TODAY

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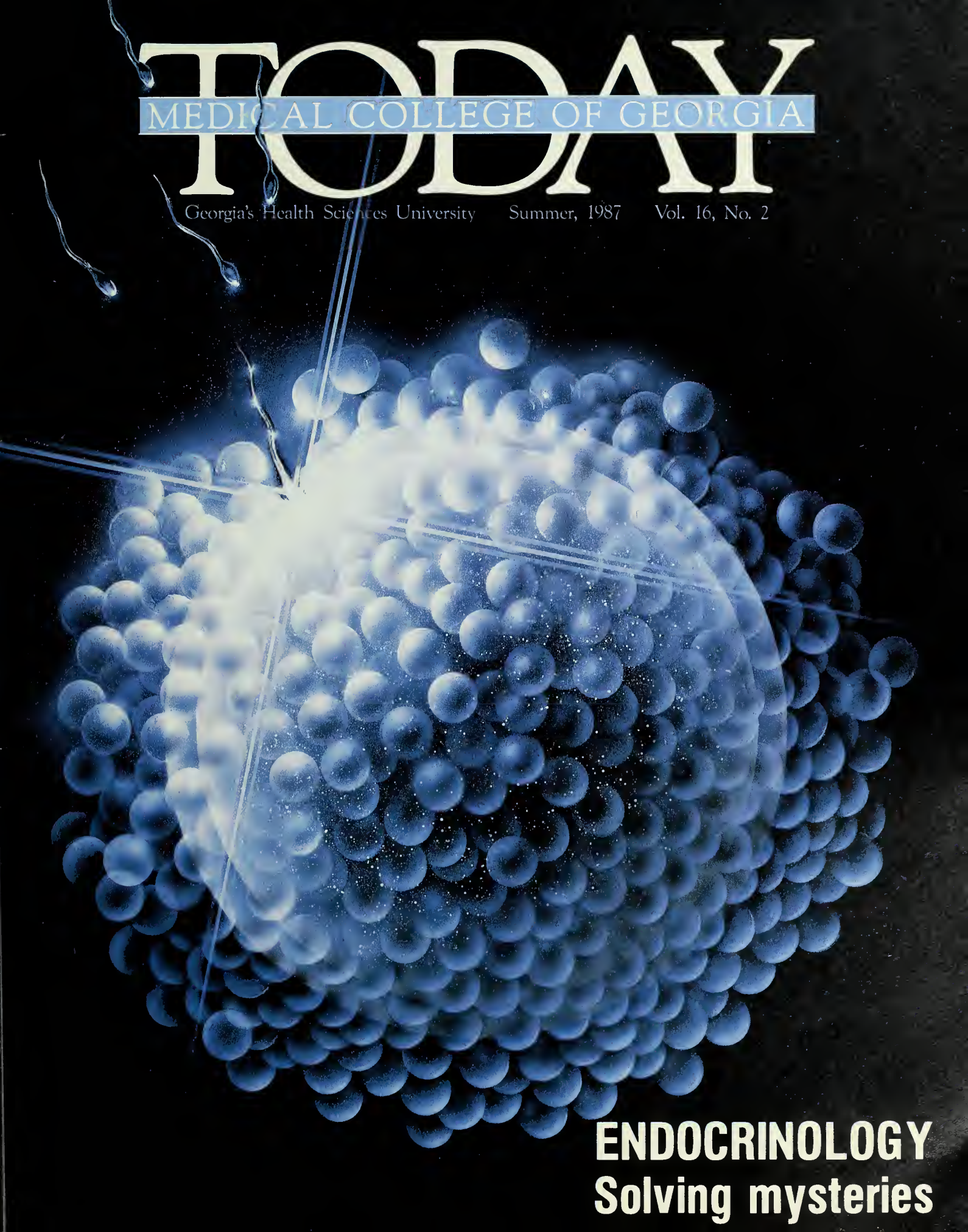

ENDOCRINOLOGY
Solving mysteries

Dr. William Hoffman explains growth chart to Crystal Atkinson and her mother, Belinda Boatright

Endocrinology at the Medical College of Georgia is nothing if not diverse.

From its infancy in 1946, the MCG department devoted to the study of the body's internal secretions has branched out into sections of reproductive endocrinology, metabolic and endocrine disease and pediatric endocrinology.

This summer issue of *Medical College of Georgia Today* examines the people, the services and the research that have placed MCG in the forefront of endocrinology.

Embryo freezing, which offers childless couples a higher success rate for in vitro fertilization, has been a service at MCG since 1984. In October, a Savannah couple is expecting what will be MCG's third successful birth from that program.

Pediatric endocrinologist William Hoffman helps children grow up. Literally. Some, like 13-year-old Crystal Atkinson, have a communication breakdown inside the body which creates a hormone deficiency resulting in below-average height. Synthetic hormone treatments can make the difference, as Dr. Hoffman explains.

Fast, accurate diagnosis of metabolic bone disease can also make the difference for patients with such a disease. Using equipment such as the photon absorptiometer, the MCG Metabolic Bone Disease Laboratory staff can provide the best in diagnosis to enable early treatment.

It could be said that veteran endocrinologist Robert Greenblatt made possible all the aforementioned — he founded MCG's Department of Endocrinology in 1946 and continues to make contributions after 52 years in the field. He recalls achievements and experiences in a profile in this issue.

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The Medical College of Georgia is the health sciences university of the University System of Georgia. Focusing on health care education, research and patient care, the Augusta-based institution consists of MCG Hospital, more than 80 support clinics, statewide outreach programs and the Schools of Allied Health Sciences, Dentistry, Graduate Studies, Medicine and Nursing.

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Frozen embryos

Newest option for childless couples

By Catherine Boardman

In October a baby born in Savannah will join an elite crowd. The infant will be one of about 100 in the world who have been born from a frozen embryo transfer.

Freezing embryos is an option offered at the Medical College of Georgia Hospital and Clinics in conjunction with its In Vitro Fertilization Program. MCG Hospital's in vitro fertilization team includes specialists in reproductive endocrinology and infertility, sonography, anesthesia, human egg development and hormone assays.

In vitro fertilization gives infertile couples a chance at pregnancy. During the process, eggs are retrieved from the woman and placed in a dish with sperm from the husband. After fertilization takes place and embryos develop, the eggs are transferred back into the woman. When the process goes well, the embryos implant on the lining of the uterus and a baby develops.

Couples call on MCG Hospital's in vitro fertilization program for a variety of reasons. In some cases, the woman has blocked or absent fallopian tubes which normally direct the sperm to the egg and then propel the fertilized egg into the uterus. Endometriosis, a condition in which tissue of the uterine lining grows elsewhere in the body, causes infertility in some women. Or the man may have a low sperm count.

"We usually exhaust all other methods of overcoming infertility and then we turn to in vitro fertilization," said Dr. Santiago L. Padilla, director of the in vitro fertilization program at MCG Hospital.

The Savannah couple had no options. In vitro fertilization was their only hope for pregnancy. The 23-year-old woman, who wishes to remain unidentified until her baby is born, has no functional fallopian tubes, said Dr. Padilla.

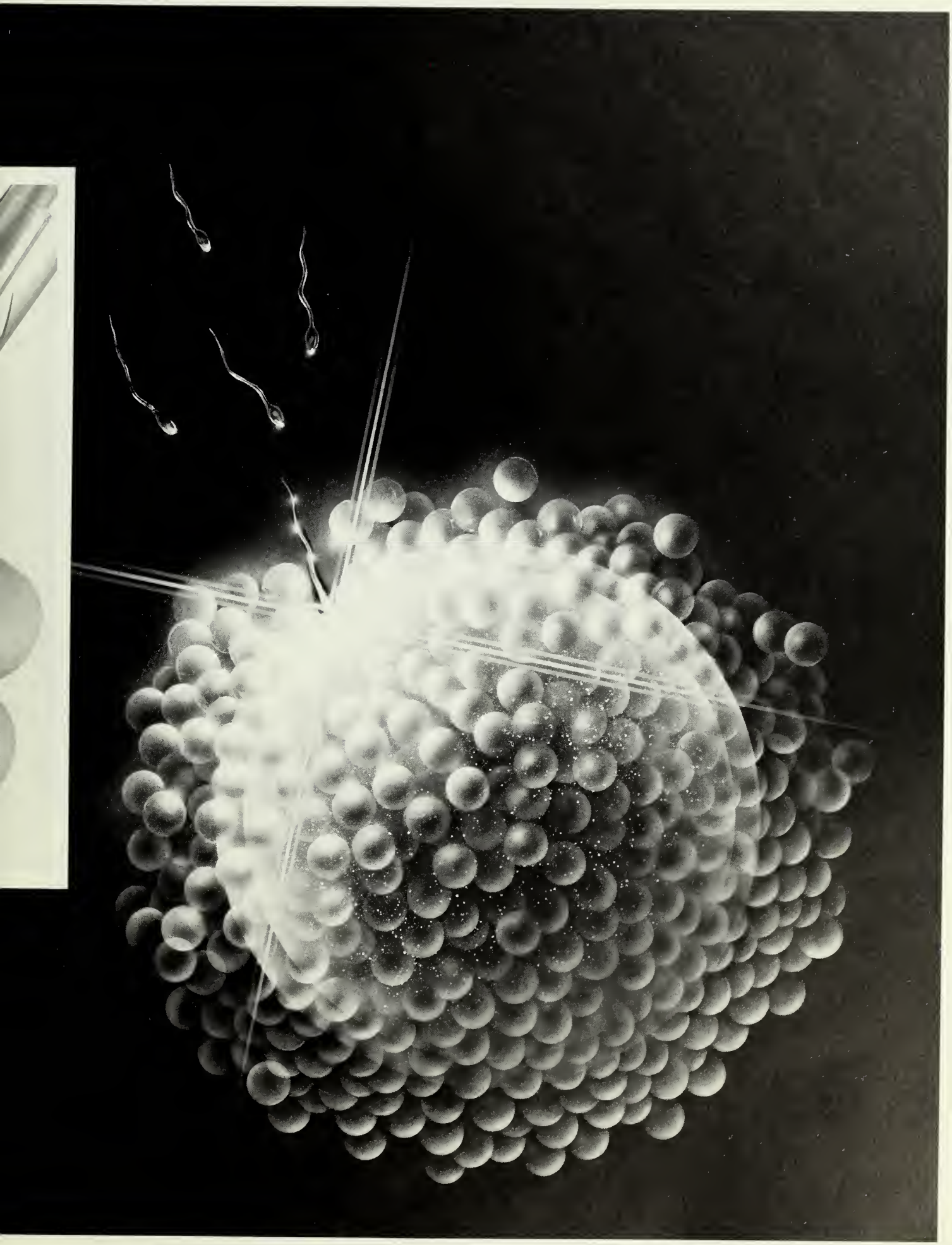
The couple's first in vitro attempt in August 1986 was unsuccessful. But MCG's ability to freeze embryos allowed them to try again six months later without having to go through the entire in vitro process. The frozen embryo was simply thawed and transferred.

Normally with egg retrieval and fertilization, several embryos result, explained Dr. Jeffrey Boldt, director of the in vitro laboratory at MCG. The optimal number of embryos to transfer to the mother is about three. Transferring more than three embryos increases the risk of a multiple pregnancy, he said.

By freezing embryos, the most effective number of embryos can be transferred to the woman while the rest are stored.

To freeze an embryo, doctors place it in a protective solution and gradually lower the temperature to minus 40-80 degrees centigrade. It is then put in a holding tank filled with liquid nitrogen,

Illustration of fertilization; (insert) Ampule containing human embryos ►



which is even colder. At that temperature, all biological activity is suspended, Dr. Boldt said.

Freezing embryos may result in a higher success rate for in vitro fertilization, he said.

During the in vitro fertilization process, the woman takes medications to stimulate egg production, which may result in a hormonal imbalance, Dr. Boldt said. By comparison, "the woman's chance of getting pregnant could potentially be better with the frozen embryo since it is transferred during her natural, spontaneous menstrual cycle," he said.

Since MCG's program began in November 1984, 45 embryo transfers have yielded nine pregnancies including the expectant mother in Savannah. Two births have occurred as well as four miscarriages and two ectopic or tubal pregnancies.

"We make a big point of very accurately telling our patients what they can expect, not only in terms of the procedure but also emotional reaction, money and the statistical probability of achieving a pregnancy and carrying to term," said Kay Craft, clinical coordinator of the in vitro fertilization program.

Ms. Craft coordinates and guides couples through the entire in vitro fertilization process. The procedure costs about $5,000.

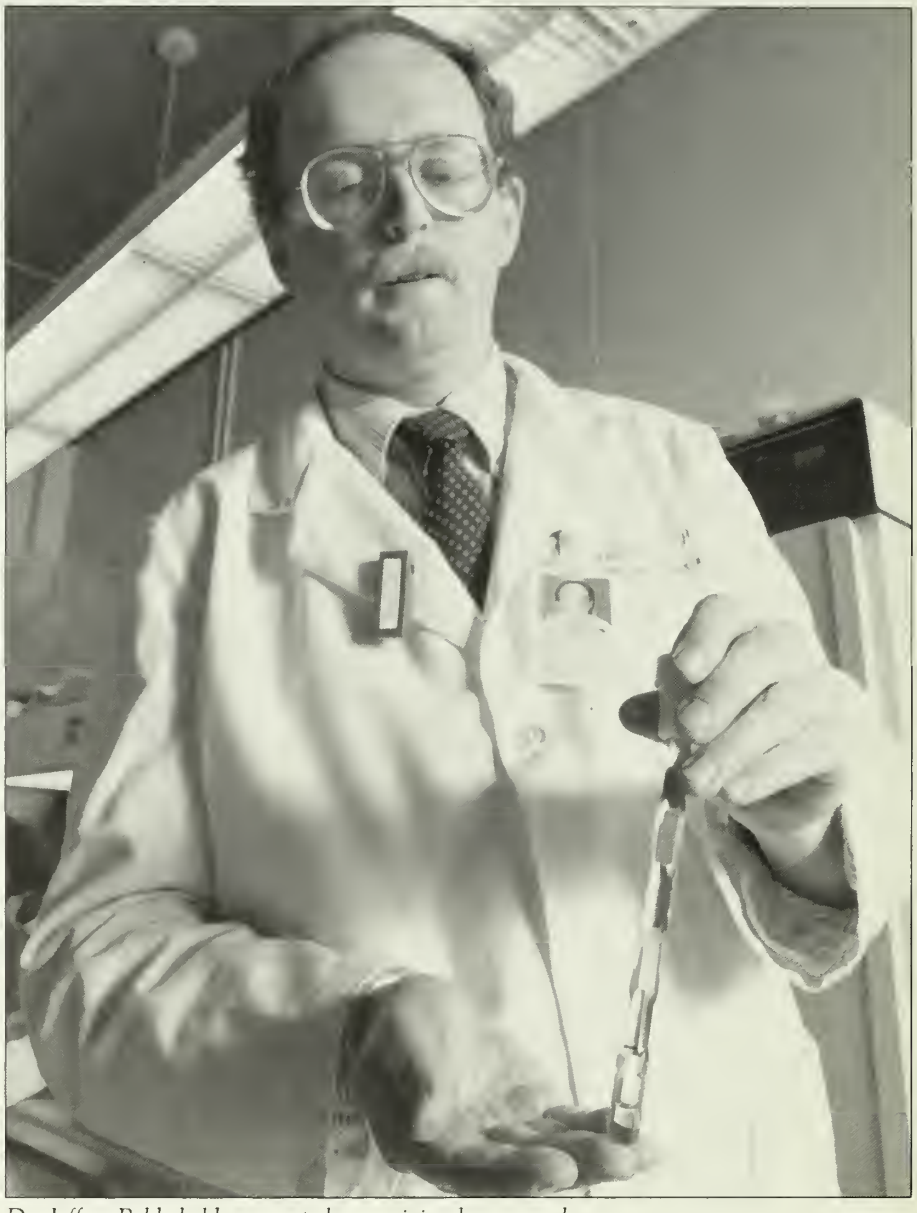
First, the woman takes medicines to stimulate multiple egg production. Next, the eggs are retrieved from the ovary by puncturing the follicle with a needle and aspirating the fluid, said Dr. Padilla.

Two methods are available for egg retrieval. One is laparoscopy, in which a tube is inserted into the lower abdomen to the ovary through a tiny incision. Or using ultrasound, a needle is placed through the bladder into the ovary. The ultrasound technique is used more often since it requires no incision, Dr. Padilla said.

While the doctor retrieves the eggs from the woman's ovaries, Ms. Craft and the husband watch a video monitor from a nearby room. She explains the process as it progresses.

Once the physician retrieves the eggs, he hands them over to the lab personnel. "We find the egg in the aspirate, put it in culture medium in a dish, process the sperm sample from the husband and inseminate the egg," Dr. Boldt said.

The egg is checked the next day for normal fertilization and is transferred to a growth medium. During fertilization, genetic material in the egg and sperm combines and rearranges. The embryo then divides. The development time is usually 48 to 78 hours. The embryo is placed in a catheter and transferred to the mother's uterus. Other embryos may be frozen for future transfers.



Dr. Jeffrey Boldt holds an ampule containing human embryos

A long two weeks must pass before the mother is tested for pregnancy, Ms. Craft said. When the process works, everyone involved is ecstatic. "The successes are indescribable," she said.

Dr. Boldt and two other researchers in MCG's in vitro fertilization laboratory are working to make the process more fruitful. They test culture and growth mediums using mouse embryos and look for possible improvements.

In November 1986, Dr. Boldt received a three-year grant from the National Institutes of Health to study the fertilization process in mice to understand the fusion activity between the sperm and egg. "It is a critical aspect of fertilization and no one has any idea what is involved in it," Dr. Boldt said.

"We're also working with mouse embryos to further develop and refine our freezing techniques," he said.

Advances may mean better odds for infertile couples to achieve pregnancy. "Unfortunately, infertility is on the upswing because of changes in lifestyle such as delayed childbearing," Ms. Craft said.

"Couples wanting children need to know they have done all they can. If in vitro fertilization works, they are happy. If it doesn't, they can give up their quest knowing they have done all that modern science has to offer," she said. ■

Physician traces clues to miscarriage

By Toni Baker

It was hardly the scenario she'd imagined.

Jill and her husband are products of big families.

Jill and her husband love each other.

Jill and her husband love children.

Their first pregnancy was not planned, but it was hardly unwelcome either.

One January day they found out they were pregnant — six or seven weeks along.

The next day Jill miscarried.

"The timing was so bizarre," said the young woman, who was willing to share her story but not her real name. The subject was too private.

"I think you grow up assuming that you are going to have children and assuming that there is not going to be any problem."

The loss came very early in the pregnancy. She hadn't felt physically different yet. She hadn't felt the baby move. But she still felt the disappointment.

The obstetrician told her to wait several months before trying to get pregnant.

Nearly 10 months later, the couple was pregnant again.

But the scenario was all too similar.

Jill still didn't feel or look different physically. "But it's more of a bitter disappointment the second time. I think you feel a sense of mourning for what could have been. You almost feel like you are setting a trend. Maybe those five children or four children or whatever that you wanted aren't going to come as readily or may not come at all, the way that you had thought."

It was at that point her obstetrician referred her to the Medical College of Georgia reproductive endocrinology clinic.

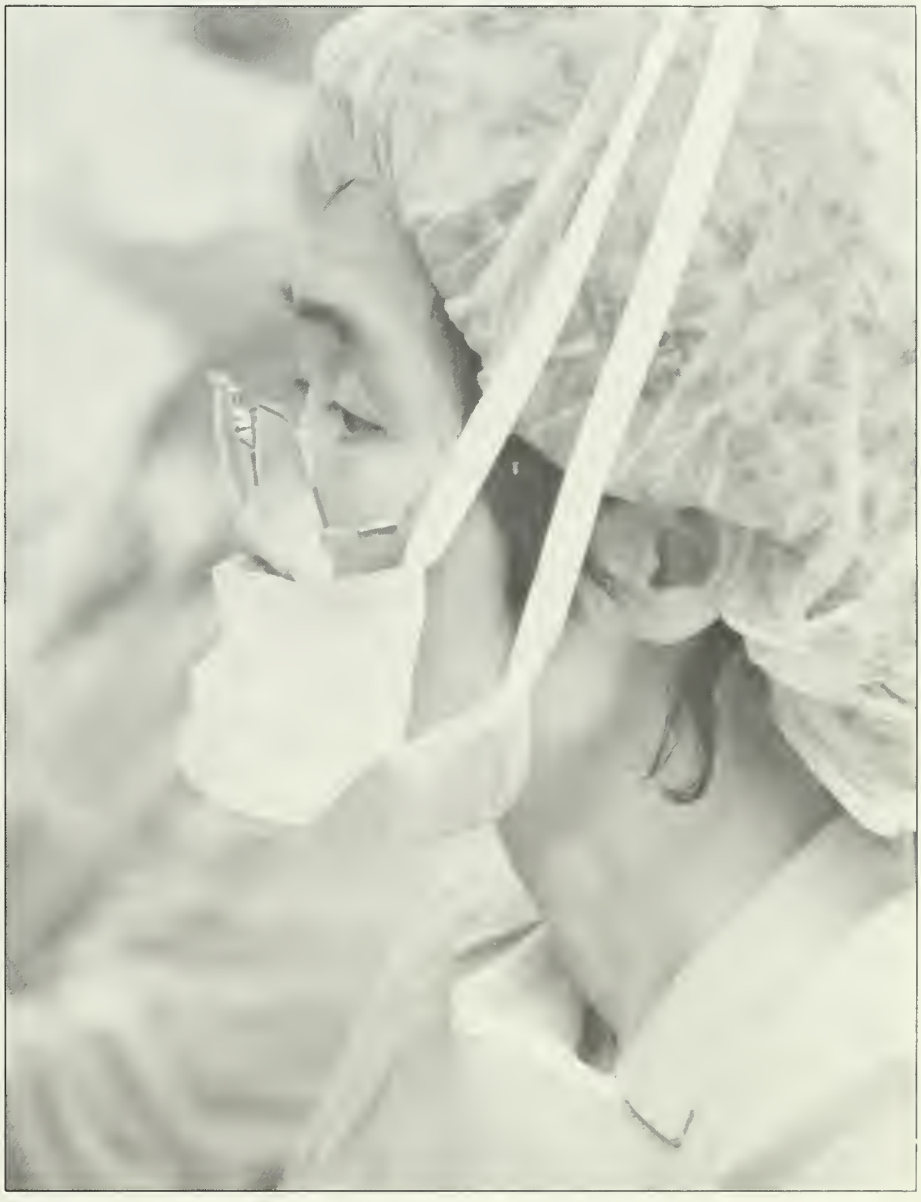
Dr. Sandra P. Tho, assistant professor of obstetrics and gynecology and expert in reproductive endocrinology at MCG, may see five new cases like this one each week in her clinic.

These women are not infertile in the classical sense.

They can get pregnant.

But they cannot stay pregnant.

When these patients get to Dr. Tho, they embark upon an exceedingly thorough series of tests to attempt to pinpoint the cause of the trouble. For a few patients it is a search that never ends.



Dr. Sandra P. Tho

In this effort to find the cause and potentially the solution for recurrent miscarriages, tests range from X-rays to complex analyses of hormonal activity and chromosomes.

When women miscarry early in the first trimester, chromosomal abnormalities are to blame in about half the cases.

Normally, an embryo — a developing baby in its first few weeks in the uterus — is formed by the combination of one egg of 23 chromosomes and one sperm of 23 chromosomes.

The single-cell, 46-chromosome embryo must divide into two and four and eight and hundreds of cells to grow. If the chromosome number is abnormal, the embryo may form, but the division process crucial to its growth may stop at any time or happen too slowly. The result is early loss of a pregnancy.

The embryo may have either too few or too many chromosomes.

When there are too few, loss of the pregnancy comes very early. "Women can be late a few days, then have a heavy

Dr. Tho won't give up on a patient...unless the patient gives up. At times, that may mean sending the patient away, until advances in treatment offer new hope.

period and never know they were pregnant," Dr. Tho said.

About six days pass between fertilization and implantation, Dr. Tho said. But current testing cannot tell if a woman is pregnant until four or five days after implantation.

"People work real hard to make a diagnosis of conception before implantation, but they are not successful," Dr. Tho said. She calls this a dark area of science.

This may be one explanation for the "unknown" loss of early pregnancies.

The difficulty in documenting too few chromosomes may be one reason there seem to be more cases of embryos with too many, Dr. Tho said.

Embryos with too many chromosomes may live longer so the pregnancy can be documented. Chromosomal studies then can verify abnormal numbers of chromosomes.

This abnormal number may be hereditary. In that case, nothing can be done to correct the problem. "We tell them they have a chance of losing, but they may not always lose," Dr. Tho said.

Couples who then choose to continue trying may never have a child. Or they may have a child who is either abnormal or perfectly healthy.

Should a pregnancy survive, say for 9 to 12 weeks, chromosomal studies can then determine if the baby is normal.

Another baseline of Dr. Tho's evaluation is detailed temperature charts tracking ovulation.

Typically from menses to ovulation is 12 to 20 days. If that period is longer, eggs may stay in the ovary too long and get too old.

Animal studies show that older eggs may have abnormal numbers of chromosomes. Although it's not completely clear why, it may be that the separation of the two members of a pair of chromosomes doesn't happen as easily in an older egg, Dr. Tho said.

It's also important to know when ovulation occurs so that couples can have intercourse close to that time. Eggs produced during ovulation then won't be too old for the sperm and vice versa.

If ovulation doesn't occur on time, Dr. Tho prescribes Clomid, a hormone that corrects that problem.

But some chromosomal problems cannot be remedied. One of these — fortunately rare — is structural abnormalities of the chromosome.

Another major reason for recurrent miscarriages can be diagnosed with an X-ray of the uterus.

This diagnostic tool looks for fibrous tissue that could keep the egg from successfully implanting in the uterus. Female embryos develop with two uteri. During development, the two uteri should fuse and the fibrous tissue between the two uteri should resorb, giving rise to a single cavity. If resorption of the two into one uterus is incomplete, fibrous tissue void of blood vessels can be present in the adult uterus. If an embryo attempts to implant in this tissue, it will die from lack of blood and oxygen. Most women don't even know they have this tissue until they attempt to become pregnant.

Fortunately, this relatively simple problem has a straightforward solution.

Doctors can insert a scope vaginally up to the uterus and clip away the tissue, avoiding major abdominal surgery.

Another potential problem lies within the uterus, but this time with the lining.

By charting ovulation, Dr. Tho can determine when to do a biopsy of the lining of the uterus to see if it is prepared to accept and nurture an egg.

The search for Jill's problem ended here. "For some reason, she does not make enough progesterone," Dr. Tho said. Progesterone is a hormone required for implantation, and it normally increases during pregnancy.

A biopsy of the lining of Jill's uterus showed that her own hormonal system was not producing sufficient progesterone. Apparently her pituitary gland was not signaling her ovaries to produce the vital substance.

Dr. Tho began treating Jill with suppositories of progesterone twice daily for 10 days, then biopsied the lining to see if it could accept an egg.

The first round of treatment was not sufficient, so Dr. Tho increased the dosage. This time the lining was ready.

Mid-March found Jill five months pregnant and rather insightful.

"I stayed real leery of another miscarriage for probably four months. I don't think you ever experience a miscarriage and get pregnant again and don't experience some semblance of anxiety or fear. You are just not naive anymore."

She had just finished taking the progesterone. She continued to take it until her placenta took over the job of producing the substance. Dr. Tho says it's rare that problems are found with the placenta making sufficient progesterone.

The young mother understands that she was one of the luckier women in the clinic. Jill only spent about a year there. She saw women who had spent six and eight years there, waiting and trying. She is pretty sure she couldn't have done that.

"I don't know how to describe it except to say that it's all consuming," Jill said. "Instead of what day of the week it is, you know you are on day 12 of your cycle. Every month it's something. You end up planning vacations, planning visits with your parents around your menstrual cycle."

Dr. Tho won't give up on a patient like Jill, unless the patient chooses to give up. At times, that may mean sending the patient away, until advances in treatment offer new hope.

"People suffer a lot. In some, we don't see the reason but they keep losing. So we have a group of patients we call unknown," the reproductive endocrinologist said.

But more often than not, the stories end happily. Dr. Tho follows mothers until the embryo is about 16 weeks old. When she is convinced everything is fine, she refers patients back to their obstetricians.

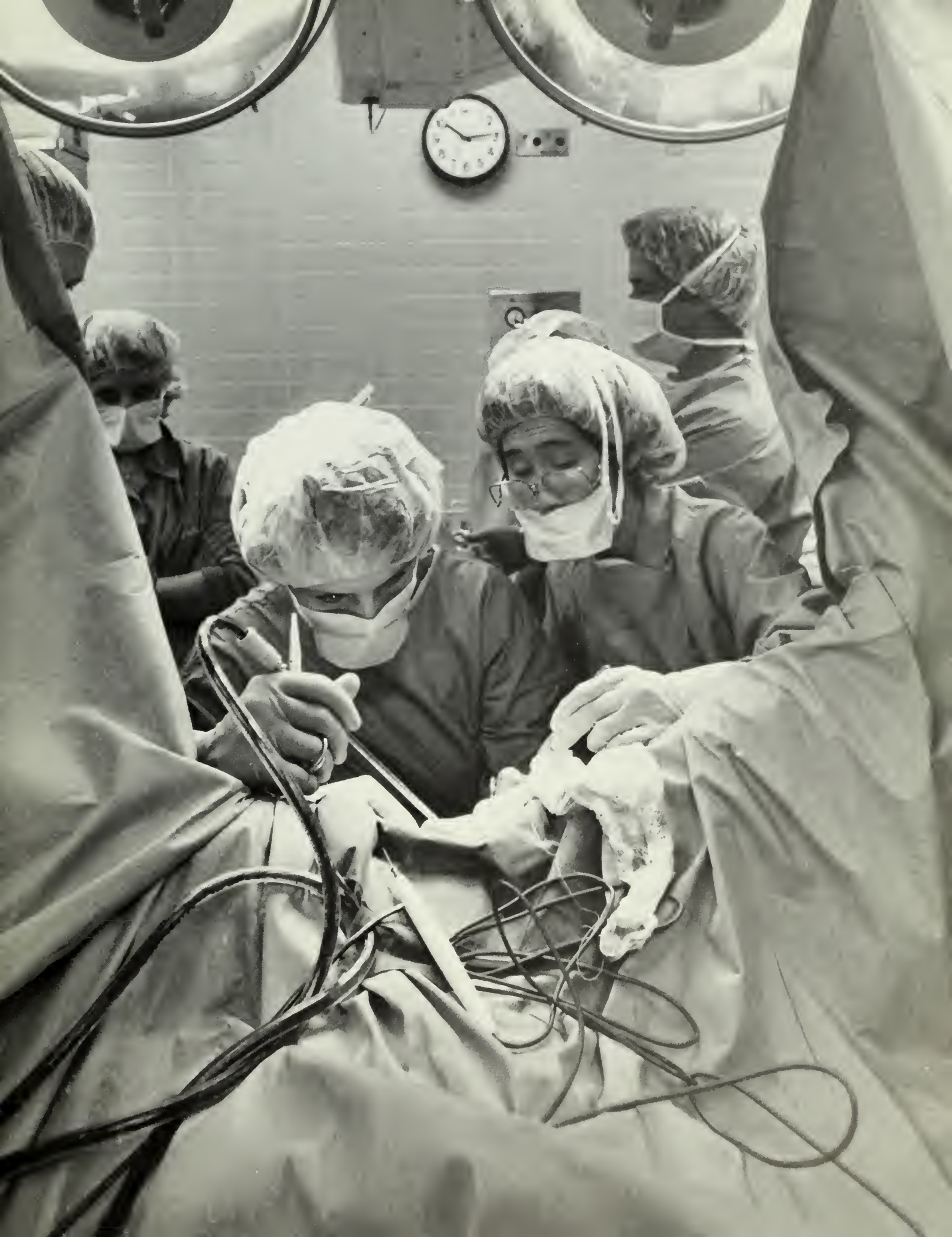
It's gratifying work, expecially at Christmastime when Dr. Tho gets pictures of babies she helped make possible.

"Right now I'm not considered high-risk anymore," Jill said. She doesn't feel high-risk either. She didn't say she doesn't worry.

"It's a whole series of ups and downs, of emotional highs and lows," she said. "I never thought it would be this way. You'd get pregnant. You'd get tickled and go out and buy baby things."

But, she says, to get where she was that mid-March day, she would go through it again. ■

Dr. Sandra P. Tho in surgery ►



Diagnosis in the womb

DNA testing dispels parents' uncertainties

By Christine Deriso

Jack and Joanne, a young married couple, find out they're expecting a baby. They're elated; parenthood has always been one of their top priorities.

But an ominous cloud is cast over their future: Joanne's family has a history of hemophilia, a disease in which blood doesn't clot properly. The disease transforms minor scratches into life-threatening crises. And it's hereditary. Is their unborn baby a victim? The uncertainty turns their elation into dread.

Jack and Joanne are fictional, but their problem is a jarring fact of life for many expectant parents. Fortunately, recent medical technology can dispel their uncertainty. Hemophilia and many other diseases now can be diagnosed within weeks of conception. Prenatal diagnostic testing can make the difference between nine months of agony and nine months of elation.

A number of fetal abnormalities can be diagnosed only by testing fetal deoxyribonucleic acid (DNA), the molecular basis of heredity, according to Dr. William J. Butler, assistant professor of obstetrics and gynecology at the Medical College of Georgia.

DNA diagnostic testing is not dependent on expression of the gene responsible for the disease, which may not occur in fetal tissue or the tissue available for diagnosis. All cells contain all genes, whether they use them or not. So with this method, for example, blood disease can be diagnosed from fetal skin cells.

Fetal DNA testing has been available for about five years, and MCG has been among the world's trailblazers in its research and application.

The most widely used method to obtain tissue for DNA analysis is amniocentesis, in which a needle is inserted into the amniotic sac around the fetus to drain fluid. Within the fluid are fetal cells shed from the skin, which can be used for the analysis. The procedure is done about 16 weeks into pregnancy.

A newer method, still in the research stages at MCG, is chorionic villus sampling (CVS), in which DNA is extracted from the trophoblast, a piece of the placenta.

Its advantage over amniocentesis is that it is performed earlier in pregnancy, at nine to 11 weeks of gestation. Its disadvantage is a higher risk of miscarriage (1 to 2 percent compared to the approximate 0.3 percent risk in amniocentesis.)

Another advantage is that trophoblast can be analyzed immediately and the results are available in a week.

The results of amniocentesis, a 15-minute outpatient procedure, aren't available for a month because the cells must be grown in culture.

"It's a long four weeks for them," Dr. Butler said.

Once the DNA is extracted, two procedures are available to test it.

Direct gene analysis to identify an abnormal gene was developed to test for sickle cell anemia at MCG by Dr. John Wilson. The method is now limited to testing for only that disease, but Dr. Butler said research may yield more far-reaching applications.

A method that can test for many abnormalities is restriction fragment length polymorphism analysis (RFLP.) This method identifies markers in DNA associated with abnormal genes. By tracing the marker, doctors can predict the presence of the abnormal gene that can't be directly detected. One disadvantage of the technique is that every family member must be tested to trace the gene. Another is that accuracy varies.

"That's the problem," Dr. Butler said. "The percentage error depends on how closely linked the RFLP is to the abnormal gene you're trying to trace through the family."

Nevertheless, RFLPs represent an enormous breakthrough in medical technology. Diseases such as thalassemias (in which defective genes limit hemoglobin synthesis), hemophilias A and B, cystic fibrosis, Duchenne's muscular dystrophy and Huntington's disease can be diagnosed prenatally.

The breakthrough of prenatal diagnostic testing leaves parents with something of a double-edged sword: invaluable information and a huge dilemma — if the fetus tests positive for an abnormality. Where do parents go from here?

Dr. William Butler and assistant Ginny Davis examine audioradiograph of DNA probe

"Women can either terminate the pregnancy or be prepared for the problem so newborn treatment can be implemented immediately," Dr. Butler said. MCG offers "non-directive" counseling, informing parents of the options and leaving the decision in their hands.

"Obviously, this is fraught with a lot of moral issues for individuals," Dr. Butler said. "A lot of parents will tell you they'll do one thing before the fetus is tested and then change their minds."

The moral dilemma is multiplied for one disease in particular: Huntington's. The fatal disease isn't manifested until one's 30s or 40s and is characterized by dementia (insanity).

Dr. Butler cited the case of a pregnant woman who sought prenatal diagnostic testing at a hospital after her father-in-law died of Huntington's. But her husband didn't want the test results revealed.

"Since his father died of it, the fetus' father had a 50 percent chance of having the disease," Dr. Butler said. "He didn't want to know. If you diagnosed the baby as having the disease, you've just given the father a death sentence."

The ultimate solution to the dilemma of diagnosing fetuses is being able to cure them. Such a breakthrough is not yet a reality.

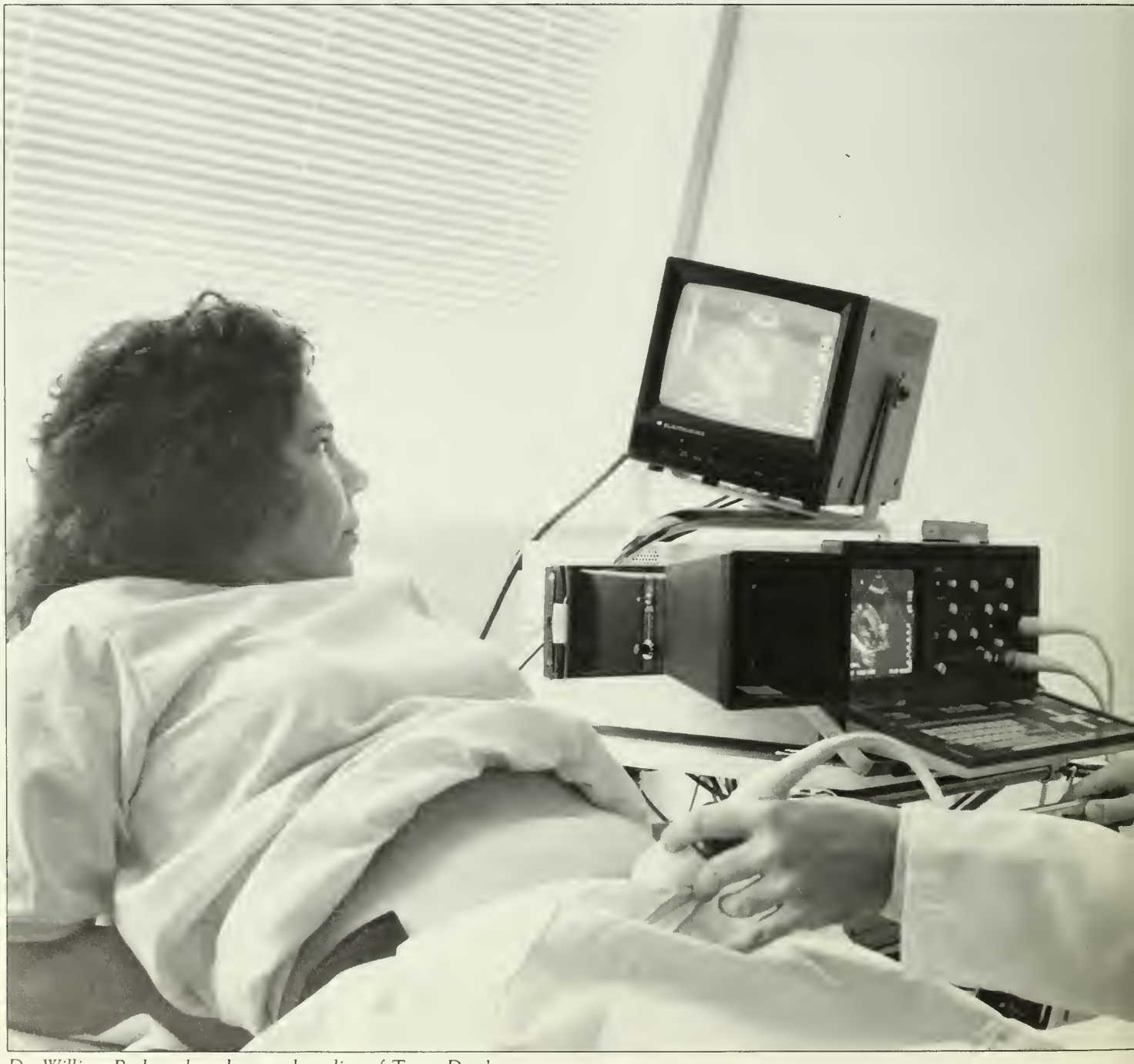
"At the moment, prenatal therapy is not available," Dr. Butler said. "But we want to move prenatal testing earlier because of the hope of gene therapy."

The first gene therapy tests will be done this year at the National Institutes of Health in Bethesda, Md., he said. Researchers will attempt to treat adenosine deaminase deficiency, the fatal immunological disease that affected the "bubble boy."

"If it works in children, it can be done in utero as well," he said. "Twenty years down the line, that's what we're aiming for." ■

Innovative surgery corrects uterine

By John Donnelly



Dr. William Butler takes ultrasound reading of Teresa Dyer's uterus

abnormality

Several years ago, after suffering two miscarriages, 33-year-old Teresa Dyer and her physician discussed the possibility of surgery to correct an abnormality in her uterus.

"At the time all I did was talk about it," Mrs. Dyer said. "I backed off from it for a few years but asked my doctor about it again last year."

Her physician, MCG graduate Dr. Charles May, practices in Macon, 20 miles from Mrs. Dyer's home in Bon Aire, Ga. He knew of a procedure, hysteroscopic surgery, being done at the Medical College of Georgia and referred Mrs. Dyer to Dr. William Butler.

"Teresa came to us in June of 1986. She was our first hysteroscopic surgery patient and the first to become pregnant," said Dr. Butler, assistant professor of obstetrics and gynecology at the Medical College of Georgia.

Since that time, six similar procedures have been done by Dr. Butler and his associates, Dr. Santiago Padilla and Dr. Sandra Tho, both assistant professors of obstetrics and gynecology at MCG. To date, no other pregnancies have occurred.

Mrs. Dyer, an engineering data specialist at Warner Robins Air Force Base, eagerly awaits the birth of her first child. Dr. May will deliver the baby in Macon.

"I have three stepsons, 15, 19 and 20, so I would prefer a girl. I could put bows in her hair," she said.

Dr. Butler feels the need to see a patient if, like Mrs. Dyer, she has had two or more spontaneous abortions. "This can indicate there is a physical abnormality in the uterus," he said. Polyps, sub-mucus myomas (benign tumors), Asherman's syndrome (intrauterine scar tissue) or uterine septa (a growth that divides the uterine cavity) are all uterine abnormalities that can lead to irregular bleeding and miscarriages. Hysteroscopic surgery can, in many cases, correct these abnormalities.

"A uterine septum, for example, can cause miscarriages because the growth reduces the size of the uterine cavity. In addition, it is very avascular — it doesn't contain many blood vessels. If an egg attaches to the septum, there will not be enough blood flow to sustain the egg and a miscarriage results. This was Mrs. Dyer's problem," Dr. Butler said.

Removal of the septum tissue from the uterus by hysteroscopic surgery means both adequate room for a developing fetus and a blood supply equal to the egg's need.

The surgery developed from hysteroscopy, a procedure allowing physicians to view the cervical canal and uterine cavity using a fiber-optic instrument. The instrument consists of a telescope, encased in a metal sheath, that receives light from an external source through a fiber-optic bundle.

The telescope is four to six millimeters in diameter, leaving room in the sheath for accessory channels to handle operating instruments and for delivering a solution to the uterus. The solution is necessary to allow dilation of the uterine cavity.

"The clear, syrupy solution dilates the uterus ahead of the hysteroscope," Dr. Butler said. The normal position for the uterus is with its front and back touching. Dilation allows the physician to view the opened uterus.

"It wasn't that much of a step from hysteroscopy to hysteroscopic surgery," Dr. Butler said. Since it was already possible to view the uterus and there was room in the hysteroscope for surgical equipment, performing the surgery was just a matter of developing the proper techniques.

"I got involved with hysteroscopic surgery because I had patients I thought it could help. It was an innovative procedure, done mostly in academic medical centers. If there are things being done that can help my patients, I want to be able to offer them."

According to Dr. Butler, early results indicate two-thirds of the patients who have hysteroscopic surgery are able to carry their pregnancies to term. "This is the same percentage as the women who have a metroplasty," he said.

A metroplasty is an operation performed through the top of the uterus to remove abnormalities inside the uterine cavity. Drawbacks to this procedure include blood loss and the necessity for a Cesarean section when the baby is born.

The patient also has to spend five to six days in the hospital and another three to four weeks at home recovering from the procedure.

"Hysteroscopic surgery can be done on an outpatient basis with two to three days recovery," Dr. Butler said. There is no accompanying blood loss and the procedure does not by itself necessitate a Cesarean section.

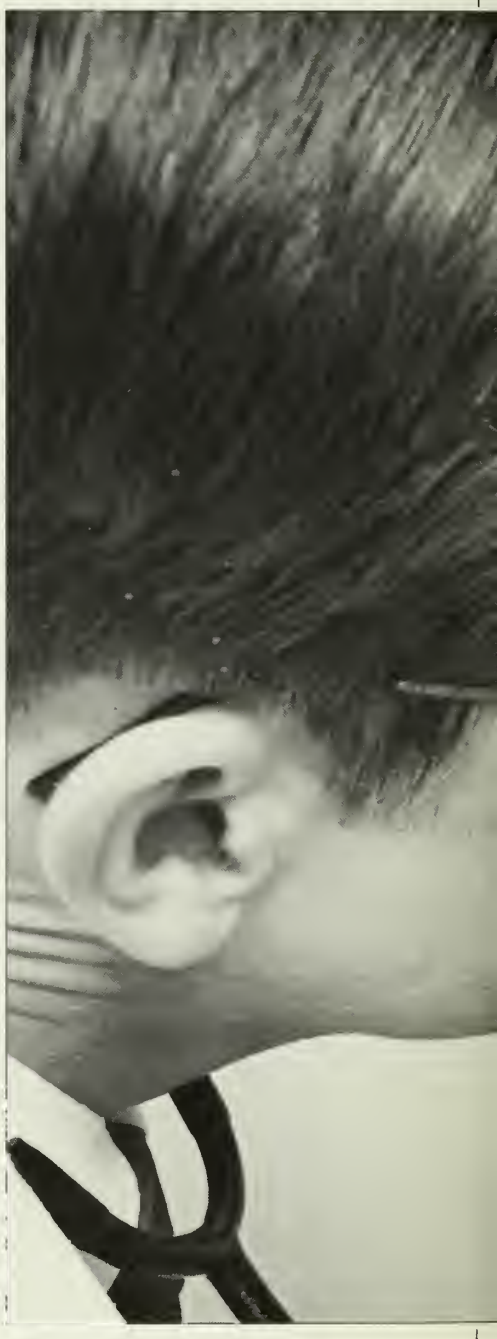
"We are very enthusiastic about this treatment," Dr. Butler said. "We won't know for sure for a few years, but the preliminary results look good."

Mrs. Dyer and her family will not have to wait 'a few years' for their results. Her due date is September 26, close to the birthday of her oldest stepson. "He was born on September 24. It would be nice to give him a birthday present," she said. ■

Playing catch-up

Correcting hormone deficiency helps children grow up

By Toni Baker



Crystal Atkinson was thrown a curve she could not catch.

It was a growth curve, the range of normal heights for growing children.

When pediatric endocrinologist William Hoffman first saw Crystal, she was 11 years old, 48 inches tall and falling farther away from that curve.

That was April 1985.

March 1987 found Crystal on the verge of 13 and only 53 inches high.

Crystal still hasn't caught the curve. But these days, she is closing in on it.

"She's always been slow as far as her growth. I just assumed she was going to be little," said Crystal's mother, Belinda Boatright.

Mrs. Boatright will never forget the beauty contest Crystal entered at age 11. Crystal seemed a small, delicate doll compared to her peers.

At about that time, Crystal's pediatrician, Dr. Sudhakar M. Reddy from Statesboro, Ga., showed Mrs. Boatright the curve that Crystal couldn't catch.

"Dr. Reddy said if anybody could help Crystal, it would be here," said Mrs. Boatright, sitting in the Medical College of Georgia pediatric endocrinology clinic where she and Crystal have been regulars for nearly two years.

At the Medical College of Georgia, Crystal met Dr. Hoffman, and she and her mother embarked upon a growing process for Crystal's body and for both their minds.

They have learned that in the complex growth process, Crystal has a breakdown.

The process begins in the brain, where neurotransmitters that help millions of cells communicate also assist in the release of growth hormone releasing factor.

When the brain's hypothalamus releases growth hormone releasing factor, one function of the pituitary gland is activated. The pituitary, a gland at the base of the brain which is about the size of a finger tip, then activates a series of glands throughout the body. One product is growth hormone.

But another conversion must take place.

Growth hormone must be converted to somatomedin-C, which stimulates cells to grow.

The bad news is that this usually harmonious communication between the brain and body can be interrupted. The breakdown can occur at nearly any point within this complex system.

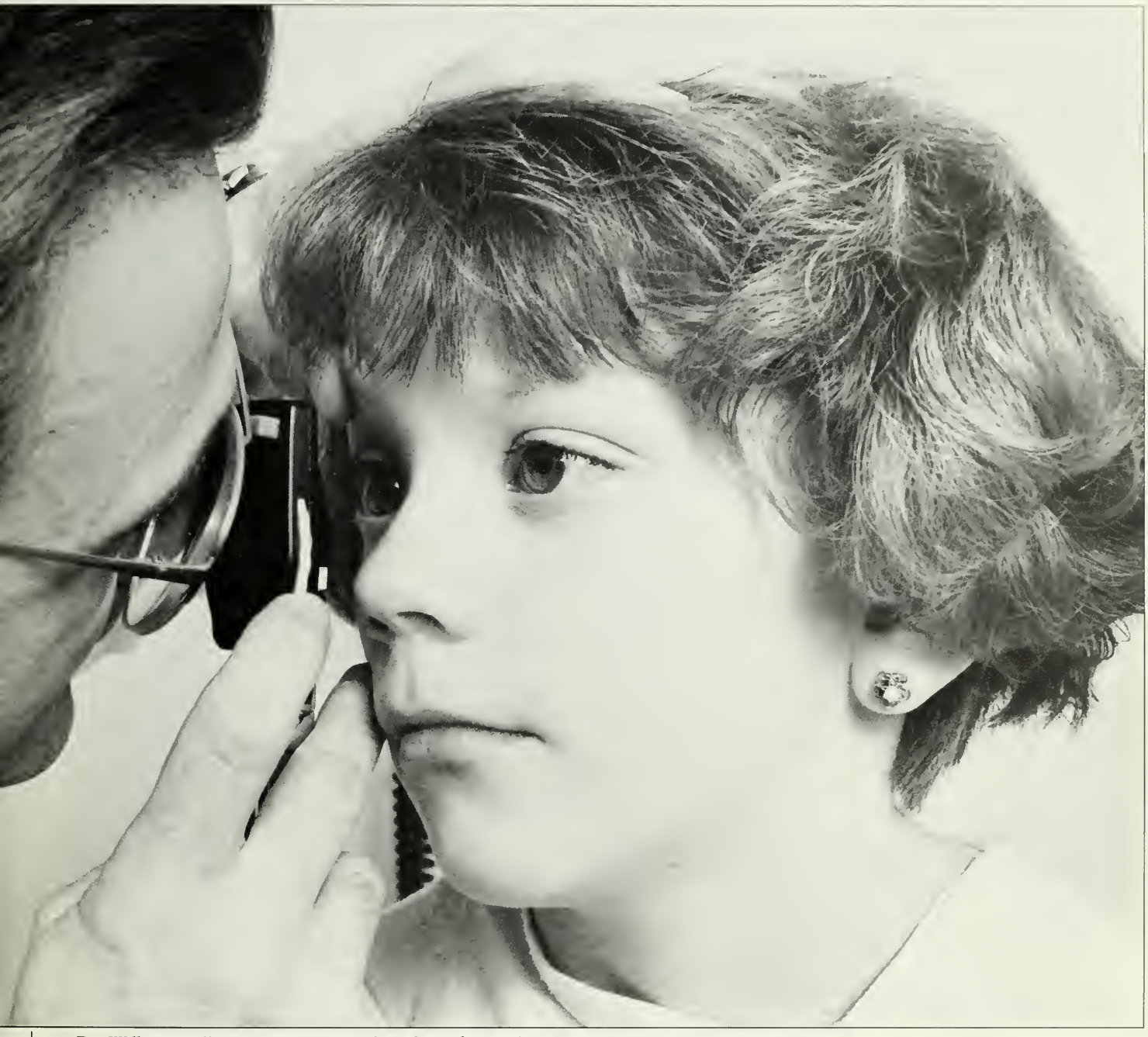
"Some of these children don't have the neurotransmitters to cause the release of growth hormone releasing factor and others don't have the releasing factor in their hypothalamus," Dr. Hoffman said. "Also, there are children who don't have the ability to produce growth hormone and others who produce normal amounts of growth hormone, but who can't produce somatomedin-C.

"Most of them fall into that nebulous category of idiopathic. We don't know why they are deficient," Dr. Hoffman said.

No matter where the breakdown occurs, the basic results are the same.

Children like Crystal don't grow normally and therefore can't realize their height potential.

"We are talking about individuals who at full height may just exceed four feet as an adult," Dr. Hoffman said. "They are always different. They are always singled out both outside and within the family — the child who is teased by his taller younger sister because he can't turn on the basement light."



Dr. William Hoffman examines Crystal in the pediatric clinic

Dr. Hoffman treats about 15 children and adolescents for growth hormone deficiency. They are the patients in whom he has ruled out numerous other problems such as tumors that might interfere with growth.

Despite the mystery and complexity of the growth process, Dr. Hoffman maintains that identifying problems with growth is a rather straightforward matter that goes back to the growth curve.

Despite the sometimes dramatic short stature of these patients, problems may go undetected.

Dr. Hoffman says that happens when linear growth — a cornerstone of pediatrics — is ignored.

"The usual story is, 'Don't worry Mrs. Jones, your child will grow,'" Dr. Hoffman said.

Dr. Hoffman has had growth hormone deficient patients referred to him after they have completed puberty. By then, linear growth has stopped. All he can do is tell them the problem and that it's too late for help.

The fact is that these young people frequently don't begin to show growth hormone deficiency until after the first three years of life. Often, parents don't really notice a problem until after their children start school and they see them with other children the same age.

Once a child is referred to Dr. Hoffman, he again begins with the basic tools of medicine.

"The cornerstone evaluation is a careful history and a physical, not a laboratory test," he said.

It may just be that the child is going to be short because of an inherited trait. Or maybe he's just slow to grow. Possibly the child has a kidney problem that is stunting his growth or a gastrointestinal disorder. Chemotherapy or radiation therapy

given to battle childhood cancers also can damage the pituitary and stunt growth.

If the child's short stature is related to some problem other than growth hormone deficiency, Dr. Hoffman wants to know that so he does not needlessly put a child through rigorous pharmacological tests.

Once the growth hormone deficiency has been pinpointed, other complicating factors may be explored.

About half the time, the only deficiency is the lack of growth hormone, Dr. Hoffman said.

But in other cases, the same system breakdown that has caused growth hormone deficiency also has created havoc elsewhere.

As a master gland, the pituitary is involved in the activity of a number of other glands including the thyroid, adrenal glands and gonads.

That's why some children like Crystal may have other related deficiencies as well.

Crystal also is hypothyroid: deficient in the pituitary hormone that stimulates the thyroid. The thyroid in turn normally produces hormones that fuel the whole body. She must take medicine to do what her pituitary and thyroid cannot do.

Her adrenal gland also does not function correctly. When Crystal is exposed to stress, her pituitary is not able to stimulate the adrenal gland and so produce increased amounts of cortisol, which is needed to help the body cope. Should Crystal face a stress, such as a bad infection or surgery, she requires a shot of cortisone. Crystal wears a medical alert necklace so that others will know this. Mrs. Boatright also has made the situation quite clear to teachers and others who spend time with Crystal.

She also was hypoglycemic, lacking sufficient sugar in the blood. To maintain a normal blood sugar, a balance must be maintained between insulin, the hormone which helps the body use sugar, and the body's counter-regulatory hormones. Among the counter-regulatory hormones are growth hormone and cortisol.

When the balance between insulin and these hormones goes awry, blood sugar levels go awry as well. Crystal now has her hypoglycemia under control largely through her treatment for her primary problem, growth hormone deficiency.

Treatment includes three weekly injections of a synthetic growth hormone identical to the hormone normally produced by the body.

Giving this synthetic hormone is the preferred treatment for nearly all children who are growth hormone deficient regardless of where the problem occurs.

The Medical College of Georgia is participating in a clinical trial of this synthetic hormone which is produced by bacteria using recombinant DNA techniques. In early efforts to treat growth hormone deficient children, growth hormone was taken from the pituitaries of human cadavers. However, the Food and Drug Administration withdrew this source of human hormone after several children died from viruses contracted from human growth hormone. MCG did not use growth hormone obtained from cadavers.

When Crystal and her mother make their sojourns to Augusta from nearby Emanuel County, they bring a cooler to take back the precious synthetic substance.

Mrs. Boatright has learned to give the injections. "I cried and cried the first time. She didn't cry," mother said of daughter. Now Crystal has learned to help her mother give the shots. "I need three hands," Mrs. Boatright said.

Dr. Hoffman's goal is to continue to help Crystal to grow to at least 5 feet. "The average young woman stops growing at 15 1/2 and men at 17 1/2," Dr. Hoffman said. "But Crystal has greater growth potential than most 13-year-old girls. It's as if she were 9," he said.

"An additional limiting factor may be if she needs assistance through puberty," Dr. Hoffman said.

That would mean Dr. Hoffman also may have to help her with this process.

In a sense, the delayed onset of puberty may be an asset to Crystal because it gives her more time to grow.

A new and important development is that now there is help for children who are growth hormone deficient and go through puberty either early or at a normal age.

Through a joint program between MCG and Massachusetts General Hospital, Dr. Hoffman can offer these patients a hormone to block pituitary action triggering puberty. This treatment buys time for some children to grow.

Despite all that can be done for these children, some cannot be helped within the confines of current technology. For example, a small percentage of children make growth hormone but are not able to convert it to somatomedin-C.

But Dr. Hoffman says the final chapter has not been written on helping people struggling to overcome short stature.

"Individuals who are specialists in growth problems in children are really writing a new chapter in growth," he said. "In the past, we said this is the way you are and there is really nothing that can be done. But now we can assist an increasingly significant number of children in achieving a more socially acceptable height.

"An exciting prospect, with no immediate clinical relevance, is the opportunity to treat children with disproportionate short stature — short trunks or short limbs. Recent research has shown that there are numerous growth factors known to affect bone growth, structure and bone modeling. In the future, as our knowledge increases and the availability of these growth factors increases, we may be able also to help those children," Dr. Hoffman said.

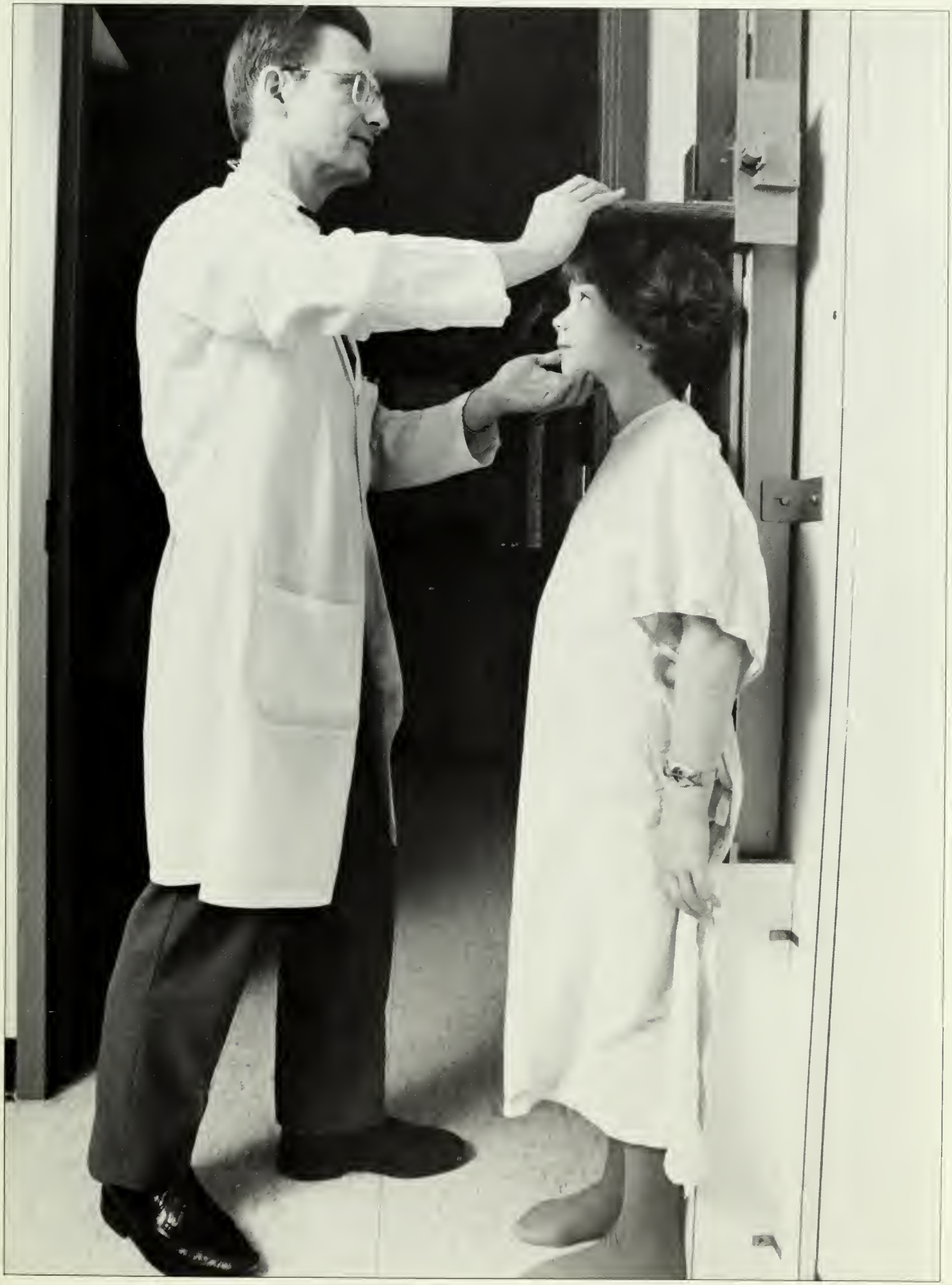
"You have to make the best of it and do what your doctor tells you to do," Crystal's mother said. "I'm trying my best, but I worry all the time about her. If something happens to her, I handle it, then I fall to pieces."

There are still many worries. Mother worries about Crystal starting high school. She worries about her dating or not dating. She worries about her firstborn who still looks so much younger than her peers. She worries that Crystal will act younger as well.

"My pitch to them is that there are many ways to grow and that we are going to help you in one of these ways," Dr. Hoffman said. "But even if we are not totally successful with linear growth, you know that there are other ways to grow and we expect you to be successful in other ways."

"It's been hard," Mrs. Boatright said. "I do a lot for her I shouldn't. But she does a lot for me. I love her. I just hope I can raise her and she can learn to take care of herself, fend for herself as an adult and have a happy, healthy future with a husband." ■

Dr. Hoffman takes measurements as part of Crystal's physical exam ►



Partners for life

Diabetes center focuses on care, education, outreach

By Christine Deriso

Dr. Max E. Stachura refers to his mission as a marriage, and he takes his vows very seriously.

"Taking care of a diabetic is like getting married," said Dr. Stachura, chief of the section of metabolic and endocrine disease in the Medical College of Georgia Department of Medicine. "It's till death do you part, and no matter how hard you work at it, something's always going wrong. And if you assess it honestly, both are to blame. We marry our patients till death do us part."

His partners in wedlock are the eight other staff members of the Medical College of Georgia Comprehensive Diabetes Care Center and the diabetics they treat.

The center is in its infancy, but it has been a concept at MCG for years.

"Before the center, we had nurses and a dietitian working with diabetics along with the doctors, but it wasn't organized," said Dr. Thomas A. Huff, professor of medicine in the section of metabolic and endocrine disease and a center staff member. "It's been a center of interest to me since I came to MCG in 1971. We have been laying the groundwork for a change to a formal structure for the past couple of years."

The groundwork began when Dr. Stachura came to MCG from the University of Chicago in 1982. While in Chicago, he and his peers had begun compiling information for diabetics. The problem was getting it to them. He moved before he could resolve the dilemma in Chicago, but MCG became the beneficiary of his experience.

Dr. Stachura's concept of an information center may seem baffling. As long as a doctor is informed, isn't that all that matters? Not in the case of a diabetic.

"If you come to me for pneumonia, I can fix it and off you go. The problem with diabetes is you have to live with it for a lifetime," Dr. Stachura said. "A diabetic has to deal with every little thing day in and day out. Things that the body does for healthy people don't happen for a diabetic; they have to be managed."

Diabetes occurs because the pancreas stops making the hormone insulin (called insulin-dependent diabetes) or because insulin is not used effectively (non-insulin dependent.) The condition is incurable but controllable through diet, exercise and perhaps prescribed medication or insulin.

Because lifestyle is so critical to controlling diabetes, a patient's health is very much in his own hands, supplemented with knowledge and treatment of his caretakers. Therefore, the diabetes center revolves around three concepts: patient care (inpatient and outpatient), education of both patients and caretakers, and an outreach program.

"The center isn't so much a physical location as it is a way of handling diabetics," said Dr. Robert Chadband, assistant professor of medicine in the section of metabolic and endocrine disease and director of the center. Its staff members work out of offices in the Veterans Administration Hospital and the MCG Hospital and Clinics, but their common goal binds them together.

The center is based on standards developed in 1985 by an American Diabetes Association committee developed to approve diabetes educational programs in the United States. The MCG center will apply for national recognition in 1988, according to center coordinator Gwen Gore, an instructor of medicine in the section of metabolic and endocrine disease.

Patient care consists largely of providing lifestyle guidelines and assisting patients with compliance, a process the center's staff hopes to refine.

"Patient compliance is critical to any kind of diabetic problem," Dr. Huff said. "Our goal is to do what's optimal in terms of the disease but to maintain the patient's freedom to live as fully as possible. In order to get compliance, we almost have to construct a prison, and a diet shouldn't be a prison. What's the alternative? That's the kind of thing we've got to deal with in setting up a program — addressing the nuts

Members of the MCG Comprehensive Diabetes Care Center are, from left: Dr. Thomas Huff, Dr. Robert Chadband, Ms. Gwen Gore and Dr. Max Stachura

and bolts of the nutritional aspects of diabetes and looking for new medications."

Based on the belief that better patient education results in higher compliance, the center will offer patient classes four days a week to assess individual needs and incorporate them into the program.

"I think the center's biggest service will be provided by the teaching classes," Dr. Chadband said. "The best method of getting control is getting patients informed. I can't get patients to change their behavior, but I can get them to want to try."

Ms. Gore said the classes will begin as soon as a classroom facility is available. The classes must continue for at least a year before the center can apply for national recognition.

For diabetics who can't come to the classes, the center is bringing the classes to them in a unique way. The staff has compiled information about diabetes in a textbook and a resource manual which they have given to every county extension agent in Georgia.

Dr. Stachura said the agents were receiving calls for information and weren't equipped to give it.

"The volume got so big that agents were smart enough to say, 'We don't know this stuff.' They asked us for an hour's training and we said, 'My God, you can't learn this stuff in a lifetime. Let's form a partnership,'" he said, adding that the liaison is the only one he knows of in the United States.

MCG staff members also give the agents a six-hour course on diabetes.

The center's outreach program also is an educational device. Center staff members travel statewide teaching doctors, nurses and nutritionists updated diabetes information. They also help the caretakers develop programs of their own.

"What I try to emphasize most is that diabetic complications can be prevented or (are) modifiable," Dr. Chadband said.

Dr. Stachura acknowledged that the center requires a great deal of work, but the staff members' preoccupation with the project seems to preclude dwelling on obstacles.

"I hope it becomes one of the premier high points of what the Georgia medical community can offer the state," he said.

Dr. Huff concurred, adding that aiding diabetics continually will help offset related medical problems later in life.

"I want my greatest impact to be on the front end of diabetes treatment," he said. "The point is that, by golly, these folks can live, and they can live pretty darn well." ■

Asking the right questions

Lab's advanced equipment diagnoses bone disease

By John Donnelly

What a photon absorptiometer does probably means little to anyone who's not a physician. But to patients with metabolic bone diseases, it can mean early diagnosis and relief from pain.

The Medical College of Georgia has been at the forefront of advances in metabolic bone disease treatment, being one of the first institutions in the U.S. to integrate new equipment such as the photon absorptiometer and treatment procedures into clinical use.

Osteopenia is the generic term used for metabolic bone diseases which include osteomalacia (a softening and bending of the bone caused by a vitamin D deficiency) and its childhood form, rickets; osteitis fibrosis (resorption of calcified bone and replacement with a fibrous tissue, caused by excessive secretions of the thyroid gland) and osteoporosis (skeletal atrophy or reduction of bone).

The most prevalent form of osteopenia in the U.S. is osteoporosis, accounting for more than 90 percent of all cases. As people with this disease age, their skeletons may weaken and cause back pain and fractured bones.

Diagnosing such diseases hasn't always been efficient.

"When I finished my residency in 1973, the major tool in determining bone loss was the X-ray," said Dr. Robert S. Weinstein, associate professor of medicine and director of the MCG Metabolic Bone Disease Laboratory.

"For an X-ray to be effective, 40 to 50 percent of the bone mass has to be gone. We couldn't tell what was happening within the bone until well past the time when frac-

Dr. Robert Weinstein examines a bone specimen on image analyzer.

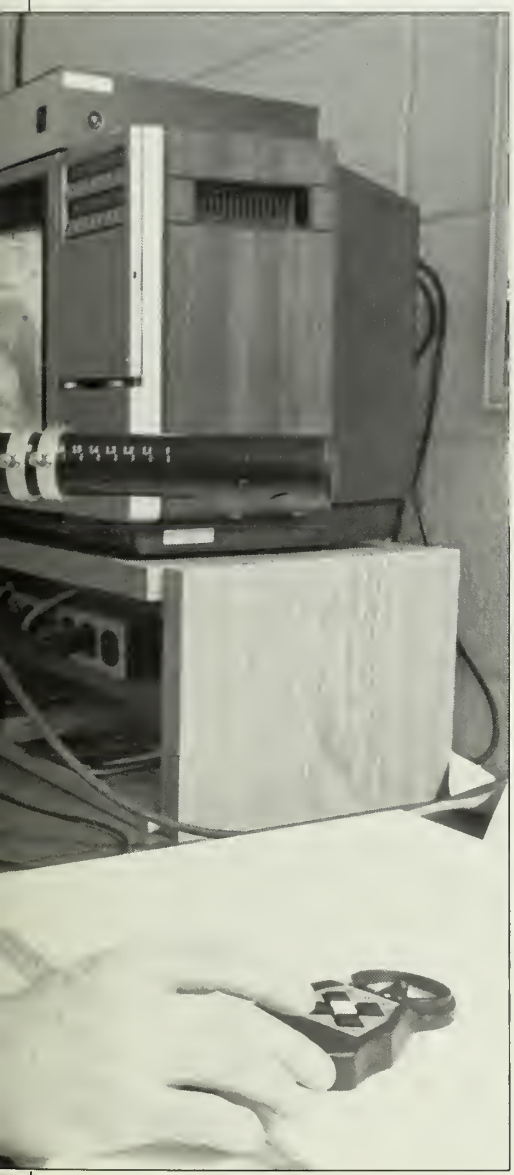
tures could occur," Dr. Weinstein said.

Metabolic bone disease is caused by abnormal concentrations of hormones. As a systemic disease, it affects all the bones.

Most bone disease can be treated but not reversed, Dr. Weinstein said, "therefore by the time X-rays detect any damage, it is usually too late for restoration of the skeleton."

Along with the X-ray, a test to determine the amount of calcium in the bone — the total serum calcium concentration — was done. This also was not very precise, according to Dr. Weinstein.

"Not all calcium is biologically important," he said. "Forty percent is bound to protein and is inert. Another 10 percent is bound to citrates, phosphates, bicarbonate and lipids, and is also inert.



"Only half of the calcium in the body is ionized and this is the only biologically important part to us," he said. "A physician had to be a detective to determine the fraction of the total serum calcium that was ionized."

The first advance in obtaining early, accurate measurement of bone degeneration was photon absorptiometry or densitometry. The Medical College of Georgia had one of the first units in the country and "when I arrived in 1977, it was already a routine test," Dr. Weinstein said.

The MCG densitometer is a single photon absorptiometer. "It was the first technique used and remains the instrument which gives the most reproducible results," Dr. Weinstein said.

This is how it works: the photon absorptiometer has a C-shaped bracket into which the patient places his arm. A radioactive source is at one tip of the "C" and a detector is at the other.

"The absorptiometer scans the bone and gives a reading of its exact density," Dr. Weinstein said. "In this way, we can detect a problem when there is still time to effectively treat it. The machine can detect a reduction in the amount of bone decades before it would appear on an X-ray."

A drawback to using the single densitometer is that the bone measured by the instrument is a peripheral one. "We are using the bone of the arm to infer the degree of density of the spine or the hip — the bones most likely to be affected by osteoporosis," Dr. Weinstein said.

Using dual photon absorptiometry or quantitative CT, these bones can be measured directly. Dr. Weinstein prefers single densitometry for several reasons.

"First of all there is the cost factor. A measurement in our lab costs around $47. Either of the other techniques will run from $200 to $300. Then there is the matter of time. Our procedure takes roughly 15 minutes while both the other methods require 30 to 45 minutes," he said.

Other advantages of the single densitometery process include the machine's portability, the ease of quality control maintenance and less variability in the results. The patient also receives a lower level of radiation.

The radiation a patient receives during a single densitometery bone scan is small, roughly equivalent to that of a dental X-ray, according to Dr. Weinstein.

Metabolic bone disease patients are diverse, Dr. Weinstein said. They are referred from a variety of disciplines, including pediatrics, obstetrics and gynecology, nephrology, neurology and rheumatology.

Among patients known to be susceptible to metabolic bone diseases, such as those with chronic renal disease, serial readings help determine the exact trends of a bone disorder. "We do the whole dialysis unit here at MCG every three months," Dr. Weinstein said.

In a way, Dr. Weinstein said, the photon absorptiometer is like a blood pressure cuff — "it can tell you there is a problem, but it can't tell you why the problem exists."

To determine what causes the reduction in bone material, Dr. Weinstein and his colleagues use an ion-specific electrode that is coupled to a microcomputer.

"This allows us to measure the ionized calcium in a very small sample of serum. Every sample is compared to a standard before reporting results on unknowns. The machine can pick up abnormal levels of calcium that couldn't otherwise be detected.

"What really makes me proud is that when I was a resident, this form of calcium measurement was strictly a research tool; now it is being used as a routine clinical tool. It has also aided our ability to teach students more about metabolic bone diseases," Dr. Weinstein said.

When the result is outside normal ranges, the serum sample is further examined and the concentrations of immunoreactive parathyroid hormone and the active metabolites of vitamin D are measured.

"These are the principle calcium-controlling hormones," Dr. Weinstein said. "Changes in their concentrations can aid us in finding out what's wrong with the patient."

If the reason for the bone disease is still unknown, Dr. Weinstein performs a bone biopsy. This outpatient procedure uses a local anesthetic and is no more troublesome than having blood drawn, he said.

The biopsy is taken from the easily accessible anterior hip bone (ilium) because it causes the body no loss of structural support.

Dr. Weinstein and his group have developed a specific technique for cutting the biopsy sample.

"We use a sledge microtome to cut the bone," he said. "The sample has been embedded in an extremely hard plastic — methyl methacyrate — that holds the bone so tightly the architecture of the bone tissue sample is superbly preserved."

The section is then mounted on a slide

and examined under the microscope.

"We can determine the relative and absolute quantities of mineralized bone as well as the size of the various bone cell populations," Dr. Weinstein said.

This quantification used to be done through a grid in the microscope eyepiece. Now, however, a miniature television camera is attached to the microscope and linked with a computer.

"The image analysis was derived from the technology developed for studying satellite photographs," Dr. Weinstein said. "With it, we can measure the number of osteoclasts — bone resorbing cells — in minutes. It used to take hours. It is the most advanced method in use today."

The rate of bone growth can also be determined from a bone biopsy. "We use the drug tetracycline, administered orally, as a tissue-time marker to determine the rate of skeletal formation," Dr. Weinstein said.

Tetracycline is absorbed by the newly mineralized bone and, when viewed under ultraviolet light, shows up as bright lines on the bone's calcification front. The drug is given twice at a 14-day interval, and by measuring the distance between the two lines the physician can calculate the rate of bone mineralization.

This measurement is important, Dr. Weinstein said, because many metabolic bone diseases are disorders of the rates of bone mineralization and bone function.

"We read bone biopsy slides for hospitals all over the country. They send them here because we developed many of the techniques for routine clinical use."

Patients with some metabolic bone diseases have benefited significantly from the technology available in laboratories such as Dr. Weinstein's.

"Osteomalacia is being cured. It was once thought to be a rare disease. We are finding that is not so. It was there all along but we just didn't know how to look for it until this technology became available," Dr. Weinstein said.

"Paget's disease of bone can now be successfully treated. We know we can usually take the pain out of that disease," he said.

More is also becoming known about osteoporosis, perhaps the most generally recognized form of metabolic bone disease.

"We couldn't get anywhere with it (treating osteoporosis) without this stuff," Dr. Weinstein said of the laboratory's equipment. "With it, we are beginning to ask the right questions in order to begin to treat it." ■

Surgery solves the problem of too much calcium

By Catherine Boardman

The hazards of calcium deficiency are often heard, but many people face an opposite problem. Their blood has too much calcium from a disease known as hyperparathyroidism.

Hyperparathyroidism is an overactivity of the parathyroid glands which regulate the body's calcium level. The parathyroid glands normally are located near the thyroid gland in the middle of the neck. Most people have four parathyroid glands that are small, flat, bean-shaped and reddish-brown to yellow in color.

In the 1920's, physicians discovered that these glands could become overactive and cause bone disease, kidney damage, severe abdominal pain and fatigue.

"That's only 67 years to know this disease. That's a relatively short time since hyperparathyroidism occurs in about one of every hundred hospital patients," said Dr. Robert S. Weinstein, associate professor of medicine and director of the Metabolic Bone Disease Laboratory at the Medical College of Georgia Hospital and Clinics.

Hyperparathyroidism predominantly affects women ages 50-70, Dr. Weinstein said.

"The symptoms of hyperparathyroidism are so nonspecific that it often is difficult to blame the patient's symptoms on the disorder," he said. Fatigue and weakness are the primary symptoms. Some patients can become comatose if calcium levels are severely elevated.

Since the disease is most often found in middle-aged to elderly patients, the symptoms of hyperparathyroidism have been incorrectly attributed to old age, Dr. Weinstein said.

However, this occurs less often now because the disease is found much earlier and physicians are more aware of the condition. Routine blood and urine tests include calcium measurements and often detect problems.

Other clues also lead to the diagnosis of hyperparathyroidism. Approximately 20 percent of people with hyperparathyroidism also have kidney stones. Therefore, "people with kidney stones are a good group to examine to find cases of hyperparathyroidism," Dr. Weinstein said.

After high calcium levels are detected, other tests are performed to confirm the diagnosis of hyperparathyroidism. This involves a very sensitive assay of the serum ionized calcium and parathyroid hormone taken from the parathyroid gland. These assays are routine procedures in MCG Hospital's Metabolic Bone Disease Laboratory.

Surgery is the only known treatment for hyperparathyroidism.

"When hyperparathyroidism was found 20 years ago, it was so severe that it was clear surgery was required," Dr. Weinstein said.

Since the disease is detected earlier and more frequently today, "the problem now is to decide who would benefit from surgery," Dr. Weinstein said.

Dr. Weinstein follows many patients with hyperparathyroidism for years, monitoring their bone density and kidney function. He advises patients against taking vitamins, calcium supplements and dairy products. Also, he recommends drinking lots of liquids, except milk.

"When following patients with hyperparathyroidism, we try to intervene before any serious damage occurs," Dr. Weinstein said.

MCG Hospital's success in treating hyperparathyroidism is due to a team approach. Dr. Arlie R. Mansberger Jr., professor and chairman of MCG Hospital's Department of Surgery, and Dr. Weinstein are the main players on MCG's team. Dr. Mansberger assists in diagnosing the disease just as Dr. Weinstein is present in the operating room when the glands are removed.

The two physicians decide together, after consulting a pathologist, how much parathyroid tissue and which glands are to be surgically removed.

"The surgeon who does parathyroid

Dr. Arlie Mansberger in surgery

surgery is on the spot, not from the standpoint of removing the parathyroid tissue, but because he has to know the embryology, the anatomy and the variability of location and number of parathyroid glands," Dr. Mansberger said.

The number of parathyroid glands can vary from two to six, while their location can vary from the hypopharynx in the throat to the mediastinum near the heart. "Also, they are small and may be encased in a layer of fat which disguises their distinguishing color and shape," he said.

Two kinds of primary hyperparathyroidism exist, Dr. Mansberger said. Parathyroid ademonas are tumors growing from a normal gland which suppress the size and growth of the other parathyroid glands. When found, adenomas are completely removed. The other condition is hyperplasia, in which all parathyroid tissue is overproductive, not just a single gland.

In hyperplasia, the amount of tissue removed varies among patients. Generally, the weight of one normal parathyroid gland (50 milligrams) is allowed to remain.

"Ideally, all parathyroid tissue is identified and biopsied. Then Dr. Weinstein and I decide what is to be removed," Dr. Mansberger said.

In the series of patients Drs. Mansberger and Weinstein have treated together since 1977, 85 percent had adenomas and 15 percent had hyperplasia.

Dr. Mansberger carefully details the surgical procedure for all patients considering parathyroid surgery. A small horizontal incision is made in the neck. Scarring is minimal because the skin is loose and the blood supply excellent. The surgeon explores the neck until he finds the parathyroid glands, then removes the prescribed amount of tissue.

Blood loss during parathyroid surgery is minimal. "It has to be a bloodless operation because the surgeon depends in part on color identification to find parathyroid tissue. Any blood staining just makes it more difficult to find the tissue," Dr. Mansberger said.

Best of all, little pain is involved. For the patient, parathyroid surgery is relatively simple, Dr. Mansberger said. Most patients suffer from a sore throat but are walking around and eating a regular diet the next day. They usually leave the hospital three days after surgery.

Ionized calcium levels are monitored daily after the surgery and usually return to normal within two to three days, Dr. Weinstein said.

After surgery, many patients experience dramatic increases in strength. "Patients will realize they have been fatigued for years because of hyperparathyroidism but didn't realize it," Dr. Weinstein said. ■

Clinician, scholar, pioneer

Endocrinologist Robert Greenblatt is all three

By Gwen Corinth

He is the father of endocrinology at the Medical College of Georgia — indeed, the founder of the nation's first independent endocrinology department in 1946. Endocrinology had yet to be recognized as a genuine science then, and Robert B. Greenblatt found he had to ruffle a few feathers to get his fledgling department off the ground.

It all started from a misunderstanding.

When the chief of obstetrics and gynecology witnessed Dr. Greenblatt giving a patient the unheard-of dosage of 25 milligrams of progesterone, he promptly reported the "infraction" to then-dean of the School of Medicine Lombard Kelly.

"Unless you understand endocrinology, it sounds horrendous," admitted Dr. Greenblatt.

What the senior physician didn't know is that during the last trimester of pregnancy, a woman metabolizes roughly a thousand milligrams of progesterone each day, Dr. Greenblatt said. The increased production of progesterone prevents menstruation, so the extra dosage successfully halted the patient's uterine bleeding. (Dr. Greenblatt pioneered the arrest of abnormal bleeding with progestational agents and in 1942 won his first medal for his work on uterine bleeding — the Crawford W. Long Gold Medal.)

Summoned to Dr. Kelly's office after the incident, Dr. Greenblatt got good news instead of a rebuke.

"Dr. Kelly (who had worked in endocrine research under the famous Dr. Papanicolou of Pap Test fame) said, 'I'm going to take it on my own to promote you to full professorship with your own department and your own budget,'" Dr. Greenblatt said.

Endocrinology, the science of the body's internal secretions, had come into its own at the Medical College of Georgia.

"In those days, most clinicians didn't understand endocrinology. They thought it was a form of quackery," Dr. Greenblatt said.

Which may explain the reception the researcher got in 1961 when he presented the startling news that a chemical agent, clomiphene citrate, which had been found to inhibit ovulation and spermatogenesis in laboratory rats, could actually be used to treat infertility since it stimulated ovulation in non-ovulating women. Dr. Greenblatt discovered this while conducting clinical trials with the agent as a contraceptive drug. As a result, women around the world have benefited from this "fertility pill."

An editorial in the *Journal of the American Medical Association* hailed Dr. Greenblatt's finding as the most important breakthrough in reproductive endocrinology in 20 years, but skepticism still prevailed. Invited to address the New York Obstetrical Society on clomiphene, he wasn't prepared for the response.

"I've never taken such a ribbing and such sarcasm in all my life," he said. "They just wouldn't believe it."

Testing and retesting accepted knowledge is part of research, and it is part of Dr. Greenblatt's own research philosophy.

"Anybody in research has to seek the unknown," he says. "And what is known, he has to make sure it is so."

After 50-plus years in medicine, this octogenarian has made quite a few contributions to knowledge about reproductive endocrinology. He considers clinical research his forte and still sees as many as 20 patients a day in the 15th Street clinic he operates with associates R. Don Gambrell and P.K. Natrajan.

Over the years, Dr. Greenblatt has made discoveries regarding the use of estrogens to treat symptoms of menopause and the use of androgen, to treat sexual dysfunction in women (having proved with the help of Dr. Virendra Mahesh that the ovary secretes androgens as well as estrogens and progesterone). He also helped to discover a cure for the venereal disease granuloma inguinale, which is now almost completely eradicated.

Along the way he has taught the art of research to 82 postdoctoral fellows from 23 countries. In 1985, the International Society of Reproductive Medicine met in Augusta to honor his 50 years in medicine. Thirty-five of those 82 research fellows attended. They're scattered around the nation and the world, and some of them are now distinguished scientists in their own right:

Dr. Ricardo Asch, a professor of reproductive endocrinology at the University of Southern California, is inventor of a modified in vitro fertilization method called the Gift Procedure, involving laparoscopic insertion of egg and sperm into the fallopian tube. Dr. Somnath Roy is director of the All India Research Institute in New Delhi. Dr. Paul McDonough is chief of the reproductive endocrine section in the MCG School of Medicine's Department of Obstetrics and Gynecology. Dr. Jean-Joel Leng is chief and professor of obstetrics at the University of Bordeaux, France. Dr. Arturo Zarate is chief of endocrinology at the University of Mexico. And Dr. Greenblatt's associate since 1979, Dr. Gambrell, who worked with him as a research fellow from 1969 to 1971, is internationally known for his studies on the protective action of progesterone in preventing breast and endometrial cancer.

"He's very dynamic," Dr. Gambrell said of his mentor. "He's just a natural born

◄ *Dr. Robert Greenblatt*

leader — very progressive and almost aggressive."

Indeed, Dr. Greenblatt shows no sign of letting up as he approaches his 81st birthday. His latest research project involves studies of a hormone, B-hCG (human chorionic gonadotropin), which is present during pregnancy and is also produced by certain malignant tumors. Dr. Greenblatt, working with MCG's Dr. Tom Abney, found that cysts of the breast produce bioactive hCG. They believe the test may be a marker for eventual development of breast cancer in these patients.

When not working on medical research, Dr. Greenblatt is usually researching one of two other favorite topics: history and the Bible. He has published four of what he calls paramedical books on those subjects, the most recent being "Sex and Circumstance: Humanity in History," a compilation of 44 vignettes of famous historical characters along with Dr. Greenblatt's modern diagnoses of their physical ailments.

Some of his tales are startling proof that truth just may be stranger than fiction. He proposes, for example, that Queen Elizabeth I was called the virgin queen because she never menstruated and Napoleon Bonaparte died of an endocrine disturbance, not arsenic poisoning as was popularly believed.

"It's historical sleuthing," Dr. Greenblatt said of his side interest.

In June he and wife Gwen went to England for his induction into the Royal College of Obstetricians and Gynaecologists, the latest in a string of international honors which also include the Chevalier of the French Legion of Honor, received in 1973.

"I'm very pleased because I've received honorary memberships in almost every important country in the world except England," he said. "I think it was very nice the Royal College honored an American. Maybe it's because I'm a Canadian!"

Although now an American citizen, Dr. Greenblatt was born a British subject in Montreal. He decided early on his professional direction — with a little prodding from his mother.

Dr. Robert Greenblatt

"She said to my brother, 'Michael, you're going to be a lawyer. Bobby, you're going to be a doctor.' We followed my mother's orders."

After finishing medical school at McGill University in Montreal in 1932, Dr. Greenblatt received a research fellowship at the University of Montreal, followed by a residency in Boston, then cut short an appointment at Englewood General Hospital in Englewood, N.J., to come to MCG early in 1935.

He started out earning $75 a month as a pathology research fellow and ob/gyn resident. At 34, he became a professor of experimental medicine, the forerunner of endocrinology.

Today, endocrinology "is one of the most elite disciplines of medicine," according to Dr. Greenblatt.

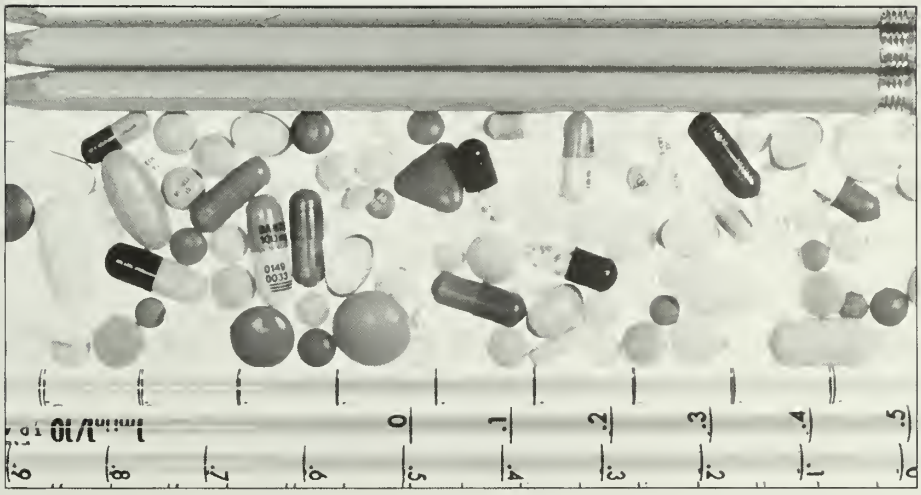
"To get into the Endocrine Society, you might have to wait five years and be a top notch scientist and clinician," he said. That means establishing exacting credentials and being senior author of at least five publications.

"We started the first individual department of endocrinology in the United States. Here at MCG, there are three subdepartments in ob/gyn, pediatrics and medicine, along with a basic one — the Department of Physiology and Endocrinology.

"Today, every medical school has one or more endocrine departments. Isn't it amazing how the world has turned?" ■

Answering questions in the laboratory

By Gwen Corinth



Around the world, researchers in reproductive biology are seeking ways to accomplish seemingly paradoxical purposes: safer, more effective contraception and treatments for infertility.

The paradox, however, doesn't exist. Both contraception and infertility are linked through control of ovarian and testicular functions. Where there is understanding of those functions, there can be manipulation to promote either contraception or fertility.

Researchers at the Medical College of Georgia are continuing a tradition of excellence in those areas by seeking new knowledge in the control of ovulation and spermatogenesis by the anterior pituitary and higher brain centers, ovum pickup and transport and fertilization and implantation.

MCG has a history of accomplishment in reproductive biology and endocrine research. During the early 1970s, Drs. Virendra Mahesh, now chairman of endocrinology and physiology, and Robert Greenblatt, then chairman of endocrinology, were among the first to discover that patients with large polycystic ovaries and facial hair may produce large amounts of androgens in the ovary. Androgens are normally produced in very small quantities in women and large quantities in men. Among other actions, they are responsible for facial hair growth. Subsequent methods of diagnosis and management have been based on these studies. Dr. Mahesh and his group then used several animal models to study causes of polycystic ovarian disease.

Drs. Mahesh and Greenblatt also were among the first to use a chemical agent, clomiphene citrate, to induce ovulation. The "fertility pill" is now widely used.

Research in reproductive biology brought the MCG group national and international recognition. Augusta was chosen as the site of two workshops: "Functional Correlates of Hormone Receptors in Reproduction" in October 1980 and "Regulation of Ovarian and Testicular Function" in February. The workshops were sponsored by the National Institute of Child Health and Human Development and were organized by Dr. Mahesh. More than 200 scientists and the Reproductive Biology, Reproductive Endocrinology and Human Embryology and Development study sections of the National Institutes of Health attended the February workshop.

Among several ongoing areas of research at MCG are the following stories on Dr. Thomas Muldoon's attempts to understand steroid hormone function, Dr. Thomas Mills' studies of ovarian steroids and Dr. Lawrence Hendry's use of DNA models to design drugs.

Getting all angles on steriod hormones

Dr. Thomas Muldoon believes in tackling a research question from a variety of angles. That's probably why he directs nine other researchers at work on six different projects.

He calls it a multifaceted approach to a single question: how do steroid hormones function? To find out, he is conducting experiments in areas ranging from the regulation of reproduction and fertility by steroidal sex hormones to the influence of the hormones estrogen and prolactin on normal and cancerous breast tissue.

"If something interests me and it's in the field, I'm going to go after it because that's what's fun," said Dr. Muldoon, a professor of endocrinology at the Medical College of Georgia and a biochemist by training.

Dr. Muldoon's sense of fun transfers to everything he does — from the nonsensical signs that hang in his office ("Pizza" and "Lifeguard on Duty") to the good-natured "discussions" he often has with collaborating researcher Dr. Lawrence Hendry. Dr. Muldoon is conducting animal studies to test an anti-tumor agent isolated by Dr. Hendry which appears to have a hormonal component to its action.

"Larry and I sometimes disagree on our course of action because we have a slightly different perspective," said Dr. Muldoon. "Larry tends to be more oriented toward pure chemistry. I'm trained as a biochemist."

The biochemist is interested in discovering how hormones interact with protein receptors, for example. Receptors are molecules present in certain tissues, such as the breast, which receive and respond to hormones from the blood.

Most recently, Dr. Muldoon and his co-workers have discovered a new class of receptors existing inside each living cell. These receptors are within the protein-manufacturing center of the cell, and their presence suggests a novel mechanism by which steroid hormones may exert their effects. Also, these receptors can regulate the accessibility of hormone to the nucleus, where it affects gene expression.

Another significant discovery has been that prolactin from the pituitary regulates estrogen responsiveness in breast tissue, a system previously thought to be self-regulating. This may call for a reevaluation of breast cancer treatment to include controlling prolactin as well as estrogen, which contributes to the development and growth of tumors, Dr. Muldoon said.

Breast cancer is often treated by administering anti-estrogen drugs, which are effective but have side-effects including circulatory and liver disorders, Dr. Muldoon said. He and Dr. Hendry are seeking better anti-estrogens without side-effects through a molecule model which allows them to predict function based on the model's ability to interact with DNA.

A separate study targets prostate cancer, which is not predictably responsive to hormonal therapy, Dr. Muldoon said. To find out why, he is examining how androgen and estrogen contribute to the development of tumors.

Understanding the "why" behind molecular activities gives scientists clues to developing better treatments for infertility and more effective contraceptives as well as anti-cancer drugs, Dr. Muldoon says.

"If we understand at the molecular level how these hormones are acting, we can alter patterns of the menstrual cycle and either increase or decrease fertility," he said. "We can also understand better disorders of reproductive function and perhaps develop new agents that would either be more or less effective than natural compounds."

For example, one of Dr. Muldoon's studies seeks to understand how estrogen and progesterone control the release of gonadotropic hormones which regulate ovulation. If these hormones are present in amounts that are too high or low, the menstrual cycle ceases or becomes sporadic. Administering drugs tailored to block or increase hormone production could correct this.

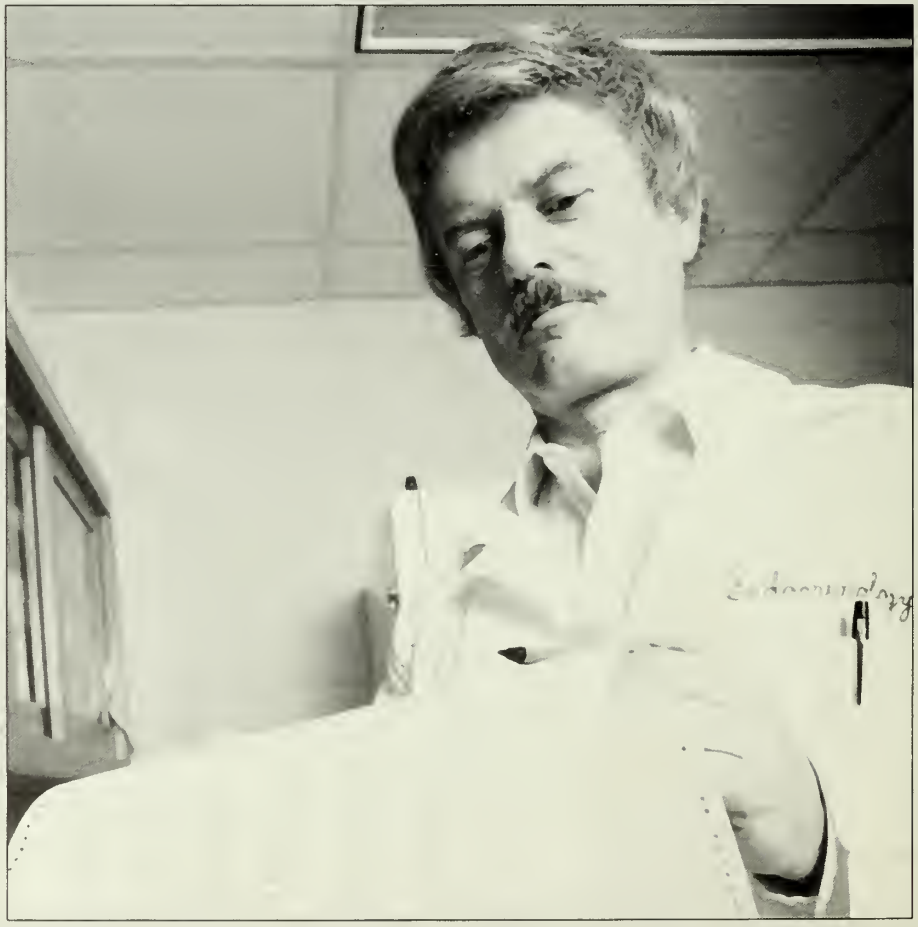
Dr. Muldoon meets weekly with his research staff to discuss their work. The projects are interrelated, and the researchers work together as well as on individual projects.

"I have the hardest time because I have to know what they're all doing," he said.

Travel can sometimes interfere with that, he said. This year, for example, he may attend seven professional meetings around the U.S. and the world.

"I have to really get things organized so the labs operate smoothly," he said. He returns full of news about what's going on in other laboratories and ready to hear from his own researchers.

"They make me feel indispensable," he said. "They have a million questions when I get back."



Dr. Thomas G. Muldoon

Examining follicle influences in the ovary

One good question naturally leads to another for Dr. Thomas Mills — that is, if the subject is the complex chain of events inside the female ovary.

Dr. Mills has been studying ovarian steroids, the hormones involved in the growth and release of the egg, since the early 1970s. Now a professor of endocrinology in the Medical College of Georgia Department of Endocrinology and Physiology, he began working with steroids during postdoctoral studies at Ohio State University and the University of Miami.

Since coming to MCG in 1971, Dr. Mills has been principal investigator of several studies of hormonal influences on the growth of the ovarian follicle, which contains the egg. Most recently, he has sought to discover if the steroids estrogen and progesterone act within the ovary to inhibit follicle growth.

It's established scientific fact that ovarian steroids play a part in the interdependent relationship among the hypothalamus region of the brain, the pituitary gland and the ovary. The pituitary is prompted by the hypothalamus to produce follicle stimulating hormone (FSH) which in turn triggers the follicle in the ovary to grow and nourish an egg. When the follicle is fully grown, the pituitary is triggered to produce luteinizing hormone (LH), which then causes ovulation, releasing the egg. After ovulation, the follicle becomes the corpus luteum and secretes estrogen and progesterone, which halt the pituitary secretion of LH and FSH.

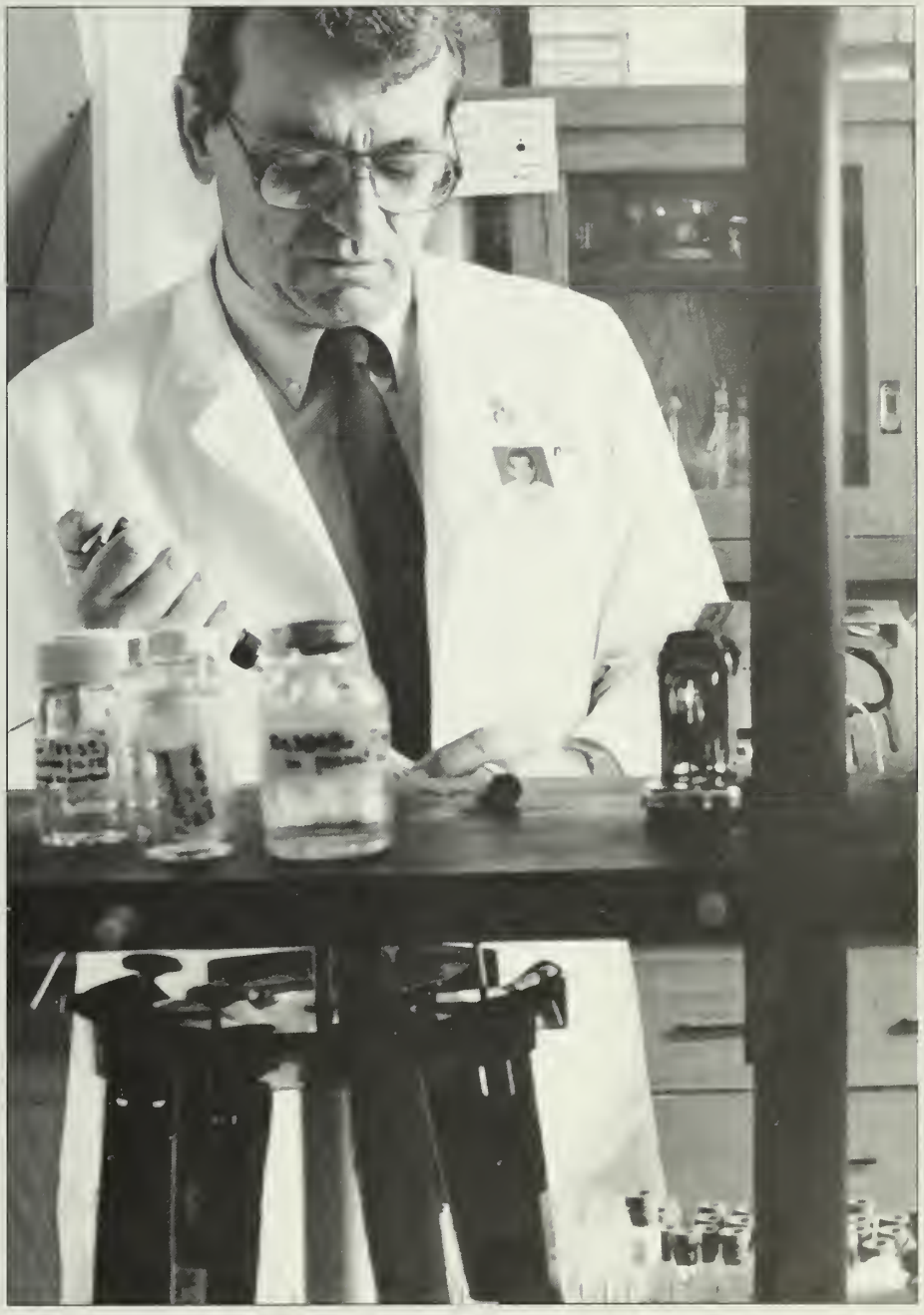
With this process sufficiently explained, Dr. Mills decided to go a step further.

"We're asking a slightly different question: are steroids like progesterone acting back on the ovary to inhibit its function?" he said.

Based on studies in rabbit models, Dr. Mills believes the answer is yes.

Dr. Mills already suspected a link between progesterone and inhibition of follicle growth. He knew that progesterone is present in the ovary during pregnancy when the follicle stops growing. He also had observed that implanting pellets of progesterone in rabbits that were not pregnant resulted in halting follicle growth.

To prove the theory, researchers in Dr. Mills' lab induced ovulation in rabbits, then surgically destroyed all but one follicle in one ovary in each animal. The remaining follicle became a corpus luteum, producing progesterone and preventing further follicles from growing in the same ovary — good evidence of intraovarian action of progesterone inhibiting follicle production, according to Dr. Mills. The ovary without a corpus luteum continued to produce follicles.



Dr. Thomas Mills prepares serum samples for an assay

What Dr. Mills has learned may prove useful in developing better contraceptives and in treating infertility.

"It represents another level of control of ovarian function (so) there is the possibility of manipulating the process," he said.

But the conclusion to these experiments has given rise to another question: how is progesterone transported from the corpus luteum out into the ovary?

Three possibilities exist, Dr. Mills said: progesterone may be distributed by diffusion, in the blood, or by the lymphatic system. He and cardiovascular physiologist Dr. William Jackson, whose specialty is microcirculation, are considering a collaboration to find out.

"This vascular connection ... is something new for me, and that's exciting," he said.

Predicting biological activity based on genetics

Coffee cans filled with multicolored plastic "atoms" line the shelves of the room Dr. Larry Hendry calls "the magic kingdom." Beside them are models made from those atoms, each neatly labeled according to structure as a bile acid, a prostaglandin or an estrogen.

The shelves of bright yellow, blue and red models make the room look like a toy closet. But Dr. Hendry, associate professor of medicine, endocrinology and physiology at the Medical College of Georgia, uses them for serious purposes: studying genetic structure and using it to predict the biological activity of molecules.

What Dr. Hendry has learned since beginning his studies in 1975 has become a technology that can be used to design new pharmaceuticals. In 1981, he patented that technology and later, with the aid of Augusta attorney J. Milton Martin Jr., launched Stereochemical Genetics, Inc., (SGI) to develop and sell pharmaceuticals made with his technology. SGI's agreement with MCG allows the corporation total control of Dr. Hendry's technology but gives MCG joint publication rights and 10 percent of the corporation's income. Since SGI's founding, that percentage has amounted to $20,000.

Using models of a compound's molecular structure, Dr. Hendry predicts how the compound will function based on how it fits into DNA, the nucleic acid bearing the genetic code for each living cell. The DNA models contain spaces into which the molecules may or may not fit. By first discovering what molecules fit into those spaces and then manipulating atoms within the space, he can increase or decrease the activity of the molecule. Resulting predictions must then be tested in animal studies.

Using this principle, SGI consultants design new compounds and contract the testing with laboratories at MCG and other universities. Dr. Hendry is SGI's chief research consultant, and he is assisted by four others.

SGI's mission is to develop safe, effective pharmaceuticals, Dr. Hendry said. These may function as agonists, which resemble the parent molecule, or antagonists, which are unlike the parent. Researchers can also design compounds with limited side effects after first making predictions based on what happens when specific molecules are inserted into DNA.

Some of the drugs being tested include antidepressant, antidiabetic, antithyroid and contraceptive agents. Another is an antitumor compound called phenacyperidone, which appears to have hormonal qualities and has been isolated in human plasma. Dr. Thomas Muldoon, a professor of endocrinology at MCG, is collaborating with Dr. Hendry to test phenacyperidone in rats and mice. So far, those studies show the compound prevents tumors, but long-term clinical studies are needed, Dr. Hendry said.

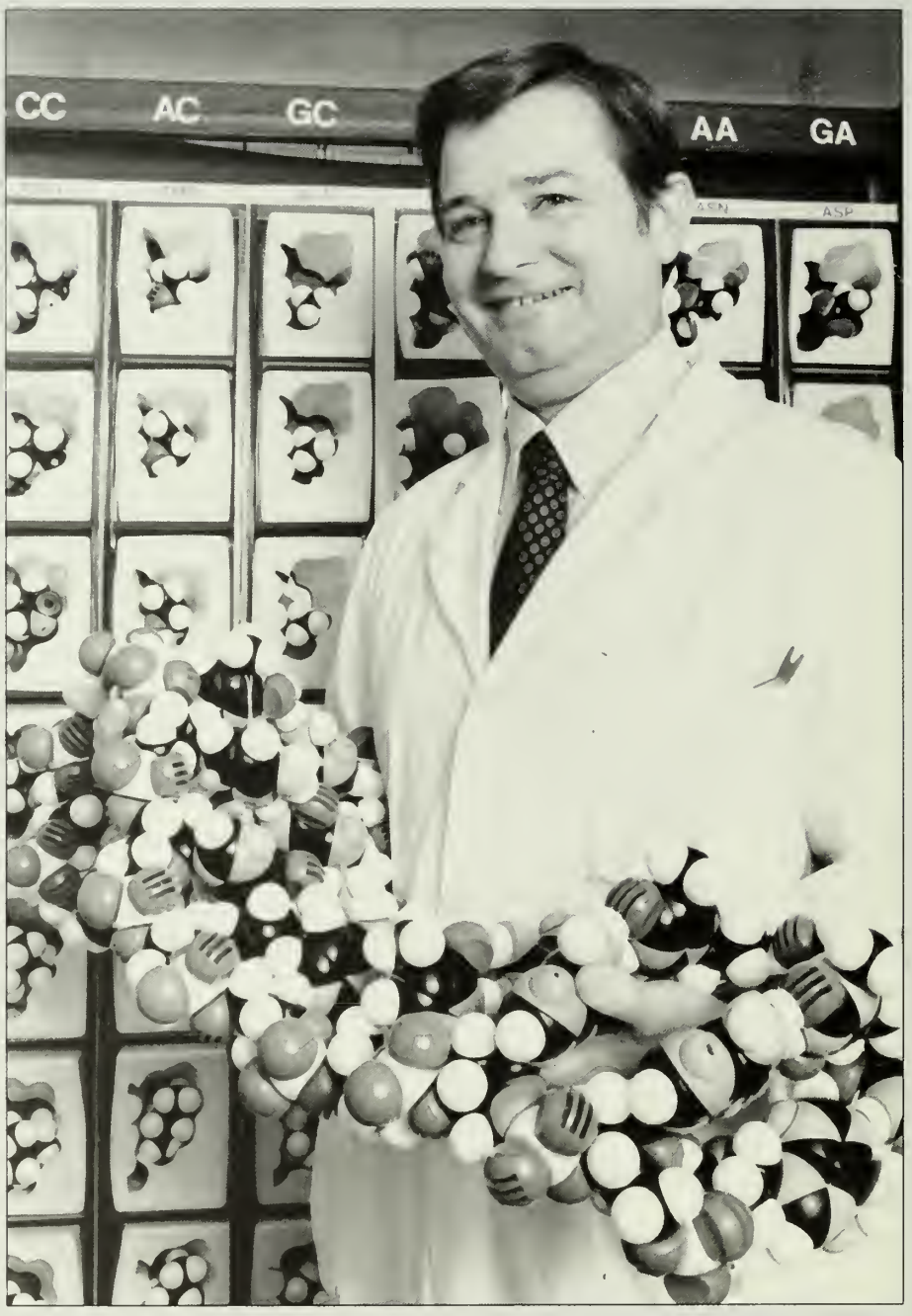
But the technology has implications beyond drug design, Dr. Hendry said.

What he discovers about how molecules are made in nature and about how compounds work may show that these actions are not simply accidents.

"What we're dealing with is a biochemical law," Dr. Hendry said.

For example, it's known that amino acids are part of the genetic code for proteins. Dr. Hendry has found that amino acids also fit into DNA, as do molecules such as sugars. Based on this, he predicts there's also a genetic code for carbohydrates.

Another implication is that changes in the DNA which alter the fit of various molecules may be involved in the pathophysiology (or changes in function occurring during a disease) of certain diseases. ■



Dr. Laurence Hendry with a DNA model

Giving

Supporters of the Medical College of Georgia are being encouraged to name MCG Foundation, Inc. as the beneficiary of gifts in wills and other trust arrangements.

The Board of Regents of the University System of Georgia recently requested that individual colleges and universities within the system encourage their supporters to name tax-exempt foundations at particular schools as beneficiaries of such gifts. This procedure is expected to ease the administrative aspects of managing the gifts.

A gift made to any unit within the system is technically the property of the Board of Regents. The regents take official action to designate gifts for their intended purposes.

Officials at MCG created MCG Foundation, Inc. in 1954 to administer its gifts. If you have provided for the Medical College of Georgia in your will, please check with your attorney to insure the Medical College of Georgia Foundation, Inc. is properly named.

If you are now preparing your will and are considering naming MCG as a beneficiary, feel free to contact our offices at (404) 828-2515 for assistance. We can provide information on designating uses for the funds, honoring loved ones, receiving tax benefits or other aspects you and your attorney may discuss.

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