Radiation Dose Estimates for the Carbon-14-Labeled Urea Breath Test

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The use of the ^{14}C-urea breath test for diagnosis of *Helicobacter pylori* infection in gastric mucosa has gained widespread acceptance and utilization. In order to obtain regulatory approval for this procedure, new dose estimates were required. Previous radiation dose equivalent estimates for males only were based upon data published in 1975 for bicarbonate metabolism. Since that time, calculational techniques for dose estimation have been significantly improved and the organ masses of Reference Man updated. We have calculated dose estimates for males and females who test positive (HP+) and negative (HP−) for gastric *H. pylori* infection. Our results indicate that the urinary bladder wall receives the highest absorbed dose in all four of the above subject populations (HP− males = 0.14 mGy/MBq; HP− females = 0.19 mGy/MBq; HP+ males = 0.10 mGy/MBq; HP+ females = 0.14 mGy/MBq). Gonadal absorbed doses were similar to those previously estimated (testes < 0.065 mGy/MBq and ovaries < 0.084 mGy/MBq, respectively).

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Helicobacter pylori (HP) associated gastritis is present in about 20% of adult Americans (*1*) and may predispose them to both peptic ulcer disease and gastric cancer (*2,3*). *H. pylori* produces urease, which allows the presence of gastric urease activity to be used as a marker for the infection (*4,5*). Gastric urease can be detected noninvasively by measuring isotopic CO_2 excretion in breath after oral administration of ^{13}C- or ^{14}C-urea (*6,7*). Although the ^{13}C test is more difficult, proponents of the test have promoted it on the basis of safety because the isotope is nonradioactive. The ^{14}C test, however, may also be safe because, unlike previous ^{14}C breath tests in humans, ^{14}C-urea does not have a major route for entry into metabolic pathways and is rapidly excreted as either $^{14}CO_2$ in breath or as unchanged ^{14}C-urea in urine (*8*). Thus, the radiation doses resulting from these newer ^{14}C breath tests are likely to be lower than those from older ^{14}C breath tests and cannot be easily extrapolated from calculations done on other types of breath tests.

In the past, most radiation dose estimates for ^{14}C-labeled urea breath tests were based upon the data and calculations of Yap et al. (*9*) who reported dose equivalents for only four tissues; bone, fat, lung and gonads (Table 1).

The protocol of Yap et al. (*9*) involved the injection of 5.74 MBq (155 μCi) of $Na_2{}^{14}CO_3$ with measurement of breath CO_2 excretion for 5 hr in five healthy subjects. An equation was derived describing the CO_2 excretion rate during the initial 5 hr of the study. These dose equivalents were calculated by assuming the residual ^{14}C activity, after 5 hr, followed the biological model of Committee II of the International Commission on Radiological Protection [ICRP II, (*10*)]: bone 10%, T_B = 40 d; fat 60%, T_B = 12 d and remainder of the body 30%, T_B = 10 d.

Winchell and coworkers (*12*) published a paper in 1970 that modeled the kinetics of CO_2-HCO_3^- in normal adult males as a three-compartment model with a pulmonary excretion pathway. Data of 12 subjects were collected for 120 min and mean transfer rate coefficients of the compartment model were estimated. The modeled excretion rate of Winchell et al. (*12*) closely matches that of Yap et al. (*9*) over the time period of Winchell's measurements.

The model of Winchell et al. (*12*) consisted of a low-flow compartment, a high-flow compartment and a relatively fixed compartment. This relatively fixed compartment was considered to be partially comprised of bone, although no specific fraction of the fixed activity was explicitly assumed to enter bone tissue.

The dose equivalents reported by Yap et al. (*9*) were based on experimental results and the biological model of the ICRP II (*10*). Subsequent to this publication, some organ masses (e.g., bone and fat) have been substantially revised and the accepted form of dose calculation has changed. Specifically, n, the relative damage factor for radionuclides in bone (n = 5 for ^{14}C in ICRP II) is no longer in use, thus resulting in the effective energy now

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TABLE 1
Dose Equivalent Estimates for Subjects Given $H^{14}CO_3^-$ Intravenously*

Organ	mSv/MBq	mrem/μCi
Fat tissue	0.75	2.8
Bone	3.1	11
Lung	0.10	0.38
Gonads	0.06	0.23

*Yap et al. (*9*).

being considered to be equal to the actual beta energy for ^{14}C. These changes have demonstrated the need for a comprehensive update of the dosimetry for this procedure, especially when one considers the presence of a biokinetic model for $Na_2{}^{14}CO_3$-CO_2 and the increasing use of the ^{14}C-urea breath test. We have developed a comprehensive biokinetic model of ^{14}C-urea ingestion, metabolism and excretion based upon recent experimental work and modifications of existing bicarbonate and urea biokinetic models. This model was used to estimate the radiation absorbed doses to male and female populations who test HP+ or HP− with the ^{14}C-urea breath test.

METHODS

Work by Marshall and Surveyor (*8*) has indicated that the amount of urea metabolized to CO_2 depends on the presence or absence of HP in the gastric mucosal surface. Their data showed that HP− subjects excreted 70% of the ingested urea intact via the urinary pathway with the remaining ^{14}C (30%) exhaled in the form of CO_2. Subjects who were HP+ excreted 40% of the ingested urea intact in the urine with the remaining ^{14}C (60%) exhaled in the form of CO_2.

The radiation absorbed doses resulting from an oral administration of ^{14}C-urea (^{14}C-urea breath test) were calculated from a combination of models of bicarbonate and urea metabolism. Because the fraction of ingested urea converted to bicarbonate depends on the presence or absence of HP, we calculated the residence times for injections of 100% ^{14}C-urea and 100% ^{14}C-bicarbonate. The resultant residence times are then apportioned from the two models according to the metabolic fate of the ingested ^{14}C-urea. For example, adding 40% of the urea model residence times to 60% of the bicarbonate model residence times would yield the correct residence times for an HP+ person. It was assumed that urea and bicarbonate absorption and metabolism were not gender-dependent.

Bicarbonate Model

Our model of bicarbonate metabolism is shown in Figure 1. Compartment 1 represents organs that receive high rates of blood flow and Compartment 2 represents organs receiving low rates of blood flow. Compartment 3 represents the remainder of the body which contains bone. We have slightly modified the model of Winchell describing $Na_2{}^{14}CO_3$-CO_2 kinetics to include a return pathway from the "relatively fixed" compartment (No. 3) back to the high-flow compartment (No. 1). ICRP Publication 30, Part 3 recommends that the biological removal half-time of carbon incorporated into the "relatively fixed" compartment be set equal to 60,000 min (*13*) or 1,000 hr. Therefore, we set the transfer rate coefficient for the return pathway equal to the biological removal rate, i.e., $k_{13} = 0.6931/1000\ hr^{-1}$.

The k_{ij}'s are the fractional transfer rate constants between compartments and k_{E1} is the fractional rate constant for excretion (breath) into the environment. Numerical values for the fractional transfer rate coefficients are as follows: $k_{12} = 4.02\ hr^{-1}$; $k_{21} = 2.742\ hr^{-1}$; $k_{13} = 0.0006931\ hr^{-1}$; $k_{31} = 0.306\ hr^{-1}$ and $k_{E1} = 1.65\ hr^{-1}$. All k_{ij}'s except k_{13} were reported by Winchell et al. (*12*)

Several assumptions regarding fractional blood volume and blood flow were made as described by Powers et al. (*14*). Of the total blood volume, 0.265 is contained in the heart and arterial side of the circulatory system; 0.196 in the pulmonary circulation and 0.539 in the venous side of the circulation. For dosimetric purposes, the source organs were the lung and spleen (two high blood flow and content organs) and the remainder of the body. Powers states that 0.163 of the total blood volume is contained in the low flow organs with the remaining 0.837 distributed as pulmonic (0.196) and splenic (0.032). The remaining 0.609 is contained in all other high flow tissues (*14*).

The equations describing the rate of change of tracer concen-

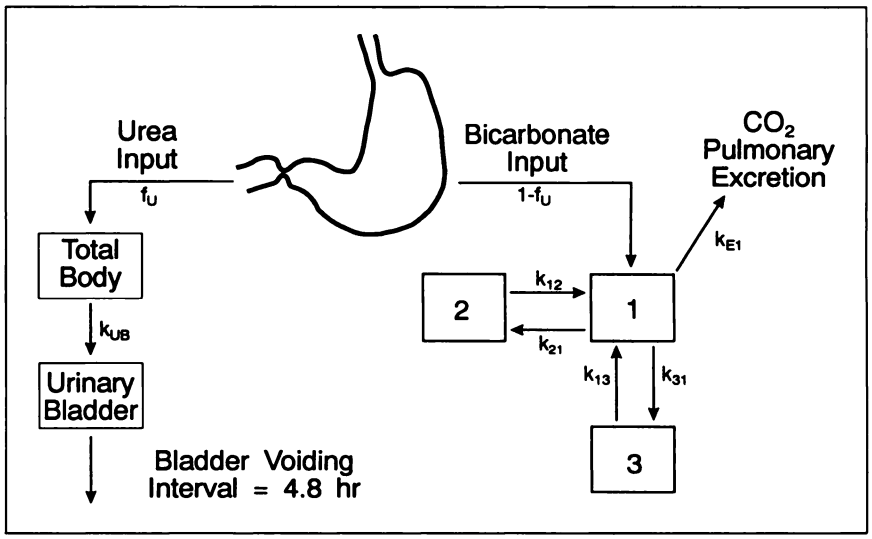

FIGURE 1. Carbon-14-urea breath test compartmental model. The model consists of two sub-models: a gastric urea absorption/distribution/excretion model and an adaption of the compartmental model of Winchell et al. (*12*) to include washout of bicarbonate from the fixed space (compartment 3). Compartments 1, 2 and 3 are high blood flow tissues, low blood flow tissues and a "relatively fixed" group of tissues, respectively. Numerical values for the fractional transfer rate coefficients are given in the Methods section. The bicarbonate and urea are absorbed from the stomach with a removal rate of 9.0 hr^{-1} (T_B = 4.62 min). The fraction absorbed in the form of urea, f_u, is equal to 0.4 and 0.7 in HP+ and HP− subjects, respectively.

tration in the three compartments were solved analytically. The resultant eigen values and eigen vectors of the solutions (Equations 1–3) were integrated ($0 \le t \le \infty$) to yield residence times for all three compartments. Radioactive decay ($T_{1/2}$ = 5730 yr) was neglected as it makes no impact on the effective removal rate constants.

$$q_1(t) = 0.2810 \cdot e^{-0.666 \cdot t} + 0.7189 \cdot e^{-8.052 \cdot t} + 5.55E-5 \cdot e^{-0.00058 \cdot t} \quad \text{Eq. 1}$$

$$q_2(t) = 0.5442 \cdot e^{-0.666 \cdot t} - 0.5443 \cdot e^{-8.052 \cdot t} + 8.14E-5 \cdot e^{-0.00058 \cdot t} \quad \text{Eq. 2}$$

$$q_3(t) = -0.1292 \cdot e^{-0.666 \cdot t} - 0.0273 \cdot e^{-8.052 \cdot t} + 0.15654 \cdot e^{-0.00058 \cdot t}, \quad \text{Eq. 3}$$

where t is hr.

Compartments 2 and 3 were considered (dosimetrically) to be the remainder of the body. The residence time for compartment 1 was apportioned to lung ($\tau_1 \cdot 0.196/0.837$) and spleen ($\tau_1 \cdot 0.032/0.837$) with the residual fraction of τ_1 lumped with the remainder of the body.

Urea Model

Studies by Marshall et al. (*7*) have indicated that the absorption of the ingested ^{14}C-labeled urea is essentially complete within 20 min. The assumption that 95% of the administered dose, both bicarbonate and urea, is absorbed in 20 min implies a biological half-time of 4.62 min. This results in a calculated stomach residence time of 0.11 hr. Delluva et al. (*15*) demonstrated that urea is not hydrolyzed by mammalian cells and always indicates the presence of bacteria. In unpublished studies from the University of Virginia, three HP− subjects excreted more than 75% of ingested urea in a three-day urine collection. We assume that the remaining urea was hydrolyzed by bacterial organisms in the gut and that the CO_2 was excreted in the breath. This assumption has been made by other authors who have investigated urea metabolism in humans (*16*). The absorbed (and unmetabolized) urea was assumed to be excreted from the remainder of the body with a 6-hr half-time via the urinary pathway (*14*). Therefore, k_{UB} = 0.116 hr^{-1}. The residence times for the urinary bladder contents were calculated using the dynamic bladder model of Cloutier et al. (*17*) with a voiding interval of 4.8 hr.

The MIRDOSE3 software, (Radiation Internal Dosimetry Information Center at the Oak Ridge Institute for Science and Education, Oak Ridge, TN) was used to calculate the absorbed doses. The specific absorbed fractions of Cristy and Eckerman (*18*) for the adult male and female were used.

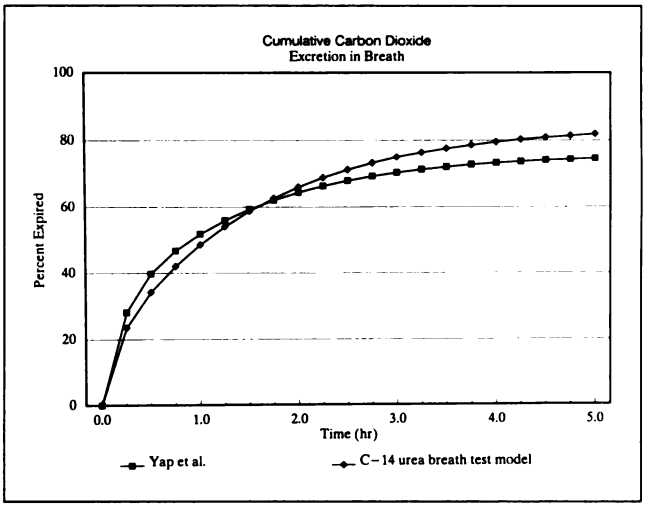

FIGURE 2. Comparison of the percent of injected bicarbonate excreted in the breath of human subjects. The data of Yap et al. (*9*) (squares) were measured for 5 hr. The percentage of the bicarbonate, produced by urea metabolism, that our model predicts to be exhaled in the form of CO_2 is also given (diamonds). There is good agreement between the measurement and our model prediction.

RESULTS

Figure 2 compares the cumulative breath excretion of $^{14}CO_2$ reported by Yap et al. (*9*) and this report. The residence times for the modified bicarbonate model, urea model and the ^{14}C-urea breath test (HP+ and HP− subjects) are listed in Table 2. The results of the dose calculations for oral administration of ^{14}C-urea in males and females are contained in Tables 3 and 4, respectively. The absorbed dose to females is slightly higher than that for males because of the general tendency toward smaller body and organ masses in females as compared to males (*18*). The urinary bladder wall received the highest dose

TABLE 2
Residence Times for Bicarbonate Model, Urea Model and ^{14}C-Urea Breath Test Model in HP− and HP+ Subjects

Organ	CO_3^{-2}-CO_2 (hr)	Urea (hr)	HP−* (hr)	HP+† (hr)
Lung	0.146	—	0.044	0.088
Spleen	0.024	—	0.007	0.014
Remainder of body	269	8.66	86.8	165
Stomach	—	0.11	0.11‡	0.11‡
Urinary bladder	—	2.62§	1.83	1.05

*Urea excretion = 70%; CO_2 excretion = 30%.
†Urea excretion = 40%; CO_2 excretion = 60%.
‡Gastric absorption rate equivalent for HP− and HP+ subjects.
§4.8-hr bladder voiding interval.

TABLE 3
Radiation Absorbed Dose Estimates for the ^{14}C-Urea Breath Test in Females

	HP−		HP+	
Target organ	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi
Stomach	3.0E-02	1.1E-01	5.0E-02	1.9E-01
Lungs	1.9E-03	7.1E-03	3.8E-03	1.4E-02
Ovaries	4.4E-02	1.6E-01	8.4E-02	3.1E-01
Red marrow	5.6E-02	2.1E-01	1.1E-01	3.9E-01
Bone surfaces	4.2E-02	1.5E-01	7.9E-02	2.9E-01
Spleen	1.7E-03	6.2E-03	3.3E-03	1.2E-02
Testes	4.4E-02	1.6E-01	8.4E-02	3.1E-01
Urinary bladder wall	1.9E-01	6.9E-01	1.4E-01	5.0E-01
Uterus	4.4E-02	1.6E-01	8.4E-02	3.1E-01
All others	4.4E-02	1.6E-01	8.3E-02	3.1E-01
	mSv/MBq	rem/mCi	mSv/MBq	rem/mCi
Effective dose equivalent	4.9E-02	1.8E-01	8.0E-02	3.0E-01

(D_{UBW}) in all subject populations (D_{UBW} < 0.19 mGy/MBq).

DISCUSSION

Our model predicts that the cumulative pulmonary excretion of CO_2 at 1 hr postadministration is 49%. The model of Yap et al. (*9*) predicts a value of 52%. Recent work (*19*) reported a 1-hr cumulative excretion value of 58% for a bolus injection of ^{11}C-labeled CO_2/bicarbonate solution. We feel that these data (*9,19*) support the model of CO_2/bicarbonate used for this report.

Our results indicate that for the ^{14}C-urea breath test, the urinary bladder wall (dose < 0.19 mGy/MBq) receives the highest dose. Yap et al. (*9*) reported that the bone received the highest dose equivalent (3.1 mSv/MBq). The absorbed dose (mGy/MBq) and the dose equivalent (mSv/MBq), although numerically equivalent for ^{14}C, are not the same quantity, though they are related. Yap et al. (*9*) estimated the dose equivalent for bone and lung to be higher, relative to our results, by factors of at least 39 and 26, respectively. The absorbed dose to bone for our model is due to activity in the remainder of the body, of which bone is a constituent. Estimates of gonadal dose from Yap et al. (*9*) were similar to our results. The above comparisons were made of Yap's data with our dose estimates for the HP+ female. Comparisons with the other three subject populations show an even greater difference.

The largest calculated effective dose equivalent for the ^{14}C "Microdose" breath test (HP+ female) is 0.080 mSv/MBq. The effective dose equivalent (global mean) to an average person from natural sources was recently reported by UNSCEAR to be 2.4 mSv/yr (*20*). Approximately 800 ^{14}C-urea "Microdose" (*21*) breath tests (37

TABLE 4
Radiation Absorbed Dose Estimates for the ^{14}C-Urea Breath Test in Males

	HP−		HP+	
Target organ	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi
Stomach	2.3E-02	8.6E-02	3.9E-02	1.4E-01
Lungs	1.3E-03	4.6E-03	2.5E-03	9.2E-03
Ovaries	3.4E-02	1.3E-01	6.5E-02	2.4E-01
Red marrow	4.5E-02	1.7E-01	8.6E-02	3.2E-01
Bone surfaces	3.1E-02	1.1E-01	5.8E-02	2.2E-01
Spleen	1.1E-03	4.2E-03	2.2E-03	8.3E-03
Testes	3.4E-02	1.3E-01	6.5E-02	2.4E-01
Urinary bladder wall	1.4E-01	5.2E-01	1.0E-01	3.8E-01
Uterus	3.4E-02	1.3E-01	6.5E-02	2.4E-01
All others	3.4E-02	1.3E-01	6.5E-02	2.4E-01
	mSv/MBq	rem/mCi	mSv/MBq	rem/mCi
Effective dose equivalent	3.8E-02	1.4E-01	6.2E-02	2.3E-01

TABLE 5
Urinary Bladder Wall Dose for a 2.0-Hour Bladder Voiding Interval

Subject	mGy/MBq	rad/mCi	%Reduction*
HP− male	0.066	0.25	53
HP+ male	0.061	0.22	42
HP− female	0.087	0.32	53
HP+ female	0.079	0.29	42

*Compared to dose for a 4.8-hr bladder voiding interval.

kBq per test) would generate the same effective dose equivalent. Therefore, it may be concluded that the relatively few ^{14}C-urea breath tests an individual may receive per year will contribute insignificantly to their radiation exposure.

Prudent radiation protection practice seeks to reduce all absorbed doses to as low as reasonably achievable (ALARA). Reducing the bladder voiding interval to 2 hr would decrease the dose to the urinary bladder wall by 42%–53%. Table 5 illustrates the substantial reduction in absorbed dose to the bladder wall for a 2.0-hr bladder voiding interval as opposed to the 4.8-hr voiding interval.

In conclusion, we have calculated a comprehensive set of absorbed dose estimates for a ^{14}C-labeled urea breath test to HP+ and HP− males and females based upon a metabolic model of bicarbonate kinetics and measured urea metabolism. For a 37-kBq administered dose, these estimates are substantially lower than previously calculated and approximate those received from natural sources in an 11-hr period. Dose to the lung and bone were estimated to be substantially lower than previously thought; dose to the remainder of the body was three-fold lower and the urinary bladder wall was determined to receive a higher dose than bone.

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REFERENCES

1. Graham DY, Malaty HM, Evans DG, Evans DJ, Klein PD, Adam E. Epidemiology of Helicobacter pylori in an asymptomatic population in the United States. *Gastroenterology* 1991;100:1495–1501.
2. Peterson WL. Helicobacter pylori and peptic ulcer disease. *N Engl J Med* 1991;324:1043–1048.
3. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991;325:1127–1131.
4. McNulty CA, Wise R. Rapid diagnosis of Campylobacter-associated gastritis [Letter]. *Lancet* 1985;1:1443–1444.
5. Marshall BJ, Warren JR, Francis GJ, Langton SR, Goodwin CS, Blincow E. Rapid urease test in the management of Campylobacter pyloridis-associated gastritis. *Am J Gastroenterol* 1987;82:200–210.
6. Graham DY, Klein PD, Evans DJ, et al. Campylobacter pylori detected noninvasively with the ^{13}C-urea. *Lancet* 1987;1:1174–7.
7. Marshall BJ, Plankey MW, Hoffman SR, et al. A 20-min breath test for Helicobacter pylori. *Am J Gastroenterol* 1991;86:438–445.
8. Marshall BJ, Surveyor I. Carbon-14 breath test for the diagnosis of Campylobacter pylori associated gastritis. *J Nucl Med* 1988;29:11–16.
9. Yap SH, Hafkenscheid JCM, Goossens CMIC, Buys WCAM, Binkhorst RA, Van Tongeren JHM. Estimation of radiation dosage and transmutation effect of ^{14}C involved in measuring rate of albumin synthesis with ^{14}C-carbonate. *J Nucl Med* 1975;16:642–648.
10. International commission on radiological protection report of committee II on permissible dose from internal radiation. New York, New York: Pergamon Press; 1959.
11. International commission on radiological protection No. 23; report of the task group on reference man. Oxford, England: Pergamon Press; 1975.
12. Winchell HS, Stahelin H, Slanger B, Fish M, Pollycove M, Lawrence JH. Kinetics of CO_2-HCO_3^- in normal adult males. *J Nucl Med* 1970;11:711–715.
13. International commission on radiological protection No. 30, Parts 1 & 3; limits for intakes of radionuclides by workers. Oxford, England: Pergamon Press; 1981.
14. Powers WJ, Stabin M, Howse D, Eichling JO, Herscovitch P. Radiation absorbed dose estimates for oxygen-15 radiopharmaceuticals ($H_2{}^{15}O$, $C^{15}O$, $O^{15}O$) in newborn infants. *J Nucl Med* 1988;29:1961–1970.
15. Delluva AM, Markley K, Davies RE. The absence of gastric urease in germ free animals. *Biochem Biophys Acta* 1968;151:646–650.
16. Hansen BA, Vilstrup H. Increased intestinal hydrolysis of urea in patients with alcoholic cirrhosis. *Scand J Gastroenterol* 1985;20:346–350.
17. Cloutier RJ, Smith SA, Watson EE. Dose to the fetus from radionuclides in the bladder. *Health Phys* 1973;25:147–161.
18. Cristy M, Eckerman KF. Specific absorbed fractions of energy at various ages from internal photon sources. Oak Ridge National Laboratory Report ORNL/TM-8361 Volumes 1, 5 & 7; 1987.
19. Shields AF, Graham MM, Kozawa SM, et al. Contribution of labeled carbon dioxide to PET imaging of carbon-11-labeled compounds. *J Nucl Med* 1992;33:581–584.
20. Sources, effects and risks of ionizing radiation. In: *United Nations Scientific Committee on the Effects of Atomic Radiation 1988 Report to the General Assembly, with annexes*. New York: United Nations; 1988.
21. Marshall BJ, Hoffman SR, Sarosiek J, McCallum RW. A microdose, capsule-based, ^{14}C-urea breath test for *H. pylori* [Abstract]. *Gastroenterology* 1991;100:A118.