is transferred from the warm blood of the subcutaneous vascular plexus to the cooled esophageal membranes. This mechanism is coupled with panting, gular flutter, and postural adjustments. The latter mechanisms cannot, alone, maintain body temperature in the ringdove.

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References and Notes

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2. This is a domesticated African collared dove of uncertain ancestry. D. Goodwin [*Pigeons and Doves of the World* (British Museum of Natural History, London, 1967), pp. 129–130] considers it derived from *Streptopelia roseogrisea*. J. L. Peters [*Check-List of Birds of the World* (Museum of Comparative Zoology, Cambridge, England, 1961), vol. 3, p. 92] puts it with *S. decaocto*.
3. A. M. Lucas and P. R. Stettenheim, *Avian Anatomy: Integument* (Handbook 362, Department of Agriculture, Washington, D.C., 1972), pp. 262 and 485–635.
4. The plexus is noted in L. H. Hyman [*Comparative Vertebrate Anatomy* (Univ. of Chicago Press, Chicago, 1942), pp. 351–354]. It is also mentioned by J. N. Langel in an early description of the sympathetic innervation of the avian vascular system [*J. Physiol. (London)* **30**, 221 (1904)]. J. Baumel of Creighton University found this plexus independently and is engaged in an extensive exploration of its structure.
5. L. Weiss and R. O. Greep, *Histology* (McGraw-Hill, New York, 1977), pp. 414–415.
6. Doves examined were *Columba livia*, *Zenaida macroura*, *Leptoptila verreauxi*, and *Goura crista*. The plexus is absent in the sand grouse *Pterocles decoratus*, whose position within the Columbiformes is often disputed.
7. The description of a "nape-cheek rete" in the helmeted guinea fowl *Numida meleagris* by T. M. Crowe and A. A. Crowe [*J. Zool.* **188**, 221 (1979)] is intriguing, but insufficient for comparison with the plexus described here.
8. Both male and female doves inflate the esophagus when cooling. During cooling, the internal choanae appear to be blocked by the tongue (A. S. Gaunt and S. L. L. Gaunt, unpublished observation). How the esophagus is inflated and how the inflation is maintained with an open bill during heat stress is not readily apparent. The striated muscle of the integument may be involved in the pulsations of the inflated esophagus.
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Bladder Cancer and Artificial Sweeteners: A Methodological Issue

The appropriate conclusions to be drawn from the data on artificial sweetener use and bladder cancer reported by Wynder and Stellman (*1*) are quite different from those stated in the report.

The authors say that "these findings are essentially in agreement with results obtained during an earlier phase of the study." In October 1977 [reference 15 in (*1*)] Wynder reported a "crude" relative risk (*RR*) of 1.87 for 260 males with bladder cancer. Later, for a series of 420 cases including the original 260, he found the crude *RR* to be 1.85. When a series of "adjustments" was made the *RR* fell to 1.43. A matched-pair analysis incorporating additional adjustment cut the *RR* further to 1.13. In a later sample of 312 male bladder cancer patients—the study reported in the main text (*1*)—the *RR* is 0.93, on the basis of similarly matched controls. While the adjusted values may be in agreement, the drastic reduction of the *RR* from the values first reported can hardly be called "essential agreement."

There are two explanations of what the statistical adjustments have done here. One is that they have removed a spurious effect. The other is that they have thrown out the baby with the bath water. As is well known, "matched pairs" such as the Miettinen procedure (*2*) used here can produce a serious loss of statistical "power" (ability to detect effects). Miettinen has emphasized this in previous arguments with me (*3*). The Mantel-Haenszel test (*4*) has the same weakness (*5*). This loss of power is especially severe when the covariables are "confounded" (related to each other). While the issues are generally discussed in statistical jargon, the point can be made in plain English.

The problems are especially acute in these data. Cigarette smoking is known to be a major factor here. It is a factor in both the cases and the controls. Thus 61 percent of the controls have cancer, 23 percent at a site which is more closely related to cigarette smoking than bladder cancer is. This confounding is especially troublesome when, as here, the authors propose to study "cocarcinogenesis" (the combined effect of smoking and artificial sweetener). Moreover, they are dealing with a series of hospitals where both the cases and the controls are markedly different in character from one hospital to another.

In a situation like this, matching on confounded variables (for example, hospital and hospital room status, as was done here) can easily match out the effect that is under study or can introduce random effects that will overwhelm weak real effects (when the *RR* is less than 2) (*6*).

The progression of the *RR*'s from 1.87 down to 0.93 strongly suggests that this is exactly what has happened here.

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The downward shift of the adjusted *RR*'s in our earlier study [reference 15 in (*1*)] typifies the classical effect of adjustment for confounding variables in "removing a spurious effect," which is the straightforward explanation we favor for the changes in *RR*. Furthermore, we now know the source of the confounding: it arose from the selection bias that resulted from oversampling controls from lower socioeconomic county and Veterans Administration hospitals, while the cases came largely from upper socioeconomic hospitals, such as Memorial Hospital in New York. On the other hand, it is difficult to see how "overmatching," a rare enough artifact in epidemiological studies of this magnitude, could have affected that study, inasmuch as matching was not employed in the initial selection of controls but only in a post hoc analytical procedure to control for several confounding variables at once.

Our second study (*1*) was carried out in a substantially more homogeneous set of hospitals and with rigorous matching of controls to cases prior to interview. The distributions of usage, quantity, and duration of tabletop sweetener consumption among these controls so closely resemble the corresponding distributions in a much larger and geographically diffuse stratified population sample, as reported by Hoover and Strasser (*2*) in a separate study of bladder cancer and artificial sweetener use, that it would be difficult to maintain that prematching forced an unusual distribution on them; therefore, the possibility that overmatching occurred in our second study is remote.

In all population strata in that study, sweetener use among controls slightly exceeded that among cases; that is why the *RR*'s were all below 1.0. Point estimation of *RR*'s as the ratio of discordant

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pairs was dictated by the matched design (*3*). We can imagine that some statistical procedure more powerful than standard Mantel-Haenszel and Miettinen tests might narrow the confidence intervals a bit, but it would not alter these point estimates by much.

Adjustment of the *RR*'s for tobacco use provides an adequate test for confounding. With subjects categorized either as non-, ex-, or current cigarette smokers or as pipe or cigar smokers, the adjusted *RR*'s were 0.97 for males and 0.76 for females, practically unchanged from their original values. Thus, tobacco use was not a confounder.

We appreciate Bross's concern that we not overlook potential artifacts or alternative interpretations of our data, but having reexamined them we see no reason to change any of our conclusions.

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N-Acetylglucosamine-6-Sulfate Sulfatase Deficiency Reconsidered

In 1978 two papers were published by our group (*1*) indicating the existence of two *N*-acetylglucosamine-6-sulfate sulfatases, specific respectively for the glucose or galactose configuration of their substrates. While extracts of skin fibroblasts derived from Morquio patients were found to be defective in *N*-acetylgalactosamine-6-sulfate sulfatase, those of a patient (G.G.) affected by a mucopolysaccharidosis clinically and radiologically different from those already known were reported to be defective in *N*-acetylglucosamine-6-sulfate sulfatase.

During 1978, as S. Toma proceeded to the purification and characterization of the two postulated enzymes, some discrepancies with our original results became evident, namely (i) the 6-sulfated hexosaminitols were poor substrates for the postulated enzymes; (ii) [1-^{3}H]-galactitol-6-sulfate was not hydrolyzed by any preparation of *N*-acetyl-galactosamine-6-sulfate sulfatase, either crude or purified; (iii) fibroblast line GM 2243 (which allegedly represented G.G.'s fibroblasts deposited in the Human Genetic Mutant Cell Repository, Camden, N.J.) was found to have normal *N*-acetylglucosamine-6-sulfate sulfatase activity with several substrates, such as *N*-acetylglucosamine-6-sulfate labeled in the acetyl group with ^{14}C or ^{3}H, *N*-acetylglucosamine-6-sulfate β-1 $\rightarrow$ 3-[1-^{3}H]galactitol, and *N*-[1-^{3}H]acetylglucosaminitol-6-sulfate.

We reviewed all the original data concerning the enzyme studies performed on G.G. and his parents; everything seemed to be in order to justify the original conclusions, except that we found the results of the enzyme measurements performed on a leukocyte extract of G.G.'s father to have been manipulated: what should have been low, defective values had been corrected and presented as "heterozygous" values.

Considering the possibility that an accidental exchange of G.G.'s fibroblasts might have occurred, we secured a frozen pellet of G.G.'s original fibroblasts, derived from a biopsy performed elsewhere about 2 years before the patient came to our attention. Enzyme studies done in parallel with this line and line GM 2243 repeatedly indicated that both had comparable, normal activity of *N*-acetylglucosamine-6-sulfate sulfatase.

By then, R. Matalon informed us that in his laboratory line GM 2243 had shown normal *N*-acetylglucosamine-6-sulfate sulfatase activity, with oligosaccharides derived from keratan sulfate used as a substrate. Recently, H. Kresse provided us with a copy of a manuscript demonstrating the existence of two different *N*-acetylglucosamine-6-sulfate sulfatase enzymes, specific for 6-sulfated residues present in heparan sulfate and in keratan sulfate. In his laboratory, line GM 2243 was normal in both enzyme activities.

We have not found a satisfactory explanation for the original results related to patient G.G., and the possibility that they were fabricated must be considered. If they were, as the senior member of the group I would wish to assume the responsibility for reviewing the original data with excessive enthusiasm and with a criticism not suited to uncover a scientific fraud. At the same time, I would like to apologize for all inconvenience caused to the scientific community.

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