vaccination among patients hospitalised with pneumococcal infection with that in age- and underlying disease-matched controls lacking pneumococcal infection. If the vaccine is effective, the percentage of vaccinated individuals will be lower among those with pneumococcal infection. In the indirect cohort analysis, the ratio of pneumococcal infections caused by types included in the vaccine to those caused by types excluded from the vaccine is contrasted in vaccinated individuals and in controls. If the vaccine is effective, the ratio will be lower among its recipients. Among several such studies, the aggregate efficiency of the vaccine has ranged between 60 and 70%, consistent with an average exposure to 4 pneumococcal types represented in the vaccine.[34-37] Few data are available on the duration of protection and on the need for revaccination. In one case-control study,[37] there is little evidence of declining immunity 3 to 5 years after immunisation at ages 45 to 50 years, whereas among those aged 85 years and older, evidence of protection declines rapidly and is no longer apparent after 5 years. Data on the immunogenicity of vaccine readministered 5 to 8 years after an initial injection of the vaccine are also limited, and the results of several small studies have been variable.[38,39] Current recommendations for readministration of pneumococcal vaccine at intervals of 5 to 7 years are, accordingly, in need of further study to determine their utility. Revaccination, however, is a safe procedure.[40]

Acceptance of pneumococcal vaccine, slow initially, has received added impetus from the recent rapid increase in the number of pneumococcal iso-

lates manifesting resistance to one or more antimicrobial drugs. In addition, it would seem desirable that the age recommended for the initial administration of pneumococcal vaccine be lowered to 45 years in light of evidence of the better responsiveness of the mammalian immune system early in life.[41]

3. Pneumococcal Polysaccharide Protein Conjugate Vaccines

Because infancy and early childhood are periods in the human life span when the incidence of pneumococcal infections is among the highest,[1] the redevelopment and relicensing of polyvalent vaccines of pneumococcal capsular polysaccharides led to their use in several controlled trials, which were not notably successful in individuals at these stages of life.[42,43] The results of these studies should, perhaps, not have been surprising. In 1937, Davies was one of the first, if not the first, to vaccinate infants under the age of 15 months with a pneumococcal capsular polysaccharide, that of type 1.[44] Only 1 of the 15 recipients of the polysaccharide showed an immunological response. In 1944, Hodes et al. reported that children aged 3 to 9 years developed mouse protective antibodies after injection with whole killed type 1 pneumococcal cells, although they responded poorly to a similar vaccine of pneumococcus type 6.[45] Infants 3 to 18 months of age failed to respond to either vaccine.

Bacterial capsular polysaccharides are thymus-independent antigens, the responses to which are characterised by development late in ontogeny and by lack of immunological memory.[46] The solution to the problem of successfully immunising humans in the first year of life lay in extrapolations from laboratory observations made in the 1920s and 1930s. The demonstration by Heidelberger and Avery[20,21] that the type-specific capsular antigens of the pneumococcus were polysaccharides led to unsuccessful attempts by Avery and Morgan[47] to immunise rabbits with them. Subsequent studies of Avery in collaboration with Goebel,[48,49] however, revealed that, if the capsular polysaccharide was linked chemically to a protein, the rabbit would respond with the production of type-specific anticapsular antibodies protective against infection. By contrast, the mouse, as reported by Schiemann and Casper,[22] could be immunised by injection of type 3 polysaccharide alone, an observation confirmed by Schiemann with the polysaccharide of pneumococcus type 2.[23] Although Schiemann failed, like his predecessors, to immunise rabbits with the same type 2 antigen, he attributed his failure perhaps to the use of too small an amount.

Concomitant with the redevelopment of vaccines of pneumococcal capsular polysaccharides, attempts were being undertaken to develop an effective vaccine against *Haemophilus influenzae* type b, then the most common cause of bacterial meningitis in the first 2 years of life. Like pneumococcal capsular polysaccharides, that of *H. influenzae* type b proved to be a poor antigen in those in the age group at greatest risk. By drawing on the earlier laboratory observations and linking the same polysaccharide chemically to a protein such as tetanus toxoid, diphtheria toxoid or to a nontoxic variant of diphtheria toxin, safe and highly antigenic vaccines resulted[50,51] which, since their introduction, have largely eliminated both the carriage of, and disease caused by, *H. influenzae* type b[52] in populations in which they are used extensively.

The success of these conjugate vaccines has provided the impetus to develop similar vaccines of pneumococcal capsular polysaccharides. The problems posed in their production include the following: the choice of polysaccharides to be included in the vaccine and their degrees of polyvalency; the protein or proteins with which the capsular antigens are to be conjugated; and the method used to link the two essential components of the vaccine, either directly or through an intermediary compound.

A number of such vaccines are currently under development,[53-56] the polyvalency of which has ranged from 4 to 9 polysaccharides of the types most frequently responsible for paediatric infection: types 3, 4, 6B, 9V, 14, 18C, 19F, 19A, 23F.

Phase I and II clinical trials of several of these preparations, both in older children and in infants 6 to 12 months of age, have shown them to be both safe and antigenic, and field trials to assess their efficacy are currently in progress. The results of one such trial involving 37 000 infants in Northern California, half of whom were inoculated with a heptavalent pneumococcal vaccine at ages 2, 4 and 6 months with a booster at 12 to 15 months, the other half with a conjugate group C meningococcal vaccine, have recently been reported.[57] The results are highly encouraging. All 22 cases of invasive pneumococcal disease occurred in the control population, which finding is indicative that prevention of pneumococcal infection in the first 2 years of life, caused by types represented in the vaccine, is highly probable if the findings are confirmed by other trials. Few data are currently available on the immunogenicity of polysaccharide conjugate vaccines in the elderly, but those extant suggest that they will offer little or no advantage over the corresponding polysaccharide antigens for individuals in the later years of life.[58,59]

Finally, it should be noted that, although pneumococcal components other than capsular polysaccharides, including several surface proteins, pneumolysin and C polysaccharide, continue to be studied as potential vaccines or components of vaccines,[60] none has been shown in comparative studies in laboratory animals to have efficacy comparable to that of capsular antigens. At present, it appears unlikely that any will replace capsular polysaccharides in the prophylaxis of pneumococcal infection.

4. Conclusion

As the millennium approaches, it is apparent that the uneasy relationship between man and the pneumococcus will persist, becoming more troublesome to the therapist in the face of pneumococcal resistance to antimicrobial drugs. After nearly a century of vaccine development, prevention of the preponderance of pneumococcal infections now seems feasible with the administration of conjugate pneumococcal vaccines in infancy and of capsular polysaccharide vaccines at, or shortly after, puberty. Although there will continue to be occasional vaccine failures and infections caused by the less invasive pneumococcal types not represented in the vaccines, significant reduction of the burden of pneumococcal infections now seems to be within man's grasp.

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Correspondence and reprints: Dr *Robert Austrian,* Professor and Chairman Emeritus, Department of Molecular and Cellular Engineering, The University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6088, USA.