

6. Musher DM, Mediwala R, Phan HM, Chen G, Baughn RE. Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. *Clin Infect Dis* 2001;32:534-8.

The editorialists reply:

*To the Editor:* In our editorial, we quoted Levy, who estimated that in 1996 160 million prescriptions were written for antibiotics in the United States and more than 50 million lb (22.7 million kg) of antibiotics was produced for use in people, animals, and agriculture.<sup>1</sup> Approximately half those antibiotics (25 million lb [11.4 million kg]) were used by people. Because there are no specific data on prescribing profiles for the U.S. population, we calculated an average from the data: 25 million lb for 275 million people, or 9 lb (4.1 kg) per 100 persons per year. If 80 million prescriptions (half the total) were for use in people, the use of similar calculations would yield a value of 29.1 prescriptions per 100 persons per year.

The congressional Office of Technology Assessment estimated that in 1985, 17.6 million lb (8.0 million kg) of antibiotics was prescribed for use in animals alone — for treatment, disease prevention, and growth promotion.<sup>2</sup> Assuming that equal quantities (17.6 million lb) were used for people in 1985 and that such use has increased over the past 15 years, we find that there is consistency in the pattern of the various gross estimates.

Nevertheless, Dr. Wilbur's point about our ability to estimate the average use per person or use per prescription without available data is well taken. Referring to data from the Office of Technology Assessment, the Institute of Medicine in 1998 reported annual antibiotic use in humans in different terms: approximately 190 million defined daily doses were used in hospitals, and approximately 145 million courses were used in the community.<sup>3</sup> If one third to one half of the 35 million patients who are hospitalized in the United States each year receive antibiotics, the number of defined daily doses would be 16.3 to 10.9 per person. However, some patients in critical care units and others who have immunosuppression with fever and neutropenia receive multiple antibiotics at high doses for weeks at a time, far exceeding the average use. In a study of eight intensive care units, Gaynes and Monnet reported that the use of vancomycin ranged from 10 to 70 defined daily doses per 1000 patient-days and the use of third-generation cephalosporins ranged from 17 to 154 defined daily doses per 1000 patient-days.<sup>4</sup> Wide variation in use among outpatients must also occur.

We conclude that a large tonnage of antibiotics is prescribed for people in the United States. Measures of use vary considerably from study to study. Most important, precise profiles of the distribution of antibiotics and the number of prescriptions written for people in the community, hospital, or extended care facilities are unknown and await accurate national surveillance.

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1. Levy SB. Antibiotic resistance: an ecological imbalance. In: Ciba Foundation. Antibiotic resistance: origins, evolution, selection and spread. Chichester, England: John Wiley, 1997:1-14.

2. Antibiotics in animal husbandry. In: Office of Technology Assessment, Congress of the United States. Impacts of antibiotic-resistant bacteria. Washington, D.C.: Government Printing Office, 1995:155-66.

3. Institute of Medicine, Forum on Emerging Infections. Antimicrobial resistance: issues and options — workshop report. Washington, D.C.: National Academy Press, 1998:40.

4. Gaynes R, Monnet D. The contribution of antibiotic use on the frequency of antibiotic resistance in hospitals. In: Ciba Foundation. Antibiotic resistance: origins, evolution, selection and spread. Chichester, England: John Wiley, 1997:47-60.

## Cellular Telephones and Brain Tumors

*To the Editor:* The article by Inskip et al. (Jan. 11 issue)<sup>1</sup> provides reassuring findings that cellular-telephone use is not associated with an increased risk of brain tumors, but the study has some limitations that are due to its retrospective design. Exposure was assessed by interviews, and recall bias, one of the main pitfalls in case-control studies, may be a problem because patients with brain tumors can have impaired memory.

Since telephone companies keep very accurate records of the calls of their customers, it would have been possible to document cellular-telephone use objectively if these data were accessible. Although legal problems might arise, most subjects would probably consent to the retrieval by investigators of data on the total duration of their calls, with no further details. The telephone companies should certainly be blinded to the health status of the customers whose data they provide. Because of the objectivity of billing records, such a design could provide more reliable data on the association between cellular-telephone use and brain tumors.

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*To the Editor:* The study by Inskip et al. has a number of serious deficiencies. The hypothesis that was tested was that there is no association between the frequency of brain tumors (as determined by hospital admissions) and ever having used cellular telephones regularly. Consider the possibility that before the diagnosis of a brain tumor, a physician had advised each of these patients to purchase a mobile telephone for use in emergencies. If that had been the case, the study would have found an increased relative risk in users of cellular telephones, but the causality would have been reversed. I wonder whether the authors have considered the possibility that there might be confounding due to the use of a cellular telephone on the advice of a physician. (Among the controls, a considerable proportion of the patients had cardiovascular diseases — a circumstance in which the purchase of a cellular telephone is often recommended.)

It is indispensable in case-control studies to ensure that the condition under investigation precedes the disease outcome. The most important factor in analyzing the possible contribution of cellular-telephone use to brain tumors is latency. For some brain tumors, the interval between malignant transformation and clinical symptoms or diagnosis can exceed 10 or even 20 years.<sup>1-4</sup> The study did not have

sufficient power to detect a substantially increased risk if exposure to a cellular telephone is considered as contributing to malignant transformation. Such a contribution of exposure to tumor development was not even addressed, let alone tested, by the authors.

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1. Simmons NE, Laws ER. Glioma occurrence after sellar irradiation: case report and review. *Neurosurgery* 1998;42:172-8.
2. Daentzer D, Boker DK. Strahleninduziertes Meningeom 20 Jahre nach Operation und hochdosierter Radiatio eines Ependymoms. *Zentralbl Neurochir* 1999;60:27-32.
3. Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* 2000;95:2770-5.
4. Strojjan P, Popovic M, Jereb B. Secondary intracranial meningiomas after high-dose cranial irradiation: report of five cases and review of the literature. *Int J Radiat Oncol Biol Phys* 2000;48:65-73.

*To the Editor:* The results of the study by Inskip et al. include a possible 60 percent increase in the incidence of glioma resulting from reported short-term use of cellular telephones. This increase may not rise to the level of statistical significance, but given the low power of the study, which is due, in part, to the truncated nature of the study period, the authors' reassurances are hard to accept. The broad confidence intervals underscore the deficiencies and uncertainties that undermine the authors' conclusions.

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The authors reply:

*To the Editor:* Our study was conducted in response to the concern that brain cancers diagnosed in the early 1990s might have been caused by cellular telephones. The upper confidence limits in our study indicate that if there was such an effect, it was small. We found a relative risk of glioma of 0.9, with an upper 95 percent confidence limit of 1.6, associated with more than 100 hours of cellular-telephone use, and a relative risk of 0.5, with an upper limit of 1.3, associated with more than 500 hours of use. The absence of a dose-response relation for any measure of the level of use argues against an association.

We acknowledged the possibility that our study was conducted too early to detect an effect. Insofar as it is not known at what stage in carcinogenesis, if any, radio-frequency radiation might act, it is not clear what we should expect in terms of an induction period, nor that ionizing radiation should serve as the model, as implied by Kundi.

Kundi's suggestion that there might have been a high rate of cellular-telephone use among the controls with cardiovascular disease is not supported by our data. The relative-risk estimates were insensitive to the inclusion or exclusion of any subgroup of controls. The duration of symptoms before admission to the hospital was less than one year for more than 90 percent of the controls, and the exclusion of cellular-telephone use within the year preceding admission did not materially change our findings.

Erman et al. suggest that cellular-telephone use might have been underreported among patients with tumors because of mental impairment, and they advocate the use of billing records to assess cellular-telephone use. Mental impairment, rare in acoustic neuroma and less common in younger than in elderly patients with glioma or meningioma,<sup>1</sup> is unlikely to have affected substantially the responses of the heaviest cellular-telephone users — namely, young and middle-aged patients. Billing records have been judged inadequate for the assessment of exposure in case-control studies.<sup>2,3</sup> Cellular-telephone service providers typically maintain detailed billing records for a maximum of one year; those records often include only outgoing calls and do not identify the user of the telephone.<sup>2,3</sup> Regardless of the limitations of billing records as compared with data from interviews, it is reassuring that a recent cohort study that used service-provider records<sup>4</sup> had similar findings.

We see the timing of our study relative to the explosive growth in the use of cellular telephones as its most important limitation. A recently launched, multicenter study<sup>3</sup> will have greater statistical power to assess risks associated with long induction periods and the use of digital telephones. However, given the extent of exposure to cellular telephones in the population, one would want to identify any excess risk at the earliest possible time.

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1. Kleihues P, Cavenee WK. Pathology and genetics of tumours of the nervous system. Lyon, France: International Agency for Research on Cancer, 1997.
2. Dreyer NA, Loughlin JE, Rothman KJ. Epidemiological safety surveillance of cellular telephones in the US. *Radiat Prot Dosim* 1999;83:159-63.
3. Cardis E, Kilkenny M. International case-control study of adult brain, head and neck tumours: results of the feasibility study. *Radiat Prot Dosim* 1999;83:179-83.
4. Johansen C, Boice J Jr, McLaughlin J, Olsen J. Cellular telephones and cancer — a nationwide cohort study in Denmark. *J Natl Cancer Inst* 2001; 93:203-7.

## Allergy and IgE Antibodies

*To the Editor:* Allergic symptoms are the result of an inflammatory process triggered by an allergen or allergens to which a patient has generated antibodies after a previous exposure. Dr. Kay's review article on allergic diseases (Jan. 4 issue)<sup>1</sup> recognizes only the action of IgE in the inflammatory process and erroneously identifies a response mediated by type 2 helper T cells (Th2) as an exclusively IgE response, ignoring the other epitopes. This may be the result of using immediate hypersensitivity skin-prick tests as the sole means to detect the patient's allergic reactivities. Such tests detect only IgE antibodies. I believe the article is seriously flawed because it ignores the most efficient inflammatory antibodies generated on exposure to antigen — namely, IgG and IgM.

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1. Kay AB. Allergy and allergic diseases. *N Engl J Med* 2001;344:30-7.