CLINICAL CONFERENCE

Genital Abnormalities in Infants Associated with Administration of Progesteroids* to Their Mothers

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PRESENTATION OF CASES

Dr. Sheldon G. Leibow: Case 1. The first patient is an infant girl who was first seen here on October 6, 1958 at the age of 2 months by Dr. Gardner. She was referred for evaluation because of an enlarged clitoris present since birth.

The child was born on August 5, 1958, the ninth pregnancy of a 39-year-old mother. Her mother had a history of three spontaneous abortions, two of which had preceded the birth of the patient. In view of this obstetric history, her mother was given hormone therapy in her second month of pregnancy (December 9, 1957). Treatment consisted of: U.S.P. desiccated thyroid, 65 mg/day; 17-alpha-ethinyl-19-nortestosterone (Fig. 1), 5 mg twice daily; and diethylstilbestrol 5 mg twice daily. On December 30, diethylstilbestrol was increased by 5 mg/day, once weekly, until a daily dose of 75 mg was achieved. The other hormones were continued at the original dosage. All therapy was discontinued in the thirty-fifth week of gestation.

Two other developments of interest occurred during this pregnancy. Glycosuria was noted for the first time during the second month and was treated with a 1,500 calorie diet and 27 units of isophane (NPH) insulin daily. There was no antecedent history of maternal diabetes, and insulin was not required after termination of the pregnancy. The child's mother fell during her fifth month of pregnancy, developing some spotty vaginal bleeding which ceased promptly after several days of bed rest.

A full-term infant weighing 3,430 gm was delivered on August 4, 1958. The neonatal course was uneventful. There were no episodes of diarrhea, vomiting, fever or dehydration.

The mother was apparently well and had no evidences of masculinization. Five siblings of the patient were well and apparently normal. Their ages ranged from 19 to 6 years (3 girls and 2 boys). There was no family history of endocrine disease and, specifically, none of abnormal genitalia.

The patient was first seen as an outpatient at 2 months of age. Her development had been normal. There had been no progression in the size of her clitoris nor had she developed any other evidences of virilization. Her height was 61 cm (97th percentile). Her clitoris was 2.5 cm long and 1 cm in diameter (Fig. 2). There was no visible urethral orifice in the phallus. The labia majora were somewhat enlarged with some rugae. Gonadal masses were not palpated in the labia nor in the inguinal canals. The introitus appeared normal except for minimal posterior labioscrotal fusion. Abdominal masses were not felt. There was no pubic hair nor other evidence of virilization, except as noted. The remainder of the examination was normal. A smear of the buccal mucosa by the Barr technique revealed the nuclei of cells to be chromatin-positive, as is seen in females.

She was admitted to Syracuse Memorial Hospital on November 17, 1958, at the age of 2 months, for further studies. She had done well without any evidence of progression of virilization. The systolic blood pressure by palpation was 80 mm Hg. The weight of 7.03 kg was at the 75th percentile level, and the

* The term "progesteroid," as used in this Clinical Conference, refers to the entire group of progesterone-like compounds currently used in prenatal therapy (including progesterone itself). The term "progestin" has been similarly employed by some authors, but its usefulness is vitiated since it is a trade-marked designation for one brand of progesterone.

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height of 61 cm was also 75th percentile for her age and sex. The physical examination was unchanged. Blood count was normal; roentgenograms of hand and wrist revealed a normal bone age. Four 24-hour urine samples analyzed for 17-ketosteroid excretion yielded no measurable 17-ketosteroids. She was discharged on November 20, 1958 with a diagnosis of non-adrenal female pseudohermaphroditism associated with maternal ingestion of progestoids during pregnancy.

The child was readmitted to the hospital on June 16, 1959, at the age of 10 months for a clitorectomy. There had been no progression of virilization. Physical examination revealed a height of 78.7 cm (97th percentile) and a weight of 10.4 kg (75th percentile). Physical findings were unchanged. There were no palpable abdominal masses. A midline structure thought to represent uterus was palpated by rectal examination. No adnexal masses were felt. Laboratory studies showed a normal hemoglobin; leukocyte count, 20,200/mm³; differential count revealed 23% neutrophils, 73% lymphocytes, 1% monocytes, 2% eosinophils, and 1% basophils. A repeat leukocyte count was 18,600/mm³; with a similar differential. A culture from the throat grew no pathogens. The child appeared well, and the elevated leukocyte count remained unexplained. Urinalysis was normal. Roentgenograms of the hand and
wrist showed a carpal age of 1 year and a phalangeal age of 16 months, representing an average bone age of 16 months. A clitorectomy and vaginal plastic procedure were performed by Dr. Lawrence K. Pickett on June 18, 1959. The child was found to have a separate vagina and urethra. She was discharged on June 22, 1959.

Cases 2 and 3. We will include in our discussion two other children who were hospitalized for study. Their cases will be summarized briefly. Both had a history of progesteroid administration to the mother during pregnancy. Case 2 was a newborn infant at the time of her transfer to our hospital. She had an imperforate anus, absent urethral meatus and an enlarged phallus surrounded by labioform structures. There were no palpable gonadal masses in the labia nor in the inguinal canals. At surgery, a bicorntuate uterus, a vagina without external vaginal orifice, and grossly normal tubes and ovaries were found. A definitive corrective procedure for the imperforate anus and a suprapubic cystotomy were performed by Dr. Nicholas M. Stahl. The cells in a buccal smear were chromatin-positive. The 24-hour urinary excretion of 17-ketosteroids was normal. The child had a normal 5-year-old sister. Her mother had received 250 mg of 17-alpha-hydroxyprogesterone, intramuscularly, every 2 weeks from the eighth to thirty-second week of pregnancy.

Case 3 was seen recently at the age of 10 months. She had a history of clitoral enlargement since birth, without evidence of progression or other evidences of virilization. Her mother had received progesteroid therapy for recurrent abortion. Her first pregnancy aborted spontaneously at about 3 months gestation. Her second pregnancy resulted in a normal female infant. Her second pregnancy is of interest in that she bore an unaffected female infant despite administration of 17-alpha-ethinyl-testosterone from the fourth to sixteenth weeks. However, the doses administered were small, 5 mg every other day. Her third pregnancy aborted. Her fourth pregnancy, Case 3, had clitoral enlargement. A progesteroid, 17-alpha-ethinyl-19-nortestosterone, had been given during this pregnancy from the sixth to thirty-second week, starting with a daily dose of 20 mg which was periodically reduced. On examination, Case 3 had no palpable gonadal masses, and there were no labioscrotal changes. The cells from a buccal smear were chromatin positive. Height and weight were in the 97th percentile. The bone age was normal. The child's clitoral enlargement had become less obvious with general body growth and enfolding of the clitoris by the labial folds. The clitoris had apparently remained unchanged in size.

DISCUSSION

Dr. Leibow: Wilkins and his group in 1958 called attention to the association between masculinization of some female infants and administration of progesteroid to their mothers during pregnancy. These authors were careful to note that this was only an association; the causative relation, if any, had not been proven. The report considered 21 cases of female infants with partial masculinization. All of them had phallic enlargement and some had varied degrees of labioscrotal fusion. The mothers of 18 of the infants had received steroid hormone therapy during pregnancy. In some cases progesteroids alone were given and others had received progesteroids plus diethylstilbestrol. One case had received testosterone as well as a progesteroid.

There is some basis in animal experimentation for implicating progesterone in fetal masculinization. Greene et al. noted the chemical similarity of progesterone to androgenic agents. They administered progesterone to intact infant male rats and found that this resulted in heavier ventral prostates, with histologic evidence of increased secretory activity, as compared with their untreated and castrated litter mates. When newborn rats were castrated and given progesterone from the day of castration, a normal prostatic appearance and secretion were maintained; the untreated and castrated litter mates developed prostatic atrophy. Several authors who attempted to duplicate these results were unsuccessful, but Greene et al. suggested the failures were due either to inadequate doses of progesterone, or to the route of administration of the progesterone (rubbing in the hormone cutaneously produced less masculinization than subcutaneous administration), or to...
using different organs in evaluating the response.

Greene et al. emphasized the differing responses of different organs in the same animal, noting that, although the ventral prostate of the newborn castrated rat was quite sensitive to progesterone, the seminal vesicles were not. Consequently, progesterone produced an increase in the weight of the prostate but not of the seminal vesicles. Therefore investigators using weight of the seminal vesicles as a guide in rat-response studies reported no effects following progesterone administration. Four newborn female rats of two litters received gradually increasing doses of progesterone for the first 30 days of life. In each case the clitoris was about three times as large as the clitoris of two untreated controls. There was no comment about any other genital abnormalities in these rats. In a subsequent article Greene et al. noted that adrenalectomy of castrated rats did not in any way interfere with their response to progesterone. Thus the response of the ventral prostate to progesterone was apparently not mediated through the adrenal cortex.

Embryologic studies by Jost and by others indicated the existence of a critical period in the differentiation of the internal and external genitalia, beginning with gonadal differentiation, then genital duct differentiation, and finally reaching external genital development. Jost showed that androgen administration at any stage of fetal or postnatal development can produce phallic enlargement. (This will be borne out in subsequent discussion of androgen and progesterial administration in human case reports.) However labioscrotal fusion has a more limited critical period and presence of such fusion suggests excessive androgenic activity before the stage of fetal development when differentiation of the female external genitalia is completed. In human females, the vulval vestibule containing separate urethral and vaginal orifices is completely formed by the twentieth week. Therefore, the presence of any degree of labial fusion would suggest that action of whatever masculinizing influence has played a role occurred before 20 weeks gestation.

Various agents had been implicated in female nonadrenal masculinization long before reports on progesterials were published. A number of cases of androgen administration to mothers resulting in fetal female masculinization had been reported. Zander and Müller described a masculinized infant who was the product of a pregnancy during which the mother had received an androgen from the sixth month of pregnancy until term, for breast carcinoma; the infant had clitoral enlargement with no labial or other abnormalities. In another case testosterone was given to the mother from the fourth month to term for a pruritic skin condition; the infant exhibited clitoral enlargement and labial hypertrophy but no labial fusion. Grunwaldt and Bates reported on a female infant with complete labioscrotal fusion; the mother had received a single intramuscular injection of 100 mg of testosterone in the tenth week of her pregnancy and continuing with 30 mg/day, orally, of methyltestosterone for 51 days—the hormone was given for nausea with vomiting and weakness. Testosterone was stopped because the mother developed “hoarseness.” Her infant showed phallic enlargement with complete labioscrotal fusion. The urethra was phallic, no gonads were palpated either in the labia or in the inguinal canals, and rectal examination revealed a midline structure thought to represent a uterus. The cells in the buccal smears had a positive chromatin pattern. Urinary excretion of 17-ketosteroids in 24 hours was normal. Visualization of the bladder and vagina was achieved by instillation of radio-opaque dye into the phallic urogenital sinus. Exploratory laparotomy demonstrated normal uterus, tubes and ovaries (histologically proven). Hayles and Nolan reported an infant whose mother received, methyltestosterone in Linguits (20 mg/day) from the second month of pregnancy to delivery, as treatment for alopecia. There were signs of virilization.
in the mother—deep voice, hirsutism, and clitoral enlargement. The female infant had a large clitoris with chordee, complete labial fusion, and a urethral opening at the base of the phallus. Initially, this infant was diagnosed as a male with hypospadias and cryptorchidism. However, at 7 months of age, she was studied further. A positive chromatin pattern was found in cells from a buccal smear, urinary excretion of 17-ketosteroids was normal, and at laparotomy uterus, ovaries and tubes were found.

It is noteworthy that of the four cases just described, the two infants whose mothers received androgens at 2 months and 2½ months gestation, respectively, had complete labioscrotal fusion and phallic enlargement; whereas the two infants to whose mothers such therapy was given later in pregnancy (4 and 6 months) had phallic enlargement without labioscrotal fusion. The clinical patterns of these four examples are compatible with the experimental evidence which suggests that androgenic effects toward the end of the twentieth week of gestation are less likely to interfere with labioscrotal development.

One other cause of maternal virilization which can affect the infant is arrhenoblastoma, a masculinizing ovarian tumor. A child was reported whose mother had a cesarean section at 37 weeks gestation for progressive virilization. An ovarian arrhenoblastoma was found and removed, and the infant was delivered. The infant showed phallic enlargement and almost complete labioscrotal fusion, with a urogenital sinus at the base of the clitoris. An exploratory laparotomy was done on the infant at 3 years of age and completely normal internal genitalia were found.

In cases of testosterone administration and in cases with arrhenoblastoma, the mother as well as the fetus was masculinized, whereas all of the cases reported associated with progesteroid administration have had no instance of maternal virilization.

To review the cases of Wilkins et al. in more detail: 21 female infants were discussed by him and in 18 of these the mothers had received progesteroids during pregnancy. The mothers of the remaining three infants had not received progesteroids or other hormones, and it is of interest that in these three instances the infants had extensive masculinization with complete labioscrotal fusion as well as phallic enlargement. Of the 18 cases exposed to progesteroid in utero, 6 had no labial fusion, 7 had slight fusion characterized by a thin crescent across the posterior fourchette but with separate urethral and vaginal orifices, 4 had marked fusion with a small meatus near the phallic base representing a urogenital sinus, and there was 1 case with extensive fusion and a phallic urethra. The analysis by Wilkins et al. of these 18 cases revealed that all severe cases (that is, those with extensive fusion) had a history of progesteroid therapy to the mother early in pregnancy. In 4 of the 5 cases, progesteroid therapy had been started at 4 weeks and in 1 case at 6 weeks gestation and had been continued to 20 to 36 weeks gestation in the various cases. The most severely involved infants were those of mothers who had received the largest doses of progesteroids, with initial doses of 50 to 200 mg daily, and an ultimate daily dose of 200 mg/day in all cases. All of the mothers of the severely affected infants had also received progesterone or 17-hydroxyprogesterone intramuscularly for varying periods, and none of the mothers of this series had received diethystilbestrol. The progesteroid given orally in all cases was 17-alpha-ethinyltestosterone. One mild case of phallic enlargement without fusion occurred in the infant of a mother who had received very large doses of 17-alpha-ethinyltestosterone, in the range of 120 to 340 mg/day. This was in the dosage range given to mothers whose infants had severe masculinization. However, in this instance the progesteroid had been started at 18 weeks of pregnancy, well toward the end of the critical period of labial differentiation; treatment had been continued until 36 weeks. Thus this infant demonstrated, by these minimal effects, that
there may be a relationship not only to intensity of dose but to the exact gestational time when progesteroids are first administered. The mothers of most of the mild cases in the series of Wilkins et al. received only 20 to 40 mg of progesteroid daily. A few had received diethylstilbestrol as well. In these cases, in most instances, treatment had been started between 4 and 10 weeks gestation. In the exceptions, one mother had been receiving progesteroid before conception, and hormone therapy was continued; and in the case of the other mildly affected infant, large doses of progesteroid had been given to her mother but not until late in pregnancy (18 weeks). All these infants had a positive chromatin pattern in cells from a buccal smear.\textsuperscript{1,10,13}

In connection with differential diagnosis, if the child is thought to be a female pseudohermaphrodite, congenital adrenal hyperplasia must be excluded. This was done in all three of the cases presented herein by history of lack of progressive virilization, by lack of a family history where there were several siblings in a family, and by the presence of normal excretion of 17-keto-steroids. With the exclusion of congenital adrenal hyperplasia, another possibility is true hermaphroditism in which definite diagnosis requires nuclear chromatin studies\textsuperscript{10-14} and surgical exploration with gonadal biopsy. In both maternal testosterone administration and maternal arrhenoblastoma, virilizing effects of some degree usually occur in the mother.

Several writers\textsuperscript{5,13} suggest that in case of a reliable history of progesteroid administration during pregnancy and a female infant with only phallic enlargement without labial fusion, there is no need to explore surgically. However, if more extensive virilization is present (extensive labial fusion), some advise exploration and gonadal biopsy. Another diagnostic aid of value, which may obviate the need for exploration, is instillation of radio-opaque dye into the urogenital sinus to outline bladder and vagina. The consensus is that in the cases exposed to progesteroid in fetal life normal female development is to be anticipated. Surgery may be needed to correct the genital abnormality.

The mechanism by which progesterone has its effect in these cases is unknown. One hypothesis is that there is abnormal placental transmission of steroid hormones in some mothers, which could lead to fetal masculinization. Another possibility is that there may be abnormal degradation of progesteroids in some mothers, leading to the production of steroid intermediates which cause fetal masculinization.

There is one report\textsuperscript{19} of a mother who had received progesteroid during two pregnancies in both of which masculinization of a female infant occurred. Bongiovanni et al.\textsuperscript{14} have reported four cases of masculinization of female infants collected from three clinics, wherein there was a history of administration of diethylstilbestrol alone during pregnancy; no other factors were found to explain the observations. The mother of one infant with phallic enlargement and extensive labial fusion had received 5 to 15 mg/day of diethylstilbestrol from the seventh to twentieth weeks of pregnancy. Another mother had received 25 mg/day of diethylstilbestrol from the fourteenth to the twentieth weeks, for vaginal bleeding. Her infant had clitoral enlargement with only minimal labioscrotal fusion. In a third case, diethylstilbestrol had been given from the thirteenth to thirtieth week of gestation in doses started at 10 mg/day and increased gradually to 75 mg/day. This infant had clitoral enlargement. The fourth infant's mother had received diethylstilbestrol from her four to ninth week of pregnancy. This infant had clitoral enlargement and extensive labial fusion. All infants were proven to be females. In the two instances where diethylstilbestrol was started at the fourth and seventh weeks, there was labial fusion as well as phallic enlargement. In the two instances where diethylstilbestrol had been started later in pregnancy (during the thirteenth and fourteenth weeks) phallic enlargement was unassociated with labial fusion.
A review of White's data on pregnant diabetic mothers who had received daily intramuscular injections of diethylstilbestrol and progesterone revealed that therapy was started from onset of pregnancy to 10 weeks gestation, and was continued until term; 380 such cases were discussed. This study was oriented more toward fetal survival than development of genital abnormalities, but there was no mention of genital anomalies in the infants of these mothers. Bongiovanni et al. make reference to 950 cases from Joslin's clinic in Boston; they could find no reports of external genital anomalies in these cases.

Dr. Neil Stewart: Dr. Gardner, would you like to make some comments now?

Dr. Lytt I. Gardner: I think it would be appropriate to mention the distribution of these cases. We know that only a very small percentage of mothers who receive progestin have children with abnormal genitalia. This immediately brings us to considerations of the epidemiologic pattern of the disease. Why is it that all of the children of mothers who get progestin do not have abnormal genitalia? This is reminiscent of the studies on primaquine sensitivity. There the original observation was made that some United States soldiers in the Pacific theater, who received primaquine, developed jaundice; most of these troops did not develop jaundice. Out of that original observation has evolved a most important study of the distribution over the world of the trait of primaquine sensitivity, now known more specifically as glucose-6-phosphate dehydrogenase deficiency. Is the tendency for these infants under discussion today to have abnormal genitalia a result of a genetically-determined predisposition of their mothers to metabolize the progestin in such a fashion that androgenic compounds are delivered into the environment of the fetus?

Dr. Stewart: I have asked Dr. Hughes to give the obstetric viewpoint on the subject.

Dr. Edward C. Hughes: This is a field of therapy that we have all wondered about, and like every new thing (particularly the use of these new progestins), they are given on an empiric basis by many people. I was asked to discuss the use of these steroids during pregnancy. We are using them less and less during pregnancy, because we have never been impressed by the action of either diethylstilbestrol or progesterone in the preservation of an abnormal pregnancy. Chorionic gonadotrophin is secreted by the cytotrophoblasts of the chorion, and the peak of secretion is reached about the fifteenth to sixtieth day of the pregnancy—the amount of secretion then decreases gradually and remains at a low level throughout normal pregnancy.

The secretion of progesterone by the cerv...
pus luteum of the ovary during the first trimester of pregnancy increases steadily. During the last two trimesters, the placenta continues to secrete progesterone in increasing amounts. If implantation and chorionic function are abnormal, and chorionic function becomes depressed, the pattern of secretion of both chorionic gonadotrophin and progesterone is diminished. This indicates that the embryo will not grow well and that a blighted ovum is in the making. I don't care whether you give progesterone, diethylstilbestrol, chorionic gonadotrophin, thyroid, adrenal extracts, vitamin C or sawdust, the outcome will be the same. The chorion will be poorly formed and consequently these patients are going to abort. They will have a blighted ovum. There is no sense in giving these people these expensive drugs when they have no effect.

I think we should consider this relationship when trying to give substitution therapy in the sort of cases that are under discussion. In Case 1, it is my estimate that the conception probably occurred November 15. The patient began to receive 17-alpha-ethinyl-19-nortestosterone about December 9 or 6, which is very early. Medication was given at the transition time of the embryo, when it is very sensitive to hormones. This compound definitely should never be used during pregnancy, as far as I can see, because of the androgenic effect. Testosterone, which is in the same category, should also not be used during pregnancy. What we want progesterone and estrogen to do is to improve the blood supply to the decidua so that more nutrition can be furnished to the growing chorion and the growing embryo. The progestoid and testosterone have just the opposite effect on the endometrial glands. And so we would never use testosterone or testosterone-like substances, particularly during the first part of the pregnancy. Estrogen does increase blood flow to the decidua and may be less dangerous than the testosterone compounds. So far as we are concerned, these steroids are used very infrequently to preserve a pregnancy. There was an article published within the last month or two on about 2,000 patients who had vaginal bleeding during the early part of gestation, who were given nothing, and still went to term and delivered a good percentage of normal children. Comparable groups given progesterone did not have any better fetal survival rate. I think that the use of these steroids has been overstressed.

**Dr. Stewart:** We have Dr. Pickett with us to comment on the surgical aspects of this condition.

**Dr. Lawrence K. Pickett:** The surgeon generally comes in not for the cause and effect relationship, but to alter structurally what has happened already. It is most important that we investigate these cases very completely, because there is a significant legal aspect to the removal of organs which may later be useful. We here are particularly fortunate in being able to single out and recognize (by making accurate determinations of the urinary excretion of 17-ketosteroids) those offspring who are changed structurally by the presence of virilizing adrenal hyperplasia. These are in contrast to the group of cases that we have mentioned here with exogenous drug effect. We have seen these three cases and several others who developed genital abnormalities associated with use of progesterone or similar substances during gestation.

Mothers are quite sensitive about such children. When a mother is considered to have a female child, and a baby-sitter comes and changes the diaper and sees what would pass for a pretty good male, then alone the grapevine in the town the word gets out that she is harboring a monster. The parents in one case had to leave the town and go to another village to live because the curiosity was such that everyone wanted to be baby-sitter for them, and their life was ruined. Other mothers have become so sensitive that they won't let anybody be a baby-sitter; until appropriate external alterations are made surgically, they will not let anyone else change the diapers, and they are totally bound to these children.

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One mother used a sling in which she suspended the baby like a papoose over her shoulder, when she went to the supermarket; never was this baby out of physical contact with her in the first year of life, until they were finally directed toward surgical correction.

The problem is one of trying to recreate a more normal-appearing anatomy. Figure 2 shows a foreskin with a well developed glans and the urethra opening below. Though there is some fusion across below the urethra, there is a separate vagina. In patients with virilizing adrenal hyperplasia, the androgenic influence has been effective during fetal development; in these patients there is a urogenital sinus, which branches off with a vagina coming off this common urogenital sinus, and a urethra extending on into the bladder. In the individuals whose mothers have received progestins during pregnancy, where the influence starts somewhat later in gestation, one will find separate orifices for the vagina and the urethra. Clitorectomy is done to make this seem to be a more normal clitoris, and also some plastic work is done on the labioscrotal fusion to give a more normal vaginal orifice; this is not definitive. I suspect the reconstruction will have to be redone following puberty, because the changes that take place at puberty will be extensive. I am impressed that there is little progression in the size of the clitoris in those individuals who have had progestins-induced hypertrophy of the clitoris. In those individuals who have virilizing adrenal hyperplasia, there is considerably greater hypertrophy of the clitoris, and I wonder whether we aren't trying surgery too early in the progesting group. We haven't seen very many of these latter, but we have seen enough to get the impression that plastic surgery might not always have to be done in this particular group.

Case 2 has a clitoris or a phallus, a large orifice just below the pubic bone and a bladder which empties through the phallus. The vagina is present as are a bicornuate uterus, tubes and ovaries, and there is a blind anus entering the vagina. Imperforate anus with recto-vaginal fistula, a vaginal-urethral fistula and a urethro-clitoral fistula makes up the total description. This particular child has had the anus repaired; the urethra comes out the clitoris. The vagina is still associated with the urethra in the hidden state and will be exteriorized as soon as the child grows up somewhat. This mother is most anxious to know what part (if any) the drug played in the abnormalities.

**DR. JULIUS B. RICHMOND:** I might just make some brief comments. As we've been listening to this very comprehensive presentation, I have been thinking of the interaction of various factors: the quality of the stimulus biochemically; or the intensity or quantitative aspects of the stimulus which we often speak of as the “dose,” and, as Dr. Leibow indicated so well, the timing of exposure to the stimulus. Then Dr. Gardner and Dr. Hughes introduced an emphasis on the biologic substrate on which the stimulus acts. One of our problems clinically is to evaluate just in what order and to what degree these factors are interacting.

All of these factors are of some consequence in connection with psychologic considerations relating to surgical corrective procedures. I think Dr. Pickett has raised a very interesting point; that is, whether if we permitted these children to go on without surgical correction, growth generally would render the prominence of the clitoris a little less apparent. However it seems to me, from a developmental point of view, and because of all the anxiety that centers about sexual development particularly, early correction is probably indicated. I think that by performing the procedure in the period of infancy we minimize the possibility of psychologic sequelae, since there will probably be little recall or memory for the event.

This could get us into a very extended discussion concerning some of our concepts of infant development. Briefly, it is our

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belief that, during the period of infancy, the relationships which the infant develops in a general sense with its parents—in other words, the over-all experiences—probably have more consequence for later development than any one specific experience, such as the trauma of surgery. Of course, we all acknowledge that Dr. Pickett's surgery isn't very traumatic regardless of the child's age. However, in the period beyond infancy, it may be that the child's own recall for the experience may have much more specific connotation. Also, by early correction the parental anxiety may be abbreviated and its intensity lessened. This is a matter about which we need a good deal more information. Our current practices are based on conjecture stemming largely from retrospective psychiatric observations rather than on the direct accumulation of data. I hope that we—and others—will be in a position to accumulate such data in the future.

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