if one accepts the premise that chemotherapy and other means of treating neoplasia are capable of initiating clinical herpes zoster. None of these cases came to diagnosis because of the herpes; one was clinically recognized two months before the onset of herpes zoster, and the other seven had been diagnosed as cancer at least five months earlier.

Riegelman is correct in indicating that the main issue is the detection of undiagnosed cancers as the result of evaluating herpes zoster. By definition, however, these are neoplasms that are found concurrently with or shortly after the diagnosis of herpes. Thus, the subsequent risk of cancer during the time immediately after the onset of herpes zoster is the critical value. We found four cases of cancer in the first year after the diagnosis of herpes — no more than the number expected. The specific tumors involved (one patient each with cancer of the breast, colon, lung, and ovary) did not seem unusual. Consequently, we stand by our conclusion that the risk of cancer after herpes zoster is not elevated and that the routine workup of patients with herpes zoster specifically to exclude the possibility of occult cancer does not seem justified.

M. W. RAGOZZINO, M.D.
Framingham, MA 01701 Framingham Union Hospital

L. J. MELTON, III, M.D.
L. T. KURLAND, M.D.
C.-P. CHU, M.S.
H. O. PERRY, M.D.
Rochester, MN 55901 Mayo Clinic

COMBINED BETA AGONISTS AND METHYLXANTHINES IN ASTHMA

To the Editor: The growing practice of combining beta-adrenergic agonists and methylxanthines for the treatment of chronic asthma has evoked a caution from the Food and Drug Administration because of evidence that coincident administration of these drugs in animals produces myocardial ischemic changes in some of them.[1] The letter by Nicklas et al. of the FDA (August 26 issue) commented on the response to their warning, postulated that a subgroup of patients with asthma might be unduly susceptible to toxic effects of the drug combination, and emphasized the need for careful studies to establish whether this postulate has clinical importance.[2]

We had previously raised this same possibility when we noted an apparent increase in deaths from acute asthma in young people in New Zealand at a time when the use of combination theophylline and beta-agonist therapy was increasing rapidly.[3] The hypothesis raised considerable comment, to which we have replied.[4] Since then, an increased frequency of fatal asthma in patients 5 to 34 years old has been statistically confirmed in a recent study in New Zealand, where the death rate for this disorder has risen from 1.4 per 100,000 in 1975 to 4.1 per 100,000 in 1979.[5] Although combination bronchodilator therapy with beta agonists and theophylline was uncommon in 1975, it is increasingly being perceived as the therapy of choice for many asthmatics. A number of alternative explanations for this precipitate increase in fatal asthma must of course be considered: a change in the prevalence or severity of the disease, substitution of theophylline for corticosteroids, or prolonged delay in seeking medical help when the usual medication has failed. However, most of the patients described in our original communication who died suddenly were using theophyllines and beta agonists as their sole therapy.

J. D. WILSON
D. C. SUTHERLAND
University of Auckland
Auckland, New Zealand School of Medicine

1. Interactions between methyl xanthines and beta adrenergic agonists. FDA Drug Bull. 1981; 11:19-20.
2. Nicklas RA, Whitehurst VE, Donohoe RF. Combined use of beta-adrenergic agonists and methyl xanthines. N Engl J Med. 1982; 307:557-8.
3. Wilson JD, Sutherland DC, Thomas AC. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? Lancet. 1981; 1:1235-7.
4. Sutherland DC, Wilson JD. Theophylline, beta-agonists and fatal asthma. Lancet. 1981; 2:988.
5. Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Asthma mortality: a new epidemic in New Zealand. Br Med J. 1982. (in press).

ELECTRICAL PROPERTIES OF TRACHEAL EPITHELIUM IN CYSTIC FIBROSIS

To the Editor: As reported by Knowles et al. in the issue of December 17, 1981, in vivo measurements of potential difference across the trachea in patients with cystic fibrosis were significantly greater than in control subjects. ($P<0.05$).* Superfusion of the luminal surface of the trachea with amiloride (10^{-4} M) reduced the potential difference by 85 per cent in patients, as compared with 25 per cent in controls, suggesting that the increased potential difference in cystic fibrosis is due to an increase in amiloride-sensitive sodium absorption.

Less than three hours after the death of a 29-year-old man with cystic fibrosis, we mounted epithelial sheets from the posterior membranous portion of his trachea in Ussing chambers under short-circuit conditions. The average resting values for short-circuit current and conductance in three tissues were 21.4 $\mu A \cdot cm^{-2}$ and 4.05 $mS \cdot cm^{-2}$, respectively. Amiloride (10^{-4} M) placed on the luminal side of two tissues decreased the mean short-circuit current by 61 per cent (Fig. 1), the potential difference by 60 per cent, and conductance by 12 per cent. Changing the bathing medium did not reverse the effects of amiloride, and serosal amiloride did not affect the short-circuit current. The addition of dibutyryl-cyclic AMP (10^{-3} M) and then bumetanide (10^{-3} M) to the lumen or serosa or

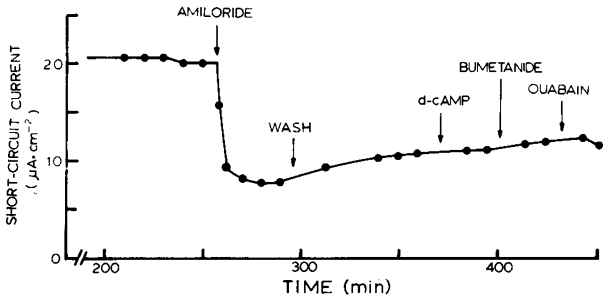

Figure 1. Response of Short-Circuit Current to Post-Mortem Administration of Various Drugs in Tracheal Epithelium from a Patient with Cystic Fibrosis.

Arrows indicate addition of amiloride to lumen (10^{-4} M), dibutyryl-cyclic AMP (10^{-3} M) to serosa and lumen, bumetanide (10^{-3} M) to serosa, and ouabain (10^{-4} M) to serosa. Each symbol represents the mean value in two tissues.

both did not alter the current. Adding serosal ouabain (10^{-4} M) caused only a gradual decline in current over the next 30 minutes.

Our observations lend support to Knowles' conclusion that in cystic fibrosis the trachea absorbs Na^+ chiefly through an amiloride-sensitive pathway. Since cyclic AMP and bumetanide did not change the short-circuit current, it is unlikely that this trachea actively secreted Cl^-. The relative lack of effect of ouabain may have been due to a reduction in sodium influx caused by the combination of amiloride and bumetanide. The large changes in the short-circuit current and potential difference when a small reduction in conductance occurs indicate that measurements of changes in potential difference alone may accurately reflect the transcellular ion-transport properties of this tissue.

IAN NATHANSON, M.D.
J. H. WIDDICOMBE, D.PHIL.
BRIAN DAVIS, M.B., CH.B.
University of California,
San Francisco, CA 94143 San Francisco

*Knowles M, Gatzy J, Boucher R. Increased bioelectric potential difference across respiratory epithelia in cystic fibrosis. N Engl J Med. 1981; 305:1489-95.

The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: Nathanson et al. provide evidence that the short-circuit current and transepithelial electric potential difference of tracheal epithelium excised from a dead patient with cystic fibrosis are sensitive to exposure of the luminal surface to amiloride (60 per cent inhibition). The relevance of these observations to our report is unclear. Although inhibition of short-circuit current was responsible for the reduction in potential difference in the excised trachea, the decrease in potential difference was intermediate between the values that we measured in our patients (85 per cent) and normal subjects (25 per cent) in vivo. There is no previous experience with autopsy material, and the bioelectric properties of tracheal tissues from "normal" subjects have not been reported.

However, there is a larger problem with in vitro studies when only bioelectric properties are recorded. The interactions between Na^+ and Cl^- flows across respiratory epithelia, as well as the effects of amiloride on these flows, are complex.[1] Specifically, Na^+ absorption accounts for more than 80 per cent of the resting short-circuit current of mammalian bronchi, but amiloride induces only about a 50 per cent decrease in the current and potential difference.[2-4] Measurements of unidirectional ion flows have revealed that amiloride abolishes Na^+ absorption and that the remaining short-circuit current reflects the induction of Cl^- secretion. These observations raise the possibility that the greater potential difference and efficacy of amiloride that characterize respiratory epithelia in vivo in cystic fibrosis may involve interactions between both Na^+ and Cl^- permeation. The first clue that the Cl^- permeability of respiratory epithelium may be abnormal in this disease came from in vivo studies. Superfusion of the luminal surface of nasal[5] and bronchial[6] epithelia with Cl^--free solutions induced a much greater hyperpolarization in normal subjects than in those with cystic fibrosis. Maneuvers to minimize the contribution of Na^+ to the diffusion potential (e.g., pretreatment with amiloride) produced similar results. More recently, we found that nasal epithelia excised from four patients with cystic fibrosis had a higher potential difference in vitro than comparable tissue from nine control subjects.[7] The raised potential difference appeared to result largely from reduced conductance, and the short-circuit current was quite variable (see below). Absorption of Na^+ was the only active ion flow across the diseased and the normal epithelia. Movement of Cl^- was passive in both groups, but the magnitude was smaller in the patients' epithelia. Amiloride was more efficacious at reducing the short-circuit current in the patients' tissues, but the reduction in conductance was similar in the two study groups. Amiloride inhibited active Na^+ flow across epithelia from both patients and normal subjects but induced Cl^- secretion only in the controls' epithelium. Consequently, a raised potential difference and increased amiloride efficacy are typical of the respiratory epithelia in cystic fibrosis in vivo and in vitro. In addition, the degree of Cl^- permeability is abnormally small. The greater efficacy of amiloride may reflect the small resting Cl^- permeability of the luminal membranes of epithelial cells, which prevents Cl^- secretion after drug treatment. The role of Cl^- secretion in the maintenance of normal liquid balance across airway epithelia in vivo has not been determined. If secretion makes an important contribution, then its absence in cystic fibrosis could lead to a greater ("excessive") net absorption of salt and water and dehydration of mucus macromolecules on the airway surface.[8] In addition, we have not ruled out the possibility that Na^+ absorption by respiratory epithelia in cystic fibrosis is abnormally high. The resting active Na^+ transport and short-circuit current of tissue excised from subjects with cystic fibrosis varied, ranging from 0.25 to more than 7 $\mu eq/cm^2 \cdot hr$, the highest values that we have observed in human respiratory epithelia.

A better understanding of the basic defect (or defects) in cystic fibrosis will require direct evaluation of ion flow across many more tissues.

MICHAEL R. KNOWLES, M.D.
JOHN T. GATZY, PH.D.
RICHARD C. BOUCHER, M.D.
University of North Carolina–Chapel Hill
Chapel Hill, NC 27514 School of Medicine

1. Boucher RC, Narvarte J, Cotton C, et al. Sodium absorption in mammalian airways. In: Quinton PM, Martinez JR, Hopfer U, eds. Fluid and electrolyte abnormalities in exocrine glands in cystic fibrosis. San Francisco: San Francisco Press. (in press).
2. Boucher RC, Gatzy JT. Effect of amiloride and mucosal sodium removal on canine bronchial ion transport. Fed Proc. 1981; 40:447.
3. *Idem.* Characteristics of sodium transport by excised rabbit trachea. J Appl Physiol. (in press).
4. Knowles MR, Murray GF, Shallal JA, Gatzy JT, Boucher RC. Ion transport in excised human bronchi and its neurohumoral control. Chest. 1982; 81S:11S-3S.
5. Knowles M, Gatzy J, Boucher R. Relative ion permeability of normal and cystic fibrosis nasal epithelium. Clin Res. (in press).
6. *Idem.* Amiloride sensitivity and ion permeabilities of cystic fibrosis and normal human bronchi. Clin Res. (in press).
7. Knowles M, Spock A, Fischer N, Stutts M, Gatzy J, Boucher R. Amiloride effects on bioelectric properties and ion flows across nasal epithelia excised from cystic fibrosis and normal subjects. Clin Res. (in press).
8. Boucher RC, Knowles MR, Stutts MJ, Gatzy JT. Epithelial dysfunction in cystic fibrosis lung disease. Lung. (in press).

THYROTOXICOSIS FACTITIA

To the Editor: Mariotti et al. (August 12 issue)[1] report markedly elevated serum triiodothyronine concentrations in six patients with factitious thyrotoxicosis and attribute these to increased peripheral 5′ deiodination of thyroxine. However, since these subjects were taking excessive doses of desiccated thyroid, a marked contribution to the raised triiodothyronine levels may have been from the medication itself, since this preparation has a high[2] and variable triiodothyronine content.[3] For these reasons this product is no longer recommended for clinical use in the United Kingdom.

Whereas ingestion of massive amounts of thyroxine will elevate serum triiodothyronine into the toxic range, presumably through peripheral metabolism,[4] smaller increases in serum thyroxine in patients receiving oral thyroxine replacement may not be accompanied by a rise in serum triiodothyronine above normal limits. We have measured serum triiodothyronine levels in 58 healthy subjects maintained on oral thyroxine replacement for hypothyroidism with doses of thyroxine ranging from 150 to 300 μg daily, in all of whom the serum thyroxine level was above the normal range (60 to 150 nmol per liter). None was taking any drug known to interfere with peripheral thyroxine metabolism, and all were clinically euthyroid. The mean serum thyroxine level (± 1 S.D.) was 182 ± 24 nmol per liter (range, 152 to 246); the mean serum triiodothyronine level was 2.62 ± 0.40 nmol per liter (range, 1.8 to 3.6; normal euthyroid range, 1.2 to 3.1). In only 7 of the 58 serum samples (12 per cent) was the triiodothyronine level above normal. There was no correlation between the serum thyroxine level and the serum triiodothyronine level ($r = 0.23$, not significant). Presumably, under these conditions of moderate hyperthyroxinemia, homeostatic mechanisms involved in thyroxine metabolism are responsible for maintaining serum triiodothyronine levels within normal or nearly normal limits.

If similar mechanisms operate at thyroxine levels greatly above normal, then one might expect to find the ratio of serum thyroxine to triiodothyronine in patients taking pharmacologic doses of thyroxine (as opposed to thyroid extract) to be higher than the ratio in patients with "genuine" thyrotoxicosis, in whom there is marked thyroidal secretion of triiodothyronine. In a group of 31 patients with untreated thyrotoxicosis due to Graves' disease the mean ratio of thyroxine to triiodothyronine was 28 ± 10 (range, 11 to 57), whereas the patients with hyperthyroxinemia described above had a mean ratio of 70 ± 12 (range, 48 to 114). The patient described by Nyström et al.,[4] who had taken more than 10 mg of thyroxine, had a serum thyroxine level of 1460 nmol per liter and a serum triiodothyronine level of 11.6 nmol per liter, giving a ratio of 126, which is well outside the range for the thyrotoxic patients.

Hence, if estimations of serum thyroglobulin are not available, the ratio of thyroxine to triiodothyronine may prove useful in distinguishing factitious thyrotoxicosis due to thyroxine ingestion from other forms of hyperthyroidism.

C. J. PEARCE, M.R.C.P.
Harrow, Middlesex HA1 3UJ, R. L. HIMSWORTH, M.D.
England MRC Clinical Research Centre

1. Mariotti S, Martino E, Cupini C, et al. Low serum thyroglobulin as a clue to the diagnosis of thyrotoxicosis factitia. N Engl J Med. 1982; 307:410-2.