time highly entertaining. It is also viewed with delight by adults. This 1-h program is aired on educational stations as well as by some commercial stations; 80% of these stations are showing it twice a day. It has been estimated that 80% of Boston's preschool children are watching it. One may speculate that the program has a great impact on the child's motivation to learn creatively and joyfully.

Dr. RICHMOND: Efforts are being made to try to evaluate this program. I am not in a position to comment on it very fully, since I have had no direct involvement with the program. This is a good example of the mass media having made a good effort to utilize professional opinion, both in the design of the program and in efforts to evaluate it. I anticipate that we will be getting some data from the planners and producers of the program.

14 *Evaluation of Treatment of Thyrotoxicosis in Children and Adolescents with Radioactive Iodine.* ALBERTO HAYEK, EARLE M. CHAPMAN and JOHN D. CRAWFORD. Harvard Med. Sch., Massachusetts Gen. Hosp., Children's Service, Boston, Mass.

LYTT I. GARDNER (State University of New York, Upstate Medical Center, Syracuse, N.Y.): I agree that the children who have already been treated with radioactive iodine should be followed very carefully. I would question whether additional children should be treated until one has exhaustive follow-up on the children already treated. I submit that a mean follow-up of 9.2 years is not adequate to draw the conclusion that radioactive iodine therapy is to be rated as safe as other modes of therapy now available.

Dr. HAYEK: Our conclusion was based on all adequate data thus far published. We were cautious in admitting that 'up to date' the results have been quite satisfactory when one compares the complications from radioiodine with those observed after surgery and drug therapy in this disease. A great deal more information could be gained were some organization such as the American Academy of Pediatrics to collect data on all the children who have been treated with radioactive iodine; a comprehensive survey would increase by 10- or 20-fold the number of children reported and probably the mean follow-up time.

DELBERT A. FISHER (UCLA School of Medicine, Harbor General Hospital, Torrance, Calif.): Just a comment relating to Dr. GARDNER's. The incidence of hypothyroidism after radioiodine therapy in the adult is usually related to the dose of radiation, in rads, to the gland. The conventional dose is about 7,000 rads. The incidence of hypothyroidism with 7,000 rads is generally considered to be 5–10% the first year, and 1–3% additional per year thereafter. Your incidence of 30% at 10 years is about equivalent to this. I think this implies that there will be a progressive increase in the incidence of hypothyroidism in these patients.

Dr. HAYEK: I mentioned the data of BELING and EINHORN [Acta radiol. *56:* 275 (1961)], predicting an incidence of hypothyroidism of 6.5% for the first year with an increase of 3% per year leading to a 30% figure for the 7-year-posttreatment period. Our incidence is similar, but it should be noted that for the last 7 years only one case of hypothyroidism has developed in our patients. It was during this period that we began to use lower doses of radioiodine together with stable iodine. Perhaps these measures have contributed to the reduction of hypothyroidism occurring in the first decade posttherapy. Comparable results have been reported by HAGAN *et al.* [New Engl. J. Med. *277:* 559 (1967)] in adults treated at the Massachusetts General Hospital.

Dr. FISHER: Your 6-mCi dose, and now maximal 5-mCi dose, amounts to how much estimated radiation per gland? Now the trend is to use lesser doses of radioiodine, something on the order of 3,000–3,500 rads and with such doses the incidence of late hypothyroidism is reduced to about one-third.

Dr. HAYEK: The amount of radiation delivered by radioactive iodine to the thyroid is related to the gland's weight, its rate of turnover and the biological half-life of $^{131}I$. Unfortunately, we all lack a precise way to estimate the first parameter. A dose of 60–80 μCi/g to a gland weighing between 40 and 50 g with a high uptake and rapid turnover will give a radiation dose to the thyroid of about 5,000 rads and probably in the vicinity of 5–6 rads to the rest of the body. I would like to stress that doses as small as 2 mCi have been successful in obtaining remission when stable iodine has been used concomitantly.

EDNA SOBEL (Albert Einstein College of Medicine, New York, N.Y.): I think that the point at difference may be whether one is thinking in terms of the number of thyroid tumors found or in terms of elapsed time. Even if complete follow-up information on all the children who had been treated with radioactive iodine in the past 30 years were now collected, I do not believe that we could be satisfied about the risk of eventual malignancy. Only two of your patients had been treated more than 22 years ago. The only thyroid tissue examined histologically was diagnosed as a benign adenoma, 17 years after treatment. This just is not long enough. DOLPHIN's compilation [Health Physics *15:* 219 (1968)] shows that thyroid nodules developed in 19 of 32 individuals who had been exposed to radioactive iodine under the age of 20, and that only one of the nodules was malignant. He mentioned that more cancers could be expected, because the follow-up time was just over 12 years.

The argument that many internists pose to pediatricians who are concerned about thyroid nodules and cancer is that thyroid cancer does not kill. Thyroid cancer may not kill adults, but it does kill children. Papillary and follicular thyroid cancers are relatively indolent, and most adults reach the end of their life expectancy for other reasons before they die of the cancer. That is not true of children. Calculations made from WINSHIP's data (Amer. J. Surg. *102:* 747 (1961)], as they are cited by DOLPHIN, indicate that 55 of 554 children in whom papillary or follicular carcinoma of the thyroid gland was diagnosed before the age of 15 were dead 21 years later, before they had reached the age of 36.

I would like to state that we are very patient in our use of antithyroid drugs. One boy is now in his 6th year of treatment with propylthiouracil, and seems to be almost over his disease. This therapeutic plan was difficult, but perhaps I can feel confident that I will not die before he dies of a thyroid cancer induced by treatment I recommended.

I wish I could be as sure as you are that radioactive iodine is a safe treatment; certainly it would be a great deal easier than a medical program for both patient and physician.

Dr. HAYEK: Most therapeutic procedures that doctors undertake for the well being of a patient carry a risk. In the case of radioactive iodine, we are all aware of its potential complications and we are on the lookout for them. Only more data such as those presented here

will give an answer to this problem. I agree with you that the safety factor has not been completely resolved and until it has, this treatment will remain controversial. With the information available at this time children under the age of 5 years and those exhibiting very large goiters requiring a higher $^{131}I$ dose should probably be treated with surgery or the antithyroid drugs.

In our experience, cancer of the thyroid in children carries an excellent prognosis providing that the cancer is restricted to the thyroid gland and is detected early. It is of interest to note that the incidence of thyroid cancer in the adult population has not increased since the introduction of radioactive iodine in the therapy of this disease.

ALLAN L. DRASH (The Children's Hospital of Pittsburgh): I am concerned about the statistical handling of your data. In the follow-up analysis you have not made any consideration of the age of the patient at the time of $^{131}I$ administration. Information gained from experience with external irradiation and the induction of thyroid carcinoma should be applicable here.

As is well known, thyroid carcinoma in the child and young adult is highly correlated with exposure to external irradiation. Although many of the cases resulted from radiation exposure during the first year of life, thyroid carcinoma has clearly resulted from external irradiation occurring any time prior to adolescence. The onset of adolescence appears to carry with it a relative resistance to the induction of neoplastic change in the thyroid gland.

Do you have follow-up data comparing those who received $^{131}I$ in the preadolescent period with those who were adolescent or postadolescent at the time of radiation exposure? It would appear judicious to refrain from using $^{131}I$ therapeutically in preadolescent thyrotoxic patients until the outcome in adolescents and young adults is unequivocally settled.

Dr. HAYEK: We have treated in this series only 3 patients under the age of 10 years. Their follow up is 28, 10, and 1.5 years. With regard to the susceptibility of children to thyroid cancer after external radiation, it is quite evident that this is closely related to the age at exposure. The younger the child the higher his susceptibility. As you recall, the original observation of the relationship was made in children who were treated with external radiation for 'enlarged thymus' very early in childhood. DOLPHIN, analyzing HEMPELMAN's data on 2,878 children with this history, has pointed out that almost all children were irradiated prior to 6 months of age. This group of patients had 41 tumors, 19 malignant and 22 benign. The reason why most of our treated patients were preadolescents or adolescents largely reflects the higher incidence of the disease in this particular age group. Most people would agree that thyrotoxicosis in the young occurs with an incidence of about 70% in the 10–18 year group, 20% for the 5–10 year group, and less than 10% for children under age 5 years.

DAVID W. SMITH (University of Washington School of Medicine, Seattle, Wash.): The type of genetic damage due to $^{131}I$ therapy is most likely to be recessive single gene mutations and these will generally *not* be appreciated in terms of the incidence of birth defects in the offspring of irradiated parents. Actually, the deleterious effect of such recessive mutations would probably not be appreciated for generations to come and thereby creates an almost impossible situation for follow-up in the human. The dangers of $^{131}I$ relative to genetic mutation should be studied more completely in rapidly reproducing animals before their use is seriously considered in the human who is of reproductive age. Adding the unknown carcinogenic aspect to the concern for genetic mutation, I strongly oppose the therapeutic use of $^{131}I$ in prereproductive and reproductive ages.

I would be in favor of using other modes, surgically and medically, in handling this condition in individuals who are prereproductive in time.

Dr. HAYEK: I hope more data on this point can be gained by study of the progeny of the Japanese population affected by the atomic bombings.

JOHN D. BAILEY (Hospital for Sick Children, Toronto, Ont.): Did the patients treated with radioactive iodine have measurements taken of their TSH levels or their response to TSH after treatment?

Dr. HAYEK: The TSH radioimmunoassay has been available to us for the last 2 years. In those patients in whom TSH was measured, $T_4$ values declining into the hypothyroid range were associated with rising levels of TSH. It should be noted that these patients were receiving $^{127}I$ at the time they became chemically hypothyroid. Discontinuation of stable iodine brought the $T_4$ back to normal, with a decline in the TSH value towards physiologic levels. We have observed few patients, years after treatment with radioactive iodine, in whom euthyroidism appears to be maintained at the expense of TSH overstimulation, as measured by an increased concentration of the trophic hormone in peripheral blood.

Dr. BAILEY: I would like to propose that patients treated with radioactive iodine be treated with thyroid therapy after treatment, because although they may be clinically and biochemically euthyroid, these patients lack thyroid reserve, and they are being maintained by maximal TSH stimulation. They gradually show up as being clinically hypothyroid. Secondly, it exposes a damaged thyroid gland to high levels of TSH and excess stimulation, which may increase the incidence of thyroid problems in the posttreatment group.

Dr. HAYEK: In the patient showing chemical hypothyroidism 2–3 months after therapy, TSH is regularly high. However, as pointed out before, thyroid indices generally return to normal followed by a decline in the TSH. These patients probably do not require thyroid replacement therapy.

Concerning your second question, Dr. MALOOF has coined the term 'prehypothyroidism' for those patients in whom euthyroidism is maintained at the expense of TSH overstimulation. You may be right in assuming that replacement therapy may reduce the incidence of thyroid abnormalities in these patients. We do not have sufficient data, but it seems that, if untreated, these patients will eventually become hypothyroid.

Chairman FORBES: You indicated a radiation dose to the thyroid on the order of 5–5,000 R, but do you have any idea what the dose is to the stomach, the kidneys, and the gonads?

Dr. HAYEK: The dose of radiation to kidney, stomach, and gonads is probably less than 7 rads. Since radioiodine not trapped in the thyroid gland is promptly excreted in the urine, we give these children a moderate water load to enable them to void frequently and reduce the retention time of radioiodine in the bladder, thus decreasing radiation to the gonads.

President RICHARD L. DAY (New Rochelle, New York): I want to comment about the comments on this paper. I had responsibility for this program, I was very interested in this paper—I wanted to hear it presented —but more particularly I wanted to hear the com-

ments. It seems to me worthwhile to review what has been said. It was said by a geneticist that the kind of defects one would expect would be recessive, and would not appear in the first generation. Not only that; there has to be consanguinity; and even in Hiroshima, recessive traits from the bomb are not showing up despite a higher rate of consanguinity than in the United States. So, to discover the recessive defects that are caused by radiation is virtually impossible. I do not think Dr. HAYEK will live long enough to find out whether any have been induced.

Secondly, the interval between the stimulus and the possible cancer is totally unknown, as far as I know, from any data that you have. We have no idea whether you need to wait 8 years, 18 years, or 50 years.

So I would like to urge that those people, and there seem to be several, who are using this method of treatment do what HAYEK suggested; namely, see if there cannot be a follow-up of children who received this treatment in several centers years ago, and make a study like the one on cancer of the thyroid in relation to radiation of the thymus.