The effective biological monitoring of astronauts during long-term flights represents a new aspect of environmental and human toxicology. Iodine compounds, used by the National Aeronautics and Space Administration (NASA) as water disinfectants during extended space missions, can be a potential human hazard (1,2). Exposure to excess iodine through foods, dietary supplements, topical medications, or iodinated contrast media widely used in clinical diagnostics can produce toxic responses in humans including thyroiditis, goiter, hypothyroidism, hyperthyroidism, sensitivity reactions, and acute responses (3–6).

An important aspect of biological monitoring of astronauts is to identify a method that can recapitulate exposure to toxic substances during the mission. Potential media include blood, saliva, urine, and hair. Not all of these media, however, can be easily collected and stored during long-lasting space missions. According to numerous studies, human hair can be a useful medium for biological monitoring (7–10). Hair has the potential to incorporate chemicals transported from the bloodstream into the follicle and subsequently into the hair shaft. Thus, with a growth rate of approximately 1 cm/month, even a short length of hair can recapitulate blood levels over periods of several months (9).

In our previous studies (11), we demonstrated that human hair transplanted onto nude mice can be used to evaluate human exposure to different toxic substances. This unique system maintains human hair characteristics and incorporates toxic substances in a fashion identical to that seen in humans in vivo. The presence of excess iodine in hair has been reported in several animal and human studies (12–17), but this medium has not been critically evaluated as an indicator of iodine exposure. NASA has been using saliva for clinical monitoring of drugs (18), and this medium also should be considered because it is noninvasive and high iodine concentrations are found in saliva (19,20).

Urine is widely used to estimate iodine status in subjects with dietary iodine deficiency, and the guidelines for minimum iodine concentrations in urine have been already established (21,22). Nevertheless, data on iodine levels in urine are scarce. Under space laboratory conditions, iodine analysis in plasma, due to very low concentrations, as well as the other laboratory tests (i.e., triiodothyronine, thyroxine, or thyroid-stimulating hormone levels) will be difficult to perform.

Iodine forms a variety of ions and compounds when added to drinking water (23,24). Recycling systems now being planned for long-term flight missions will lead to further iodine-containing by-products. The bioavailability of these by-products, and even their chemical identity, is not known. Thus, biological monitoring is the only means to determine tissue burdens of iodine.

The primary objective of this study was to evaluate the usefulness of hair, saliva, and urine for biological monitoring of iodine in order to establish guidelines for assessing astronauts’ exposure to iodine in drinking water. This was accomplished by studying iodine elimination in human and in vivo iodine incorporation into human hair, both in humans and in a human hair/nude mouse model, after single-dose and prolonged exposure.

**Material and Methods**

We monitored iodine in blood, saliva, urine, and hair in five patients with a diagnosis of thyroid carcinoma. Four weeks after a total thyroidectomy the patients received a therapeutic, single oral dose of 150 mCi Na\(^{131}\)I, carrier-free (Iodotope, Squibb Diagnostics, Princeton, New Jersey). Elimination of iodine in blood, saliva, urine, and hair was determined for 3 days during hospitalization and when available over the next week. During hospitalization, blood was collected once a day, saliva twice a day, and urine twice a day in precise 2-hr collections (2 hr after empying the bladder), after obtaining written consent. We measured \(^{131}\)I using a Packard \(\gamma\)-scintillation counter. Creatinine levels (Sigma, St. Louis, Missouri) were measured in urine. Comparison of mean half-time (T\(_{1/2}\)) values of iodine elimination in blood, saliva, and urine was performed using the \(t\)-test. The relationship of iodine concentration among blood, saliva, and urine was analyzed with Pearson’s correlation coefficient, and pertinent \(p\)-values were calculated using linear regression. A \(p\)-value <0.05 was considered statistically significant.

Iodine incorporation into hair was evaluated using hairs plucked 2, 20, 24, 48, and 52 hr after iodine administration. Hairs were processed for autoradiography with Kodak X-OMAT film, exposed for 48 hr at room temperature, and developed.
ulate stability of iodine incorporation, hairs were washed with acetone, ethyl ether, or 1% nonionic detergent solution for 1 hr, rinsed three times with deionized water, and air dried. We measured iodine levels after the washing procedure as a percentage of initial concentration.

We used the human scalp/nude mouse model to study incorporation of iodine into hair during continuous iodine exposure. Ten 5-week-old male BALB/c nu/nu nude mice obtained from NIH Taconic Farm (Germantown, Maryland) were housed in metabolic cages in a clean room (bioBubble, Inc., Fort Collins, Colorado) in a 12-hr light/12-hr dark cycle at 25°C with free access to tap water and mouse chow (Purina Mills Inc., Richmond, Indiana).

Human tissue collection conformed to current recommendations of the National Institutes of Health and recommendations of the University of Rochester's Committee on Investigations Involving Human Subjects. Human scalp skin grafts were transplanted subcutaneously using pentobarbital for anesthesia (60 mg/kg).

We administered Na125I (Nal, Fisher Scientific, Pittsburgh, Pennsylvania; Nal125I carrier-free, Dupont, Wilmington, Delaware) solutions to animals using subcutaneously implanted ALZET osmotic pumps (model 2002; 10 mg I/ml, 100 μCi/ml). Biopsies from grafts of human scalp and mouse skin were taken 2 weeks after cessation of exposure, embedded in plastic, and processed for autoradiography with Kodak NTB-2 film emulsion, exposed for 7 days at 4°C, and developed. Sections were then stained with toluidine blue and mounted with Permount (Fisher Scientific).

Results

Table 1 shows half-time (t1/2) values in blood, saliva, and urine of all patients. Mean t1/2 values were similar: in blood 14.6 ± 3.8 hr, in saliva 13.7 ± 2.9 hr, and in urine 14.3 ± 3.6 hr (differences were not statistically significant).

The iodine elimination in blood, urine, and saliva of patient J.W., administered a single dose of 150 mCi 131I, is shown in Figure 1. In the first 3 days, iodine in all patients was eliminated in the highest concentrations in urine and saliva, showing first-order elimination. Levels of iodine in blood were about 30 times lower than in saliva and urine. Iodine concentrations in saliva were only slightly higher than in urine. Despite different magnitudes, the pattern of elimination was similar for all three media.

Correlation coefficients between iodine elimination in blood and saliva, blood and urine, and saliva and urine, with relevant p-values, were calculated separately for all patients (Table 2). Levels of iodine in various media were highly correlated. Mean correlation coefficients (r) between iodine elimination in different media were for blood/saliva 0.99, blood/urine 0.95, and saliva/urine 0.97. The small number of cases did not allow us to obtain statistical significance in all correlations (Table 2).

Comparison of elimination curves in the urine of one patient with or without creatinine correction is shown in Figure 2. The absolute value of iodine concentrations in urine revealed marked variability, which was corrected by adjusting for creatinine levels.

Although the rapid elimination did not allow us to monitor iodine concentrations in patients' hair over a long period of time, the autoradiographic studies of hair demonstrated augmented accumulation of iodine in the hair root (Fig. 3). Repeated measurements over a 52-hr observation period showed an increase in iodine 131I uptake into the hair root with time. Iodine was also found along the hair shaft 52 hr after iodine administration (Fig. 3), indicating external iodine contamination of hair.

To study stability of iodine incorporation into human hair, root hairs obtained from 131I-treated patients were washed with ether, acetone, or 1% detergent solution (Fig. 4). Washing with ether and acetone did not change iodine concentrations in the hair root, whereas soaking with detergent solution removed the majority of iodine (about 50%).

Autoradiographic studies of human scalp transplanted onto the nude mouse performed 2 weeks after cessation of daily exposure (Na125I, 10 mg I/ml, 100 μCi/ml for 1 month) did not show iodine accumulation along the hair shaft (data not shown).

Discussion

Astronauts consuming water disinfected with iodine must be monitored to prevent the occurrence of adverse health effects.
our knowledge, the usefulness of hair, saliva, and urine for evaluating human exposure to iodine had not been studied.

There are many controversial data on uptake of iodine into the hair follicle. Leblond (12) postulated that iodine in hair occurs in inorganic form (iodide) and can be related to the iodine content of the diet. Brown-Grant et al. (13,14) showed that iodine in hair occurs at the site where initial stages of keratin formation take place and that iodine incorporation can be associated with the binding to sulfhydryl groups in the prekeratogenous zone of the hair root. More recently, Jones et al. (25), after in vitro iodination of wool fibers, found a high iodine content in the orthocortex of the wool shaft associated with tyrosine-rich proteins. Contrary to these findings, Wright (15) demonstrated iodine incorporation into the rat hair follicle in the region where protein (keratin) formation is complete, at the level of the sebaceous gland. These data are supported by the observation of Abdel-Dayem et al. (17), who reported a single case of a significant amount of 131I detected along the hair shaft of a Bedouin woman, scanned 7 days after the administration of 50 mCi of 131I in a single therapeutic dose. This case indicates iodine contamination of the hair shaft from sweat or sebum. Bate et al. (26) noted that since many elements present in hair are also present in sweat, which comes into contact with hair, this external contamination may provide an "absorptive origin" for many elements found in hair.

Our data confirmed that in vivo iodine binding to the human hair root occurs mostly on the surface of the hair and that the iodine detected should be considered external contamination that can be removed by washing (Fig. 4). Because the hair grows 0.3–0.4 mm per day, the labeling over 9 mm in 3 days suggests external contamination. The amount of iodine that remains in hair could be due to incomplete washing. These results were further supported by data obtained from our unique experimental model, human hair growing on nude mice. Autoradiograms of human hair after continuous, 1-month exposure of mice to high doses of iodide did not show iodine incorporation along hair shaft (data not shown). A different medium therefore should be considered for biological monitoring of iodine exposure in astronauts.

We found that high iodine concentrations in saliva parallel iodine excretion in urine and blood (Fig. 1) and can provide information about the level of exposure, in agreement with other studies (27). If appropriate corrections are made for saliva flow rate (28), saliva should prove useful for biological monitoring of astronauts. Saliva has been shown to be an excellent biological monitoring medium for acetaminophen in astronauts (18).

Numerous studies have shown that daily urine iodine excretion can be accepted as a satisfactory index of iodine intake (4,5,21,22), but there are limited data on iodine concentrations after exposure to excess iodine. Grasso et al. (29) reported high concentrations (more than 1000 μg l/g creatinine) of iodine in the urine of patients admitted to the hospital for nonthyroidal diseases. In the few reports on controlled human exposure to excess iodine in drinking water (30,31), iodine concentrations in urine exceeded 1000 μg l/g creatinine. Philips et al. (32) reported thyrotoxicosis in England caused by high iodine concentrations in milk when cattle feed was supplemented with iodine. Nelson et al. (33) demonstrated a strong correlation between urinary iodine excretion and iodine content of milk. A good correlation between iodine dose administered to vol-

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**Figure 2.** Comparison of 131I elimination curves in urine of patient J.W. after a single, oral dose of 150 mCi 131I, 2-hr urine collection.

**Figure 3.** Autoradiogram of hair of patient J.W. Iodine accumulation in hair roots increased after a single administration of 150 mCi 131I. Hair samples collected at (A) 2 hr, (B) 20 hr, (C) 24 hr, (D) 44 hr, and (E) 52 hr after iodine administration.

**Figure 4.** Removal of 131I from human hair after washing with ether, acetone, or 1% detergent solution as a percentage of initial concentration of 131I in unwashed hair (100%).
unters in drinking water and urinary iodine excretion was observed by Robinson et al. (personal communication). From these reports and from our data, we conclude that urinary iodine determinations seem to be the most reliable biological index of iodine exposure in humans.

It should be pointed out that there are some controversies regarding the units in which iodine urinary excretion should be expressed. Some data reported excretion relative to creatinine excretion, others on the basis of 24-hr urine collection or iodide excretion per kilogram body weight (22). Our data showed clearly that due to large variations in iodine excretion, the assessment of iodine in urine should be adjusted for creatinine excretion (Fig. 2).

It should be stressed that there are no recommendations for maximum safe concentrations of iodine in urine associated with excessive iodine intake. According to recent reports of the Food and Nutrition Board of the National Academy of Sciences, a daily iodine intake in adults ranging from 50 to 2000 μg of iodine/day has no adverse effects in healthy individuals (21). Since NASA uses iodine concentrations in drinking water of 2 mg/l (J), the daily average intake can easily exceed acceptable values.

In summary, we conclude that hair cannot be used as a medium for biological monitoring of iodine in humans. Salivary iodine levels showed promising correlation with the other media, and saliva has the advantage of offering noninvasive collection in space. The established indicator that can provide satisfactory information about exposure to iodine is urine, when adjusted for creatinine, but more studies on the relationship among urine levels, body concentrations, and thyroid function should be done to evaluate risk assessment of astronaut exposure related to iodine in drinking water.

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