GENETIC ASPECTS OF PEDIATRIC ENDOCRINOLOGY
Summary of a Round Table

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Introductory Remarks

DR. GARDNER: Historically pediatricians have been in the vanguard of the social and scientific forces improving the health and well-being of their patients—the children of this country. Indeed, we have the heavy responsibility of carrying on the proud tradition of our professional great-grandfather, Dr. Abraham Jacobi, who came to these shores in the aftermath of the German Revolution of 1848, and who eventually rose to the presidency of the American Medical Association.1 As the pioneer in American pediatrics, Jacobi never failed to let his position be known on controversial issues. His intuitive Jeffersonian grasp of the democratic process facilitated his rôle in the early development of pediatrics here. Jacobi's coat has, in a sense, fallen upon our shoulders, and American pediatrics must continually be on the alert to live up to what he would have expected of us.

Therefore let me come directly to the problem at hand. As we know, the relative number of children with congenital defects in our hospitals is very much greater than 25 years ago. Recently in our hospital we tabulated the cases over a 5-month period, and found that 30% of the pediatric in-patients were there because of congenital defects. This apparent increase is almost certainly due in large part to the reduction in patients with infectious disease, but the figure of 30% still must remind us that the care of children with congenital defects is a field of major importance in modern pediatrics. How many of these defects are genetically determined is not known for sure, but certainly a considerable part of this group of patients represents inherited disease. As is obvious from the syndromes we will take up in this endocrine round table, nearly every one of these conditions is genetically determined, that is to say, the result of a mutation which has taken place in the human hereditary material.

With this "load of mutations" to deal with in our pediatric services, naturally any public health measures to prevent further increase in the mutation rate are very much in order. It is now common knowledge that ionizing radiations, in the form of x-rays, fall-out radiation, etc., cause an increase in the mutation rate. This has been carefully quantitated in a number of animal forms, and a straight-line relationship has been found to exist between total radiation and mutation rate. The more radiation there is, the more mutations occur.2

Our colleagues in roentgenology have become acutely aware of this problem, and are making great efforts to reduce the x-ray exposure of patients to the absolute minimum. Public health laws are restricting the use of x-ray apparatus to trained personnel. So there is good reason to think that progress is being made to reduce human exposure to x-rays and to medically used radioisotopes.

There is one other source of human exposure to radiation about which something could be done, and that is the radiation exposure brought on by fall-out from the testing of nuclear bombs. Unfortunately little progress has been made in reducing human exposure to this form of radiation. Russia has just resumed a series of tests,

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which means that we are still playing this Alphonse-Gaston game of genetic roulette.

The relevance of this increase in radiation (and therefore increase in mutation rate) to the field of pediatric and child care can be immediately seen from the following.

Dr. J. F. Crow, Professor of Genetics at the University of Wisconsin, has estimated that if the world's population is exposed to 0.1 roentgen per person over a single period of 30 years, there will be produced a total of 80,000 gross defects in the living children of future generations. In addition he estimated a total of 700,000 lethal mutations (i.e., deaths) for future generations as a result of this irradiation. Dr. Linus Pauling, Professor of Chemistry at the California Institute of Technology, recalculated these data on the basis of a 1958 estimate of fall-out radioactivity. Dr. Pauling concluded that if the present rate of testing were continued, each such year would result in 8,000 gross defects in the living children of future generations (or a total of 240,000 produced by a 30-year period of testing).

It must be noted that the foregoing calculations refer only to the immediate radiation produced by the relatively short-lived isotopes of a bomb explosion. This is, in a sense, the first phase of genetic damage caused by weapons testing.

The second phase of genetic damage appears to be caused by the effect on the hereditary material of the long-lived isotope, C\textsuperscript{14}. This isotope has an average life of 8,000 years. During all this period of time the human hereditary material is irradiated, and the mutations thereby produced are permanently inherited. The most recent publication of the Atomic Energy Commission estimates that the C\textsuperscript{14} produced from bombs alone to date (excluding the current U.S.S.R. series) might cause 100,000 gross genetic defects in the living infants and children of future generations. A very much larger number of genetic lethals (fetal, neonatal and childhood deaths) were estimated from this C\textsuperscript{14} irradiation. All the agencies which have participated in these calculations have emphasized the large uncertainties and difficulties involved in estimates of genetic damage. Nevertheless there is little doubt of the general nature of the conclusion. The problem is now mostly one of interpretation. It is understandable that the military mind would take the point of view that the genetic casualties are only a very small aspect of the whole weapons testing program.

On the other hand, because the cost of these "casualties" is measured in helpless infants and children, the pediatrician is liable to take a very different point of view. We are the custodians of an ancient precept that holds all life to be important, that heeds the words of Maimonides, the physician: "Thy eternal providence has appointed me to watch over the life and health of Thy creatures." It is said that the present situation is a philosophic dilemma. If this be so we are equipped with a rich tradition to exert a force for the benefit of humanity.

**Hypopituitarism**

**Dr. Rosenthal:** The diagnosis of hypopituitarism originating in childhood is relatively easy in the patient over 20 years of age. The diagnosis is more difficult in younger children, and careful differentiation must be made from primordial disturbance of growth, constitutional delay in rate of growth, and growth failure secondary to serious organic disease. The presence of a severe delay in bone age, normal body symmetry, and evidence of secondary hypoadrenalism and hypothyroidism may aid in early diagnosis. Some patients present evidence of a pituitary tumor, although in most instances the cause of hypopituitarism is not known. Increased sensitivity to insulin and abnormal excretion of a standard water load may help in the early establishment of the diagnosis of hypopituitarism. A good clinical method for the assay of growth hormone is badly needed.
The recent demonstration by Raben* of stimulation of the growth of a hypopituitary dwarf over a period of 10 months, by the intramuscular injection of human growth hormone two or three times a week, is of great interest. Other workers have also demonstrated physiologic effects of human growth hormone in man. Human growth hormone is not available for general clinical use. It is unlikely that it will become available in the near future. Animal growth hormones appear to be of no value in the treatment of human patients.

Treatment for hypopituitarism should not be instituted unless the diagnosis is definitely established. Treatment before the normally expected age of puberty, as suggested by some workers, is not recommended. For males of pubertal age, treatment with testosterone enanthate (200 mg) intramuscularly each month is recommended. For females of pubertal age, oral treatment with methyl testosterone (10 mg daily) and with a suitable estrogen is recommended. Fairly good sexual development should result from this therapy, although the patients obviously remain infertile. For psychologic reasons, treatment at the usual age of puberty, as recommended recently by Martin and Wilkins,* is suggested instead of treatment at a later age which was previously recommended. It is doubtful, however, that therapy with its resulting growth spurt causes any increase in height over that which would have eventually been attained without treatment.

**Dr. Gardner:** Hypopituitarism has causes which sometimes can be readily demonstrated. We should be aware of the possibility of a suprasellar cyst. Roentgenograms of the skull in this syndrome will usually demonstrate calcification in the suprasellar region and/or flattening of the sella.

**Pheochromocytoma**

**Dr. Rosenthal:** Cone, Allen and Pearson* in a recent review of the literature were able to find 34 cases of pheochromocytoma reported in children under the age of 14 years. The average age of onset was 9 years. The youngest child was 18 months. The tumor was confined to one adrenal in 16 cases and involved both adrenals in 7 cases. In seven cases the tumor was not in the adrenal. In four cases the tumors were in the adrenal and also in an extra-adrenal site. The disease may be familial. The presacral injection of air may localize the tumor; the test may be misleading and in these patients carries a definite risk.

In the management of these patients before surgery the oral administration of Regitine® (phentolamine) may be useful in the control of the hypertension until definitive surgery is performed. In those rare cases in which both adrenal glands are involved with tumor, bilateral adrenalectomy may be necessary. Appropriate preoperative medication and postoperative adrenal corticosteroid substitute therapy are indicated.

**Dr. Gardner:** It should also be mentioned that removal of a pheochromocytoma may result in prolonged hypotensive shock even when a constant infusion of norepinephrine is provided. Dr. Robert E. Greenberg and I have recently described such a case in our report of the eighth known affected kindred.~ In this family, father and son were both affected. The father showed severe hypotension after removal of a left-sided pheochromocytoma in spite of norepinephrine therapy. His son, age 3½ years, also had a left-sided pheochromocytoma removed, but interestingly enough the child did not exhibit postoperative hypotension.

**Dr. Keagy, Altoona, Pa.:** Will essential hypertension respond to Regitine®?

**Dr. Gardner:** Usually not. But the surest way to diagnose pheochromocytoma is by measurement of catechol amines in the urine. Figure 1 shows a typical Regitine® response in a case of proven pheochromocytoma. Primary aldosteronism may also be a cause of unexplained hypertension. The serum potassium levels are usually low, although occasional values may be normal. Conn recommends that a series of serum potassium levels should be done before ruling out primary aldosteronism.
Familial Goitrous Cretinism

Dr. Rosenthal: The symptoms of hypothyroidism do not differ in goitrous cretinism from those of sporadic athyreotic cretinism. A more suitable designation for goitrous cretinism is cretinism caused by biochemical abnormality in the synthesis of thyroid hormones. In goitrous cretinism the goiter usually develops later in childhood. Goitrous cretinism appears to be genetic in origin.

In goitrous cretinism the radioiodine uptake of the thyroid gland may be elevated or in the normal range. The protein-bound iodine in blood serum is usually low but may be normal or even elevated. Goitrous cretinism, according to Stanbury, can result from one of several biochemical abnormalities in the synthesis of thyroxin. The thyroid gland may lack the oxidative enzyme so that, while it can trap iodine, it cannot produce iodotyrosine. The thyroid gland may lack the enzyme which causes coupling of iodotyrosines to form iodothyronines. The gland may lack the enzyme dehalogenase so that monoiodotyrosine and diiodotyrosine escape into the blood and insufficient thyroid hormone is produced. There are also other less common biochemical abnormalities responsible for goitrous cretinism. In the diagnosis of goitrous cretinism secondary to a lack of oxidative enzyme, the discharge of trapped $^{131}$-iodide from the thyroid gland by potassium thiocyanate is a useful test. More elaborate diagnostic methods are necessary to establish the metabolic block in other cases.

Dr. Stanley Steinberg, Washington, D.C.: Can the measurement of protein-bound and butanol-extractable iodine be done with accuracy in a small hospital?

Dr. Gardner: Unless the local laboratory facilities are unusually excellent, it is recommended that these determinations be sent to laboratories which make a specialty of these measurements.

Dr. Keagy, Altoona, Pa.: Does the bone age respond to thyroid therapy?

Dr. Gardner: Yes, improvement in bony maturation occurs very readily under thyroid treatment. But bone age may not be used alone to judge adequacy of therapy, because one may find normal bone ages in a child who is not being treated with sufficient thyroid.

Dr. Joan Brady, Rockland Co., N.Y.:
Does the cholesterol level go up in a hypothyroid child who is not treated?

**Dr. Gardner:** For reasons not clearly understood, untreated hypothyroid infants in the first year of life do not show elevated serum cholesterol values. Figure 2 shows this point very strikingly. It can be seen that after 1 year of age there is a maturation of the cholesterol metabolic defect, with abnormally increased values in evidence.

**Dr. J. Dick, Levittown, N.Y.:** Would you comment on the so-called metabolic insufficiency syndrome?

**Dr. Gardner:** In my opinion the syndrome of "metabolic insufficiency" as applied to children is a figment of medical semantics and has no existence in fact.

**Intersexuality**

**Dr. Rosenthal:** Male pseudohermaphroditism results from failure of the fetal testis to cause male differentiation. Female pseudohermaphroditism results from partial virilization of the fetus by androgens produced by its own adrenals or derived from the mother. In true hermaphroditism, the pathogenesis is failure of normal differentiation of one or both gonads in accordance with the genetic sex. Most cases of gonadal dysgenesis (previously known as ovarian agenesis) appear to result from early degeneration of the fetal testes, so that the fetus (like Jost's rabbit fetuses which were castrated in utero), develops as female. Some cases of testicular dysgenesis appear to result from abnormal differentia-

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**Fig. 2.** Concentrations of cholesterol in plasma of infants and children with untreated hypothyroidism. The failure of the young hypothyroid infants to show increased values for serum cholesterol is obvious. The open circles represent previously treated children who had not received thyroid therapy for 6 weeks or longer.
tion of the undifferentiated gonads into testes in individuals of female genetic sex. Pathogenetically these cases appear to be related to true hermaphroditism.

As a result of the work of Barr and his colleagues, it is now possible to determine the genetic sex of an hermaphrodite. By buccal mucosal smear or by skin biopsy, a chromatin mass can be detected in the nuclei of a high percentage of the cells of those of female genetic sex, but not in the cell nuclei of those of male genetic sex. Individuals with a high percentage of cells with these chromatin masses are called chromatin positive, and those whose cells do not have the chromatin mass are called chromatin negative. This test for genetic sex is simple to perform and is useful in the diagnosis of clinical cases of intersexuality. Careful attention must be paid to the proper preparation of smears and biopsies in order to avoid errors.

Male pseudohermaphrodites are sex chromatin negative. Female pseudohermaphrodites are either chromatin positive or negative. Most cases of gonadal dysgenesis are chromatin negative. Many cases of testicular dysgenesis are chromatin positive.

In the diagnosis of hermaphroditism consideration must be given to the nature of the genitalia, the character of the gonads, the genetic sex, the secondary sex characteristics and the gender rôle. The determination of the urinary excretion of 17-ketosteroids and of pregnanetriol are most useful in the diagnosis of virilizing adrenal hyperplasia. Exploratory laparotomy and gonadal biopsy are necessary for diagnosis in the cases of hermaphroditism but should not be necessary for diagnosis in the cases of female pseudohermaphrodites secondary to congenital adrenal hyperplasia.

Wilkins et al. have recently shown that female pseudohermaphroditism may result from masculinization of the female fetus as a result of the administration of certain progestins to the mother during gestation. The drugs involved, among which were 17-ethinyltestosterone and progesterone, had been used in cases of threatened or habitual abortion. It is important that all pediatricians be aware of this syndrome.

In cases of hermaphroditism the diagnosis should be established as early as possible so that definitive sex assignment can be made after a consideration of all factors involved. The nature of the internal and external genitalia are of prime importance in this regard. The development of gender rôle is dependent in large part upon assigned sex. Change of sex assignment is particularly undesirable after the age of 18 months, and should be avoided unless there are extraordinary circumstances.

In gonadal dysgenesis, the presence of under stature, pterygium colli and other anomalies may suggest the diagnosis. It must be remembered that female patients with the pterygium syndrome may not necessarily have gonadal dysgenesis.

It is emphasized that the virilization of females with virilizing adrenal hyperplasia, due to a congenital defect in the synthesis of hydrocortisone by the adrenal, may not be present at birth but have its onset in childhood. These cases can be differentiated from cases of adrenal tumor by the method of Gardner and Migeon. The urinary excretion of 17-ketosteroids is depressed by the administration of cortisone or one of its analogs in virilizing adrenal hyperplasia but not in virilizing adrenal tumor. The cases of tumor usually excrete excessive amounts of dehydro-epiandrosterone.

Unless the sodium-losing form of congenital adrenal hyperplasia is recognized and treated vigorously in infancy there is a high mortality. The diagnosis is particularly difficult in male infants, because there is no genital abnormality at an early age. Vigorous treatment with intramuscular cortisone, sodium chloride, and desoxycorticosterone acetate is recommended. After the needs for desoxycorticosterone are determined, infants can be conveniently maintained on the drug by injection of desoxycorticosterone trimethylacetate approximately every 4 weeks as an alternative to
the insertion of pellets of desoxycorticosterone acetate. During the second year of life desoxycorticosterone can be discontinued in most instances, but it must be administered to maintain electrolyte homeostasis in an occasional patient. By the second year of life cortisone or one of its analogs should be administered orally. In case of stressful circumstances this dose of cortisone should be increased and if necessary administered parenterally. Cortisone must be continued throughout life in these patients.

With proper psychologic preparation, clitoridectomy and plastic reconstruction of the genitalia may be performed in females with virilizing adrenal hyperplasia without fear of causing psychologic disturbances. In some instances clitoridectomy may be avoided by early treatment with cortisone. Normal sexual maturity and fertility may be expected if treatment is started early. If treatment with cortisone is started late in childhood when the bone age is already advanced, isosexual true precocious puberty should be anticipated as a result of therapy.

Virilizing Adrenal Hyperplasia

Dr. Gardner: Although Dr. Rosenthal has already touched on some of the problems of the female with this syndrome, a few general remarks about the classification of the syndrome would seem to be in order. Roughly, there are five categories into which this syndrome can be divided:

1) First there is the usual type, which simply shows the results of virilization, without excessive sodium loss or other complications. This type may be either congenital or postnatal.

2) Secondly there is the so-called "salt-loser," which is the patient with virilization described above plus crises of excessive sodium loss.

3) Thirdly there is the type showing virilization plus hypoglycemia.

4) A fourth type shows virilization plus hypertension.

5) Lastly, a newly described fifth subtype shows virilization plus episodes of periodic fever. These paroxysmal episodes are characterized by high fever, pains in the abdomen and head, hypotension, flushing of ears and face, and prostration. It now appears that endogenous liberation of etiocholanolone is responsible for the paroxysms of periodic fever in this subvariant of virilizing adrenal hyperplasia.

Bioassay of Insulin

Dr. Feinberg: Several methods of assaying insulin in blood and other body fluids have been proposed. There is described below a method at present under study, based on an immunologic principle.

In this immunologic method an antiserum to insulin is prepared by immunizing guinea pigs to insulin. Insulin antigen for the test is prepared by adsorbing insulin on tannic acid-treated sheep erythrocytes. This converts the ordinary sheep erythrocyte into a cell coated with the specific antigen, in this case insulin.

All sera used in the test are heated at 56°C for 30 minutes to inactivate complement, and adsorbed with washed sheep erythrocytes in order to remove any nonspecific antisheep agglutinins. Serial dilutions are made in Houssay cat serum in order to eliminate any insulin in the system other than that from the patient's serum or on the sensitized sheep erythrocytes. The antiserum guinea pig serum is then added, and the system incubated. If insulin is present in the serum being assayed, it will neutralize the antibody. The sheep erythrocytes on which insulin has been adsorbed are then added. If there remains free antibody, hemagglutination will occur. If insulin in the serum being tested has neutralized all or part of the antibody, hemagglutination will be completely or partially inhibited. The amount of insulin in the serum can thus be estimated.

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