I would like to make it clear that we are not suggesting that the lack of positive findings here applies to comprehensive care programs in general. We suggest only that this approach be used to submit comprehensive care to a truly rigorous evaluation of its effectiveness.

BARBARA M. KORSCH (Children's Hospital, Los Angeles, Calif.): If, as has been stated, this may not have been an example of truly comprehensive care, in that it was not delivered by a health team and did not start at birth, on the other hand, it did seem to isolate the factor of continuous medical care by one physician. Here again, it seems to me that there are other studies, like the one by CHARNEY *et al.* where continuous care by a particular pediatrician did seem to make for increased compliance with various medical regimes studied previously.

So it is not a simple situation, even if you say that you are simply introducing the factor of the continuous relationship with a doctor. The question is: Can you legislate this in a hospital setting at one moment, and produce a change, or can you not?

To document the study, you may need larger numbers of cases, because in our earlier work on compliance with medical advice we did have some very discouraging months during the first few hundred cases, and finally the zeros before the ones began to appear after we were well beyond 600 or 700 patients. This was an outpatient department. I do not think that the findings in this number necessarily mean that you might not get a real difference.

There are several other points that interested me. I would be very curious to do some studies on the actual interaction between the physicians in the two systems and their patients, because our work has shown some statistically significant differences in patients following medical advice which could be predicted on the basis of specific attributes of an individual interaction of a new physician with a new patient around an illness, and I would be curious to see how the physicians in the two groups relate to patients, and how they communicate with their patients.

Finally, lest someone get the impression that the fact of having a continuous relationship with a doctor like this does not improve patients' follow-through on medical advice. When we started our studies we had done some work that suggested that perhaps the social distance between the physician and the patient might make the patient more compliant, in the sense that he is a big authority, and you cannot get too close to him, and maybe what he says might be more important, and therefore you were anxious to do what he said. We found exactly the opposite to be true in our compliance study; namely, that effect, and friendliness, and conversation other than strictly medical conversation, had a positive effect on compliance.

EDGAR J. SCHOEN (Kaiser Foundation Hospital, Oakland, Calif.): The authors considered they were delivering comprehensive care. Did the patients?

You mentioned that two senior residents were used. What was the total number of physicians involved in this work? Also, at the end of the study, were the patients asked at any point if they knew the name of their doctor?

Dr. GORDIS: The same two physicians provided all the care for the comprehensive care group. In response to your second question, on the identification of the physician by the patient, there were significant differences between the two groups in the percentage of who could correctly identify their physician by name.

NICHOLAS M. NELSON (Boston, Mass.): I would like to suggest that your slide which showed an increase in noncompliance in both the experimental and control groups is yet another demonstration of the uncertainty principle, or as it is sometimes known, the Hawthorne effect; namely, that it is impossible to observe the phenomenon without changing the phenomenon observed.

President DAY: I think we will have to close the discussion.

3 *Differences in Glycolysis Between Fetal and Non-fetal Fibroblast Cell Lines.* ANTOINETTE CONDON, FRANK A. OSKI, SALVATORE DIMAURO and WILLIAM J. MELLMAN, Depts. of Ped., Neurol. and Med. Genet., Univ. of Pennsylvania.

WALLACE W. MCCRORY (New York Hospital, Cornell Medical Center, NewYork, N.Y.): The demonstration of a difference in channeling of glucose metabolism into the hexose-monophosphate shunt and the Krebs-TCA pathway in fetal and adult cells in tissue culture is in agreement with similar findings of Dr. E. SCHUBERT in the Department at Cornell. Dr. SCHUBERT's studies were done on kidney tissue in differing periods from fetal life to maturity in the rat. The changes correlate with the growth program of the organ with maturation. The activity of the hexose-monophosphate shunt is highest in proliferating cells and falls to adult values when growth by hyperplasia ceases (about 40 days after birth). What I find especially interesting is your data showing fetal cells continue to demonstrate this metabolic pattern in tissue culture if I understood your comments. Did you find that fetal cells remained 'fetal' in this regard in serial tissue culture?

Miss CONDON: Yes.

LEONARD PINSKY (Lady Davis Institute, Montreal, Que.): Miss CONDON and her associates have shown us once again that cultured human fibroblasts are not the dedifferentiated masses they were thought to be a few years ago. In other words, the age of the donor and, perhaps, the anatomic site of the parental tissue may confer heritable properties on the cell strain developed.

I wonder if the speaker has had any experience with newborn fibroblasts. I have the feeling that fibroblasts derived from newborns, and particularly newborn foreskin, have many of the properties she has described for her fetal strains. It would be important to know if this is true because one frequently sees cell strains derived from human foreskin used as controls in studies dealing with fibroblasts cultured from adult skin.

Miss CONDON: We have no experience with foreskin from newborns.

4 *Prenatal Diagnosis of the Mucopolysaccharidoses by a Chemical Method.* REUBEN MATALON, C. B. JACOBSON and ALBERT DORFMAN. Univ. of Chicago, Dept. of Ped. and the Joseph P. Kennedy, Jr. Mental Retardation Res. Center, Chicago; and George Washington Univ. Med. Center, Washinton, DC.

IRWIN A. SCHAFER (Cleveland Metropolitan General Hospital, Cleveland, Ohio): Dr. TAKEUCHI in our laboratory has been working with amniotic fluid. She has analyzed a much smaller number of normal controls, but can confirm your results with one minor exception. We find in normal amniotic fluid a small amount of heparitin sulfate. I think chemically the material that we get off the column is not as yet as well characterized as some of the material with which you have worked.

We have also been able to confirm—probably the same specimen that you analyzed—the difference in distribution of acid mucopolysaccharides in the Hurler amniotic fluid.

There is only one problem that is still a little bothersome to us, and that is the question of expressing the results in terms of volume, since I am not quite sure whether there might be differences in concentration, water content, of amniotic fluid which might artifactually influence the results.

Dr. MATALON: I have discussed this problem previously with you, Dr. SCHAFER, and I agree with you that one might add more criteria for expressing these data.

I would like to stress again that in the Hurler amniotic fluid the problem is not a problem of concentration only, but it is again a problem of total different distribution. In none of the amniotic fluids did we find any suggestion of this amount of heparitin sulfate; as you will recall, normal amniotic fluids have almost 80% of their polysaccharide as hyaluronic acid.

The second thing you mentioned is that you detected some heparitin sulfate. We did the same thing you mentioned, and found a reactive substance in all the amniotic fluids; however, this substance was not true heparitin sulfate, because it gave reaction in the zero time, which heparitin sulfate does not.

5 *Intravascular Coagulation and Fibrinolysis in Human Renal Disease.* E. RICHARD STIEHM, JON I. SCHEINMAN, CARL W. TRYGSTAD, LINDA S. KUPLIC and DAVID T. UEHLING, Dept. of Ped., Univ. of Wisc. Med. Sch., Madison, Wisc. (introduced by Arthur J. Moss).

JAMES J. CORRIGAN, Jr. (Emory University School of Medicine, Atlanta, Ga.): What happens to the fibrolytic split products in inflammatory disease in general? Can you venture a guess as to what the half-life of the split products might be? And, in studies that we have done and reported by others, we have noted that there is a high titer of a material that is antithrombin in the alpha-2-macroglobulin fraction in addition to the antiplasmin; so that thrombosis in the nephrotic syndrome is probably not simply on the basis of elevated antiplasmins.

Dr. STIEHM: Fibrin split products increase in inflammation and infection. Using a sensitive technique like hemagglutinin inhibition, elevations of fibrin split products are frequently noted; this may be a useful test for sepsis. The half-life of fibrin split products is from 3 to 6 h. Limited studies on antithrombin levels in the nephrotic syndrome have disclosed no abnormalities; I will await your data with interest.

LYMAN A. PAGE (Stanford University School of Medicine, Palo Alto, Calif.): Is defective fibrinolysis seen as nonnephrotic hypoalbuminemia and analbuminemia?

The second question is whether you have tried to correlate the presence of fibrin split products in the urine with the extent of renal failure. It seems to me you are drawing some important inferences from the absence of correlation between urinary and plasma fibrin split products.

Dr. STIEHM: In patients with chronic renal disease with low albumin, there was no defect in fibrinolysis. We have not studied any patients with analbuminemia.

In any type of chronic renal failure urine fibrin split products may be elevated; therefore, when one is using urine fibrin split product levels as an indicator of transplant rejection, one should take into consideration the degree of azotemia. A urine fibrin split product level is significant only if it is markedly above what we would expect from other uremic patients with the same degree of renal failure. Currently we are relating levels of azotemia with urine fibrin split product levels.

HAROLD M. MAURER (Medical College of Virginia, Richmond, Va.): Have you used the ethanol gelation test to detect intravascular coagulation? How sensitive is this test compared with the test for fibrin split products in serum?

Dr. STIEHM: We have had limited experience with this procedure. The ethanol gelation test is positive in marked intravascular coagulation with defibrination. I do not believe, on the basis of limited studies, that it is of value in the study of subtle and localized intravascular coagulation.

GERALD S. GILCHRIST (Children's Hospital of Los Angeles, Los Angeles, Calif.): I noticed that 37% of the patients had fibrin split products in their serum. Larger numbers have it in their urine. Can you explain the large percentage of serum positive patients in the light of the apparent defect in fibrinolysis? Secondly, with regard to the hemolytic-uremic syndrome, I find difficulty in accepting your classification of the syndrome as a manifestation of generalized intravascular coagulation. Most studies would support the concept that this is a localized phenomenon with no consistent evidence of vascular involvement outside of the kidney.

Dr. STIEHM: There is a disagreement whether fibrin split products can occur in the presence of a defective fibrinolytic system. In my experience, I have never seen a fibrinolytic system so defective that fibrin split products are not generated even in the presence of markedly decreased plasminogen levels. Fibrin split products may be falsely negative if insensitive techniques such as agar diffusion are used. Secondly, I regard the hemolytic-uremic syndrome as an illness not limited to the kidney, with central nervous system and peripheral vascular involvement. At autopsy I believe there is evidence for intravascular coagulation.

JACK RESNICK (Naval Hospital, San Diego, Calif.): What type of correlation do you find between the biopsy evidence of fibrin or fibrinogen in the kidney, and the urine and serum fibrin split products?

Dr. STIEHM: We have not as yet had extensive experience correlating urine fibrin split products with biopsy evidence of deposited fibrinogen. We have found poor correlation between serum levels of fibrin split products and immunofluorescent evidence of a fibrinogen.

6 *Functional Asplenia in Sickle Cell Anemia—A Reversible Defect.* ALLEN D. SCHWARTZ, HOWARD A. PEARSON, JOSEPH H. ZELSON, RICHARD P. SPENCER and SORRELL L. WOLFSON. Depts. of Ped. and Nucl. Med., Yale Univ. Sch. of Med., New Haven, Conn.

LOUIS K. DIAMOND (University of California Medical Center, San Francisco): Shortly after hearing of this work of Dr. SCHWARTZ and Dr. PEARSON, we had the opportunity to study two children in one family with severe sickel cell anemia. The younger, a 12-year-old girl, had a spleen that was easily palpable two to three finger breadths below the costal margin. The older boy, 16 years of age, had an even larger spleen at an age when it is usually fibrosed and not palpable. He had had more than 30 admissions in the first 10 years of his life, several of them with pneumonia, one of them with pneumococcal pneumonia and septicemia.