LYMAN A. PAGE (Stanford School of Medicine, Palo Alto, Calif.): Do you have data on whether the reduced size of other organs is due to reduced cell number?

Dr. KNITTLE: We have no data now. We have organs in the deep freeze, and we will be doing DNA and protein ratios to determine cell number and size.

- 12 *Defective Coenzyme Biosynthesis in B₁₂-dependent Methylmalonicaciduria*. MAURICE J. MAHONEY, MILDRED C. STAMBAUGH and LEON E. ROSENBERG. Depts. of Ped. and Med., Yale Univ. Sch. of Med., New Haven, Conn. (introduced by C. D. Cook).

Chairman GILBERT B. FORBES: Would you like to multiply vitamin B₆ by a factor of 2 and talk about vitamin B₁₂?

CHARLES R. SCRIVER (Montreal Children's Hospital, Montreal, Que.): If only I had half the expertise to attempt it! The authors have presented a beautiful piece of work and there is nothing I can say to add to it.

I would like to ask about something that may be of interest in the future, and which could be one of the legacies of your observations. When these patients respond to the administration of vitamin B₁₂, you are also giving an atom of cobalt for every molecule of vitamin B₁₂. About 3 years ago, in Quebec we had an epidemic of cobalt toxicity with cardiomyopathy. Do you know whether long-term administration of vitamin B₁₂ to your patients will also give them a load of cobalt that may actually be toxic? Do you think this is a danger?

Dr. MAHONEY: I believe we will need a long follow-up period to answer that question. The cobalt atom is held in a tight organic complex in the cobalamine molecule and the cobalamine molecule is rapidly cleared from the blood by renal excretion. Thus we can hope that the cobalt load will not reach a high toxic level.

We have treated the first patient described for over 2 years with twice a week injections of 1 mg of cyano-B₁₂. At times we have substituted the same amount of the coenzyme, deoxyadenosyl-B₁₂.

- 13 *Extending the Evaluation of the Effects of Early Enrichment*. JULIUS B. RICHMOND and BETTYE M. CALDWELL. Upstate Med. Center, Syracuse, NY, and Univ. of Arkansas.

ALEXANDER DRESCHER (Albany Medical College): Do you feel that 0.5 h/week may provide the placebo effect of a caring and concerned adult, rather than any other educational phenomenon?

Dr. RICHMOND: I think this is an important issue. Many of the home 'tutoring' programs that are currently in process, that of WEIKART and several others, stem from the concern over the importance of parent involvement. The impact programs have on parents, and what it does to their attitudes and care of the child, may indeed be the important issues. These are some of the problems that remain to be solved. This suggests that we need alternate programs to explore a variety of approaches.

MARSHALL KLAUS (Case Western Reserve University, Cleveland, Ohio): Historically, it has been of interest to see what is important in pediatrics and how pediatrics has changed over the years. What does the teacher usually do during the half-hour?

Dr. RICHMOND: First, I would suggest that I do not know that we should generalize from this half-hour. Remember, in the program it was the lead teacher who knew these children well and who visited the children at

home. I think that the emotional factors as well as the content of what was presented would be extremely important. I also preface my comments by indicating that our numbers are small and we could rely on only one highly skilled tutor.

Also, I might say that this was a dimension of the program that was not originally planned. In our early days we were not heavily invested in home tutoring. We were rather invested in the group care program, so that at the time we undertook this we did not have an available pool of tutors. We, therefore, used the teacher who was the most skilled and who knew these children, to go into the home.

LEONARD M. LINDE (University of California Medical Center, Los Angeles, Calif.): I have been working this past year with the disadvantaged student as he applies for medical school, and one of the problems that we have encountered is that the tests are made up by advantaged people. I am wondering if the disadvantaged student is not learning some other kinds of skills that allow him to cope with his own environment, miserable as it may be, that may be missed in the testing.

In other words, how do you test for what this disadvantaged child has to know to get along? And is it possible that the tests, made up by advantaged people are merely testing something that advantaged children learn?

Dr. RICHMOND: I think this is a very important question, and certainly relates to the whole matter of the testing of cognitive function. Certainly, no one has been successful in developing a test that is free of cultural bias. We use tests that are the best that we have. We do feel, and other data that we have concerning social and psychological functioning of these children indicates, that there are many other gains beyond the cognitive. As a matter of fact, ZIGLER and BUTTERWORTH, in New Haven, and others have become very interested not only in following cognitive function, but also in learning something more about motivation. If we achieve cognitive gains and do not build in motivation for continued learning we have significant losses as a consequence.

As you point out, we are not suggesting that these children are incapable of learning. But they may be incapable of learning what is required of them in the one social institution that we require all of them to attend, the schools. We made that judgement in the middle of the last century, and we are programming some of our children to fail in those institutions.

CHARLES D. COOK (New Haven, Conn.): We have heard a good bit about the interrelationship between nutrition and growth and intelligence. I wonder if you have any information about the growth of these children, so that we could see the relation between the developmental quotient that you measured and their growth.

Dr. RICHMOND: We do have such data. I am not prepared to comment on it at this time, however. The nutrition of our children generally was reasonably good. That is, we have not encountered any striking deviations. Although we are dealing with quite a low income population, nutritionally they seem to be in rather good condition.

HANIA W. RIS (University of Wisconsin Medical School, Madison, Wisc.): Are you planning to use the television program 'Sesame Street' as an enrichment program for the preschooler?

This is one of the most creative and imaginative educational programs for children, which is at the same

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 $\mu\text{Ci/g}$ 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