

**Dr. Henry W.
Foster, Jr.**

BOOK V

1st installment of
Writings

Writings and Speeches of Henry W. Foster, Jr., M.D.

Articles

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Dr. Henry Foster is an accomplished clinician and researcher in the fields of obstetrics and gynecology. In his 38-year career, he has written on a variety of topics, with a particular focus upon the diagnosis and management of high risk pregnancies. He is not just a doctor and scientist, however; Dr. Foster is also the sponsor of a successful, community-based teen pregnancy prevention program, and has written extensively about this program and about access to health care for the under-served.

Dr. Foster is the author of four textbook chapters relating to high risk pregnancies, including two chapters on the particular issues surrounding sickle cell disease and pregnancy. He has published widely about pregnancies in patients with sickle cell anemia, and has studied diagnostic tools for use in management of the disease. In his writings on sickle cell anemia, Dr. Foster demonstrates his awareness of the agonizing family planning decisions faced by sickle cell patients in light of the life-threatening risks to them of childbirth, and discusses the importance of high quality, non-directive family planning counselling. One of the goals of his research is to maximize a patient's chances of bringing a pregnancy safely to term.

Dr. Foster has also written on the physiology and management of complications of pregnancy, including toxemia (a non-specific syndrome which can result in convulsions, coma, or death), abdominal pregnancy, early cervical cancer, Meigs' Syndrome (a rare type of ovarian tumor), thalassemia syndrome (a genetic

disorder affecting the rate of hemoglobin production) and endometrial stromal sarcoma (a cancer of the uterine lining). In particular, Dr. Foster has maintained a research focus upon the amniotic fluid and how analyzing its characteristics can be useful in the diagnosis and management of high risk pregnancies.

In his community, Dr. Foster has devoted himself to helping those less fortunate and, in particular, to preventing teen pregnancy. Dr. Foster has written a great deal based upon his experience with Meharry Medical College's "I Have a Future Program," whose development he spearheaded. The program fosters the values of self-esteem, physical and mental well-being, completion of school, development of job skills, sexual responsibility, self control and ability to handle interpersonal conflict, the value of helping others, positive social values, and family values. Locating the program in community sites allows for interaction with the teens' families and a better opportunity to involve parents and siblings, an important aspect of the program.

Dr. Foster has also written about the medical and social barriers to the health of urban infants, stressing the importance of quality pre-natal care. His research has suggested that African-Americans and whites will give birth to equally healthy children where the socioeconomic status of the two groups is the same for a sustained period of time. Both in his practice and in his writings, Dr. Foster has promoted greater access to health care and greater efforts to fight infant mortality.

While acknowledging that this country has been a world leader in its concern for medical ethics, Dr. Foster remains vigilant in safeguarding the ethical conduct of research. He is committed to protecting the vulnerable from being used inappropriately as research subjects, and his writings reflect his strong beliefs regarding informed consent. Throughout his career, Dr. Foster has emphasized the importance of providing information and counselling so that patients can make informed decisions about their health care.

Abdominal Pregnancy

Report of 12 Cases

HENRY W. FOSTER, M.D., and DONALD T. MOORE, M.D.

ABDOMINOCYESIS, a dangerous complication of pregnancy, is rare and, hopefully, will become even more infrequent as obstetric care improves. At present, however, most of the patients seen on our obstetric service are from the lowest socioeconomic strata in this country and, on occasion, rival some of the most primitive of cultures. Consequently, the occurrence of this condition is relatively frequent here, as compared to most series reported, since these patients are often not seen in early pregnancy when the condition can be prevented.

To us, the term abdominal pregnancy means pregnancy within the peritoneal cavity; consequently, we have tried to exclude patients with advanced tubal, ovarian, or intraligamentous pregnancy. Almost always, abdominal pregnancy follows early tubal abortion or rupture of a tubal pregnancy, with secondary implantation on the peritoneal surfaces. Primary abdominocyesis, if it occurs at all, is extremely rare and virtually impossible to prove except when experimentally produced in the laboratory animal.⁹ However, Teneblatt, in a review of the literature, reported 25 patients in whom no evidence of previous implantation could be established. Rarely, abdominocyesis

has followed early rupture of a cesarean section scar.

DATA ON CASES

Incidence

The ratio of abdominal pregnancies to total deliveries varies widely; however, a frequently quoted figure is 1:15,000.³⁻¹⁴ Eastman states that it occurs approximately once in every 15,000 pregnancies. Beacham *et al.*² reported an incidence of 1 per 3371.75 total deliveries.

In our series, there were 13,635 total deliveries during the 15-year period Jan. 1, 1951, through Dec. 31, 1965. During this time, there were 12 abdominal pregnancies, giving an over-all incidence of 1 per 1136. However, when the data are further analyzed, the ratio shows a trend toward decreasing frequency of this condition (Table 1). Although our series is too small to be statistically significant, the lowered frequency could represent improved antenatal facilities and care.

Age

No designation of age for abdominal pregnancy appears in much of the literature. However, Henderson and Wilson noted that the age was above the average for pregnancy in general. The ages of the 12 patients in this series ranged from 19 years to 38 years. The average age was 28.4 years and the median age was 29.5 years. The largest

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TABLE 1. INCIDENCE OF ABDOMINAL PREGNANCY OVER A 15-YEAR PERIOD

Time period	Total deliv.	Abdom. pregn.		Ratio of occurrence
		No.	%	
1951-1955	4,225	5	41.7	1:845
1956-1960	4,068	4	33.3	1:1017
1961-1965	5,342	3	25.0	1:1780
1951-1965	13,635	12	100.0	1:1136

number of patients (5) were in the age group 30-34 years (Fig. 1).

Gravidity

Among the 12 patients there was a total of 32 pregnancies, including the abdominal pregnancy. The average gravidity was 2.2 per patient. Three of the patients had had a previous tubal pregnancy, and 3 had not been previously pregnant.

Diagnosis

Of our 12 patients, 2 were in the first trimester, 7 in the second, and the remaining 3 carried to term. Unfortunately, a definite diagnosis of abdominal pregnancy was made only twice prior to laparotomy. It was strongly suspected in another patient, and advanced tubal pregnancy was diagnosed in 2 others. Certainly, one of the reasons for the diagnosis being so often missed was a low index of suspicion due to the rarity of this condition.

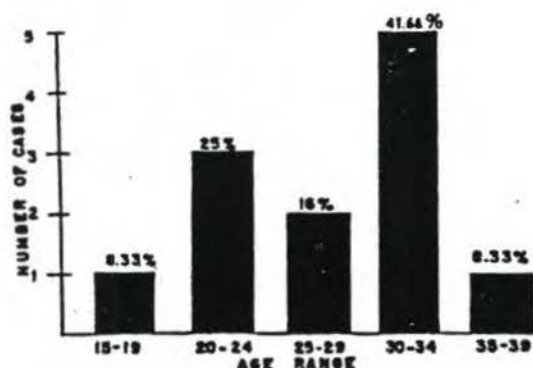


Fig. 1. Age range of 12 patients with abdominal pregnancy

Actually, the diagnosis of abdominocyesis is not difficult if only it is considered. Certain factors are highly suggestive. Unusual abdominal pain, distinctively palpable fetal parts, history of abnormal vaginal bleeding early in pregnancy, abnormal lie of fetus, and painful fetal movements are all frequent findings. A high or displaced cervix² is said to be a frequent finding although this was not documented in any of our patients.

The clinical signs and symptoms most often present were amenorrhea and pain which occurred in all 12 patients (Fig. 2). Nine patients (75%) had abnormal vaginal spotting or bleeding early in pregnancy. There were no other consistent signs and symptoms. One patient experienced false labor, 1 passed a decidual plug, and another had refractory diarrhea. None of our patients experienced any significant intra-abdominal blood loss prior to laparotomy.

When the clinical picture is suggestive, X-ray study is the next logical step in diagnosis. In abdominocyesis, the fetus most

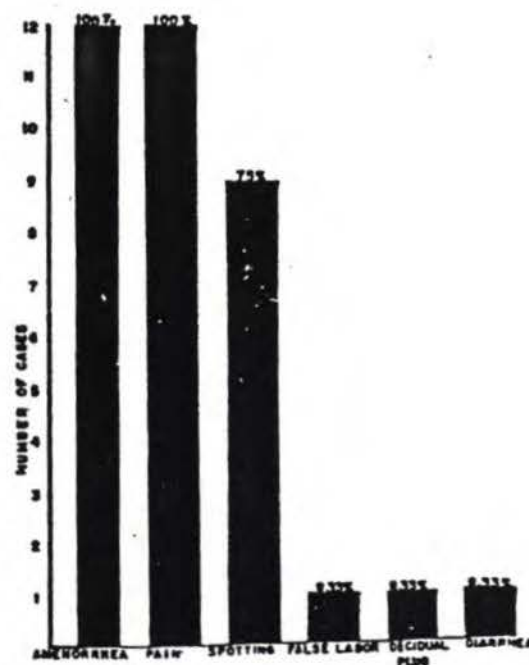


Fig. 2. Clinical symptoms of patients with abdominal pregnancy.

often assumes a transverse or oblique lie. Other factors often noted radiologically are the absence of a uterine shadow around the fetus, maternal intestinal shadows intermingled with fetal parts, and fetal parts overshadowing the maternal vertebrae on lateral views. The latter does occasionally occur with sacculization of the uterus, though this condition is even more infrequent than abdominocyesis. Certain refined X-ray procedures such as aortography,³ uterine phlebography,¹² hystero-graphy,¹ and isotopic placentography⁶ are valuable aids in establishing a diagnosis. However, these procedures are highly specialized and can be hazardous when injudiciously employed by unskilled personnel.

In our patients, X-ray studies could be documented in only 3. A positive diagnosis of abdominal pregnancy was made in 1 patient. In another, it was considered "equivocal," and in the third, the diagnosis was not made.

Other diagnostic aids employed are an oxytocin test,⁴ colpocentesis, and culdoscopy.

Surgical Management

Once a diagnosis of abdominocyesis is made, operation should be done with dispatch. However, there may be an occasional circumstance when a course of observation could be justified. The hazards of hemorrhage from removal of the placental site can be just as catastrophic at 28 weeks as at term.⁸ The major risk, then, in allowing a patient to continue to term is the possibility of intraperitoneal hemorrhage. This did not occur in any of the patients in this series. Henderson and Wilson noted 4 such patients who were deliberately allowed to proceed to near term. No intra-abdominal hemorrhage occurred between the time of diagnosis and the termination of pregnancy. Our general policy is to intervene as soon as the diagnosis is established or strongly suspected.

Management of the placenta at laparotomy is by far the greatest problem in treatment.

Factors which influence the decision are the location and accessibility of the blood supply and the size, shape, and vitality of the placenta. In most circumstances, it is probably best to avoid any unnecessary exploration of the surrounding organs. The infant is delivered, the cord tied with absorbable suture close to its insertion, and the abdomen closed without drainage. The only maternal death in our patients occurred in 1951, as the result of an unsuccessful attempt to remove a term placenta. The hemorrhage which followed was cataclysmic. Nevertheless, postoperative morbidity is considerable and maternal death may be more likely when the placenta is left in place.^{2,9}

Hreshchyshyn *et al.*¹⁰ recently used Methotrexate (formerly called Amethopterin)* to treat a placenta left in place in a patient with abdominal pregnancy. This approach seems rational since this anti-folic-acid compound is known to be effective in destroying trophoblastic tissue. In their patient, there was a sharp decrease in the chorionic gonadotropin titer and decrease in size of the placental mass, as well as clinical improvement of the patient.

As mentioned, there was 1 maternal death in our series. There were 8 placentas removed and 4 left in situ. One of the latter 4 patients developed peritonitis 8 weeks post operation, and another developed a placental cyst and intestinal obstruction requiring subsequent operation and removal of the cyst. The other required no subsequent treatment and presented no significant problems of management.

Fate of the Fetus

Three of the 12 patients in this series carried living fetuses to 39+ weeks. Two were completely normal and survived. One possessed multiple congenital anomalies of the left arm and left side of the face, succumbing 6 hr. after delivery; the amniotic

* Lederle Laboratories, Pearl River, N. Y.

sac was not intact, as it was in the 2 who survived.

Five other infants were known to have been born alive but died shortly after birth. The records were incomplete for the remainder. The amniotic sac was reported intact in 4 of the 5 patients.

SUMMARY AND CONCLUSIONS

We have reviewed the records of 12 patients with abdominal pregnancy accumulated over a 15-year period (1951-1965). The 2 most recent ones were managed by the authors. Every attempt has been made to eliminate advanced tubal, ovarian, and intraligamentous pregnancies.

The gravity of this condition is again emphasized. Prompt termination of pregnancy is the proper course, but we recognize possible exceptions to this general principle.

Most often, the placenta should be left in place because of the inability of the obstetrician to ligate its blood supply. However, when this can beyond all doubt be safely accomplished, the placenta should be removed. Convalescence is stormy and morbidity higher when the placenta is not removed.

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Toxemia of Pregnancy: A Continuing Challenge

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IN recent years, toxemia as a cause of maternal death has declined from second to third. However, toxemias of pregnancy still complicate seven to eight per cent of all pregnancies in this country and far more than this in the southern states. They account for one-third of all the annual maternal fatalities, but too often underemphasized is the fact that they cause at least 30,000 yearly perinatal deaths. This alone makes the entity a continuing challenge. The challenge will persist until the etiology of this disease complex has been solved.

At our hospital, there has been no significant decline in the incidence of toxemia. This is due to three basic reasons: 1) ours is primarily a referral hospital; 2) the majority of our patients are socio-economically depressed; and 3) a large number of primigravidas are cared for (42 per cent). During the previous year, there were 1,811 admissions on our service. Five hundred and seventy of these patients had toxemia of pregnancy, constituting 31.4 per cent of the admissions.

Difficulties are often encountered in defining and classifying this disease. To us, toxemia is a pregnancy syndrome characterized by edema, hypertension, proteinuria and a complex of symptoms which may terminate in convulsions, coma and death. Those of us who treat these patients know that the signs and symptoms are nonspecific and the prepregnancy state usually unknown. This renders accurate classification extremely difficult. Of the many schemes of classification proposed, we now employ the one set forth by the American Committee on Maternal Welfare.

PATHOPHYSIOLOGY

All the signs and symptoms of toxemia can be explained by abnormal sodium retention and generalized vasoconstriction. Abnormal sodium retention results in excessive weight gain with subsequent edema formation. Vasoconstriction causing

a decreased blood flow to any given area explains the other abnormalities. When this vasoconstriction is at the cerebral level, ischemia is produced which if unaltered leads to convulsions. Increased peripheral constriction accounts for the elevated arterial pressure. Vasoconstriction of the afferent arterioles of the kidneys explains the decreased urinary output seen. Consequently vasoconstriction is by far the most important abnormality. This factor is responsible not only for the damage done to the vital organs of the mother but also for the damage done to the fetus.

The etiology of this disease is unknown. We do not know the precise relationship between abnormal sodium retention and generalized vasoconstriction. There is a growing body of evidence which implies that alternation of the renin-angiotensin-aldosterone system is involved.¹ It is suggested that under the influence of the adrenal-cortical hormones, sodium and water retention may actually accumulate within the blood vessel walls reducing their caliber thereby leading to edema and hypertension.²

There is an increasing body of evidence which suggests a relationship between toxemia and vitamin B₆ deficiency.³ It is well established that pyridoxine or vitamin B₆ is important in brain metabolism in the formation of gamma amino butyric acid, a neuronal inhibitor. Such a deficiency may lower the threshold for convulsions.

There are numerous organ morphologic changes that accompany toxemia and eclampsia. The placenta has a tendency towards premature aging with syncytial degeneration and fibrin replacement, reduction of the intervillous space, ischemia, necrosis and infarction. The brain shows edema, and there may be hemorrhage throughout the brain substance, varying from petechiae to extensive subarachnoid hemorrhage. The heart and lungs may show small petechial hemorrhages. Sometimes there is evidence of myocarditis and usually pul-

monary edema. The hepatic lesion which was once thought to be pathognomonic shows hemorrhagic necrosis located in the periphery of the hepatic lobule. Probably, the most characteristic are the renal lesions. Electron microscopy reveals that there is a reduction or occlusion of the glomerular capillary lumina as a result of extensive increase in the cytoplasm of their endothelial cells. There is no abnormality of the basement membrane as was once thought with light microscopic studies. Most striking is the fact that postpartum, these changes show complete reversibility to a normal state. Also seen in the kidney of the eclamptic patient in addition to the features mentioned is the deposition of fibrin in the renal glomeruli with resultant cortical necrosis. Exhibited are certain features which implicate disseminated intravascular coagulation or a Schwartzman-like reaction.⁴ Other situations that have been suspected as possible causes of toxemia include environmental, nutritional, and immunological factors.

MANAGEMENT OF PRE-ECLAMPSIA AND ECLAMPSIA

In the strictest sense, the management of pre-eclampsia begins the moment the physician accepts the responsibility of treating any expectant mother. Prevention is the bedrock of exemplary management. The family history, past history and dietary habits should be well explored. Detailed inquiry about dietary habits creates in the patient an awareness of the importance of reduced caloric intake. Currently in obstetrical practice, the ill effects of excessive weight gain may have been overly dramatized but with good effect. Unlimited food intake enhances any tendency towards pre-eclampsia. Sodium intake is proportionally greater with increased food intake; consequently, reduced caloric intake tends to secondarily decrease salt on sodium intake. This combination of factors certainly provides in part the basis through which antenatal care exerts its prophylactic influence in pre-eclampsia.

According to the classification set forth by the American Committee on Maternal Welfare, pre-eclampsia is subclassified as mild and severe and, of course, the treatment for the two is different. Pre-eclampsia is said to exist when any one or more of the following are present: 1) systolic blood pressure of 140 mm. or more, or a rise of

30 mm. or more above the usual level; 2) diastolic blood pressure of 90 mm. or more or a rise of 15 mm. or more above the usual level; 3) proteinuria of a significant degree (greater than 1 plus); and 4) persistent edema of the hands and face.

The blood pressure readings must be obtained on at least two occasions, six hours apart with the patient at rest. Also, proteinuria must be observed in clean urine specimens on two or more successive days.

We do not feel that every patient with pre-eclampsia must be hospitalized. This must, however, be individualized. What influences this decision most will be the number and severity of the criterion present. The age, parity and the patient's mental grasp of the situation. Prior to the development of thiazide diuretics, this position was much more difficult to defend. Now, however, we sometimes justifiably embark on a course of conservatism and manage these early symptoms on an outpatient basis. There are some who even go a step farther and employ the thiazides prophylactically in what they consider the pre-eclampsia-prone patient.⁵

Before the thiazides were available, the aim of therapy was directed towards control of the arterial blood pressure, proteinuria and seizures. Presently, the primary aim of our therapy is prompt control of sodium retention before vasoconstriction has had time to develop. The effectiveness of the thiazides in accomplishing this has frequently eliminated the need for other treatment. Most fortunate, too, is the fact that drug resistance is seldom a problem. Any of the thiazide derivatives can be employed. On an out-patient basis, we favor chlorthalidone (Hygroton)* because of its long action. It can be effectively administered once daily in 50 mg. dose. Most other thiazide diuretics must be prescribed twice daily, somewhat decreasing patient acceptance. We recognize no other superiority of chlorthalidone and all of these drugs can cause hyperglycemia and hyperuricemia.

We restrict sodium only in that we advise the patient not to salt her food after it is cooked. No other therapy for these non-hospitalized patients is employed.

When the patient with mild pre-eclampsia requires hospitalization, her therapy often differs

* Geigy Pharmaceuticals, Ardley, N. Y.

little from the outpatient regimen. However, in addition to the thiazides, the patient receives mild sedation in the form of phenobarbital, 60 mg. three times daily. She also follows complete bedrest except for bathroom privileges. Hydralazine (Apresoline)[†] is worthwhile and is sometimes used. We do not use Reserpine for any of our antepartum patients because of its relationship to catecholamine depletion and irreversible hypotension occasionally encountered with the anesthesia of surgery.

Mandatory hospitalization is required in severe pre-eclampsia. Severe pre-eclampsia is said to exist when any one of the following is present: 1) blood pressure: systolic greater than 160 mm. Hg., diastolic greater than 110 mm. Hg. (on two occasions, at least six hours apart with the patient at rest); 2) proteinuria—five gms. or more per 24 hours (3 plus to 4 plus); 3) oliguria—less than 400 ml. per 24 hours; 4) cerebral or visual disturbances, and 5) pulmonary edema or cyanosis.

Once a patient is hospitalized and therapy begins, convulsions should rarely occur. Our objective in managing patients with severe pre-eclampsia is to first control the symptoms and then terminate the pregnancy. We are convinced that these fetuses do not significantly increase in weight and their intrauterine environment is a greater hazard than an incubator in our nursery.

On admission, the patient receives a single 15 mg. dose of morphine sulfate. She is given magnesium sulfate 20 ml. (10 ml. in each gluteus muscle) of a 50 per cent solution. This 10 gm. dose is repeated every four-eight hours as blood pressure response and patella reflexes indicate. This dosage may be reduced to 10 ml. of a 20 per cent solution. As a rule, we limit our total amount of magnesium sulfate to 120 gms. by the time of delivery is effected. Magnesium sulfate is the backbone of our therapy. The magnesium ion is well suited for the job. It acts as a mild sedative, a diuretic and is known to inhibit impulse transmission at the myoneural junction, thereby raising the threshold for convulsions.

The patient is placed at strict bedrest. She is given a high protein 500 mg. sodium diet. Intake and output are strictly recorded. She is weighed daily and a seizure tray is placed at her bedside.

We employ thiazide diuretics such as hydrochlorothiazide, 50 mg. twice daily. Also hydralazine, 50 mg. two to four times a day is given.

She should have daily urine examinations for protein and specific gravity and daily hematocrits are performed. We give 2,000 ml. dextrose 10 per cent in water with multivitamins added. Most patients improve during the next 24-28 hours. This is manifested by diuresis, weight reduction, improvement in hematocrit and modest reduction in blood pressure. Fortunately, most of these patients are in the 34th week of gestation or more. Consequently, the decision to empty the usually irritable uterus is not difficult. Intravenous oxytocin, if not contraindicated, is employed to induce labor. This is coupled with amniotomy. Cesarean section is done only for obstetrical indications. When the patient has not reached the 34th week of gestation, the problem is compounded. However, even here we still prefer to empty the uterus and usually do. Occasionally, there are exceptions and we allow the pregnancy some additional progression.

Eclampsia is a disease of neglect. There are virtually no exceptions to this statement. Also, it is mostly a disease of the young primigravida. To both the laity and the physician there are few clinical pictures more terrifying than an eclamptic seizure. Padded tongue blades are used to prevent self-injury to the oral passageways. Active convulsions are controlled by the slow intravenous injection of amobarbital (Amytal)* not exceeding 500 mg. Morphine sulfate 15 mg. is administered intramuscularly. Every effort should be made not to repeat these two drugs. Excessive sedation increases perinatal loss.⁶ Following a convulsion an airway should be maintained, suctioned as indicated and oxygen administered.

Again, magnesium sulfate is by far the most important drug. A 10 gm. dose is given intramuscularly as with severe pre-eclampsia, but as often as every three hours depending upon patellar reflexes, respiratory rate, urinary output and blood pressure response. Calcium gluconate must always be at the patient's bedside in case of magnesium sulfate overdosage.

An indwelling catheter is placed in the urinary bladder and urinary output frequently monitored.

[†] Ciba Pharmaceutical Company, Summit, N. J.

* Eli Lilly and Company, Indianapolis, Ind.

TABLE 1.—INCIDENCE OF ECLAMPSIA OVER A 3-YEAR PERIOD

Time Period	Total Deliveries	Cases of Eclampsia	Ratio of Occurrence	% of Deliveries
1965	1169	18	1:64	1.53
1966	1345	10	1:134	0.74
1967	1512	12	1:126	0.79
1965) 1967)	4026	40	1:100	1.0

Fluid balance is maintained by closely measuring the 24-hour output and adding the insensible loss and then replacing this amount with dextrose 10 per cent in water.

We have not used diuretics in the eclamptic patient. Some even feel that these drugs are contraindicated having occasionally precipitated the so-called low salt syndrome and in others acute pulmonary edema from fluid immobilization.⁷

Specific antihypertensive therapy consists only of hydralazine, either intramuscularly or in intravenous drip and the blood pressure is titrated. This form of treatment is especially indicated if cerebrovascular accident is thought to be likely. Digitalis preparations are employed when indicated.

Sedation consists of up to 180 mg., with phenobarbital intramuscularly every four hours. Tranquilizing drugs are not used. Induction of labor is started 18-36 hours after the last seizure. Cesarean section is done only for obstetric indications. Irrespective of the unripeness of the cervix, an amniotomy is done and intravenous oxytocin administered with the usual safeguards. In these patients, it is an exception indeed when vaginal delivery cannot be safely accomplished.

A three-year experience involving 40 eclamptic patients at our hospital bears out many of the factors pointed out in this presentation. Table 1 shows the incidence of eclampsia and the time period involved. It is generally accepted that the incidence of eclampsia in this country is about one in every 1,000 to 1,500 deliveries.⁸ Our figures show an overall incidence of one in every 100 deliveries. The reasons for this are pointed out earlier.

Other features to which we have alluded show that 70 per cent of our patients were primigravidae and 90 per cent were gravida III or less. In addition

TABLE 2.—DEATHS IN TOXEMIA OF PREGNANCY

Case Number	Age at Death	Fetal Status	Death Cause	Time in Hospital
90956	19	Term (Survived)	Anuria Coma	48*
94485	17	Still-Birth	Anuria Coma	5*30'
98552	29	Premature (Survived)	Anuria Coma	24*36'
102570	39	Fetal Death in Utero	C.V.A.	3*22'

tion to low gravidity, these patients are usually young. Seventy per cent of these patients were 20 years old or less and 90 per cent were 25 years or younger.

As expected, most seizures occurred in the antepartum period. The number of convulsions was usually determined by the time the patient reached the hospital. Only two patients had a subsequent seizure once treatment was instituted.

In all but one instance, the route of delivery was vaginal. In the exception, the indication for abdominal delivery was not eclampsia but cephalopelvic disproportion.

It is interesting to note that extreme hypertension, systolic or diastolic, is not a necessary requisite for the younger patient to convulse; in fact, it appears the exception. In many of the older patients, pre-eclampsia was superimposed on a pre-existing hypertension.

The perinatal mortality was 32.5 per cent with the greatest portion occurring as stillbirths⁹ and three neonatal losses. One fetus was lost to follow up and, therefore, considered statistically as non-surviving.

There were four maternal deaths constituting 10 per cent of the cases (Table 2). As can be seen from the elapsed time in the hospital until death, at least two and possibly three of these patients were moribund when admitted. In one patient, 18 convulsions were documented and none had fewer than eight.

SUMMARY

Though declining, toxemia of pregnancy continues to contribute greatly to maternal and fetal wastage, especially in certain groups and geographic areas. Moreover, this disease will continue to be a challenge until its etiology is found and its

effects eradicated.

An elementary review of the pathophysiology involved has been presented. Some of the clinical features and a method of management are presented. However, it is recognized that there are many other satisfactory methods of management, especially since all treatment is empiric.

Forty eclamptic patients treated over a three-year period at the John A. Andrew Memorial Hospital, Tuskegee Institute, Alabama are reviewed. The high morbidity and mortality, both maternal and fetal, are examined and re-emphasized.

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Twin Pregnancy: A Three-Year Report

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TWIN pregnancy, because of the associated increased maternal and fetal morbidity, is a distinctly abnormal condition. The anatomic and physiologic capacities of the human female reproductive system are unduly stressed when called upon to bear more than one offspring at a time. The problems of twinning encountered at the John A. Andrew Memorial Hospital over a 36 month period are presented. All phases of the reproductive process, antepartum, intrapartum and postpartum are adversely affected by plural gestation as well as the outcome of the fetus. Some of the biologic factors involved in twinning and some of the complications encountered in their management are reviewed in this paper.

In 1895, Hellin postulated that twins occurred once in every 89 births, triplets in 89 births squared and quadruplets in 89 births cubed. Since that time, this so-called "Hellin's Law" has been repeatedly tested and has more or less stood the test of time, although it is more of a biological approximation rather than a mathematical law.¹

An ethnic variation in frequency of plural births is a well recognized fact. It occurs most frequently among the black race, least often in Orientals with Caucasians occupying an intermediate position. Heredity, age and parity in addition to race all have a positive affect on the incidence of twinning.

At our hospital during the three-year period, January 1, 1966, through December 31, 1968, there were 4,198 births. During this same period, there were 52 twin deliveries, an occurrence of one set of twins for every 80 single births. There were no triplets or higher multiple births.

Twin pregnancy may occur in one of two ways. It may result from the fertilization of two separate ova or from a single ovum, producing fraternal or identical twins, respectively. With fraternal or double ovum twins, the ova may be derived from two separate ovaries, the same ovary or even a single graafian follicle. Approximately

two-thirds of twins are fraternal or the double-ovum type. Single ovum or identical twins which comprise the other one-third are not influenced by heredity, race, age or parity. These four factors influence only double ovum twinning.

To establish zygosity in twins at birth is not always a simple matter and often cannot be done. It could not be established in 20 per cent of cases at Chicago Lying-In Hospital, a center specializing in this type abnormality.² However, there are some characteristics to be pointed out that are helpful. First, if the twins are of the opposite sex, they are not identical. If of the same sex, they may be either. When there is a single, non-fused placenta with a single chorion, the twins are identical. If there are two separate placentas, the twins may be either fraternal or identical. If conjoined, the twins are identical.

In identical twinning, whether there be one or two placentas is determined by the time or stage at which the germ disc splits into two. If the splitting occurs early, before there is an embryo or a placenta, the separation is complete and each half of the germ disc may then go its separate way and develop quite independently. The result is the formation of identical but dichorionic twins with separate placentas though the twins originated initially from a single ovum. If zygosity cannot be definitely established at birth, there are other modalities that can be employed later. Some of these techniques are comparing all blood factors, major and minor, which must correspond completely if the twins are derived from one ovum. Another method is comparison of hand and foot prints. Also, reciprocal skin grafting is a technique employed. The graft behaves like an autograft when the twins are identical.

As mentioned above, certain conditions predispose to multiple gestation; i.e., strong family history, increasing age and increasing parity. Consequently, one can be alerted to the greater prob-

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females. In 31 cases, both fetuses were of the same sex and 21 of opposite sex.

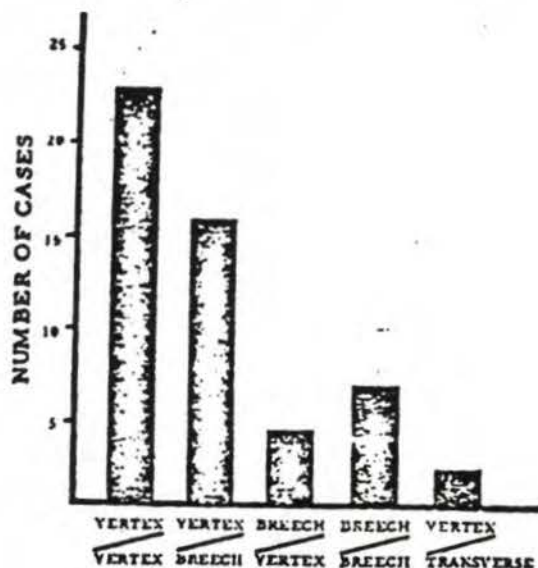


Fig. 1—Fetal Presentations

The most well established abnormality associated with twinning is the enormous fetal wastage. The perinatal loss is most severely affected by prematurity (Fig. 2). Of the 104 infants in this study, 64 or 61 per cent weighed less than 2,500 gms. In

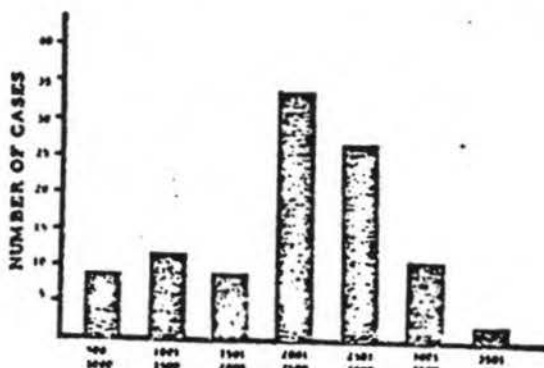


Fig. 2—Birth Weight (in grams)

only 15 of our 52 cases (28.8 per cent) did both fetuses weigh more than 2,500 gms. as contrasted to 27 cases (51.9 per cent) where both infants were premature. In 10 cases, one-half of the in-

fants were over 2,500 gms. and the other one-half weighed less than this.

The perinatal loss was 17.3 per cent. Nineteen of the 104 infants succumbed. There were nine fetal deaths and 10 neonatal deaths. Usually with twinning about two-thirds of the perinatal loss is due to neonatal deaths and only one-third due to stillbirths. Nonetheless, it is acknowledged that premature twin infants are more durable than their single born premature counterparts. This was true in this series.

In most studies, the fate of the second twin is more precarious than that of the first. Eleven of our 19 non-surviving fetuses were second born.

There were no maternal deaths.

SUMMARY AND CONCLUSION

An elementary review of the biological principles of twinning has been presented. The resultant abnormalities associated with the antepartum, intrapartum and postpartum phases of the reproductive process are highlighted. A three-year survey of twin pregnancies at the John A. Andrew Memorial Hospital is reviewed. It is concluded that twin pregnancy is a distinctly abnormal condition contributing directly to increased maternal morbidity and perinatal mortality.

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Meigs' Syndrome Complicated by Pregnancy

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Meigs' Syndrome Complicated by Pregnancy

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IN 1937, Meigs and Cass reported seven cases of fibroma of the ovary accompanied by ascites and hydrothorax. Though rare, the importance of this condition should be fully appreciated. Solid tumors are far less common than benign cystic tumors and for that reason, should be generally considered as potentially malignant. Meigs' Syndrome, therefore, points out the fact that a solid ovarian neoplasm can be responsible for ascites and hydrothorax and yet be completely benign.

Since 1937, there have been many subsequent reports of this condition. However, its association with pregnancy is, indeed, an infrequent occurrence. During the 35-month period from January 1966, through November 1968, computer analysis of the world literature revealed but a single naturally occurring case of Meigs' syndrome and pregnancy co-existing. The author here adds another case to the literature.

CASE REPORT

O.B., a 35-year-old unmarried black woman, gravida 9, para 5, abortus 3, was admitted on Feb. 15, 1968, having been referred from her county health department with a diagnosis of "polyhydramnios." She was well until three weeks prior to admission, at which time her abdomen began to enlarge rapidly. Her last normal menstrual period had begun sometime in Nov. of 1967. A week after the onset of her abdominal enlargement she developed increasing chest pain, shortness of breath and nausea and vomiting which followed most meals. She denied other gastrointestinal, renal, cardiovascular, respiratory or pelvic complaints.

Her past medical history and systems review were essentially noncontributory and her previous pregnancies were uncomplicated aside from three spontaneous abortions occurring in the first trimester. However, her social history revealed that she was the head of a two-room household composed of one adult, that being herself, and four children ranging in age from three to 16 years. She was unemployed and received no welfare assistance.

On admission, her blood pressure was 110/80, temperature 98.4, pulse 75 minutes, weight 205 pounds, and height 64 inches. Positive findings were limited to the lungs, abdomen and pelvis. The lower one-fourth of the left lung field presented percussion dullness both anteriorly and posteriorly. There were no rales or rhonchi

and the right side was completely clear to percussion and auscultation. The abdomen was markedly distended to the xiphoid process approximately the girth of a term pregnancy, but different in contour. No fetal heart tones were audible and there was a positive fluid wave. On the left side, mostly in the lower quadrant, there was a firm ballotable mass whose size could not then be ascertained. Pelvic examination revealed a normal introitus. The vaginal mucosa was blue and the cervix was soft, blue and enlarged with the external os closed. The corpus and adnexa could not be accurately assessed, nor could the origin of the ballotable mass be established.

Hospital Course: Hematologic studies revealed the following: Hemoglobin 10.4 gms.%, hematocrit 36 vol.%, white cell count 8,450, blood type O-Rh positive, and sickle cell preparation negative. Other test results were: pregnancy test positive; creatinine .95; potassium 3.1 mEq/L; chloride 96 mEq/L; carbon dioxide 21 mEq/L; total serum protein 5.9 gms.%, albumin 1.9 gms.%, globulin 4.0 gms.%, amylase 26 units, urinalysis—pH 5.0, specific gravity 1.023, albumin trace, glucose negative, acetone negative, and numerous white blood cells. Papanicolaou stain of the ascitic fluid showed Class I (absence of neoplastic or atypical cells), many mesothelial cells, histiocytes and lymphocytes. Anterior-posterior and lateral x-ray views of the pelvis revealed no fetal skeleton and only "a general haziness over the abdomen due, very likely, to a mass or ascites or both. Chest x-ray on Feb. 23, 1968, showed the left costophrenic angle to be filled with a density and some fluid extending up the lateral chest wall from the surface of the density (Fig. 1). The electrocardiogram was reported as normal.

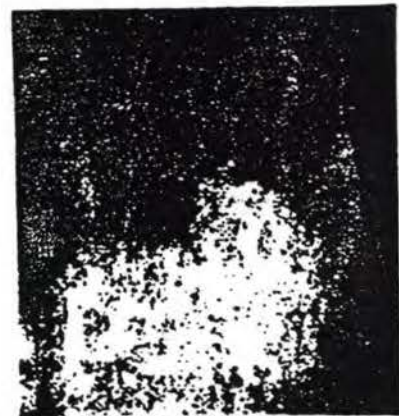


Fig. 1. Chest x-ray showing a density in the left costophrenic angle and fluid extending up the lateral chest wall.

On Feb. 26, 1968, abdominal paracentesis was performed and 2,500 mls. of a straw colored fluid were removed. Repeat pelvic examination at this time revealed more clearly a pelvic mass thought to be at least 12 cm. in diameter. Medical and urological consultations were obtained and on March 8, 1968, an exploratory laparotomy was performed. Upon entering the peritoneal cavity, a serosanguinous fluid was encountered which measured 1,500 ml. Arising from the left infundibulopelvic ligament completely replacing the ovary was a solid ovoid mass measuring 25.0 x 20.0 x 12.0 cm. and weighing 2,200 gms. Its surface presented rough excrescences and extensive loose omental adhesions. The uterus appeared gravid though no corpus luteum could be identified. A total abdominal hysterectomy, right salpingo-oophorectomy, left salpingectomy, left ovarian cystectomy and partial omentectomy were performed (Fig. 2).

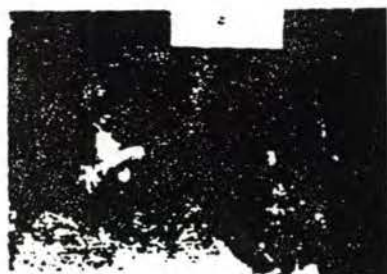


Fig. 2. Specimens removed at surgery. The ovarian mass is noted on the left and the uterus with the fetus are on the right.

Her postoperative course was one of progressive improvement and she was discharged completely asymptomatic on her 9th postoperative day. Estrogen replacement was instituted prior to discharge. She has since been seen on several occasions and eight months later remained asymptomatic.

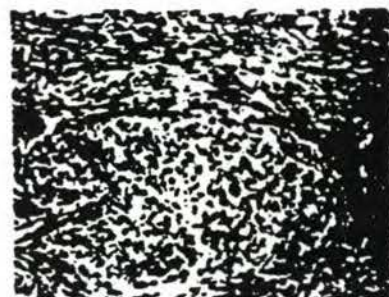


Fig. 3. Photomicrograph of the ovarian fibroma. Note the uniformity of the cells. H. & E. X350.

Pathological diagnoses were: Fibroma of ovary (Fig. 3), intrauterine gestation approximately 18 weeks, chronic cervicitis, normal ovaries and oviducts and hemorrhagic omentum.

COMMENTS

The size of the ovarian fibroma would indicate that it antedated the pregnancy even though the ascites and hydrothorax did not become manifest until the pregnancy was well established; consequently, it is felt that this is a case of Meigs' syndrome complicated by pregnancy rather than the reverse.

Approximately 40 per cent of all ovarian fibromas over 6.0 cm. in diameter will be accompanied by excessive peritoneal fluid. The added element of fluid in the pleural cavity appears with only 3 per cent of cases and the association with pregnancy is indeed a most infrequent occurrence.

Unfortunately, at our hospital, immediate frozen sections are not available. At laparotomy, the solid tumor, the extensive excrescences and omental adhesions pointed to a strong possibility of malignancy; consequently, total extirpation of the pelvic organs was carried out. The dismal social history made this decision just a bit less difficult.

In addition to the solid ovarian tumor, ascites and hydrothorax, this case fulfills a fourth criterion set forth by Meigs in 1954, that of being cured after removal of the tumor.

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MATERNITY AND INFANT CARE AT TUSKEGEE INSTITUTE

by

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During the past twenty-four years, the obstetrical service of the John A. Andrew Hospital has been actively engaged in the conduct of a Maternal and Child Health Care Program. The original program which commenced in 1947, involved eight counties which are in close geographic proximity. It was financed with an unmatched Federal Grant under Title V, Part I, Sec. 502 (b) of the Social Security Act. The program's objective then was basically to treat complicated obstetrical patients and sick infants up to one year of age. It was not highly innovative nor really broad in scope. It functioned, however, in the capacity of only health care delivery for only a short period of time. The Macon County Medical Care of MCMC Program, as it became known soon, began to serve as a vehicle for training Tuskegee Institute nursing students both on an outpatient and inpatient basis. This was followed closely by the establishment of a certified school of nurse midwifery, and in 1949, an obstetrical residency affiliation was established with Meharry Medical College. The John A. Andrew Clinical Society utilized much of this MCMC Program in its continuing education for health practitioners.

Although this program quickly broadened in its scope and objectives, the funding was in no way proportionately increased. We now admit more than 2500 patients annually and we are anticipating nearly 2000 annual deliveries; our outpatient clinic has more than doubled. Nonetheless, we moved forward, and Tuskegee Institute with its keen sense of community responsibility bore most of this increased financial demand. However, it became more and more apparent that increased funding would be essential if we were to continue to function in an effective capacity. In 1970, a Maternal and Infant Care Grant Project #556, was funded by the Department of Health, Education, and Welfare with Tuskegee Institute putting up the required matching funds when no public funds could be found.

Today, our objectives are much broader in scope—our health care delivery is comprehensive in approach and our areas of teaching have increased. Our objectives now place primary emphasis on the prevention of maternal and infant complications through the early identification of patients with a high potential for complications. In addition to healthier mothers, there is a reduction in the incidence of mental and physical

retardation in the infants. This is quite a different concept than that of twenty-four years ago when we were funded to treat obstetrically complicated mothers and sick infants up to the age of one year.

Our method of health care delivery today is multidisciplinary involving, in addition to physicians, public health nurses, social workers, nutritionists, and a variety of supporting administrative and clerical personnel. Only this comprehensive approach can effectively achieve our objectives. Our Maternity and Infant Care Project is also unique in that unlike most existing M & I Programs, ours provides its own inpatient services thereby maintaining a total continuity of the patients care.

Our Maternity and Infant Care Project presents an excellent vehicle for teaching both inpatients and outpatients. Presently we continue to train Tuskegee Institute nursing students. In addition to training residents in obstetrics and gynecology, we have conducted a medical student affiliation with Meharry Medical College since 1967, and we are hopeful of establishing the same with Howard and Emory Universities. Nutritionists and dietitians are now training in our outpatient clinics as a part of RMP. A half dozen major publications have come from the obstetrics and gynecology service in the past five years thereby indirectly contributing to the continuing education of practicing physicians.

In spite of these accomplishments, however, our future needs are increasing and require increasing funds. There are two types of barriers that prevent health services from reaching the patient. First, attitudinal barriers which preclude the patient's being motivated to seek the needed service. This barrier in our part of the country, especially, is created primarily by cultural and economic isolation. The erosion of this barrier can be speeded with an increase in the total number of personnel in all disciplines but especially in the area of social workers. More direct barriers, however, are what sociologists refer to as organizational barriers—those obstacles that prevent the motivated patient from receiving the desired service. These barriers, which constitute a large unmet need are many, less intangible; and, consequently, more readily identifiable. Care for our infants now still terminates at the age of one year. C and Y or Child and Youth Programs are sorely needed, but they require additional specialized personnel. Our present program needs a more realistic salary in order to attract a dentist. Ultra-modern dental equipment is needed.

Funds for our present consultant services are woefully inadequate and no provisions are made for outpatient consultations.

The quality of patient care could be increased and the cost of this care decreased if establishment and effective usage were made of intermediate and extended care facilities.

With few exceptions, the physical condition of most of our outpatient clinics is deplorable.

Funds for patient transportation must be given very high priority. The magnitude of this problem is amplified when the population density is low.

Family Planning Services need expanding. More needs to be done in the area of infertility and interconceptional nutrition.

There is a need for the re-establishment of a nurse midwifery program now that this concept is no longer in disfavor.

Finally, there is a growing need for the expansion of staff education. These are but some of our needs. We have looked briefly at the past and present status of maternal and infant care rendered by the John A. Andrew Team. We are cognizant that the future presents many obstacles; however, with our past performance, our existing resources in this community and with ample funding we are confident that we can adequately meet this challenge.

Thank You.

Presented at the Veterans Administration
Hospital, Tuskegee Institute
July, 1971

While it is quite likely that tuberculous lesions will regress in the young, deterioration tends to occur in older people, particularly in men.



PRESENT STATUS
OF TREATMENT
OF DIABETIC RETINOPATHY
by

S. H. SETTLER, M.D.
Chief of Ophthalmology
VA Hospital and
John A. Andrew Hospital
Tuskegee, Alabama

During the past five years, persons with diabetic retinopathy have been treated with an increasing number of high energy light beams. Jepson at the University of Colorado and Meyer-Schwickcraft at the University of Essen, Essen, Germany have both used the xenon-arc, high intensity, white light instrument for the coagulation of haemorrhagic diabetic retinopathy. Jepson initially used treatments scattered over several visits and then changed to massive numbers of burns at one visit. Meyer-Schwickcraft, in a recent paper given at the Chicago Ophthalmological Society, continued to advocate judicious use of coagulation limited to areas of haemorrhage.

The postulated theoretical basis underlying large numbers of burns made on diabetic retina is that the O₂ demands of the retina are decreased by the resulting areas of atrophy.

The argon laser acts in a manner similar to the xenon light coagulator. The laser has an additional advantage in that its wavelength is more specific for retinal vasculature and areas of retinal haemorrhage. Because of the extreme coherency of laser light, it is possible to focus a large amount of energy into a very small area. The laser is being used to coagulate microaneurysms close to the macula; a feat which was not possible with the light coagulator because of the diffuse nature of its burn.

The choice of patients for light coagulation or laser coagulation is best limited those persons who have early diabetic retinopathy with a preponderance of microaneurysms and haemorrhages. Usually these persons have a visual acuity between 20/30 and 20/70. An effort is made to coagulate only those areas which are not included in the nerve bundle

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A RURAL HOSPITAL AND FAMILY PLANNING

Henry W. Foster, M.D.
Chief, Obstetrics and Gynecology
John A. Andrew Memorial Hospital
Tuskegee, Alabama

INTRODUCTION BY ROBERT A. HATCHER, M.D.

Dr. Henry W. Foster hails from Pine Bluff, Arkansas. He was graduated from Morehouse College and the University of Arkansas Medical School. He had one year of surgery training prior to his OB-GYN residency at Meharry Medical College in Nashville. He is currently Chief of the Obstetrics and Gynecology Service at the John A. Andrew Memorial Hospital, Tuskegee, Alabama, and is Director of their Maternal and Infant Care Project.

I was very much impressed with you, Hank, and your service when I visited you way back in the spring of 1966 with Dr. John Thompson.

I look forward very much now to your reflections on the delivery of family planning services in your hospital.

A RURAL HOSPITAL AND FAMILY PLANNING

Even under the most ideal circumstances the problems of effectively implementing family planning are, indeed, difficult and often impossible. However, the frustration and futility so frequently encountered in family planning are only compounded when the setting is rural.

Macon County, Alabama, located in the southeastern part of the State typifies rurality and many of its problems. The County has a land area of 616 square miles. There are 24,841 inhabitants of which just over 11,000 reside in Tuskegee, the County Seat and the location of Tuskegee Institute, and Tuskegee's Veterans Administration Hospital. There is a smaller community of about 1,000 people with the remainder being scattered on mostly small farms throughout the County.

Family Planning services are also provided to Bullock County and partially to Russell County. Bullock County has a land area of 615 square miles and Russell County, a land area of 639 square miles. The population of Bullock County is 11,820, and the population of Russell County is 45,394. These three Counties very well parallel each other in their rural makeup and it is in this setting, primarily, that our family planning services are conducted.

In addition to speaking on the problems of family planning in a rural setting, I have also been asked to give a black physician's views on family planning. I shall speak to the latter aspect first.

In recent years, there has been an outcry by various groups that the intent of family planning is black genocide and that the ultimate effect will be black genocide. I must admit that these apprehensions are quite understandable and often not without foundation. In June of 1970, the First National Congress on Optimal Population and

Environment convened in Chicago, Illinois. Invited participants included about 45 blacks representing such moderate black institutions as the Urban League, Tuskegee Institute, and Howard University. Shortly after the Congress convened this group of individuals formed a black caucus on an ad hoc basis. After considering the major problems being discussed and the solutions proposed, the caucus observed that the Congress in its planning had been derelict in obtaining significant black input to reflect black interest, and that the purpose of the conference was to use those delegates invited to legitimize a pre-conceived plan of vicious extermination. If to many of you these views seem irrational, it is to some degree understandable. The majority of this Country's health providers have never even in the vaguest way planned a program of genocide for black people. What has occurred, however, is that many well intentioned family planning programs have been set up for large segments of our black population without adequate consideration of many other factors. Without consideration of such factors which I shall mention shortly, the end results of far-reaching family planning programs can have very disastrous consequences for black people. Nonetheless, I support family planning but this support is of necessity, conditional. I consider it axiomatic that the following conditions first be met: 1) that all programs be completely voluntary and that no coercive family planning programs be allowed to become a part of a National or local legislative policy; 2) that comprehensive health care be a viable component of any family planning program, and 3) that all family planning programs for blacks include blacks at all meaningful policy making and administrative levels. It is absolutely

essential that these three prior conditions be met and to do otherwise is, in my judgement, unthinkable. All too often, the family planning services being provided are not voluntary. Consumers, many times, are cajoled by not only physicians but almost any member of the family planning team. Patients are belittled and berattled, often openly, if they refuse services or even show reluctance. Far more frightening though is when coercive sterilization laws are enacted. Social welfare legislation in this form removes the right of a woman on welfare to have children.

Other areas of health care must be given as high a priority as family planning. I am cognizant of the positive aspects of family planning; but, just how far these positive aspects go in the face of deficient comprehensive health care I cannot answer. In fact, I pose the following questions: Is it wise to attempt to approach a National zero population growth in a group where infant deaths are twice the National average? 2) Might not a higher birth rate in such a group, at some point, be a protective mechanism where the life expectancy is significantly less than the National average. Too often family planning is given a disproportionately higher priority than are other essential areas of health care. In my own State, for example, I am suspect when I see extensive family planning services being provided in a locale where if the same patients become pregnant they cannot even receive obstetrical care there but must travel more than one hundred miles across the State passing numerous adequate hospitals.

Most family planning programs are predicated on the erroneous

assumption of a common national life style. Because of the difference in life styles, it is essential to include blacks at meaningful policy making and administrative levels when providing family planning services for black people. To those that are deprived socially and economically the procreative processes often become the only fulfilling life experience available. To curtail or remove this avenue of expression is often tantamount to taking away the only need for existence itself. Therefore, it is fundamental for the providers of family planning services to have this insight. Every human being has the need to feel creative. It is a drive not easily relinquished. The challenge is to continue to make available other avenues of expression for this creative need.

The problems of family planning are magnified when the setting is rural. Sociologists, when describing barriers to health care delivery, often use the terms "attitudinal" and "organizational." Generally attitudinal barriers prevent the individual from becoming motivated to seek the available service. Whereas organizational barriers keep the motivated individual from utilizing the services that are desired.

Rurality is characterized by a relatively unsophisticated folk culture and at times is actually primitive. There is a distinctive form of social organization which is seen in the institutions of family, religion, government, and education and reflects the deprivation caused by cultural, geographic and economic isolation. Because of this isolation and resulting unsophistication the rural psychology is strongly oriented to fatalism which in great part explains their strong resistance to any alteration in reproduction and the reproductive process. This factor creates a tremendous barrier to family planning motivation in this segment of our population. Any highly successful family planning program will remain unattainable so long as such strong attitudinal barriers exist.

Organizational barriers confronting the motivated rural patient seeking family planning services are numerous and weighty. However, unlike attitudinal barriers, these are less intangible and, consequently, more readily identifiable. Poverty constitutes an awesome barrier and is inseparable from all other barriers. Poverty is in no way unique to the rural setting but beyond all doubt, the depth of this deprivation here is equaled in no other quarter of our society. For Macon County, the median family income is only \$2,428.00 per year and 56.9% of the families earn less than \$3,000.00 annually.

Problems of transportation and communication are quite unique in the rural setting. The inaccessibility of health care centers characterizes rurality because of the distances involved and the absence of public transportation. Such problems constitute real barriers to health care delivery. Because of the existing poverty, the number of privately owned vehicles is quite low. Many patients hire private transportation but the cost is often prohibitive. Transportation is also hampered by an underdeveloped road and highway system in many rural areas.

The rural problems of mass communication parallel those of transportation. The literacy rate among rural dwellers is lower, consequently, the effectiveness of newspapers is much reduced. Although the distribution of radios in rural areas is relatively high, there are few television sets and telephone service is deficient. Also, in spite of the advances in rural electrification, there are still many homes that have never known this service. It, thus, becomes apparent that the mere dissemination of information is a very difficult task.

Adequate health manpower, distribution and utilization create still other unique barriers to rural health care delivery. The overall shortage of medical and paramedical personnel is well known but here again this

problem is amplified in a rural setting. In Alabama, there are 2,627 active physicians. The State Population is 3,444,165 with a ratio of one physician per 1,311 people. The National ratio is one physician per 821 people. When the distribution of Alabama's physicians is examined it is noted that the five most populous counties have 1,718 physicians and 1,432,858 people or a ratio of one physician per 833 people which compares quite favorably with the National average; however, the five counties with the least population and, of course, the most rural have but 17 physicians and 56,768 people or a ratio of just one physician per 3,339 people. The problem then of maldistribution becomes quite evident and obviously impedes greatly health care delivery among the unurbanized.

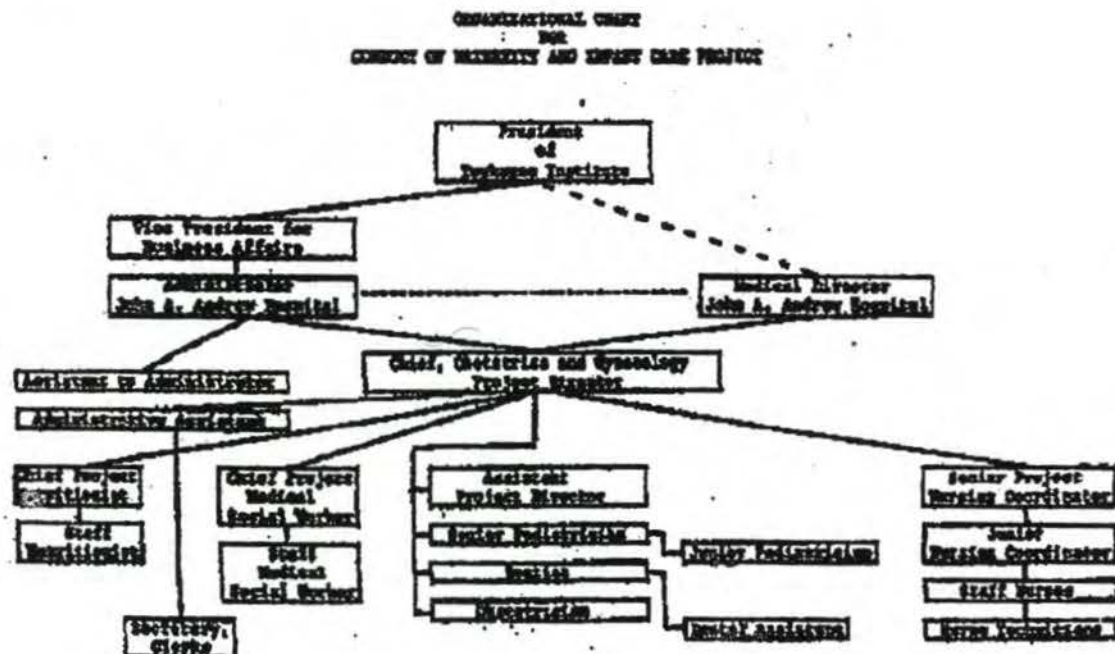
Although the setting is rural, John A. Andrew Memorial Hospital is an ultramodern 180 bed facility located on the campus of Tuskegee Institute. It is in the outpatient section of the hospital that our maternity and infant care team is based.

There are 35 positions funded in our maternity and infant care project--the vehicle through which family planning services are rendered to the three county area. (Figure 1) The organizational structure of this team is shown in figure 2. Family planning clinics are conducted independently and in conjunction with antenatal clinics. The clinic schedule is shown in figure 3 and averages 15 clinic sessions per month. All services provided outside of Macon County are performed in county health facilities with state employed public health nurses.

Prior to the completion of our new outpatient building our health care team conducted four satellite clinics away from Tuskegee but in Macon County. Although the physical condition of these satellite clinics is woefully inadequate, the State continues to use these places to

PERSONNEL FOR THE PROJECT #956

- | | |
|---------------------------------|------------------------------|
| 1. Project Director | 19. Dental Assistant |
| 2. Asst. Project Director | 20. Obstetrician |
| 3. Chief Pediatrician | 21. Staff Nurse |
| 4. Junior Pediatrician | 22. " " |
| 5. Chief Medical Social Worker | 23. " " |
| 6. Staff Social Worker | 24. " " |
| 7. Chief Project Nutritionist | 25. " " |
| 8. Staff Project Nutritionist | 26. " " |
| 9. Project Administrative Asst. | 27. " " |
| 10. Senior Nursing Coordinator | 28. " " |
| 11. Junior Nursing Coordinator | 29. Licensed Practical Nurse |
| 12. Junior Nursing Coordinator | 30. Licensed Practical Nurse |
| 13. Clerk, Medical Records | 31. Nursing Assistant |
| 14. Clerk, Business Office | 32. Nursing Assistant |
| 15. Clerk | 33. Nursing Assistant |
| 16. Clerk | 34. Nursing Assistant |
| 17. Secretary | 35. Nursing Assistant |
| 18. Dentist | |



conduct services. The physical setting is modern at our hospital as is the new health department building in Bullock County. The physical facility at the Hartsboro clinic in Russell County is inadequate and must be improved.

Since abandoning the satellite clinics in Macon County a bus route has been established where patients are picked up and returned to the same geographic location of the previous satellite clinics. This service is funded in our grant as patient transportation. Our maternity and infant care personnel physically go into Bullock and Russell Counties.

During the previous calendar year, there were 2,400 family planning visits of which 960 were new patients. In addition, through our in-patient services we performed 193 tubal sterilization procedures. These figures, though low and in need of improving, are respectable when the low population density being dealt with is realized. Moreover, this allows us to place higher emphasis on quality and comprehensive care.

In conclusion, it can be seen that most of the problems in the delivery of family planning services to minorities and to the rural have a common genesis--that of economic, social and cultural isolation. As a black physician, I well see the value of family planning, but also as a black physician I know I must be perceptive enough to distinguish family planning from population control. The latter is easily disguised as the former. They are not the same; there is a difference. Some of these differences have been pointed out here today. At Tuskegee, we have mounted an attack on health problems in general of which family planning is a part.

FAMILY PLANNING CLINIC SCHEDULE

8 A. M. to 12 Noon

- 1st & 4th Friday..... Family Planning Clinic (exclusively)
Tuskegee (Macon County)**
- Every Monday & Tuesday.... Family Planning in conjunction with
Prenatal Clinic
Tuskegee (Macon County)**
- 1st & 3rd Thursday..... Family Planning in conjunction with
Prenatal Clinic
Harteboro (Russell County)**
- 2nd & 4th Thursday..... Family Planning in conjunction with
Prenatal Clinic
Union Springs (Bullock County)**

International Efforts in Family Planning Training

HENRY W. FOSTER, MD, and SAMUEL S.O. NWOSU, ChB, MB,†
Nashville, Tenn

Abstract: It is now well recognized that worldwide population stabilization must be achieved because of the economic and ecologic dangers. Based on this premise, but being alert to the unique aspects of family planning as it relates to blacks, health professionals from several black African nations, two predominantly black institutions, and the United States Agency for International Development have joined in a common training effort to prepare personnel to meet this challenge. This effort involves education of both the provider and the consumer of health care. Fortunately, the environment that is required for training also guarantees first-rate, comprehensive health care for patients. Parenthetically, our future educational efforts are properly dependent upon the availability of adequate clinical outlets such as those of the John Andrew Memorial Hospital in Tuskegee, Ala. The performance of these health professionals has been outstanding, and we are certain that their skill will be further demonstrated when a subsequent site visit to Kenya is conducted. Perhaps with the exception of the United States and Canada, the importance of the extended role of the professional nurse is well recognized and appreciated. The level of maternal and child health in this country falls below that of many countries which make full use of the nurse practitioner. The implications for the United States should be clear.

MANKIND recently has had a rude awakening. Finally and fortunately we have recognized that this earth's natural resources are not inexhaustible. Moreover, this ever-shrinking, more complex, interdependent world continues to face new problems which are compounded as its population expands. It is estimated that in the year 1650 AD the world population was about 500 million people. It required two centuries for it to double, becoming 1.1 billion in 1850. By 1930, a mere 30 years later, it had risen to 2 billion. By 1975 the world's population will again have doubled, increasing to 4 billion inhabitants.^{1,2} Eight billion world inhabitants are predicted for the year 2010. Realizing the fundamental facts of survival, international efforts and energies are now being channeled to preclude a potentially chaotic situation. However, these factors notwithstanding, there are unique

aspects to this problem as it relates to black people both in America and in Africa.

Public opinion on the population explosion in sub-Saharan Africa varies from those who believe that Africa is underpopulated to those who claim that social and economic progress is impossible without first controlling excessive population growth. African scholars, politicians, and government officials (especially those who are not involved with economic development and planning) tend to be optimistic, while the more advanced industrialized nations of the old and new world (the "financial aid" givers) take a pessimistic view. The African's apparent resistance to population control mystified his friends of the old world. Several explanations have been offered, including cultural values, national welfare considerations, family and clan welfare, marriage adjustments, economic conditions, personality needs, and distrust of the motives of the rich nations which suddenly open their coffers for this particular cause. Population control programs are referred to

From the Meharry Medical College, Nashville, Tenn.
Presented at the Seventy-eighth Annual Convention of The National Medical Association, Inc., New York, NY.
Reprint requests to 1006 Park Ave N, Nashville, Tenn 37208 (Dr. Foster).

among Africans as an "imperialist plot" and among those in the black American community as "genocide." The fact that some countries within the continent with small and stagnant populations are not fairsing any better has not escaped their attention, nor have they failed to notice how well Britain and Japan are doing with teeming populations and scarce resources.

Is the reduction of fertility the most urgent medical problem facing black Americans and Africans? These groups are characterized by reduced life expectancy, shamefully high maternal and infant mortality, and limited access to modern medical care. In view of these factors, might not a higher birth rate serve as a necessary protective mechanism?

Being well aware of the positive aspects of family planning, the question thus boils down to its extent and priorities. The following approach to family planning is one with which we believe not many people will quarrel:

(1). Comprehensive health care for all our people.

(2) Massive educational effort: (a) to train personnel to include family planning in the comprehensive health care package they will bring to the people; (b) to educate the public (the patients) to appreciate good health and how to maintain it. The assumption is that the patient (the woman, in this instance), emancipated from her own ignorance, is likely to take over the control of her own fertility.

Family planning must always be voluntary and never be a part of governmental policy at any level. An example of the comprehensive health care, or the service portion of such an approach, is demonstrated at the John Andrew Memorial Hospital, Tuskegee Institute, Alabama, and is well documented in the publication of *Family Planning in the South*, conducted at Emory University in Atlanta, Ga., April 1972.² Meharry Medical College, through its Maternal Child Health/Family Planning (MCH/FP) Center (Tuskegee Institute M & I Project #556), and health professionals from Africa are pushing to expand the second part of the approach, *eg*, massive educational efforts for both the provider and the consumer.

Meharry Medical College has produced nearly 50% of the black doctors in the United States. The Maternal Child Health/Family

Planning Center of Meharry Medical College was funded in 1971 by the United States Agency for International Development (USAID) for training and research in MCH/FP. The center has a multidisciplinary staff which is complimented and supported by the staffs of Meharry Medical College, Vanderbilt University, Peabody College, Fisk University, and Scenic College in Nashville. The fact that Meharry graduates are predominantly black and practice almost exclusively in black neighborhoods and in the inner city eminently qualifies the college to handle this type of training and research relating to Africans.

Kenya was the first sub-Saharan African country to adopt an official population policy. It had a population of 10.9 million in the 1969 census and total area of over 500,000 sq km, or twice the size of the British Isles. The average annual per capita income is \$126. The birth rate is 51 per 1,000 of population; infant mortality is 113 per 1,000 live births, and population growth is 8.5% per year. The average life expectancy is 48 years and 47% of the population is 15 years old or under. In order to help this country carry out its population policy, six nurses and a physician were sent to the MCH/FP Center at Meharry under the auspices of USAID to be trained for teaching family planning in Kenya.

Counselling was offered at the MCH/FP Center. Instruction emphasized reproductive anatomy, physiology, and endocrinology as much as the social, cultural, and demographic aspects of human fertility. It included health education, use of communications media, and health administration (Table 1).

This part of the training lasted nine weeks—about three weeks longer than projected because of two seminars at Meharry. One was a two-week seminar for African nurse-midwives from about 17 different African countries, and the other was a seminar on health administration and planning.

Realizing the importance of adding family planning to existing health services also focused attention on the need to train more personnel and use them effectively. The MCH/FP Center at Meharry is one of a number of worldwide projects which offers university training for social workers, nurse-midwives, demographers, economists, communicators,

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SOUTHERN

INTERNATIONAL EFFORTS IN FAMILY PLANNING TRAINING—Past and Present

TABLE 1
COURSEWORK OUTLINE

Technical Background Knowledge Essential for Family Planning		Complementary Subjects Preparatory to Immediate Leadership		
Health Education		Health Administration	Demography	Economics and Social/Health Aspects of Family Planning
Laboratory, physiology, and microbiology of human reproduction	Parent motivation and recruitment	Principles	Vital statistics	Economic and sociological aspects of family planning
Birth control methods: anatomy and physiology; physiological and postcoital	Human relations	Cooperative studies of organization and delivery of MCH/FP services	Introduction to population studies	
Fertility and sterility	Teenage and marriage counseling	Resource personnel affecting the African health administrator and planner	Special cultural determinants of fertility	Relationships between family planning and sociodemographic indicators of development
Contraceptive technology	Use of media: radio, television, group meetings	Health planning and administration in Africa	Family decision-making processes	Sexual, moral, and problems of family planning in the African setting
Training methods and procedures: clinic visits, group, and individual; interviewing and counseling techniques	Media workshops	Importance of research and reports in health care administration	Evaluation	

home economists, nutritionists, family planning physicians, and administrators. The levels of training vary from seminars and short three- to four-month special programs, to masters and doctoral programs. Other American universities involved are New York (Down State), Johns Hopkins, North Carolina, Michigan, Hawaii and Harvard. Four nonuniversity organizations also involved in training are Family Health Inc., New Orleans, The Margaret Sanger Research Bureau, The Population Council, and Planned Parenthood of Metropolitan Washington. International agencies such as the United Nations Funds for Population Activities, WHO, and UNESCO have also contributed to the training effort in developing countries.

The United States has played a leading role in establishing training programs in the Philippines, Indonesia, Korea, Uganda, Kenya, and Nepal. Training for foreign nationals in the United States is a short-term expedient. The long-term objective is to develop the training capacity of underdeveloped countries while maintaining the existing links with American institutions.

Clinical Setting

There are many common problems facing the inhabitants of rural southeastern Alabama and the people of the emerging nations of

Africa. Both geographically and demographically, Tuskegee, Ala., is well suited to being a clinical training site for health planners from Africa. Tuskegee Family Planning Services are offered in a three-county, 1,900 square mile area of southeast Alabama. Macon, Bullock, and Russell counties have a combined population of 82,055 inhabitants.

Although the geographic setting is rural, John Andrew Memorial Hospital itself is a \$5 million, ultramodern, 180-bed hospital. It is in this facility where Africans receive most of their clinical experience.

There are 35 positions funded in our M & I Project #555 by a title V HEW grant. A comprehensive team of social workers, nutritionists, and public health nurses is headed by three board-certified obstetrician-gynecologists. Family planning clinics are conducted independently and in conjunction with antenatal clinics on an average of 15 per month. Outside Macon county all services are provided in the Bullock and Russell county health facilities in cooperation with state public health nurses.

African trainees receive clinic experience with both outpatient and inpatient services. In the clinic setting, they participate in family planning counseling and in patient interviews with public health nurses, nutritionists, and social workers. They perform physical ex-

TABLE 2
CLINICAL SKILLS

Skills Related to Contraceptive Counseling	Skills for Essential Reproductive Clinical Services
Interviewing techniques for taking medical and social histories	General clinical screening—Pap smear
General physical assessment	Breast cancer screening—breast examination
Private examination:	Auscultation—heart, lungs, abdomen
Menstrual examination for assessment of	Hemoglobinopathy—stickle cell test
uterine size and position	Diabetes mellitus—uric acid/blood glucose
infection of cervix	Hypertension—blood pressure reading
bleeding of the uterus	Vaginal infections—wet smear microscopy for
Cervical contraceptive methods	Trichomonas and Mycoplasma
Prescribing oral contraceptives and counseling for	Vaginal discharge—
use and associated complications	Cervical, vaginal, and rectal smears for culture
Insertion and removal of IUD and counseling for	Syphilis VDRL
use and associated complications	Pregnancy—pregnancy tests
Immediate postpartum contraceptive counseling	Obstetric and gynecologic—diet instructions
Counseling for male and female sterilization	Problems pregnancy—counseling and intensive care with
Evaluation of follow-up clinics	or without hospitalization
	Social or welfare problems—counseling and home visiting

aminations and pelvic examinations, and take gonococcal and Papanicolaou smears. Also, they learn to dispense oral contraceptives, to insert intrauterine devices, and to make home visits.

Inpatient activities include ward rounds, intrapartum and postpartum patient management, and conduction of normal deliveries and episiotomy repairs. These trainees also serve as surgical assistants in the operating rooms during surgical sterilization procedures and cesarean sections (Table 2).

The clinical performance of the health professionals trained at John Andrew Memorial Hospital thus far must be rated as superior. Many of the digital skills were acquired with remarkable speed. We are certain that this is due to the training and experience which they received in their own country, and to the excellent scholarly background given by the Meharry Maternal Child Health Care/Family Planning Center.

In Kenya, the ratio of doctors to population is 1 to 11,000, but this figure belies the uneven distribution which in rural areas may

be as low as 1 to 250,000. Although these distressing national statistics for Kenyans exceed any we encounter for blacks in this country, there are nonetheless innumerable instances when the individual suffering they represent is just as great.

The medical school in Nairobi, Kenya, is hoping to produce about 90 doctors annually soon, but it will be quite a long time before the imbalance and the shortage can be remedied. However, the extended role of the paraprofessionals in Kenya has been long established. Hence, when the Health Ministry was searching for professionals to assign for the special training program, six nurse-midwives and one physician were chosen. Judging from this training experience and performance, it was a wise decision.

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SOUTHERN

Staff conference

MEHARRY MEDICAL COLLEGE ENDOMETRIAL STROMAL SARCOMA

DR. WILBUR M. BYRD: This 67-year-old nulliparous black female was admitted to the Gynecology service from the Emergency Room of the George W. Hubbard Hospital complaining of postmenopausal bleeding and the passage of a tissue-like mass through the vagina several hours prior to admission. The mass was described as flesh-like and measured 3 x 3 centimeters. Several days prior to admission she had noted postmenopausal vaginal bleeding for the first time and the bleeding had progressively increased until severe hemorrhage occurred on the night of admission. Menopause had occurred 15 years previously and was uncomplicated. She had had no radiation sterilization.

This patient had had the usual childhood diseases. Menarche occurred at the age of 12 or 13 and was normal. The patient had never conceived although she had used no contraceptives. She denied having any surgery and had no history of previous hospitalizations except for that required for a fracture of her arm several years earlier. There was no history of allergy, tuberculosis or diabetes. Her family history and systems review were non-contributory.

Physical Examination: On admission her temperature was 99.6 F, pulse 100, respirations 18 and blood pressure 160/100. She was a well developed, well nourished black female who appeared pale and cachectic. She was oriented as to time and was cooperative. Examination of the head, nose and throat was normal. Her eyes showed bilateral arcus senilis and the fundi grade I Keith and Wagner retinopathy. The pupils reacted to light and accommodation. Examination of the lungs revealed no rales, rhonchi or wheezes. There was a normal sinus rhythm and no cardiomegaly. The PMI was in the fifth intercostal space at the mid-clavicular line. There were no palpable masses in the breasts or axillae. Abdominal examination revealed an ill-defined mass palpable in both lower quadrants. No other abnormal palpable organs or masses were felt. The skin of the labia majora and minora was thin and atrophic, and there was graying pubic hair with a male pattern. The anterior vaginal wall was relaxed to the level of the introitus. The vaginal mucosa showed thinning, reflecting estrogen deprivation. Traces of blood appeared in the vaginal vault. There were no gross lesions of the cervix which was small and normally situated, but blood was trickling from the external cervical os. The uterus was anteverted, soft and 12 to 14 weeks gestational size. It was semi-fixed, and the adnexa were normal to palpation. Rectal-vaginal examination confirmed the above findings.

Laboratory Findings: Hemoglobin was 11.6 gm/100 ml, hematocrit 35%, white blood count 14,192/cu mm and red blood count was 3.8 million/cu mm. The differential showed 83% neutrophils, 15% lymphocytes

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and 1% monocyte. Serum BUN was 34 mg/100 ml, serum chloride was 96 mEq/liter and serum sodium 140 mEq/liter. Blood and vaginal cultures showed no growth. The pathological report of the mass expelled through the vagina revealed that it was a pale, blunted cylindrical mass, composed of necrotic tissue with some endometrial elements.

Admission impressions: (1) postmenopausal vaginal bleeding; (2) intrauterine mass expelled; (3) anemia secondary to (1) and (2); (4) hypertensive cardiovascular disease; (5) uterine enlargement, etiology to be determined.

Hospital Course: After the patient's blood was typed and cross-matched for transfusion, and her hypertension was evaluated and treated, she was then taken to the operating room where differential dilatation and curettage and punch cervical biopsy were performed.

MEDICAL STUDENT: I have a question about the nulliparous history. Was this voluntary? Was she married before and had no children, or was she an old maid?

DR. HENRY W. FOSTER: She was married, and allow me to make this comment. In our population approximately 10% of married couples are infertile. However, three of these ten infertile couples are voluntarily infertile, whereas the remainder are thought to be involuntarily infertile.

MEDICAL STUDENT: I would like to know something about this mass: the size, the location, etc.?

DR. BYRD: I did not enter this information into the protocol because I was unable to answer most of these questions. I felt that there was a mass in the pelvis. It was not dramatic enough or far enough out of the pelvis for me to make a more definite determination.

DR. FOSTER: May I make a comment at this point. I have been faced with similar situations. I think that a better choice of words would be an "ill-defined mass." Sometimes you do get a fullness, but you really cannot say, for example, if it is 8 or 10 centimeters, etc. You have an impression that the pelvis is occupied by some ill-defined or non-specific fullness rather than a distinct mass. A mass, in a sense, connotes positive and definable confines while a fullness is a bit more indefinite and nebulous.

DR. BYRD: I think it might be helpful if I gave my pelvic examination findings again. On examination we concluded that the mass was in the uterus, was soft and was 12 to 14 weeks gestational size. This was about all we could determine. The tubes and ovaries were not palpable and we couldn't determine whether or

not the mass, which was movable, extended to the lateral pelvic wall.

DR. FOSTER: Dr. Byrd, were these findings confirmed on both rectal and vaginal examination, or were they by vaginal examination alone?

DR. BYRD: This was by rectal-vaginal examination.

DR. FOSTER: Are there any other questions regarding physical findings?

MEDICAL STUDENT: What is the explanation of the 14,192 white blood count?

DR. BYRD: This is a good point for speculation. Due to the fact she expelled a necrotic tissue mass from the cervix in the Emergency Room, we presume she developed some degree of intrauterine infection. At this point I think that this is about all we are free to say.

DR. CHARLES E. McGRUDER: In a case such as this, I think we should speculate about the various causes of vaginal bleeding in a postmenopausal woman. For example, women can bleed from atrophic vaginitis especially following intercourse. They may also bleed from taking estrogens but we know she did not take hormone therapy.

MEDICAL STUDENT: Would you please tell us again what was done in the hospital?

DR. FOSTER: She had a fractional dilatation and curettage. As you heard from the pathological report, the tissue was composed of necrotic material with some endometrial glandular elements. In view of the findings of a pelvic mass, postmenopausal bleeding, and the pathological report of glandular elements we must assume that the cause of her admission was related to the endometrium. Our next step must be to diagnose, confirm or rule out the possible disorders involving the endometrium which could be responsible for her symptomatology.

DR. HAROLD O. BERNARD: May I say one word here as to responsibility. I don't think we have taken everything into consideration. In view of the fact that she passed a mass, could this lady have had a degenerate myoma or an endometrial polyp that passed vaginally?

DR. FOSTER: I agree that these should be considered. She could have had a lithopedion. These sometimes erode and pass through the vagina. However, I would say from the histological report presented there is no support for these possibilities.

DR. McGRUDER: Who among the medical students wants to speculate about the diagnosis of material obtained on dilatation and curettage?

MEDICAL STUDENT: Quite possibly the specimen could have shown endometrial adenocarcinoma.

DR. McGRUDER: That is a good choice.

DR. FOSTER: Is there anyone here who would disagree with this diagnosis if we had not had a pathological report? It certainly would have been the most likely diagnosis. Nobody could argue with this, but it so happens that this is not what she had. If it had been the diagnosis, the case would not have been as interesting as it is now. What else could this lady have had?

DR. McGRUDER: I am not sure, but there are many other diagnoses which might be considered.

DR. BYRD: Okay, now I will add a few little pertinent pearls into the protocol. I think a very significant positive statement was the mention of possible radiation induced menopause. This should have given someone a hint.

DR. FOSTER: This is important information since unfortunately many years ago women received x-ray treatment for abnormal bleeding problems. This should serve as a key statement. Also what about trophoblastic disease? In this age group, of course, it would be embryonic origin as is seen in men.

DR. BYRD: One other bit of pertinent information is the character of the lesion. These lesions characteristically simulate the pregnant uterus. Her uterus was not only enlarged but it was soft. This uterus in a lady 30 years would be considered a pregnant uterus and most physicians would refuse to place an intrauterine device in such a uterus.

DR. McGRUDER: Something that wasn't mentioned in the protocol is that this lady had no chest x-ray. From what has been said thus far, my diagnosis would be uterine sarcoma.

DR. FOSTER: Dr. McGruder has the correct diagnosis. However, this woman had a rare form of uterine sarcoma. She had endometrial stromal sarcoma.

DR. McGRUDER: In all my practice I have only seen one previous case of endometrial sarcoma.

DR. FOSTER: It is good to remember there are four basic sites of origin of sarcoma in the uterus: (1) in the myometrium, (2) in the stroma of the endometrium as in this case, (3) in myomas, and (4) in any of the blood vessels of the uterus.

DR. PHILLIP A. NICHOLAS: When the

continued on page 668

TMA X-ray of the month

Loculated Pleural Effusion

(Answer on page 672.)

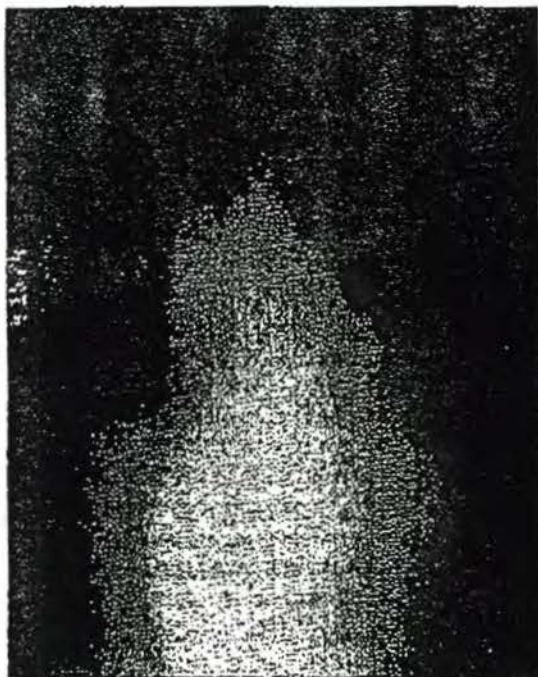


FIG. 1

Clinical Presentation

60-year-old black male with shortness of breath. Please examine the roentgenogram in Figure 1. The opacity in the right mid lung most likely represents:

- 1) Bronchogenic Carcinoma
- 2) Right middle lobe atelectasis
- 3) Bronchial adenoma
- 4) Pseudotumor

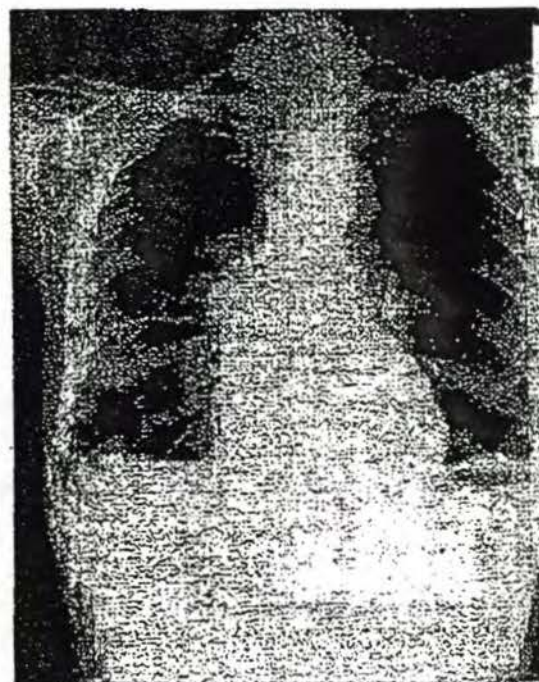


FIG. 2

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* * *

Staff Conference

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disease originates in the walls of blood vessels, the prognosis is poorest.

MEDICAL STUDENT: Do you mean in terms of years?

DR. NICHOLAS: Yes.

DR. BYRD: Within two years nearly all such patients are dead.

MEDICAL STUDENT: What about early diagnosis? Would that have helped this woman?

DR. FOSTER: I don't know. I do not believe this would affect the five year survival. You see, one of the main problems in early diagnosis is that it is difficult to accomplish and also such sarcomas are highly malignant.

MEDICAL STUDENT: Do all uterine carcinomas bleed?

DR. NICHOLAS: No, those in the myometrium do not bleed early.

DR. FOSTER: Now let us hear about treatment.

DR. BYRD: The fact that she does not have distant metastases will influence what we do. She should have a pelvic sweep, and whether or not to use irradiation postoperatively is a matter of philosophy.

DR. NICHOLAS: These tumors are characteristically radioresistant and whatever we do the prognosis is uniformly poor. However, I certainly agree that total abdominal hysterectomy with removal of the adnexa as well as postoperative irradiation should be offered this woman.

THE POOR

Franz J. Ingelfinger
Henry W. Foster
Jay Katz

FRANZ INGELFINGER

To define *the poor*, one might use the purely economic criterion. Or, from what we have heard in this Forum, one might argue that anyone who is a subject of human experimentation is poor -- that is, poor like a guinea pig. But our definition is intermediate. We shall use *poor* to encompass those populations that are deprived not only for strictly economic reasons, but because of social, cultural, administrative, and political factors.

Each of us will discuss selected major issues pertaining to the use of the poor for experimental purposes. Since the poor have been disproportionately used for experimentation -- and each of us agrees on this point -- specific illustrative cases are not short in supply. Indeed, some of the most notorious cases of human exploitation for research have involved the poor.

My two colleagues are particularly conversant with one of these, the so-called Tuskegee Study on the natural-history of syphilis. Dr. Katz was a member of the Ad Hoc Advisory Panel established by HEW to investigate this study. Dr. Foster was President of the County Medical Society in the area where the study was carried out at the time that news of it broke. I have had no such firsthand experience. However, I am not prepared to take, in the interest of fomenting controversy, the position that the poor are ideal experimental, sacrificial subjects.

Our objectives in this discussion are: to assess if the poor now are, and will continue to be, particularly exposed to use, abuse, or both as subjects of human experimentation; to examine the reasons why the poor may be more likely to be used or abused as experimental subjects; and

to explore means that could be devised to ensure that the assumption of risk by the poor does not exceed that of the rest of the population.

HENRY FOSTER

After I had agreed to participate on this panel, I felt that I could make my most worthwhile contribution, and indeed help create the Forum atmosphere, by raising an issue that had at least three components. First, I wanted to bring an issue that had some reasonable degree of feasibility to it. Second, I wanted to bring an issue that would not be agreed upon by at least one, or maybe both, of my panel colleagues. And third, I wanted to raise an issue that would not likely be otherwise raised. I think I may have been successful in the latter two.

In searching for solutions to the special problems resulting from human experimentation in the poor, their exemption from such participation, in my judgment, warrants strong consideration. In the course of my deliberations, however, it is essential to keep in mind that the concepts put forth here on this issue of such prodigious complexity are directed not to the whole of the biomedical research pool, but only to a small segment. As a physician who is also directly involved in academia, I am left with the feeling of some ambivalence following my recommendation.

In spite of the many shortcomings in the realm of human experimentation, it must be emphasized that this country's biomedical research community has been a world leader in its concern for medical ethics. As recently as 1960, no articles on this subject except in the English language could be found in the world literature. However, in spite of this concern, the thalidomide disaster and subsequent events set into motion a greater public demand for control. This demand in this country is expressed in the popular movement known as consumerism and, specifically, in that movement's concern with the right to know.

In the biomedical research community, it is expressed in the requirement for voluntary informed consent-giving on the part of patients. Given such universal concern, any perverse outcomes in research in humans today would indeed be most inopportune, especially if such research design were characterized by demonstrable disruption of the balance between risks and benefits for the patient. Parenthetically, recent untoward outcomes of this nature are in great part responsible for our being assembled here today.

In this day of heightened consumer awareness, occurrences such as the Tuskegee syphilis experiment, the injection of cancer cells into uninformed geriatric patients, and the deception of Chicano women seeking contraception cannot and will not be allowed to continue in this country. Although such cases are by far the exception, they are nonetheless very likely to be viewed by consumers as the rule. The call to consider a moratorium on the use of the poor in human experimentation thus stems as much from pragmatism as it does from altruism.

Indispensable to ethical biomedical research is the balance of two values: scientific priority of discovery; on the one hand; and humane therapeutic treatment, on the other. This has come to be known as the dilemma of science and therapy. There are those who fear for the scientific priority if there is a shift in this equation from its current status, and to exempt the poor, even temporarily, from human experimentation would create such a threat to research in the minds of some. However, if properly structured, such a moratorium would not be a hindrance; failure on the part of the biomedical sector to take such a step will have far graver consequences for both scientific and public interests and values. This alteration in policy should be intrinsic, and if the biomedical community fails to do so, we can be assured of increased hostility and of public demand for even more external control.

By some estimates it is believed that possibly 80 percent of all human experimentation that has occurred in this country involved the poor. How then can it be plausible to waive the participation of this group? The answer, in part, relates to the makeup of the group normally characterized as the poor. Although implicit in the term *poor*, as stated in my colleague's introductory remarks, it is the social and cultural deprivation that is of primary significance as it relates to this whole question, rather than the lack of economic resources per se. There are many who are classified as poor who do not suffer deep and grinding social and cultural deprivation, and therefore need not be considered for exemption.

How then is it to be determined who is so deprived, and thus subject to exemption from human experimentation? It is my belief that those incapable of clearly providing voluntary informed consent constitute this group. They are the functionally illiterate, the senile, those who do not command the English language, and certainly the mentally incompetent.

Irrespective of the definition one chooses to use, however, it is apparent that the biomedical sector has come to rely heavily and in a disproportionate fashion on the use of the poor for human research. We should be reminded that the poor constitute a relatively small proportion of this nation's total population. Moreover, we should begin to look beyond the poor for human research subjects, with the ultimate expectation that this segment of our population will dwindle.

According to the Bureau of Statistics, there were just over 24 million persons in this country classified as below low-income levels in March of 1973. Even if this number were doubled, there would still remain more than 150 million nonpoor who would be, and in fact have become, more accessible to research usage as the mode of health care financing changes -- an issue with implications of its own.

What should we hope to accomplish during the suggested moratorium? This interim should be used to reexamine those factors that tend to disrupt that balance between science and therapy, and thus restructure those mechanisms necessary to maintain that equilibrium that spawns the most favorable milieu for both humane values and scientific priority.

As with any socially structured system, conflicts develop in the application of values by those who are part of the system, resulting in compliant and deviant behavior. There are social control processes that when operative tend to preclude deviant behavior. These processes take the form of socialization or training, collaboration groups and informal networks, and forms of peer review. There is a great need for the socialization of human values in medical school and beyond, as has been pointed out so well by Renée Fox.

Studies show that the socialization of scientific values is well ahead of that of human values. Characteristics of collaboration groups and informal networks that lend to deviant behavior could possibly be improved if changes were made in the process of academic reward and advancement and in the financing of medical education. Although external pressures for peer review continue to be applied, there remain other refinements and innovations that can, and ought to, originate from within our ranks.

In conclusion, I must reiterate that our profession today is under the greatest scrutiny ever, and it behooves us to consider the measures mentioned in this presentation -- measures that should help to prevent new human catastrophes. Further disasters at this juncture will do far greater harm to the interests of biomedical research than will the exemption of a small, vulnerable segment of our population.

JAY KATZ

Should what I have to say sound like a communication from Mars, I would like to apologize beforehand.

Human experimentation can be hazardous to its subjects. Thus it is not surprising that the economically and socially disadvantaged are conscripted for research to a disproportionately large extent. Throughout history the poor have been indentured for society's most disagreeable tasks, and medical science has only followed time-honored patterns of recruitment.

It may seem regrettable that in the name of progress, science too requires its unwilling subjects. Yet for the benefit of present and future generations, science and society have always tolerated human sacrifices: the Aztec gods demanded them lest the universe fall apart; the fires of the Inquisition consumed them lest faith be diminished; and Apollo, the Physician, permitted them lest disease not be understood and conquered.

It would be an exercise in futility to curb tradition by focusing merely on the poor and insulating them from participation in research. Such a limited objective would only create new groups of cheap bodies who are not identifiable by a means test. If today's or tomorrow's poor are to benefit from our concern over their fate, we must not surround them with special safeguards, but rather look to the underlying causes that make the poor particularly, though not solely, vulnerable to exploitation in research.

Rupture of the Pregnant Uterus

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and

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RUPTURE of the gravid uterus is one of the most catastrophic events in medical practice. There is a large volume of current literature concerned with signs and symptoms, management, as well as theories of the mechanisms involved. We have correlated the experiences of the John Andrew Memorial Hospital over an 11½ year period as they relate to uterine rupture when compared to current world literature. We restricted our study to pregnancies of 20 weeks gestation or more and only complete ruptures were included. Uterine scar dehiscences, window ruptures, and minor incomplete ruptures were not included.

INCIDENCE

Rupture of the gravid uterus is thought to occur in approximately 1 per 1,500 deliveries in this country accounting for 5% of maternal deaths.¹ The highest incidence reported in the current literature is 1 per 93 deliveries as reported by Rendle-Short in Uganda.² At the John Andrew Memorial Hospital, which serves a rural and predominantly black population, there were 14 uterine ruptures among 16,264 deliveries from January 1, 1962 to June 30, 1973, an incidence of 1 per 1,162.

Yussman, who reported 28 ruptures in 34,435 deliveries, an incidence of 1 per 1,230 deliveries at the Louisville General Hospital, noted that rupture of the gravid uterus increased.³ However, Beachman, who reported 101 ruptures in 197,117 deliveries, an incidence of 1 per 1,952 deliveries at the New Orleans Charity Hospital, relates there has been a decreased incidence.⁴

There were nine ruptures in 7,240 deliveries during the time period from 1962-1967, an incidence of 1 per 804 deliveries; whereas, from 1968-1973 there were five ruptures in 9,024 deliveries an incidence of 1 per 1,805. Our figures tend to agree with the findings of Beachman. Incidence ap-

pears to be related to the classification of ruptures, socio-economic factors and availability of obstetrical care.

METHOD AND MATERIAL

All patients were black, ranging in age from 16 to 42 years, the mean age was 29.5 years. They were para 0 through para 11. The mean parity was 5.6. Uterine ruptures were classified as spontaneous rupture of the intact uterus, traumatic rupture of the intact uterus, and rupture of the uterine scar.

Attention was focused on concurrent diseases, uterine and placental abnormalities, blood loss and replacement, therapeutic management, fetal and maternal outcome.

SPONTANEOUS RUPTURE OF THE INTACT UTERUS

Spontaneous rupture of the intact uterus occurred in nine cases, representing 64.3% of our sample. All patients were in active labor. Three of these uterine ruptures were noted in the postpartum period. Seven involved the lower segment and two involved the corpus. One of the upper segment ruptures was noted to pass through the serosa and muscularis but did not involve the endometrium. This patient experienced a tearing "sensation," continued in labor and delivered a viable infant. This type of so called "external rupture" of the uterus was reported by Borenstein and Katz in 1972.⁵ The big danger here is that manual exploration of the uterine cavity will reveal an intact uterus. Age range in the group ranged from 21-39 years with a mean of 29.8 years. Parity ranged from para 3 to 16, with a mean para of 6.8.

TRAUMATIC RUPTURE OF THE INTACT UTERUS

Rupture through the lower cervical cesarean section scar was noted in three patients. No ruptures of the classical scar were noted in this group. One

rupture occurred in a 29 year old para 9 at 20 weeks gestation. The patient had had one previous cesarean section for placenta previa, there was no evidence of active labor at the time of rupture. The second patient was 42 years old, para 11 with HCVD at 36 weeks in active labor. The third patient was a 36 year old para 8 who had had one previous cesarean section for abruptio placenta. She was at term in active labor. The mean age was 35.6 years and the mean parity 6.3.

TREATMENT

Blood transfusion was instituted in all 14 patients. Three patients (22%) required less than 1000 cc of blood whereas 11 patients (78%) required 1000 cc or more blood. Eight patients (57%) experienced shock secondary to blood loss. Hysterectomy was performed on all 14 cases. Eight patients received total hysterectomy and six received supracervical hysterectomy. The condition of the patient often dictated the approach taken. The average operative time for a supracervical hysterectomy was 1.5 hours, average operative time for total abdominal hysterectomy was 2.4 hours. A right salpingo-oophorectomy was performed in one case and bilateral salpingo-oophorectomy in one case. Two cases required bladder repairs and one case required a neocystotomy and bilateral ureteral catheterization. There were two cases of renal shutdown; one case was successfully treated using the artificial kidney.

MORTALITY

There was one maternal death in our series which represented 7% of the uterine ruptures. There were nine fetal deaths representing 64.3% of the uterine ruptures. Menon reported a 10.5% maternal death rate with an 80-100 fetal mortality.⁶ Delfs and Eastman reported a 22.6% maternal death rate and a 41.5% fetal death rate. Other authors have reported a wide range of mortality figures⁷ (Table 1).

DISCUSSION

Although, our overall incidence of uterine rupture was 1 per 1,162, its occurrence decreased to 1 per 1,805 over the past 4½ years. This is explained in part by a liberally funded Federal Maternal and Infant Care Program which has greatly increased the availability and quality of obstetrical

TABLE 1.—MORTALITY FROM UTERINE RUPTURE

Author	Maternal Mortality (%)	Fetal Mortality (%)
Menon ⁶	10.5	80-100
Rendle-Short ²	36.3	82
Delfoe, Eastman ⁷	22.6	41.5
Yussman, Haynes ³	0	14.2
Hills, Foster	7	64.3

care. This program, which began in 1970, has had a tremendous impact on this patient population.

Our study revealed that youth and low parity do not confer absolute protection from this complication. However, multiparity does seem to be a predisposing factor, 10 of our patients (71.5%) were gravida 4 or more which is comparable to Margalius and Crapanzano who reported 41 ruptures in which 70% of the patients were gravida 4 or more.⁸

Rupture of the uterus associated with pitocin infusion occurred twice. Both individuals were young and of low parity. This is explained in part by a general policy of refraining from the use of pitocin in elderly gravidas and para 5 or more. Awais and Lebherz reported four instances of uterine rupture in 199 grand multiparas, an incidence of two per 100.⁹ This was with full precautions using a carefully measured oxytocic pump infusion. Therefore, one must continue to use full caution with young women of low parity and the pitocin stimulation of the grand multipara is extremely hazardous. The increased use of conduction anesthesia demands pitocin infusion must be carefully monitored.

Ritchie reported 132 women who had 233 pregnancies after rupture of the uterus in Nigeria.¹⁰ There was a 12.8% incidence of repeated rupture with two maternal deaths. There were, of course, no repeat ruptures in our series as all of our patients received hysterectomy. The choice of primary repair, or hysterectomy will depend on the character of the tear, condition of the patient and philosophy of the operator. There appears to be marked variability in the circumstances surrounding each uterine rupture. Each case must be individualized.

Prevention where applicable is most desirable and may possibly be exercised when considering candidates for pitocin, earlier use of cesarean section in multiparas with poorly progressing breech

presentation, and routine exploration of the postpartum uterus. The liberal use of blood, plasma expanders, fibrinogen, antibiotics and prompt operative intervention are necessary to save life and improve maternal outcome.

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Gestational Variation of Fatty Acid Composition of Human Amniotic Fluid Lipids

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The amount of total lipids of the amniotic fluid of normal human subjects increases progressively with gestational age and is found to be maximum in labor at term. The lecithin/sphingomyelin ratio, which invariably increases with gestational age, is 2:1 or greater beyond 34 weeks of pregnancy and becomes maximum at term labor. No definite correlation exists between the palmitic acid content of total lipids and gestational age; but the palmitic acid content of the lecithin fraction increases with gestational age and this increase is markedly accelerated near the 34th week of pregnancy. Also it is observed that the arachidonic acid of cholesterol esters increases with gestational age. Therefore, it is suggested that both the palmitic acid level of lecithin and the arachidonic acid level of cholesterol esters might serve as more reliable indices than current methods being employed for the assessment of fetal lung maturity.

ALTHOUGH 12 YEARS have passed since Helmy and Hack¹ first observed that lipids are normal constituents of human amniotic fluids, relatively little is known about the distribution, functions, chemical structures, and quantities of these lipids in amniotic fluid; even less is known about the individual fatty acids they contain.

The following published reports concern amniotic fluid lipids in human: fetal lung contributes to the formation of amniotic fluid²⁻⁴; lecithin is the major constituent of alveolar surfactant⁵ and the amount of this surfactant lipid is deficient in infants dying of hyaline membrane disease^{6,7}; the lipid contains relatively more phospholipids, free fatty acids, hydrocarbons, and cholesterol esters but smaller amounts of various glycerides⁸; total lipids, total phospholipids,

and lecithin levels are decreased in several abnormal pregnancies (prematurity, respiratory distress syndrome, hyaline membrane disease, anencephaly with polyhydramnios and diabetes mellitus)⁹; free cholesterol and unesterified fatty acids originate from placental transfer and various esterified fatty acids arise in the fetus¹⁰; the hydrocarbons and partly free cholesterol arise from vernix caseosa, and the amounts and the percentage composition of the various lipid classes do not differ with increase in gestational age⁸; the ratio of the quantity of lecithin to the quantity of sphingomyelin in the phospholipids extracted from the amniotic fluids serve as an index of the fetal lung maturity¹¹; the fatty acid composition differs between individual lipid classes and palmitic and palmitoleic acids are the major fatty acids at labor¹²; and palmitic acid serves as an index of fetal lung maturity.¹³

The observations contained in some of these studies are conflicting in nature and deserve special mention. For example, Pomerance and co-workers¹⁴ failed to find any significant variation in the content of phospholipids and triglycerides in amniotic fluids between normal and abnormal pregnancies (hemolytic disease of the newborn, toxemia of pregnancy, and diabetes). The lecithin/sphingomyelin ratio in amniotic fluids has been shown by Nakamura and his co-workers¹⁵ to be a reliable indicator of gestational age but not of lung immaturity. Furthermore, Singh and Zuspan¹² have reported that the content of total lipids of amniotic fluid increases with gestational age and reaches its maximum at term.

Thus, most published results refer to the lipid content and composition of the different lipid classes and deal very little with the distribution of individual fatty acids in various lipid classes. Moreover, little is known about whether the fatty acid composition of individual lipid classes varies with increase in gestational age. The present communication deals with the detailed human amniotic fluid lipid analysis, with emphasis on the fatty acid composition of the major lipids like cholesterol

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esters, triglycerides, free fatty acids, lecithin, and sphingomyelin at different stages of gestation.

MATERIALS AND METHODS

Preparation of Samples

Amniotic fluid was collected at Hubbard Hospital from normal patients by transabdominal and vaginal (in labor) amniocentesis at different periods of gestation. Transabdominal specimens were obtained by localizing the placenta with Doppler ultrasound and auscultation. The skin was cleansed with iodine solution. Local anesthesia was employed at the skin puncture site, and after free flow of amniotic fluid was established, 5 to 10 ml were aspirated via a #20 spinal needle and collected in sterile 10-ml glass test tubes. Any specimen which showed contamination with blood or meconium was discarded. Each fluid sample was centrifuged at 3000 rpm for 20 minutes to remove *vernix caseosa*, fetal squamous epithelial cells, and *lanugo*. The supernatant was kept frozen at -20°C until analyzed, which was within 1 week of collection. Patients were divided into four gestational groups: group I = 18 to 22 weeks (3 cases); group II = 27 to 33 weeks (4 cases); group III = 34 to 40 weeks (3 cases); and group IV = labor at term (3 cases).

Analysis of Lipids

Five milliliters of amniotic fluid were shaken in a separatory funnel for 15 minutes with 15 ml of chloroform-methanol (2:1) and centrifuged. The top layer was reextracted for 15 minutes with 10 ml of chloroform and centrifuged. The bottom layer from the second extract was mixed with that from the first one and the combined solution was concentrated. This solution contained almost all of the neutral lipids, glycolipids, and phospholipids occurring in the free state in the amniotic fluid. In order to recover the last traces of lipids which might have been still present as bound forms in the top layer from the second extract, 5 ml of distilled water were added to the top layer and the solution was adjusted to pH 3.0 by the addition of 1 N HCl. The acidified solution was then extracted three times with diethyl ether, and the ether phase was adjusted to neutral pH by repeated washing with distilled water. The washed ether layer contained almost all of the prostaglandins, if any, and trace amounts of neutral and polar lipids which originally exist in the amniotic fluid in the bound form and require acidification for release prior to extraction. This ether solution was mixed with the previous chloroform concentrate and the combined solution was concentrated and there-

after freed from the nonlipid contaminants by the application of Sephadex column chromatography.¹⁸ The eluate from the Sephadex column was evaporated to dryness in a tared container under vacuum at room temperature, and the residue was weighed after further drying in a vacuum desiccator over phosphoric anhydride. The total lipid thus obtained was dissolved in a small known volume of chloroform and an aliquot of this solution was used for separation into polar lipids ($R_f = 0$) and various neutral lipid classes ($R_f > 0$) by thin-layer chromatography (TLC) on silica gel G glass plates, using petroleum ether (bp 60–70 $^{\circ}\text{C}$):diethyl ether:acetic acid (90:10:1, v/v)¹⁹ as the solvent system for development. Various neutral lipids thus separated on the TLC plate were quantitated by the use of a Model 520A Photovolt Densitometer according to the charring-transmission densitometric procedure of Rouser and his co-workers.¹⁷ The weight of total polar lipids was obtained by difference of the weight of total lipids and the weight of total neutral lipids (hydrocarbons, cholesterol esters, ether lipids, triglycerides, free fatty acids, free cholesterol, diglycerides, and monoglycerides).

Another known aliquot of total lipid solution was used for TLC to separate phospholipids from other lipids (neutral lipids, glycolipids, and prostaglandins) using a second solvent system, benzene:dioxane:acetic acid (20:20:1, v/v).¹⁸

All neutral lipids, glycolipids, and prostaglandins (E_1 , E_2 , F_{2a} , F_{2b} , etc) migrated from the origin, while leaving phospholipids at the point of application.

It should be pointed out that this communication does not report any data on the amounts of prostaglandins and glycolipids; this will be dealt with elsewhere. The unresolved phospholipids ($R_f = 0$) from the TLC plate were scraped directly into Teflon-lined screw-cap culture tubes (16 $\times$ 100 mm) and extracted with a small known volume of methanol. An aliquot of this methanol solution was used for the detection of various phospholipids by two-dimensional TLC using the following pair of solvent systems, chloroform:methanol:conc. ammonia (65:35:5, v/v) and chloroform:methanol:acetone:acetic acid:water (5:1:2:1:0.5, v/v).¹⁹ Phosphomolybdate sprays²⁰ were used as the visualizing agent for the various phospholipids. Another aliquot of the phospholipid solution was used for the separation into various phospholipid classes by one-dimensional TLC using a solvent system, chloroform:methanol:acetic acid:water (200:120:25:15, v/v),²¹ and ultimately lecithin (L) and sphingomyelin (S) were quantitated from the TLC plate by the application of charring-transmission densitometry.¹⁷

Analysis of Fatty Acids

Fatty acid analysis was carried out on five lipid fractions: cholesterol esters, triglycerides, free fatty acids, lecithin, and sphingomyelin. These fractions were separated by preparative TLC. Aliquots of total lipid solution were applied as bands on TLC plates and developed with respective solvent systems as described earlier for separation into various neutral lipid classes and phospholipids. Absorbed layers of the resolved lipids on TLC plates were scraped directly into 25-ml round bottom flasks and saponified with 0.5 N methanolic KOH, and the fatty acids released were converted to methyl esters by heating for 5 minutes with 14% boron trifluoride in methanol.²² An aliquot of total lipid solution from each amniotic fluid was also saponified and the fatty acids obtained were methylated. The fatty acid esters were separated and quantitated by the use of a Model 7400 Packard Gas Chromatograph equipped with a flame ionization detector. The GLC analysis was carried out on a 10% diethylene glycol succinate polyester, $\frac{1}{4}$ in 6 ft column, maintained with 20 lb pressure of nitrogen gas. Temperature programming was carried out from 120 to 200 C. The fatty acid methyl ester content of aliquot used for GLC was 0.5 to 1.0 μ g. Assignments for each peak were obtained from a semilogarithmic plot of relative retention time versus chain length and degree of unsaturation of standard mixtures of fatty acid methyl esters. Peak areas were determined by multiplying the height by the width at half height. The relative percent of each fatty acid methyl ester was determined by dividing the area under individual peaks by the total peak area.

RESULTS

A significant increase in total lipids of human amniotic fluid from 22.50 to 43.73 mg/100 ml of fluid was observed during the increase of gestational age from 18–22 weeks to term (labor) (Table I). The total lipid content was not remarkably different in amniotic fluid between 18–22 weeks and 27–33 weeks of pregnancy. However the lipid level was substantially increased when pregnancy extended beyond 33 weeks. There was no significant change, however, in the total lipid content of amniotic fluid between 37–40 weeks of pregnancy and term with labor. Triglycerides, free cholesterol, cholesterol esters, free fatty acids, hydrocarbons, and polar lipids were the major lipids in amniotic fluid at every stage of gestation. Diglycerides, monoglycerides, and ether lipids were the other neutral lipids detected in most of the samples in appreciable amounts at all periods. Lecithin, sphingomyelin, phosphatidyl ethanolamine, and phosphatidyl serine were the major polar lipids at every stage of pregnancy. Other polar lipids, such as phosphatidyl inositol, phosphatidic acid, lyso lecithin, lyso phosphatidyl ethanolamine, cardiolipin, and cerebroside were also present either in trace or in appreciable amounts. Among polar lipids only lecithin and sphingomyelin were quantitated. While an increase was noted in the amounts of free fatty acids, free cholesterol, lecithin, and sphingomyelin during the advance of pregnancy from the second trimester (18–22 weeks) to the third trimester (27–33 weeks), the amounts of other classes of lipids, such as hydrocarbons, cholesterol esters, ether lipids, and to some extent tri-, di- and mono-glycerides decreased

TABLE I. LIPIDS OF HUMAN AMNIOTIC FLUID

Components	Group I (3) ^a 18–22 wk	Group II (4) 27–33 wk	Group III (3) 34–40 wk	Group IV (3) Term labor
Total lipids	22.50 $\pm$ 1.24 ^b	25.53 $\pm$ 1.01	43.43 $\pm$ 2.51	43.73 $\pm$ 3.98
Total neutral lipids	17.49 $\pm$ 1.15	16.53 $\pm$ 1.06	31.72 $\pm$ 2.85	32.61 $\pm$ 2.75
Hydrocarbons	1.62 $\pm$ 0.12	0.73 $\pm$ 0.16	1.59 $\pm$ 0.13	1.85 $\pm$ 0.20
Cholesterol esters	3.08 $\pm$ 0.28	0.80 $\pm$ 0.11	5.16 $\pm$ 0.02	5.09 $\pm$ 0.06
Ether lipids	0.53 $\pm$ 0.08	0.15 $\pm$ 0.02	0.49 $\pm$ 0.03	0.50 $\pm$ 0.03
Triglycerides	4.87 $\pm$ 0.18	4.50 $\pm$ 0.15	6.27 $\pm$ 0.13	9.91 $\pm$ 1.21
Free fatty acids	3.05 $\pm$ 0.06	5.19 $\pm$ 0.08	5.88 $\pm$ 0.09	5.83 $\pm$ 0.11
Free cholesterol	3.24 $\pm$ 0.06	4.30 $\pm$ 0.03	10.85 $\pm$ 0.91	7.55 $\pm$ 0.51
Diglycerides	0.65 $\pm$ 0.08	0.53 $\pm$ 0.07	0.99 $\pm$ 0.05	1.17 $\pm$ 0.07
Monoglycerides	0.45 $\pm$ 0.01	0.33 $\pm$ 0.00	0.49 $\pm$ 0.01	0.71 $\pm$ 0.01
Total polar lipids ^c	5.01 $\pm$ 0.11	9.00 $\pm$ 0.81	11.71 $\pm$ 0.91	11.12 $\pm$ 0.73
Lecithin	1.97 $\pm$ 0.21	4.62 $\pm$ 0.32	7.08 $\pm$ 0.43	8.13 $\pm$ 0.19
Sphingomyelin	1.99 $\pm$ 0.32	3.11 $\pm$ 0.17	2.97 $\pm$ 0.31	1.74 $\pm$ 0.18

^a = Number of cases in parenthesis

^b = Values in milligrams per 100 milliliters amniotic fluid $\pm$ SD

^c = Composed of lecithin, sphingomyelin, phosphatidyl ethanolamine, lyso lecithin, lyso phosphatidyl ethanolamine, cardiolipin, and cerebroside

phosphatidyl serine, phosphatidyl inositol, phosphatidic acid, and prostaglandins (E₁, E₂, F_{2a}, F_{2b})

TABLE 2. FATTY ACID COMPOSITION OF TOTAL LIPIDS IN HUMAN AMNIOTIC FLUID AT DIFFERENT PERIODS OF GESTATION

Fatty acid	Group I (3)* 18-22 wk	Group II (4) 27-33 wk	Group III (3) 34-40 wk	Group IV (3) Term labor
12:0 [†]	1.3 ± 0.2 [‡]	1.1 ± 0.2	0.6 ± 0.01	0.6 ± 0.01
14:0	2.4 ± 0.1	1.1 ± 0.1	1.6 ± 0.02	1.5 ± 0.1
14:1	0.8 ± 0.1	1.1 ± 0.001	0.6 ± 0.01	1.0 ± 0.1
15:0	0.9 ± 0.3	0.6 ± 0.01	0.6 ± 0.02	0.3 ± 0.01
15:1	0.4 ± 0.01	0.6 ± 0.01	0.6 ± 0.02	0.7 ± 0.01
16:0	40.6 ± 3.2	35.7 ± 2.96	27.2 ± 1.3	37.4 ± 2.4
16:1	4.5 ± 0.3	4.6 ± 0.2	3.5 ± 0.6	5.3 ± 0.8
17:0	1.9 ± 0.1	1.1 ± 0.01	1.2 ± 0.01	1.1 ± 0.01
17:1	4.6 ± 0.2	2.1 ± 0.1	1.4 ± 0.1	0.4 ± 0.01
18:0	11.3 ± 1.2	10.8 ± 1.2	13.2 ± 0.9	14.7 ± 0.8
18:1	21.9 ± 1.1	23.7 ± 1.1	28.4 ± 1.6	23.5 ± 1.1
18:2	5.1 ± 0.6	7.8 ± 0.9	11.2 ± 0.8	6.5 ± 0.6
18:3	0.8 ± 0.1	0.7 ± 0.1	1.1 ± 0.02	1.0 ± 0.08
20:0	0.3 ± 0.01	0.9 ± 0.08	0.4 ± 0.01	0.4 ± 0.01
20:4	0.7 ± 0.06	3.0 ± 0.09	2.1 ± 0.02	0.4 ± 0.02
22:0	0.9 ± 0.09	1.1 ± 0.01	1.4 ± 0.05	1.9 ± 0.2
22:5	0.9 ± 0.2	1.5 ± 0.06	1.8 ± 0.06	1.6 ± 0.3
24:0	0.7 ± 0.01	0.3 ± 0.01	1.1 ± 0.04	1.7 ± 0.2

* = Number of cases in parenthesis

† = Number of carbon atoms: number of double bonds
‡ = Percent of total fatty acids ± SD

During that period. Beyond 33 weeks of pregnancy, the amounts of all classes of lipids except sphingomyelin increased significantly. The L/S ratio showed a sharp rise with the advancement of pregnancy from 18 weeks to term in labor. Among the lipids, the quantity of lecithin only altered strikingly and became maximum during the advancement of pregnancy beyond 33 weeks. The L/S ratio was maximum at term with labor.

Table 2 shows the fatty acid composition of total lipids at different periods of gestation. Palmitic, oleic, and stearic were the major fatty acids at all stages of

gestation. No remarkable variation was noted among fatty acid composition of total lipids at different stages of gestation, except in the amount of palmitic (16:0) and heptadecenoic (17:1) acids. Palmitic acid showed a continuous drop during the advancement of pregnancy between 18-22 weeks and 34-40 weeks, followed by an increase to its original level at labor in term. The heptadecenoic acid content was decreased with increase of gestational age.

Table 3 shows the fatty acid composition of cholesterol esters. The fatty acid composition of cholesterol

TABLE 3. FATTY ACID COMPOSITION OF CHOLESTEROL ESTERS OF HUMAN AMNIOTIC FLUID AT DIFFERENT PERIODS OF GESTATION

Fatty acid	Group I (3)* 18-22 wk	Group II (4) 27-33 wk	Group III (3) 34-40 wk	Group IV (3) Term labor
12:0 [†]	0.6 ± 0.02	trace	2.5 ± 0.02	4.1 ± 0.2
14:0	3.2 ± 0.1	1.1 ± 0.0	5.5 ± 0.04	6.3 ± 0.1
14:1	1.2 ± 0.0	trace	trace	3.4 ± 0.1
15:0	1.2 ± 0.1	trace	trace	2.6 ± 0.1
15:1	0.9 ± 0.1	trace	trace	2.0 ± 0.0
16:0	20.8 ± 0.8	27.9 ± 1.9	21.1 ± 1.2	8.1 ± 0.3
16:1	3.2 ± 0.1	15.7 ± 0.9	12.7 ± 0.9	11.1 ± 0.8
17:0	1.1 ± 0.0	trace	trace	5.5 ± 0.1
17:1	1.2 ± 0.0	trace	2.9 ± 0.0	2.2 ± 0.0
18:0	5.9 ± 0.1	9.7 ± 0.6	3.1 ± 0.2	3.6 ± 0.1
18:1	25.9 ± 1.6	21.6 ± 1.5	22.1 ± 1.1	17.7 ± 1.1
18:2	21.2 ± 1.3	13.0 ± 0.8	17.8 ± 0.8	5.1 ± 0.1
18:3	4.6 ± 0.2	1.1 ± 0.02	0.6 ± 0.0	9.6 ± 0.1
20:0	0.6 ± 0.0	0.9 ± 0.0	trace	1.2 ± 0.0
20:4	1.7 ± 0.08	2.6 ± 0.1	5.9 ± 0.1	6.5 ± 0.1
22:0	2.5 ± 0.01	2.2 ± 0.0	2.8 ± 0.0	4.2 ± 0.1
22:5	3.1 ± 0.1	1.3 ± 0.1	3.0 ± 0.1	6.6 ± 0.2
24:0	1.1 ± 0.0	0.9 ± 0.0	trace	0.2 ± 0.0

* = Number of cases in parenthesis

† = Number of carbon atoms: number of double bonds

‡ = Percent of total fatty acids ± SD

esters showed continuous variation during the advancement of pregnancy. Particularly the cholesterol ester at term (labor) had a fatty acid spectrum distinct from that at any other stage of gestation. Palmitic acid content was minimum at labor and maximum at 27 to 33 weeks of pregnancy. Palmitoleic acid (16:1) showed a remarkable increase during the increase of gestational age from 18–22 weeks to 27–33 weeks and a slight decrease thereafter. Heptadecanoic acid (17:0) showed a significant increase at term in labor. Linolenic acid (18:3) content was decreased between 18–22 weeks and 27–40 weeks but was almost doubled at term with labor. Arachidonic acid (20:4), behenic acid (22:0), and docosapentaenoic acid (22:5) showed an increasing trend during the advancement of pregnancy.

Palmitic, oleic (18:1), and stearic (18:0) were the major fatty acids of triglycerides at all gestational ages (Table 4). No remarkable variation in fatty acid composition of triglycerides was noted during the advancement of pregnancy except in the amount of palmitic and myristic (14:0) acids. The palmitic acid content was decreased between 18–22 and 27–33 weeks, increased between 27–33 weeks and 34–40 weeks and decreased again between 34–40 weeks and term in labor. The myristic acid content was remarkably high (18.1%) at 27–33 weeks of pregnancy and remarkably low (1.2–3.2%) at other stages.

Table 5 shows the fatty acid composition of free fatty acids. No significant variation was noticed in fatty acid composition of free fatty acids at different stages of gestation, except in the amount of oleic and palmitic

acids. While both palmitic and oleic acids were equally the most predominant fatty acids at early stages of pregnancy, oleic acid was the most predominant one at labor in term.

Table 6 shows the fatty acid composition of sphingomyelin. The sphingomyelin contained high levels of lauric, palmitoleic, and docosapentaenoic acids in addition to palmitic and oleic acids. Myristic acid level of sphingomyelin appeared to drop with advancement of gestation. Palmitic acid level showed an increase between 18–22 weeks and 34–40 weeks, but its level was decreased at term in labor. Oleic acid content was maximum at labor and minimum at 18–22 weeks of pregnancy. The most remarkable observation was that arachidonic acid level was unusually high (30.4%) at term in labor whereas its level was very low at early stage of pregnancy. The amount of docosapentaenoic acid was lowest at labor and highest at 27–33 weeks of pregnancy.

Table 7 shows the fatty acid composition of lecithin at different stages of gestation. Palmitic acid content of lecithin showed continuous increase during the advancement of pregnancy. The rate of increase was the highest during the advancement beyond 33 weeks of pregnancy. Palmitoleic acid content in lecithin gradually increased between 18–22 weeks and 34–40 weeks, but its value drops at term in labor. The amount of lauric (12:0), myristic, linolenic (18:3), behenic, and docosapentaenoic acids dropped significantly during the advancement of pregnancy. The most interesting observation was that lecithin contains an unusually

TABLE 4. FATTY ACID COMPOSITION OF TRIGLYCERIDES OF HUMAN AMNIOTIC FLUID AT DIFFERENT PERIODS OF GESTATION

Fatty acid	Group I (3) ^a 18–22 wk	Group II (4) 27–33 wk	Group III (3) 34–40 wk	Group IV (3) Term labor
12:0 ^b	0.7 ± 0.0 ^c	3.5 ± 0.1	0.7 ± 0.0	2.9 ± 0.08
14:0	1.4 ± 0.0	18.1 ± 1.2	1.2 ± 0.0	3.2 ± 0.01
14:1	trace	trace	0.3 ± 0.0	1.5 ± 0.0
15:0	1.0 ± 0.0	0.7 ± 0.0	0.6 ± 0.0	1.4 ± 0.0
15:1	0.4 ± 0.0	trace	trace	0.4 ± 0.0
16:0	29.9 ± 1.8	16.6 ± 1.1	25.1 ± 1.5	19.8 ± 1.3
16:1	3.5 ± 0.2	5.6 ± 0.8	3.6 ± 0.1	4.1 ± 0.3
17:0	0.8 ± 0.0	0.7 ± 0.0	0.2 ± 0.0	0.5 ± 0.0
17:1	1.0 ± 0.0	trace	0.2 ± 0.0	0.6 ± 0.0
18:0	11.8 ± 0.8	8.5 ± 0.3	14.3 ± 1.1	13.2 ± 0.8
18:1	40.9 ± 3.9	16.9 ± 1.1	38.3 ± 3.2	38.6 ± 4.1
18:2	3.2 ± 0.1	6.2 ± 0.6	6.4 ± 0.3	5.4 ± 0.3
18:3	1.1 ± 0.0	6.5 ± 0.4	trace	0.9 ± 0.08
20:0	1.0 ± 0.0	0.5 ± 0.0 ^c	trace	0.2 ± 0.0
20:4	0.8 ± 0.0	6.1 ± 0.1	3.0 ± 0.01	2.6 ± 0.1
22:0	1.4 ± 0.01	2.8 ± 0.0 ^c	2.1 ± 0.02	2.7 ± 0.1
22:5	0.5 ± 0.01	6.2 ± 0.2	2.8 ± 0.01	0.6 ± 0.0
24:0	0.6 ± 0.00	1.1 ± 0.0 ^c	1.2 ± 0.01	1.4 ± 0.0

^a = Number of cases in parenthesis

^b = Number of carbon atoms; number of double bonds

^c = Percent of total fatty acids ± SD

TABLE 5. FATTY ACID COMPOSITION OF FREE FATTY ACIDS OF HUMAN AMNIOTIC FLUID AT DIFFERENT PERIODS OF GESTATION

Fatty acid	Group I (3)* 18-22 wk	Group II (4) 27-33 wk	Group III (3) 34-40 wk	Group IV (3) Term labor
12:0 [†]	1.5 ± 0.01 [‡]	0.8 ± 0.01	trace	trace
14:0	2.5 ± 0.03	5.7 ± 0.3	1.3 ± 0.01	6.2 ± 0.5
14:1	2.3 ± 0.08	1.9 ± 0.02	0.4 ± 0.0	trace
15:0	3.9 ± 0.1	1.7 ± 0.02	0.6 ± 0.0	trace
15:1	1.0 ± 0.03	0.5 ± 0.0	0.2 ± 0.0	trace
16:0	27.5 ± 1.1	18.1 ± 0.9	19.7 ± 1.8	21.2 ± 1.2
16:1	4.1 ± 0.3	3.9 ± 0.3	4.3 ± 0.3	7.3 ± 0.8
17:0	1.4 ± 0.03	3.9 ± 0.2	0.4 ± 0.0	trace
17:1	1.1 ± 0.01	1.2 ± 0.01	0.3 ± 0.0	trace
18:0	13.1 ± 0.5	13.9 ± 0.6	12.6 ± 0.9	10.9 ± 1.0
18:1	26.8 ± 1.3	18.3 ± 0.9	38.5 ± 4.2	31.5 ± 4.8
18:2	2.7 ± 0.08	5.4 ± 0.3	4.3 ± 0.3	4.2 ± 0.6
18:3	0.9 ± 0.0	2.3 ± 0.0	2.3 ± 0.2	0.8 ± 0.0
20:0	0.9 ± 0.01	1.4 ± 0.0	0.4 ± 0.0	0.6 ± 0.0
20:4	5.0 ± 0.3	9.0 ± 0.3	3.2 ± 0.1	8.0 ± 0.4
22:0	2.1 ± 0.08	5.6 ± 0.2	5.6 ± 0.2	3.6 ± 0.1
22:5	2.5 ± 0.02	4.3 ± 0.3	3.9 ± 0.3	4.3 ± 0.2
24:0	0.7 ± 0.0	2.1 ± 0.0	2.0 ± 0.0	1.4 ± 0.01

* = Number of cases in parenthesis

† = Number of carbon atoms: number of double bonds

‡ = Percent of total fatty acids ± SD

high amount of docosapentaenoic acid only at an early stage of pregnancy and virtually none at later stages (beyond 34 weeks).

DISCUSSION

The quantity of total lipids in human amniotic fluid as reported in the present study is higher than that reported by other investigators.^{8,10,12} This is probably due to the fact that the procedure used here which involves acidification extracted almost all of the bound lipids which were not considered by earlier workers.

The amount of total lipids of the amniotic fluid increase with gestational age and reaches its maximum at 40 weeks of pregnancy. In this respect, this report agrees with that of Singh and Zuspan,¹² but differs from that of Biezenski and coworkers.⁸ Also, in contrast to the findings of Biezenski et al,⁸ triglycerides and free cholesterol have been found to occur in high amounts in amniotic fluid in the present study. The present report appears to be the only one to suggest the presence of ether lipids in human amniotic fluid. Further studies are in progress to study the origin of ether lipids in

TABLE 6. FATTY ACID COMPOSITION OF SPHINGOMYELIN OF HUMAN AMNIOTIC FLUID AT DIFFERENT PERIODS OF GESTATION

Fatty acid	Group I (3)* 18-22 wk	Group II (4) 27-33 wk	Group III (3) 34-40 wk	Group IV (3) Term labor
12:0 [†]	9.8 ± 0.2 [‡]	3.8 ± 0.1	6.4 ± 0.3	7.4 ± 0.6
14:0	7.1 ± 0.3	6.6 ± 0.1	5.5 ± 0.0	trace
14:1	trace	trace	trace	trace
15:0	trace	trace	trace	trace
15:1	trace	trace	trace	trace
16:0	17.6 ± 0.6	21.6 ± 0.6	30.6 ± 1.1	14.1 ± 0.5
16:1	16.5 ± 0.8	3.3 ± 0.1	15.5 ± 0.5	8.5 ± 0.2
17:0	5.9 ± 0.2	4.8 ± 0.1	trace	trace
17:1	trace	0.4 ± 0.0	trace	trace
18:0	3.8 ± 0.1	13.7 ± 0.3	6.0 ± 0.2	4.9 ± 0.1
18:1	6.1 ± 0.1	13.6 ± 0.6	8.5 ± 0.3	19.2 ± 0.3
18:2	2.7 ± 0.1	4.6 ± 0.2	0.6 ± 0.0	3.6 ± 0.1
18:3	7.4 ± 0.2	0.6 ± 0.0	trace	0.2 ± 0.0
20:0	2.3 ± 0.08	0.7 ± 0.0	trace	trace
20:4	3.3 ± 0.07	1.5 ± 0.0	1.7 ± 0.06	30.4 ± 4.2
22:0	trace	trace	2.5 ± 0.0	1.1 ± 0.0
22:5	15.9 ± 0.2	24.8 ± 0.9	15.1 ± 0.3	7.7 ± 0.1
24:0	1.6 ± 0.08	trace	7.6 ± 0.0	2.9 ± 0.0

* = Number of cases in parenthesis

† = Number of carbon atoms: number of double bonds

‡ = Percent of total fatty acids ± SD

TABLE 7. FATTY ACID COMPOSITION OF LECITHIN OF HUMAN AMNIOTIC FLUID AT DIFFERENT PERIODS OF GESTATION

Fatty acid	Group I (3) ^a 18-22 wk	Group II (4) 27-33 wk	Group III (3) 34-40 wk	Group IV (3) Term labor
12:0 ^b	3.4 ± 0.3 ^c	trace	trace	trace
14:0	3.9 ± 0.2	trace	trace	1.1 ± 0.0
14:1	trace	trace	trace	trace
15:0	trace	trace	trace	trace
15:1	trace	trace	trace	trace
16:0	17.9 ± 0.9	20.0 ± 0.8	54.2 ± 1.3	58.1 ± 1.2
16:1	6.5 ± 0.5	7.3 ± 0.2	11.7 ± 0.6	2.1 ± 0.1
17:0	trace	0.9 ± 0.02	6.8 ± 0.08	1.9 ± 0.1
17:1	trace	0.5 ± 0.02	trace	trace
18:0	6.0 ± 0.2	9.9 ± 0.1	4.7 ± 0.06	4.1 ± 0.1
18:1	7.9 ± 0.3	15.3 ± 0.2	10.8 ± 0.02	13.9 ± 0.2
18:2	6.0 ± 0.4	9.2 ± 0.1	8.1 ± 0.01	3.8 ± 0.1
18:3	8.5 ± 0.2	trace	trace	0.6 ± 0.02
20:0	1.5 ± 0.1	trace	trace	trace
20:4	6.3 ± 0.1	11.5 ± 0.2	0.8 ± 0.01	10.6 ± 0.1
22:0	6.2 ± 0.1	trace	2.5 ± 0.01	0.6 ± 0.0
22:5	24.7 ± 0.8	25.4 ± 0.3	0.4 ± 0.0	0.6 ± 0.01
24:0	1.2 ± 0.1	trace	trace	2.6 ± 0.02

^a = Number of cases in parenthesis^b = Number of carbon atoms; number of double bonds^c = Percent of total fatty acids ± SD

amniotic fluid. The L/S ratio, which invariably increases with gestational age, is 2:1 or greater beyond 34 weeks of pregnancy and becomes maximum at term labor. This observation correlates with that of Gluck and associates.¹¹

Palmitic, oleic, and stearic were the major fatty acids of total lipids at all stages of gestation thus studied. This observation contradicts that of Warren et al.¹² who reported that heptadecanoic acid (17:0) is the most predominant fatty acid in early gestation. In the present study, heptadecanoic is found to occur in small quantities even in the early stages of pregnancy. Palmitic acid content of total lipids decreases as the gestation progresses from 18 weeks to 40 weeks and then increases in term labor almost to the same level present at 18 weeks of gestation. This observation differs from that of Warren and associates.¹² More extensive studies are therefore needed before firm conclusions are drawn relating fetal lung maturity with the quantity of total amniotic fluid palmitic acid as suggested by these investigators.

The fatty acid composition of cholesterol esters varies with gestational age. It is interesting to note that the amounts of heptadecanoic acid and linolenic acid of cholesterol esters were unusually high in term labor. Also, the amount of arachidonic acid of cholesterol esters increases with the advancement of pregnancy. It appears that the arachidonic acid level of cholesterol esters may be useful in assessing fetal lung maturity.

No remarkable variation in fatty acid composition of triglycerides and free fatty acids is noted with in-

crease in gestational age, except in the amount of myristic acid in triglycerides and the amounts of palmitic and oleic acids in the free fatty acids. It is not known why the amount of myristic acid in triglycerides is unusually high at 27-33 weeks of pregnancy and remarkably low at either earlier or later gestational periods. Of course the possibility remains that there are two pathways for the synthesis of triglycerides, one involving myristic and the other involving oleic acids (possibly palmitic acid). This myristic acid pathway may be predominant at 27-33 weeks of pregnancy. In this respect, it is worthwhile to point out a recent report of Gluck and Kulovich¹³ in which they suggested that two pathways exist for the synthesis of lung lecithin in the human fetus. One process which is active at 22-24 weeks of gestation, involves both palmitic and myristic acids; the other involves only palmitic acid, which is active at 34-36 weeks. However, no explanation can be given at the present time on a) why the amount of palmitic acid in total free fatty acids decreases with increase in gestational age, and b) why the amount of oleic acid in free fatty acids is maximum in term labor.

So far as sphingomyelin is concerned, the arachidonic acid content is unusually high at term labor and very low in early pregnancy. The opposite pattern exists in the case of docosapentaenoic acid. It appears that there may be an interrelationship between these two fatty acids in sphingomyelin and fetal maturity.

The fatty acid composition of lecithin deserves a special comment. The palmitic acid content of lecithin

increases with advancement of pregnancy. However, this increase becomes markedly accelerated at the 34th week of gestation. This observation supports the view of Gluck and Kulovich²³ that a dipalmitoyl pathway is most active at 34–36 weeks of pregnancy for the synthesis of lung lecithin of the fetus. It is therefore suggested that fetal lung maturity may be assessed by the estimation of palmitic acid in amniotic fluid lecithin.

The data presented here in relation to the quality and quantity of lipids and fatty acids and the interrelationships of the gestational age with the amount of arachidonic, behenic, and docosapentaenoic acids of cholesterol esters and palmitic acid of lecithin must be supplemented with further chemical and clinical data before final conclusions are drawn about fetal lung maturity.

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distinct categories of training: direct clinical service and consultation. Direct clinical tasks include individual, diagnostic, and family crisis intervention and day treatment. Consultation-education includes staff consultation, training, and evaluation. Agency consultation includes juvenile delinquency and drug programs, courts, police, and health programs.

Yale University's model of training with rings of clinics. Expertise was made available to hospitals and patients of Connecticut. This resembles Oregon's Continuing Program. The Oregon model has many community psychiatrists. For example, the University of California at Los Angeles has a two-year postgraduate training program leading to a master's degree in clinical psychology. The UCLA model involves teachers and investigators who are also practicing psychiatrists. The Oregon model involves giving all future psychiatric residents a community psychiatry experience to prepare them to meet the needs of the community psychiatrist.

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Biomedical Research Subjects: Who Should Be Exempt?

In recent years, biomedical research has come under ever increasing scrutiny. Such critical examination of research practices involving human subjects is currently embodied in the movement called "consumerism" and specifically in that movement's concern with the "right to know." In the biomedical research community, it is expressed in the requirement for voluntary, informed consent-giving on the part of patients. Given such universal concern, any perverse outcome in research in humans today as that witnessed with the now infamous Tuskegee syphilis study only serves as a triggering mechanism to bring about greater external control of the biomedical research community. The ultimate effect of a disproportionate degree of control over biomedical research residing outside the biomedical sector is further curtailment of essential biomedical research. Society demonstrates an ambivalence in its demands upon the biomedical research sector; there is the requirement for greater safety in medical therapeutics and simultaneously there is the demand for greater proof of the efficacy of that which we do.

Essential to all good research design is the maintenance of the balance between risks and benefits. Disruption of this balance results in either excessive risks to patients or an abatement of productive research; productive research often bears an inverse relationship to patient safety. These two values as they apply to biomedical research are viewed as the scientific priority of discovery on the one hand and humane therapeutic treatment on the other. This has come to be known as the dilemma of science and therapy. In attempting to maintain such a delicate balance, it becomes absolutely essential that the biomedical research sector put forth the greatest effort possible to minimize the likelihood of future misadventures in human biomedical experimentation. Hence, this problem can best be approached by reviewing

the characteristics of those research subjects who are most susceptible and who in the past have been victims of such untoward research.

Last February in Washington, D.C., the Academy Forum, under the auspices of the National Academy of Sciences, began to grapple with the problem by convening a conference entitled, "Experiments and Research with Humans: Values in Conflict." The speakers represented a broad spectrum of professional disciplines and viewpoints. During the two-day conference, the participants addressed the issue of populations at risk. The groups selected for special examination by the forum were the fetus, the child, the military/prisoner, and the poor. Because of their "captive" status, obviously all four groups are deserving of special consideration. However, such captive institutions or conditions as identified by the Academy Forum can on occasion very well provide a milieu for biomedical research participation which affords far more protection than many of the so-called noncaptive institutions. Admittedly, there is a demonstrable vulnerability resulting solely from being identified with a captive group. However, regarding one's suitability for participation in biomedical research, I believe the issue goes beyond captive group identification per se. The truly jeopardizing factor appears to be a deficiency or absence of those biosocial defense mechanisms essential for coping with a very complex society.

Who, then, lacks these defenses and thus should be considered for exemption from human biomedical research? Succinctly stated, they are those who are clearly incapable of providing their voluntary informed consent. Specifically, they are the functionally illiterate, the senile, those who do not command the language, and the mentally incompetent. By identifying and exempting these individuals, irrespective of their captive or noncaptive status, the probability of future human biomedical

misadventures will be greatly reduced; and, in doing so, research quality would not be compromised. Moreover, these basic criteria for exemption could be aptly applied to any individual, be he prisoner/military or poor. Although implicit is the term "poor," it is social and cultural deprivation rather than a simple lack of economic resources that is of primary significance in the case of biomedical research. There are many classified as poor who do not suffer deep and grinding social and cultural deprivation and hence need not be excluded from participation in human biomedical research. The same criteria for exemption in the case of the fetus and the child would appropriately be applied to the parents, who constitute their biological representatives and, in my judgment, their legal representatives as well.

The potential mechanism for further definition and implementation of applicable guidelines for biomedical research subjects is provided for by the action taken by Congress in July 1974 when it approved the National Research Act amending the Public Health Service Act to establish a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission is to have 11 members appointed by the secretary of health, education, and welfare. Members are to be from the fields of medicine, law, ethics, theology, biology, physical behavioral and social sciences, philosophy, humanities, health administration, government, and public affairs. Five of the members are to have backgrounds in biomedical or behavioral research involving human subjects. The commission is to conduct comprehensive investigation of the legal, social, and ethical implications of biomedical/behav-

ioral research and technology involving human subjects. Guidelines and recommendations are to be made to the secretary regarding the application of these guidelines to biomedical and behavioral research.

The duties of the commission will be multiple and will be concerned with the issues of informed, consent-giving programs involving children, prisoners, and the institutionalized mentally infirmed. Additionally, review of existing protective regulations will be conducted along with investigation of the nature, extent, and purpose of research involving living fetuses and alternate means for achieving such purposes.

Finally, the commission will make recommendations to the Congress regarding the functions and authority of the National Advisory Council for the Protection of Subjects of Biomedical and Behavioral Research to be established July 1, 1976, under Section 217(f) of the Public Health Service Act. Some of the duties of the council will be to advise and make recommendations to the secretary regarding the protection of human subjects of biomedical and behavioral research, to review policies and regulations, and to disseminate information to the public.

As can be deduced from the charge to the commission and the subsequent responsibilities of the council, clearly there will be exemptions from biomedical research. One hopes that those exemptions will be based on criteria closely paralleling those suggested in this editorial.

HENRY W. FOSTER, JR., M.D.

Member

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Removal of the Normal Uterus*

HENRY W. FOSTER, JR., MD,† Tuskegee, Ala

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Removal of the Normal Uterus*

HENRY W. FOSTER, JR., MD,† Tuskegee, Ala

ABSTRACT: The uterus is often justifiably removed when anatomically it is a normal organ. Unfortunately, such surgery often is viewed with suspicion because there is failure to communicate the justification to patients and uninformed critics. An effort is made in this manuscript to categorize procedures and thus more clearly delineate the indications for removal of the normal uterus. Reviewed is a total of 485 hysterectomies performed over a ten-year period in a medical school affiliated hospital providing training in obstetrics and gynecology for second-year residents and for third- and fourth-year medical students. Eighty-two of the 485 uteri removed (16.9%) were considered anatomically normal by the criteria set forth. The morbidity associated with these cases was minimal.

OBSTETRICIANS AND GYNECOLOGISTS must guard vigilantly against the injudicious and indiscriminate removal of the normal uterus. Failure to do so will only serve to reinforce much of the hostility and suspicion currently directed toward our discipline. However, much of the hostility and suspicion is unnecessary and exists because there is failure to communicate the concept that removal of the anatomically normal uterus can be completely justifiable. In fact, in some circumstances it is imperative that this normal organ be extirpated. Consequently, efforts must be made to inform patients and uninformed critics.

Basic textbooks of gynecology make little or no reference to removal of a normal uterus per se. Therefore, I wish to delineate more clearly those conditions under which removal of the normal uterus constitutes acceptable surgical practice. I am cognizant that this involves much that is subjective and philosophical and that there will not be unanimous agreement with the opinions presented. I hope, though, that these opinions and judgments will serve as a point of reference to place this controversial subject in better perspective and to improve communications between physicians and patients regarding this surgical procedure.

To determine what constitutes a normal uterus is not always a simple task. Nonetheless, some criteria must be set. It is estimated that the adult nulliparous and parous uteri have average weights of 60 and 90 gm respectively. It also is estimated that one out of five women past the age of 30 has either clinical or subclinical myomas.¹ For the purpose of this paper, any uterus weighing less than 150 gm, possessing no myomas greater than 4 cm in diameter, and showing no abnormal microscopic change is considered normal.

It is believed that the first hysterectomy was performed in 1843 by Charles Clay of Manchester, Eng-

land, although his patient died on the 15th postoperative day. The first completely successful hysterectomy was done by Dr. Walter Burnham of Lowell, Mass, in 1853.² However, it was well into this century before this procedure approached any acceptable mortality and morbidity figures. Thanks to the 20th Century advances in surgical technique, blood banking and infection control, hysterectomy has become a basically safe procedure, although mortality and morbidity have by no means been reduced to zero. In a large, well respected training hospital in this country, the mortality from this procedure was 0.5%.³

Moreover, the associated nonfatal complications are not to be taken lightly. Though infrequent, the most common serious complication of hysterectomy is bleeding requiring postoperative suturing in 0.8%.⁴ Other frequently encountered complications occur in the urinary tract. A study in 1962 reported a 1% incidence of unilateral ureteral ligation associated with total hysterectomy.⁵

Fistula formation frequently complicates hysterectomy. Ureteral-vaginal fistula is rare except when the ureters are skeletonized as with radical cancer surgery. Also, rarely, rectovaginal fistulas result from injury to the sigmoid colon or rectum in the course of hysterectomy.

It has been shown that laceration of the urinary bladder occurs in 2% of hysterectomies.⁶ Fistula formation here, however, can be essentially eliminated if the injury is recognized promptly and repaired properly.

Significant morbidity is thus a real threat whenever hysterectomy is undertaken and is reason enough to demand great care in patient selection.

INDICATIONS FOR OPERATION

The justification for removal of the normal uterus is clearer in some instances than in others. Table 1 lists what I have termed *established* indications for removal of the normal organ, as well as *relative* indications for this procedure.

Although hysterectomy, usually vaginal, is employed

TABLE 1. Indications for Removal of the Anatomically Normal Uterus

Established Indications	Relative Indications
Ovarian cancer	Sterilization
Oviduct cancer	Mental retardation
Vaginal cancer	Ectopic pregnancy
Chronic pelvic inflammation	Familial history of cancer
Endometriosis	Pelvic pain
Genital prolapse	Hydatid mole
	Postirradiation of uterus
	Benign ovarian disease
	Pelvic tuberculosis
	Postpartum hemorrhage
	Dysfunctional bleeding

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for sterilization it is not a universally accepted practice. Most gynecologists perform hysterectomy for sterilization only when there are other, more generalized indications for removal of the uterus. Recently, I have begun to use hysterectomy in patients with severe mental retardation. Hysterectomy can be done either for sterilization or to eliminate the menses, which is of significant hygienic benefit in these severely handicapped individuals.

Hysterectomy often is the procedure of choice in both interstitial pregnancy and ectopic pregnancy when a single remaining tube is involved and must be removed.

Whether to perform hysterectomy for dysmenorrhea or generalized intractable pelvic pain is a difficult decision because of the subjectivity of this complaint. It is recommended that a psychiatric perspective be sought when no organic cause for pain can be found.

More liberal use of hysterectomy in the presence of the normal uterus could be warranted in patients with a strong family history of genital malignancy, ie, in a sibling or parent. Such a change in philosophy may be plausible, and it is interesting to note that more women now die annually in this country from ovarian cancer than from cervical carcinoma.⁷

Fortunately, the intracavitary use of radium for the control of benign uterine bleeding has been abandoned. Studies have revealed a relatively high occurrence of carcinosarcoma in patients treated in this manner; consequently, prophylactic hysterectomy appears justified.⁸

Also, after evacuation of a molar pregnancy in a woman who has borne as many children as she desires, even in this day of effective chemotherapy, I can see no advantage in uterine conservation.

Possibly, in the patient over 35 with benign ovarian neoplastic cysts, hysterectomy should also be done. Secondary malignant degeneration may occur in any of these neoplastic tumors and they all possess a varying capacity for bilaterality.

Hysterectomy may be indicated in patients with diabetes mellitus. This consideration seems reasonable since it has been shown that the coexistence of this disease and endometrial carcinoma is frequent. It has been reported that 20% of all patients with endome-

trial carcinoma have overt diabetes and one half of these patients have abnormal glucose tolerance curves.⁹

The modern treatment of genital tuberculosis is active and prolonged therapy with streptomycin and isoniazid. However, operation becomes necessary if there is no change in the pelvic findings after four months of this regimen.

In the woman with severe dysfunctional bleeding, the number of children she has had should determine whether a hysterectomy is in order.

Again, reproductive desires dictate the course of action in severe postpartum hemorrhage. In the young patient who has further procreative desires, ligation of the internal iliac artery should be done. If necessary, both ovarian arteries in addition to both hypergastric arteries should be ligated. Pregnancy and delivery can follow these procedures and are completely uncomplicated.¹⁰

MATERIAL AND DISCUSSION

I have reviewed my experience with hysterectomy over the past ten years at the John A. Andrew Memorial Hospital in Tuskegee, Alabama (Table 2). Between May 1963 and May 1973, 485 hysterectomies were done. Of these, by the criteria set forth in this manuscript, 82 (16.9%) of the uteri removed were normal. Of these 82, 41 (50%) fell into the group defined as having established indications (Fig 1).

Pelvic inflammation by far was the most frequent

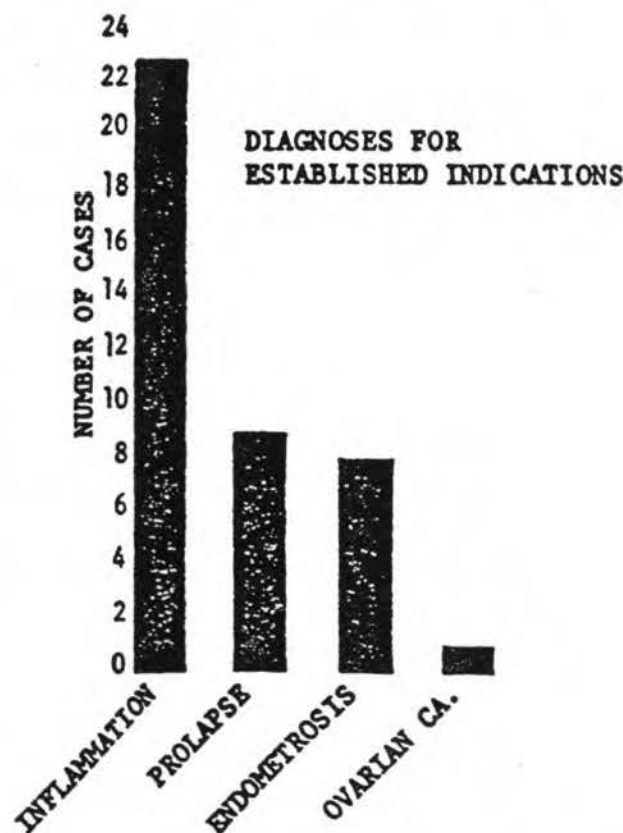


FIGURE 1. Diagnoses for established indications (n=41).

TABLE 2. Ten-Year Experience With Hysterectomy

Time Period Studied	Total No. Cases	Anatomically Normal Uteri No. Cases	% of Total
May 1963 - May 1964	64	8	12.5
May 1964 - May 1965	49	7	14.2
May 1965 - May 1966	38	7	18.4
May 1966 - May 1967	43	9	20.9
May 1967 - May 1968	50	13	26.0
May 1968 - May 1969	47	5	10.6
May 1969 - May 1970	51	6	11.7
May 1970 - May 1971	53	10	18.8
May 1971 - May 1972	38	11	28.9
May 1972 - May 1973	52	6	11.5
Totals	485	82	16.9

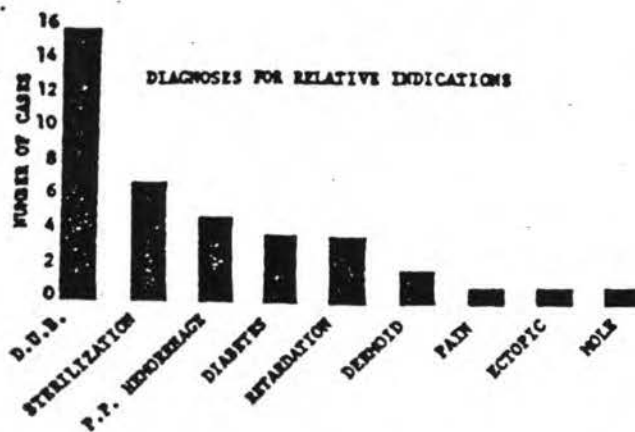


FIGURE 2. Diagnoses for relative indications (n=41).

indication for removal of the normal uterus. All nine hysterectomies for genital prolapse were by the vaginal route and were combined with anterior and posterior colporrhaphy. Of the eight cases of endometriosis (9.8%), only one patient was white. I believe the disease occurs more frequently in blacks than the literature suggests. The single case of ovarian cancer was a unilateral serous cystadenocarcinoma.

The 16 cases (19.5%) of dysfunctional uterine bleeding constituted the most frequent diagnosis in the group of relative indications (Fig 2). Admittedly, some may choose to put this diagnosis in the group of estab-

lished indications. It is interesting that only one hysterectomy (1.2%) was done exclusively for intractable pelvic pain. Certainly, many of these patients had varying degrees of pain but when more than one symptom was present, only the predominant or primary symptom was recorded as the indicated cause for operation. The single hysterectomy done for ectopic pregnancy (1.2%) was a case of intraligamentous pregnancy.

There were no fatalities among the patients having normal uteri removed. In addition, there was only minimal morbidity. Only one patient (1.2%) developed significant postoperative bleeding, which was easily controlled with several sutures placed vaginally. There was no known injury of the urinary tract, and none of the 82 patients developed any clinical thromboembolic disease.

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CHILDREN AND THE INSTITUTIONALIZED MENTALLY INFIRM

Henry W. Foster, Jr.

On July 12, 1974 the United States Congress approved public law 93-348 (H.R. 7724) amending the Public Health Service Act to establish a national commission for the protection of human subjects of biomedical and behavioral research. As a part of its charge, the Commission is to conduct comprehensive investigation of the legal, social, and ethical implications of biomedical/behavioral research and technology involving human subjects. Guidelines and recommendations are to be made to the secretary regarding the application of these guidelines to biomedical/behavioral research.

The duties of the commission will be multiple and will be concerned with the issue of informed consent-giving and programs involving children, prisoners and the institutionalized mentally infirm. Additionally, review of existing protective regulation will be conducted along with investigation of the nature, extent and purpose of research involving living fetuses and alternate means for achieving such purposes.

My charge today as a participant in this National Minority Conference on human experimentation is to examine ethical issues concerning research in children and the institutionalized mentally infirm especially from a minority perspective. And indeed such an insight is vital given the fact that the biomedical research community so often falsely and unimaginatively assumes a common national life-style in its research design. This failure to recognize the heterogeneity of the texture of this nation's social structure is in great part responsible for our being assembled here today.

Before delving further into this issue, it is appropriate to render some clarification as to what constitutes human medical research and to establish a definition of the child. Defining the institutionalized mentally infirm presents no difficulty. It is an all or none situation, however, on the other hand, if I had to define the state of mental infirmity my task would be immensely more difficult. When for example is a patient non compos mentis? How crazy is too crazy? When does the neurotic individual become incapable of providing informed consent? However, for the sake of my discussion in this manuscript, as will become evident later, the significance of the institutionalized mentally infirm, as regards their suitability for biomedical research, becomes significantly diminished.

In its broadest sense, medical experimentation on human beings is capable of occurring and indeed does occur in practically any setting where medical care is rendered. This may be in the physician's office or in the patient's home when for example the doctor has recommended, "take a couple of days bedrest," as might be advised in the case of a mild undiagnosed febrile reaction or a minor gastrointestinal upset. The issue then of biomedical experimentation in humans is basically a matter of degree and extent rather than kind. Yet for our needs, I believe the definition furnished by Irving Ladimer is suitable and is defined as "deliberate inducing or altering body or mental function, directly or indirectly, in individuals or in groups primarily for the advancement of health, science, and human welfare."¹ Such a broad definition rather well encompasses human experimentation in a context appropriate for this Conference.

Again, for the purpose of this Conference we will find the greatest utility will be achieved by utilizing the definition of the child or children as that set forth in Public Law 93-348. It reads as follows:

Individuals who have not attained the legal age of consent to participate in research as determined under the applicable law of the jurisdiction in which the research is to be conducted.

Although the definition is clear and concise and the confines are clearly drawn, the issue of informed consent-giving on the part of a minor child remains unresolved. Clearly an infant or child of 5 or 6 years cannot provide an informed consent. And in contrast, surely the adolescent of 16 or 17 years should be able to make this judgment.

Last February in Washington, D. C. the Academy Forum under the auspices of the National Academy of Sciences began to grapple with the board problem of human experimentation by convening a conference, "Experiments and Research in Humans: Values in Conflict." Considered at that two-day conference were selected groups similar to those populations at risk upon which we focus today. As a participant in that forum, I attempted to identify those groups placed at greatest risk because of their "captive state" and accordingly, recommended that a moratorium be effected in their behalf by stating and I quote, "it is my belief that those clearly incapable of providing voluntary informed consent constitute this group. They are the functionally illiterate, the senile, those who do not command the English language and certainly the mentally incompetent."² Therefore, it is my strong opinion that mental retardates, be they institutionalized or otherwise, be exemp-

from all non-therapeutic research.

As you will note, children as a group are not included in the recommended exemptions. There clearly exists the need to continue the search for better therapies and cures for the many childhood diseases that are so prevalent and devastating. Some examples would be the leukemias, bone and kidney cancers, congenital cardiovascular anomalies, sickle cell disease just to mention a few. Our charge here today is to help structure a milieu in which needed research can occur wherein risks to blacks, the poor, or other disadvantaged groups are maximally reduced.

Essential to all good research design is the maintenance of the balance between risks and benefits. Disruption of this balance results in either excessive risk to patients or an abatement of productive research; productive research often bears an inverse relationship to patient safety. These two values as they apply to biomedical research are viewed as the scientific priority of discovery on the one hand and humane therapeutic treatment on the other. This has come to be known as the dilemma of science and therapy. The avoidance of future experimental misadventures such as the now infamous Tuskegee syphilis study can in my judgment best be achieved by reviewing the characteristics of those research subjects who are most susceptible and who in the past have been victims of such untoward research--such as the categories I listed for exemption. How then do I fail to include children in those groups selected for exemption if by my own admission I cite the requirement of being able to provide an informed consent as a prerequisite to any biomedical research participation? Under these circumstances, the same criteria for exemption in the

case of the child or the fetus would appropriately reside with the parents who constitute their biological representatives and in my opinion their legal representatives as well. However, because of the differences in life styles between blacks and whites, quite possibly adulthood as a practical matter begins earlier for the former group and accordingly, a more workable definition of childhood may be appropriate.

As a black medical educator, I cannot help but feel some ambivalence on the question of biomedical research. Research or the absence thereof is inexorably tied to the financing of American medical education. The total number of medical students enrolled in United States medical schools in the academic year 1972-1973 was 13,667. Of this number 957 or about 7% of the total were Black Americans.³ Of greater significance though is the fact that over half of these black students were enrolled in Howard and Meharry, thus reducing to less than 3% the percentage of black students in American medical universities exclusive of these two predominantly black institutions.

The need for increased numbers of black physicians is greater now than it has been for many years. Theodous Thompson has recently stated, "However an examination of some recent studies on the distribution of black physicians in the United States shows that the black physician to black population ratio is less today than in 1942 even on an aggregate basis."⁴ Understandably, any steps which threatened to reduce our academic productivity causes me great concern. Certainly the overall relationship of biomedical research and the financing of medical education is in need of detailed study. The tremendous pressures which exist with respect

to the sustained thrust for the research dollar may very well create an atmosphere which frequently is to the detriment of biomedical research subjects.

A hypothetical case I believe will best serve to illustrate many of the problems of biomedical research peculiar to black children.

HYPOTHETICAL CASE

Garvey's syndrome is a disease of the central nervous system characterized by the triad of progressive loss of vision, neuropathy, and ataxia. The disease usually becomes manifest in the first two years of life and death has claimed 15% of its victims by late adolescence. The disease continues to progress wherein approximately 40% of the subjects have succumbed by age 50.

The disease effects one in 2,000 and all ethnic groups within the American population are at equal risk for the disease. Males are affected approximately one and a half times more often than females. Some limited symptomatic relief from the disease is available but there is no known cure.

A team of competent research investigators at the local University Hospital have for sometime had an interest in Garvey's syndrome. After 10 months of animal studies including primates there has emerged a new drug, NMC-76 which shows promise. In laboratory studies, it has been able to arrest the neurological progression of the disease, however, there has been some question regarding toxicity and side effects of this drug.

Consequently, the team prepared a grant application and submitted it to a federal agency and achieved funding for a three-year project to study the effect and toxicity of NMC-76.

Thirty subjects were selected for this study, twenty of which ranged in age from 15 months to 18 years and the remaining 10 patients were age 19 to 42. Twenty-six of the subjects were black, one was Chicano, and three were white. Nineteen of the subjects were males and 11 were females. All patients were registered

in either the pediatric or adult neurological ambulatory facilities of the University Hospital. The principle investigator for this research project was also the Chief of the neurological pediatric facility.

All patients and in the case of minors, their parents, were called together by an associate investigator on the grant (a pediatric neurology fellow) who carefully explained the experiment to them--that the drug NMC-76 had shown promise in laboratory studies and quite possibly could be the first definitive therapy for Garvey's Syndrome thus reducing or eliminating the devastating effects of this crippling and often fatal disease. However, it was further explained that many questions regarding this proposed therapy could not be answered with certainty until human research such as this being proposed was conducted. The subjects were advised that their participation only required the taking of pills on a prescribed schedule, periodic blood samples and follow-up. And, of course, all of this would be at the expense of the University through its grant.

Lastly, they were advised that toxic side effects in the form of skin rash and paresthesias had occurred and obviously unknown side effects could also occur. They were advised that each of them would be carefully monitored for such untoward effects and if any occurred immediate intervention would be carried out either by dosage reduction or complete withdrawal from the project.

Parents and patients were then afforded the opportunity to ask further questions and to sign the University's consent form which had been designed for this research project (that form follows this case).

As the study progressed and the dosage schedules followed, several of the children and two of the adults developed severe bone marrow depression and had to be dropped from the study, however, seven (7) of the patients not showing toxicity showed marked improvement and appeared to have their disease processes arrested. The remainder showed no toxicity or improvement, but at the conclusion of the study, the improved patients were extremely disappointed when informed that their medication was being terminated due to the FDA's failure to approve the drug for continued use.

University Hospital
and
Health Services

I, _____, have voluntarily presented myself or my minor child to participate in a program of clinical investigation described as:

ADMINISTRATION OF NMC-76
FOR GARVEY'S SYNDROME

Further, it has been explained to me that this is an experimental drug and that there are possible unknown risks and side-effects as well as possible benefits to be expected.

Additionally, I have been advised, and I understand that I/or my child can freely withdraw from this study at anytime chosen.

All questions which I have raised have been explained to my satisfaction, therefore, I hereby give my informed voluntary consent.

Signature of Patient or Legal Guardian

Date

WITNESSED BY:

In this hypothetical case there were numerous violations of the rights of the children and adults. From the very onset this grant request in its original form should never have been approved by the University's Human Investigation Review Committee, and if such a committee were properly constituted approval would not likely have been granted. It is axiomatic that such committees have the proper ethnic representation from the group being investigated. Such committees need nonprofessional input to help lessen the conflict of interest which exists when only those with research interests make these determination. A clear example is the fact that the director of the neurologic ambulatory service was also the principle investigator in this supposed research project. Built-in protective mechanisms must exist to preclude the adverse effects of interest conflicts which are, to some degree, inherent in any research design.

When this study was explained to the subjects by one of the associate investigators it should have been conducted on an individual basis with the assistance of a trained social worker and/or someone who could deal with any language barriers. The ghetto tongue most often eludes the university researcher, and vice versa.

Further, during the explanation of this research, patients were mislead when not informed that no previous human studies had been carried out with the drug. Also, any initial studies with this drug should have been restricted to adults.

From the black perspective the most glaring infringement in this hypothetical case is the fact that 26 of the 30 patients enrolled in the study (86%) were black although all ethnic groups within the American population were at equal risk for this disease. This is especially discriminatory when we as a people

comprise only 12 percent of the country's total population. Here again, economic factors relate to the method by which health care is obtained by the socioeconomically depressed thereby causing this group to have to bear a disproportionate risk.

Suppose for example during this study it was discovered that the mothers of 3 of the child subjects, who had signed the consent forms, were themselves less than 18 years of age? Should these 3 children be withdrawn from the study even if their mothers wanted them to remain because of the marked improvement they had shown?

Another possible defect in this study was patients were not informed that half of them would not receive NMC-76 but instead a placebo would be prescribed. Even when patients receive prior advice, is it just or fair to knowingly deny a potentially beneficial agent to one group and provide it for another-even if on a chance basis?

Numerous flaws were attendant to the consent form. In addition to not advising that previous studies had not been done in humans, the form also failed to specify that patients' withdrawal from the study would in no way jeopardize their ability to use other university hospital services. The consent form should also have indicated that the informing physician cannot serve as a witness to the signing. Such a witness should be an independent party. Also, such consent forms should allow for the signature of the older minor child participant, perhaps the teenager.

Additionally, it is good practice to provide the research participant with his or her own permanent copy of the consent form for further reference. Also, present on the form should be the

investigator's signature attesting to the fact that the conditions set forth in the document have been explained and that no deliberate exclusion of pertinent information has occurred.

Lastly, but very significantly is the fact that no mention was made in the consent form as to financial responsibility or liability in the event of untoward results occurring from the experiment which would require extensive and or prolonged medical care. Even for those groups of substantial financial means these become extremely important unanswered questions. Surely, the problem is compounded for the black often poor inner city dweller.

The fact that some participants in this hypothetical study developed bone marrow depression and the other participants were not informed of this clearly points out the need for effective ongoing monitoring of human research. Such monitoring must be required of all human research and structured through the grantee's human investigation review committee--one having appropriate ethnic representation.

Although the case I have presented is a hypothetical one, I am certain that those of you familiar with biomedical/behavioral research rather easily recognize the parallels that are occurring every day. We cannot and should not attempt to proscribe biomedical research--such efforts on our part would not only be unsuccessful but would not serve in our overall best interest. What we must do though is clearly highlight the transgressions that have taken place and thus define and provide mechanisms to effectively prevent their reoccurrences.

In this presentation today, I have examined the issue of human biomedical research from a general perspective and have given

special consideration to those issues which have a deeper meaning for black people and their children. I realize that I have raised many questions and answered few. Hopefully, what I have provided is food for thought which will serve as a stimulus for subsequent discussions during this Conference and will allow us to bring forward those concrete recommendations which we seek.

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Clinical Management: Sickle Cell State and Pregnancy

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Several years ago, I was appalled upon reading an article recommending primary sterilization for sickle cell disease patients. This report originated at one of this country's larger teaching hospitals caring for a sizable black population.¹ In the article, a true maternal mortality rate of 10 per cent was reported, a rate which simply is unacceptable in the contemporary practice of obstetrics. A current maternal mortality rate of that magnitude is an indictment of the care being provided by the institution.

With exemplary care, I do not believe the maternal mortality rate for the homozygous (Hb-S-S) and the doubly

heterozygous (Hb-S-C) and (Hb-S-Thal) sickle cell states should ever exceed 3 per cent in this country.

While I recognize that this is a formidable ideal, the decision to risk pregnancy is an option which can justifiably be afforded by the expectant mother. I do not believe there is an experience more significant or rewarding than reproducing one's own kind.

Indeed, one of our greatest concerns of management when sickle cell disease is a complication relates to the type of advice and counsel provided to black patients regarding potential risks they incur when pregnant. Too often, the counsel provided is highly inaccurate, misleading, and, on occasion, dangerous. In order to obtain the very best maternal and child health outcomes for these patients, there must be provided accurate screening, informed counseling, and exemplary clinical management. Without this sequential three-pronged approach, maternal mortality figures can be expected to approach those reported by Forte, et al.¹

In the George W. Hubbard Hospital of Meharry Medical College, we have a management program which we believe provides all required entities. All screening is by hemoglobin electrophoresis conducted by the Meharry Sickle Cell Center, and all direct patient care and counseling is provided by the obstetrical and social service staff of the Department of Obstetrics and Gynecology.

Our management approach recognizes no reduction of fertility or increase in either fetal wastage or maternal mortality in those pregnant patients with sickle cell trait (Hb-S-A). Urinary tract infections have been reported to be two and a half times more frequent in these patients when compared with the general population. However, improved research design is needed to be conclusive on this point. Nonetheless, there is a theoretical basis to explain this occurrence. Increased osmolality enhances sickling of affected erythrocytes, and in the kidney circulation the osmolality increases fourfold as blood flows from the cortex to the medulla. Ultimately this can lead to infection, nephron destruction, and hyposthenuria — the inability to concentrate urine — which has been reported as occurring more frequently in sickle cell trait patients.

Accordingly, urine cultures and sensitivity studies are performed on all sickle cell trait patients. Those found to have positive cultures are treated with appropriate antibiotics. Those whose cultures are negative are nonetheless treated with mild urinary antiseptic agents, e.g. methenamine mandelate-phenazopyridine (Azo-mandelamine).

In a single recent study, an increased incidence of premature rupture of the membranes in patients with sickle cell trait was reported.² However, we have not observed this phenomenon on our service. Aside from a possible increased incidence of urinary tract infection, it is our feeling that the single most significant factor in managing pregnant patients with sickle cell trait is the necessity of providing adequate genetic counseling.

Providing care for patients with homozygous or doubly heterozygous forms of sickle cell disease requires the very finest in obstetrical expertise if maximal outcome is to be achieved. For convenience, we divide pregnancy management into four phases: (1) initial visit (usually in the late first trimester or early second trimester), (2) third trimester, (3) labor and delivery, and (4) postpartum. Procedures at the patient's initial visit include repeat hemoglobin electrophoresis, serum electrophoresis, blood grouping and typing, hemogram including reticulocyte count, urine culture and sensitivity, blood chemistries, liver function tests, and consultations with hematology, cardiology, pulmonary, social and dietary services.

After taking a complete history and conducting a physical examination, the patient is evaluated and advised of the availability of pregnancy termination. If after intense counseling she chooses this option, the procedure is effected with suction curettage up to the thirteenth week of gestation (from last menstrual period). In the second trimester (after the fifteenth week) we utilize prostaglandin F² alpha preceded 12 hours with insertion of a laminaria tent. The majority of our patients, however, do not choose the option of abortion. Our fundamental management, therefore, focuses on blood replacement or exchange, prevention of infection and intense social service support.

Until recently, most centers — including our own — have utilized replacement transfusions to maintain hemoglobin levels in the 7-9 grams percent range. However, recently there have been several very encouraging reports wherein partial exchange transfusions are utilized prophylactically, rather than therapeutically with crises. A protocol for this procedure is described in a recent article by Morrison and Fish.³

The objective of this therapeutic approach is to replace initially a proportion of Hb-S with Hb-A to achieve a hematocrit of at least 35 per cent and a Hb-A content of 40 per cent. This procedure usually requires 750 to 1000 milliliters of buffy-coat poor washed red

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Sickle Cell

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cells. These values should be rechecked at six-week intervals, with a crisis, or with the onset of labor. The partial exchange transfusion should be repeated when the hematocrit becomes less than 25 per cent and/or the Hb-A content is less than 20 percent. Exchange transfusions have been utilized to varying degrees for many years, but usually were employed only with crises.^{4,5} Complications from the procedure until recently have been excessive. Preliminary reports now tend to indicate that complications are declining significantly with new and refined blood transfusion techniques.

Due to the short life span of the sickle cell erythrocyte population, folate metabolism is increased, thereby requiring folic acid supplementation. On the other hand, iron therapy is usually unnecessary and may even contribute to iron storage disease. All patients are provided prenatal vitamins.

At least 25 percent of sickle cell disease patients develop urinary tract infections, and twice this number have positive urine cultures. During initial hospitalization, kidney function is evaluated and urinary tract antibiotics in some form are provided to all patients. Cardio-pulmonary evaluation is done, and the patient is discharged to be seen at least twice monthly. Every effort is made at all times to preclude any form of infection but especially respiratory infection but especially respiratory infections.

Complications in the second trimester are not particularly common, provided the patient has been seen earlier and is followed appropriately. However, as pregnancy nears term, the likelihood of morbidity increases sharply. Toxemia of pregnancy is reported as high as 22 percent and endometritis and thrombophlebitis have been reported at 19 percent.

Although there is little in the literature to support the concept of early delivery in patients with sickle cell disease, we have nonetheless employed elective early delivery in these patients. The rationale for this third trimester management is based on the following. First, the frequency and severity of complications increase as pregnancy nears term especially in patients with hemoglobin C disease. Secondly, elective delivery obviously will not be timed to coincide with the occurrence of a crisis, which may be the situation if the spontaneous onset of labor is awaited. Further, we believe that fetal lung maturation is accelerated in fetuses of these patients.

The basic elements of third trimester management include hospitalization at 36-37 weeks, partial exchange transfusions as indicated, fetal assessment for well being and maturity and induction of labor. Amniocentesis is an acceptable procedure in these patients. Placental and fetal localization is achieved with B-scan ultrasonography. Amniotic fluid is examined routinely for its lecithin/sphingomyelin ratio, creatinine, fat cells and bilirubin. Additionally, urinary or serum estradiol levels are measured and oxytocin challenge tests are conducted. Cesarean section when employed is based solely on obstetrical indications.

Labor in these patients, either spontaneous or induced, should be managed much the same as labor in cardiac patients. Over sedation should be avoided and oxygen is administered. Epidural analgesia and anesthesia is used for labor and delivery and obviates the need for narcotics. However, fluid replacement is a critical factor and is easily mismanaged. Sickle cell disease patients frequently fall into negative fluid balance. Most have impairment of renal concentrating capacity and thus excrete excessive quantities of urine. And, as with most patients in labor, they lose their appetites and therefore have impaired food and fluid intake. Hence, intravenous fluid replacement should include not only ample amounts of water/dextrose solutions but also adequate electrolyte replacement. These patients tend to have metabolic acidosis, and correction can be achieved with lactate or bicarbonate solutions monitored with daily serum electrolytes.

Catheterization of the urinary bladder is to be avoided if at all possible, and broad spectrum antibiotics should be administered for at least 96 hours into the postpartum period. Digitalization of the patient should be done, if necessary, to prevent congestive heart failure, which occurs more frequently in the postpartum period.

Management of a crisis in the pregnant sickle cell disease patient differs little from the procedures employed in the nonpregnant state. Most crises which occur are of the vaso-occlusive type producing intense pain. Aplastic (regenerative) crises are only about one-fifth as common as vaso-occlusive crises, and acute sequestration crises are mostly confined to childhood. The basic components of crisis management include (1) analgesics; (2) partial exchange transfusions; (3) intravenous fluid and electrolyte replacement; (4) oxygen administration; and (5) elimination of infection.

Providing adequate family planning to the sickle cell patient can present an extreme challenge to the obstetrician-

gynecologist. We offer sterilization to any patient who has achieved a successful delivery. If this procedure is accepted by the patient, it is done after the six week postpartum period utilizing spinal anesthesia for surgical tubal ligation and resection. We do not recommend laparoscopic sterilizations in these patients since we require general anesthesia for laparoscopic procedures.

The intrauterine device is not used in sickle cell disease patients on our service. Endometritis frequently results from its use. This can progress to a more generalized pelvic infection including pelvic peritonitis, ultimately precipitating a crisis.

What then is our stance regarding oral steroid contraceptives? Theoretically, these drugs are contraindicated because they increase blood coagulability thereby lowering the threshold for crises. The estrogen component of this estrogen-progestin medication is the major offender. Accordingly, if used, a low dose or even better, an estrogen-free oral contraceptive is the wisest choice.

It must not be forgotten that some of the less effective but safer methods of contraception, e.g. diaphragms and condoms, are acceptable provided patient motivation is adequate. However, with such contraceptive management, therapeutic abortion clearly must be an option made available to the patient who fails at contraception.

Lastly, we make no distinction in our contraceptive management of the patient with sickle cell trait.

Over the past 20 years a vast amount of knowledge has been accumulated and a greater understanding of the entire sickle cell disease process now exists. With our improving knowledge of genetic counseling, pregnancy management, and contraceptive technique, we can expect even better maternal outcomes with this disease.

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BOOK REVIEW

Minorities in Science: The Challenge for Change in Biomedicine.

VUAYA L. MELNICK and FRANKLIN D. HAMILTON (Editors). New York: Plenum Press, 1977. 296 pp. Cloth, \$19.50; paper, \$6.95

This publication represents the collective thoughts of 35 extremely able and dedicated educators and administrators who review many social and political problems facing minority students seeking biomedical careers. Its timeliness cannot be questioned, and indeed this manuscript ought to become required reading for all engaged in biomedical education.

Although the text is presented in seven sections, basically there are but three areas of consideration: (a) documentation of the problem, (b) examination of the barriers, and (c) recommendation of solutions—immediate and long-term.

Of these three areas of consideration, documentation of the problem clearly is easiest to accomplish. The text is replete with tables, charts, and graphs depicting the paucity of native Americans, blacks, Mexican Americans, Puerto Ricans, and, to a lesser extent, Asian Americans engaged in the biomedical sciences as career choices. Blacks comprise at least 12 percent of this nation's population; however, only about 1 percent of all science doctorates are held by blacks. Even more dramatic is the observation that only about 30 Mexican American chemistry Ph.D. holders can be identified out of a total national pool of 25,000, and only 10 mathematics Ph.D. holders out of a total of 14,000. I believe that no thinking individual will gainsay these data.

Another frightening aspect brought out in this book is the apparent waning of the majority's will to address the problem. It appears there is no longer a sense of urgency in correcting these deficiencies. In 1970 a national goal of 12 percent black medical student enrollment was sought for the year 1975. Not only was this goal not reached, but also the figures decreased from a high of 7.2

percent in academic year 1974-1975 to 5.8 percent in academic year 1975-1976. This response in great part can be attributed to the general notion that there is now an overproduction of scientists and physicians in this country. For the nation as a whole this may well be true, but such conclusions are inappropriate extrapolations for minorities. Why? Our nation's poorest health care outcomes occur among minority groups. Past experiences show without question that the delivery of health care to ghetto and barrio dwellers will be provided not by middle-class, suburban-oriented physicians but instead most likely by those who themselves are products of that environment. Clearly, this is a very practical justification for increasing the numbers of minority members in the biomedical sciences.

Barriers to minorities seeking careers in the biomedical sciences begin very early in life—if not before birth and continue throughout life. The authors point to deficiencies in elementary and secondary education. Vivid examples of sociocultural biases in the classroom and elsewhere are well documented. And, of course, these barriers in elementary and secondary schools have a compounding effect; hence, minority students are handicapped in college and in postgraduate school. Tragically, the difficulties increase in an exponential fashion as the educational ladder is ascended. Many sociocultural biases were intrinsic to the old MCAT (Medical College Admission Test); hopefully, they have been removed from the new MCAT, which was introduced last year.

Appropriately, a significant section of this book explores the financial barriers which always seem to be part and parcel of minority groups. The relatively large financial support for minorities which was available just a few years ago has shrunk dramatically. A chapter is dedicated to the role of the private sector in minority education, and three chapters are devoted to federal programs—National Institutes of Health, National Institute of Mental Health, and National Science Foundation.

Book Review

The conclusion is clear—the present underrepresentation of minority biomedical scientists will be proportional to financial investment. The difficult problem of correcting these barriers is approached from a perspective of immediate and long-term solutions. For any immediate action, according to the book, there must be a reordering of priorities at the highest levels in this nation. Such a reordering would allow federal dollars to be allocated more effectively. These dollars could today be used to support minority students by providing them with financial programs to upgrade minority students and after admission to graduate school. Other actions recommended for implementation are making advisory committees more representative of minorities and vigorously enforcing affirmative action. These are but a few of the suggestions which could be implemented without any delay. Although the conference proceedings were presented too late for reference to the Bakke case, should the Supreme Court render a favorable judgment in behalf of Bakke, practically all short-term solutions are effectively negated.

Effective long-range solutions are difficult to achieve; and, of course, they are not immediately apparent. Much of the book regarding deficiencies in education and science. However, in my opinion, more attention in the early school

academic year 1974-1975 to 6.8 in the academic year 1975-1976. This great part can be attributed to the fact that there is now an overproduction of scientists and physicians in this nation as a whole this may be, but such conclusions are inappropriate for minorities. Why? The poorest health care outcomes are for minority groups. Past experience without question that the delivery of care to ghetto and barrio dwellers is not by middle-class, suburban physicians but instead most often by those who themselves are products of the ghetto. Clearly, this is a very good justification for increasing the number of minority members in the biomedical

to minorities seeking careers in the sciences begin very early in life if birth and continue throughout life. A point to deficiencies in elementary and secondary education. Vivid examples of biases in the classroom and well documented. And, of the barriers in elementary and secondary schools have a compounding effect; minority students are handicapped in postgraduate school. Tragically, difficulties increase in an exponential as the educational ladder is as any sociocultural biases were in the old MCAT (Medical College Test); hopefully, they have been removed from the new MCAT, which was last year.

Lastly, a significant section of this book addresses the financial barriers which are to be part and parcel of minority students. A relatively large financial support system which was available just a few years ago has shrunk dramatically. A chapter is devoted to the role of the private sector in education, and three chapters are devoted to federal programs—National Institutes of Health, National Institute of Mental Health, and National Science Foundation.

The conclusion is clear—the production of minority biomedical scientists will be directly proportional to financial investment.

The difficult problem of correcting deficits created by these barriers is approached from the perspective of immediate and long-term solutions. For any immediate relief to be realized, according to the book, there will have to be a reordering of priorities at the highest levels in this nation. Such a pronouncement would allow federal agencies to allocate defined dollars expressly for this purpose. These dollars could today increase recruitment of minority students by structuring special programs to upgrade minority students before and after admission to graduate school.

Other actions recommended for immediate implementation are making advisory and policy-making bodies more representative of minorities and vigorously enforcing equal employment and affirmative action programs. These are but a few of the suggestions which could be implemented without any appreciable delay. Although the conference at which these papers were presented took place in early 1976, I am nonetheless struck by but a single reference to the Bakke case in the entire text. Should the Supreme Court render a favorable judgment in behalf of Bakke, practically all short-term solutions will be effectively negated.

Effective long-range solutions are more difficult to achieve; and, of course, their effects are not immediately apparent. Much is said in this book regarding deficiencies in mathematics and science. However, in my judgment, more attention in the early school years will

have to be paid to improving simple reading skills. As pointed out in the text, programs to establish career choices in early high school are essential. Also, minority role models are needed, especially in science and medical education.

Lastly, many of the contributors express the general theme that the crucial role of black colleges has not been fully appreciated. There is a rather typical profile of blacks who hold science doctorates: "They are southern born with a baccalaureate degree from a historically black institution and then a doctoral degree from a majority institution." Accordingly, increased funding for these black institutions is an absolute requisite for any long-range plan designed to improve the status of minorities in the biomedical sciences. I am puzzled and indeed bewildered when often queried as to the need for the continued existence of the "black institution." Yet few, if any, of these inquirers would ever question the propriety as to the need for the continued existence of a Brandeis, Notre Dame, or Brigham Young university.

Melnick and Hamilton have departed themselves well in bringing together in a single volume the accounts of the Conference on Minorities in Science held as a part of the bicentennial meeting of the American Association for the Advancement of Science. Let us hope that this message reaches home.

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EDITORIAL

Why Bother with Informed Consent?

Based on the title of this editorial, one might conclude that the concept of providing medically informed consent is either optional or new. From the very onset, let me point out that both implications are false. Morally and legally, the requirement for and the provision of informed consent have existed to some degree for many years.

Prior to 1960, the physician basically felt bound only to inform the patient that a procedure or procedures were being performed and, hence, obtained the consent based upon that rather simple exchange; the patient was simply made aware that a procedure was being done. However, in 1960, this rather simplistic approach changed drastically as a result of *Nathanson v. Kline*. It was from this case that the medical profession became aware of the need to provide much more information to patients; this resulted in the creation of the so-called "collateral risk doctrine." Simply stated, the decision said that not just a physician but also the patient must possess basic knowledge about proposed procedures to make an assessment as to the risk involved. Indeed, the patient must be "informed" if he or she, along with a physician, is to be capable of rationally deciding for or against surgery based upon risk.

Following this decision of *Nathanson v. Kline*, there were numerous law suits brought forth which attempted to define how much must be told patients by doctors, but obviously none has yet accomplished this objective. The battle rages on and the question is unsettled.

Certainly much of the recent and current activity in this area is embodied in that general movement afoot in this country known as consumerism and specifically in that movement's concern with the "right to know." In the medical profession, it is emphasized in the requirement for voluntary informed consent-giving on the part of the patient. Of course, it is expected that an enlightened public will keenly concern itself with disclosure issues,

sunshine laws, and so forth. And such interest and activity have only been heightened by the recent revelation of past political concealments that occurred in our capital. If for no other reason than these, we as a profession must "bother" with informed consent.

In the years immediately following the *Nathanson v. Kline* decision, it appeared that possibly the "standard of practice" doctrine might settle the quantitative question of how much the patient needed to be told by the doctor. The standard of practice doctrine as it applied to informed consent in essence meant that the doctor was required only to disclose to the patient those informational items that were ordinarily and usually provided in a general geographic/jurisdictional area. However, as a legal concept applicable to informed consent, significant legal challenges were presented. In 1972 the cases of *Cobbs v. Grant* in California and *Canterbury v. Spence* in Washington, D. C., eliminated the standards of practice concept as an answer to the issue of information quantity. These two decisions beyond question solidly affirmed the patient's right to self-determination regarding collateral risk in those two jurisdictions. Based on these two cases, therefore, it now appears that the court will hold doctors bound to "reasonable disclosure."

As a medical educator and an operating surgeon, I think I now know what is expected by our judicial system; I simply do not know how to accomplish it. I cannot determine what constitutes reasonable disclosure, and quite frankly the courts have not helped. By its simplest interpretation, to be informed means to be knowledgeable. However, as we know, knowledge is relative and never absolute, not for the doctor and least of all for the layman on medical issues. None of us knows anything about anything. Hence, the question of disclosure to the patients boils down to how much or to what degree. The courts will not or most likely cannot tell us how much disclosure is adequate. And even if

Editorial

they could, the likelihood for inconsistency among courts is a foregone conclusion. Where are we then? Very simply, we are at the mercy of juries, judges, and arbitrators.

But as dismal as my outlook may be, I do nonetheless believe there is a faint flicker of light at the tunnel's end. I believe we can reduce our risk greatly by increasing our knowledge and understanding of the issues. For example, simply knowing some of the situations in which informed consent is either difficult or impossible to obtain is essential. It behooves us to completely understand state laws on mental competency and age limitations. The latter is of particular importance

to those who perform abortions and/or provide contraceptive services to minors. Certainly our affinity for misadventure is reduced if we are knowledgeable of particular areas of past difficulties, for example, the question of witnesses, supplemental documentation, risk versus benefit explanation.

Clearly the issue of informed consent is an unsettled one; however, we must nonetheless continue the travail; we must bother with informed consent.

HENRY W. FOSTER, JR., M.D., *member,*
Editorial Board.

Discussion of Paper Presented by Howard W. Ory

HENRY W. FOSTER, JR.

All of us who share a concern for improving the quality of contraceptive methods are indebted to the Family Planning Evaluation Division of the Center for Disease Control (CDC). The value of this unit is aptly demonstrated by the virtual elimination of deaths from spontaneous abortion that are related to the use of intrauterine devices (IUD's).

Dr. Ory is correct in that we constantly hear pleas for safer contraceptives when very clearly the ones that are in existence could be used more safely. However, the *theoretical* safety and effectiveness of these agents well exceed their actual safety and effectiveness in use. Since the Family Planning Evaluation Division seeks to eliminate the mortality and to control the morbidity that are associated with contraception by applying knowledge gained from epidemiology, I must ask: What is the limit beyond which we can expect to enhance safety given the limitations imposed by our inadequate understanding of human behavior? What role or relationship should or do behavioral scientists play in meeting the objectives of the Family Planning Evaluation Division? How many of the 50 staff members are strictly behavioral scientists? I will be keenly interested in Dr. Warren Miller's presentation on "Psychosocial Aspects of Contraception."

In examining the health effects of fertility control, Dr. Ory has labeled as highly effective the methods of oral steroid contraception, the intrauterine device, abortion, and tubal ligation, which are used by 16 million women in the United States annually. His table of methods also lists 5.7 million women who use other, less effective methods.

Discussion of Paper by Ory

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However, his table does not list hysterectomy. What is the speculated contribution of this procedure to contraception in this country? I do appreciate the difficulty in determining whether or not the procedure is performed solely for the purpose of sterilization or ostensibly for some medical indication. In some centers, hysterectomies are performed expressly for the purpose of contraception.

The widespread use of oral contraceptive hormones and their potential long-term risk has stimulated concern for contraceptive safety. The single most important unanswered question regarding steroid contraceptives is: Do they increase the risk of cancer? But, as pointed out by Dr. Ory, the period of observation has not been long enough to make this judgment. To date, the production of breast tumors by steroid contraceptives has been limited to specific strains of rats and mice. High doses of estrogen have not produced breast tumors in a variety of other laboratory animals including monkeys. Although diethylstilbestrol (DES) is not a steroid hormone, the recent report by Bibbo *et al.* (1978) on females who received this drug more than 25 years ago shows a 4.6% incidence of breast cancer for users of DES as opposed to an incidence of 3.1% for nonusers. Although this difference is not statistically significant, it is unsettling and shows the need for more answers.

There now seems to be less concern regarding the effects of steroid contraception upon the endometrium than on other genital organs. In fact, a protective result may accrue to the endometrium from combination birth control pills.

As pointed out by Dr. Ory, the published data by Beral (1975) cannot as yet be considered fully applicable to women in the United States, but without question, they probably have some applicability to this country. These data show that all cardiovascular diseases appear to be increased in users of oral contraceptives. By applying her data to Tietze's data, which show excess annual death rates (Tietze, 1977), Dr. Ory has shown that in addition to the significant difference in death rate between nonsmokers and smokers, the base rate for nonsmokers is higher than his data showed independently. I cannot question this extrapolation. As he has emphasized, firm conclusions remain yet unsubstantiated for this country.

I agree with Dr. Ory that information regarding benign liver tumors needs further explanation. However, preliminary data on the subject indicate that the practice of medicine has already been influenced favorably—few practitioners now routinely prescribe more than 50 μ g doses of estrogen for contraceptive purposes. There is one unanswered question: Is the relationship of hepatoma formation with the use of

mestranol stronger than that with the use of ethinyl estradiol, or was this artifact caused by the disproportionate use of mestranol over ethinyl estradiol in contraceptive formulae? This question and others have been addressed by Rooks *et al.* (1979).

I should like to emphasize the continued need for the requirement of prescription renewal for steroid contraceptives. This practice will afford the opportunity for continued screening for genital malignancy and other possible estrogen-related disorders.

Dr. Ory has presented a table showing the major harmful effects of IUD's, excluding death. Of these harmful effects, reference has already been made to septic spontaneous abortion. It is interesting to note the increased risk to IUD users as compared to nonusers, which is caused by the risk-modifying factors of an age of less than 20 years and nulliparity. Does this increased morbidity reflect biological differences that are not inherent in multiparous, older patients? Or is the difference in risk attributable to the dissimilar lifestyles of the two groups, e.g., greater and more varied social and sexual exposure of the younger nulliparous women, with a greater risk for contracting venereal disease? Dr. Ory also does not mention the progesterone-bearing IUD's. This is a bit unusual inasmuch as he, I, and others devoted the greater part of a recent meeting discussing this topic.

On two occasions during his presentation, Dr. Ory pointed out that little is known about complication rates of surgical sterilization. Recently, CDC has embarked upon an in-depth surveillance program. Such a response by CDC cannot be more timely in view of the fact that the 1975 National Fertility Study (Westoff and Jones, 1977) found that sterilization is now the contraceptive method of choice for couples of reproductive age married 10 years or more and that 25% of all once and currently married white couples under 45 have selected sterilization as their contraceptive method (14% female, 11.1% male). According to the National Center for Health Statistics (U.S. Department of Health, Education, and Welfare, 1976), the election of sterilization has doubled since 1965 to nearly 25% among married couples of reproductive age in the United States, thus indicating a new trend in public and personal acceptance of this contraceptive procedure.

Just over 2 years ago, we began to perform the interval minilaparotomy sterilization procedure at the gynecology service at Meharry Medical College in Nashville, Tennessee, and more recently as an ambulatory procedure performed with local anesthesia at the Planned Parenthood Affiliate of Nashville. Shortly after instituting this new surgical procedure, I reviewed the literature in an effort to gain some insights as to advantages and disadvantages of interval minilaparotomy

over other forms of surgical sterilization. Some crude comparative outcomes for these two procedures were made between the health effects of uterine perforation, bladder injury, intestinal injury, bleeding, infections, deaths, and subsequent pregnancy rates. When making these comparisons, I am fully aware that no well-structured prospective study between the laparotomy sterilization and minilaparotomy has been conducted using standardized definitions and uniformity of reporting. What I have done, however, is to compare some outcomes of several laparoscopic studies with the only available minilaparotomy study, which was conducted by Dr. V. Osathanondh of the Ramathibodi Hospital in Thailand (Osathanondh, 1974, 1976).

Table 1 compares uterine perforation, bladder injury, intestinal injury, bleeding, and infection of minilaparotomy with laparoscopic sterilization. Uterine perforation occurred almost twice as often with laparoscopy. Bladder injuries sustained during the minilaparotomy were more frequent in one and less frequent in another laparoscopic study. Intestinal injuries were less with the minilaparotomy than with all three laparoscopy series. Bleeding occurred more often with the minilaparotomy in one study and less often in another than with the laparoscopic approach.

Infections from minilaparotomies occurred more often than in any of the laparoscopic studies. However, the Ramathibodi study (Osathanondh, 1974, 1976) subdivided the infections into grossly infected (2 cases) and skin inflammation (24 cases). Four hundred sixty-six cases (16%) of the 2,786 procedures from this study were conducted in outpatient centers in rural Thailand by nonphysicians. No mortality figures were given in this study.

Table 2 presents the subsequent pregnancy rate from five laparoscopy studies. The pregnancy rate in these studies ranges from a low of 0.6% to a high of 2.8% in a study of women who used the spring clip exclusively. There is no specified time period or cutoff point by which pregnancy in these studies was measured. The question of subsequent pregnancies did not appear in the Ramathibodi study. However, Garb (1957) reported 22 pregnancies in 5,477 Pomeroy procedures yielding an overall pregnancy rate of 0.4%. Based on 10 major studies from three continents, Tietze found that 34 failures occurred with 20,000 surgical sterilizations (0.17%). In these studies, no distinction is made as to the time of the procedure, i.e., postpartum or during the interval state. With regard to any type of sterilization procedure, there remains the unclarified issue of menstrual irregularity subsequent to the sterilizing procedure and, of course, psychological sequelae, which are difficult to evaluate.

TABLE 1 Complications from Minilaparotomy Compared with Those from Laparoscopic Sterilization

Complication	Laparoscopic Sterilization				Minilaparotomy			
	Study	Total in Study	Complications		Study	Total in Study	Complications	
			Number	%			Number	%
Uterine perforation	Corson and Bolognese, 1972	1,545	9	0.58	Ramathibodi (Osathanondh, 1976)	2,786	9	0.32
Bladder injury	Corson and Bolognese, 1972	1,545	1	0.06	Ramathibodi (Osathanondh, 1976)	2,786	5	0.18
Intestinal injury	Georgy <i>et al.</i> , 1974	800	2	0.25	Ramathibodi (Osathanondh, 1976)	2,786	3	0.11
	Corson and Bolognese, 1972	1,545	3	0.19				
	Peterson and Behrman, 1971	186	1	0.53				
Bleeding	Thompson and Wheelless, 1973	3,600	11	0.3	Ramathibodi (Osathanondh, 1976)	2,786	10	0.36
	Corson and Bolognese, 1972	1,545	1	0.06				
	Peterson and Behrman, 1971	186	5	2.6				
Infection	Corson and Bolognese, 1972	1,545	9	0.58	Ramathibodi (Osathanondh, 1976)	2,786	26	0.93
	Peterson and Behrman, 1971	186	0	0				

TABLE 2 Pregnancies After Interval Minilaparotomy Compared to Those Following Laparoscopic Sterilization.

Laparoscopic Sterilization				Minilaparotomy			
Study	Number of Sterilizations	Subsequent Pregnancies		Study	Number of Sterilizations	Subsequent Pregnancies	
		Number	%			Number	%
Corson and Bolognese, 1972	1,545	3	0.19	Garb, 1957	5,477	22	0.4
Thompson and Wheelless, 1973	4,200	31	0.73	Tietze (Hellman and Pritchard, 1971)	20,000	34	0.17
Peterson and Behrman, 1971	186	1	0.53				
Kessel <i>et al.</i> , 1976	876	20	2.28				

TABLE 3 Complications of Abortion Patients, July 1, 1970 to June 30, 1971*

Patients	Complication Rates per 100 Women Obtaining Abortions			
	Total Complications		Major Complications	
	Total Patients	Local Patients with Follow-Up	Total Patients	Local Patients with Follow-Up
All patients				
<12-weeks gestation	5.2	7.8	0.6	1.1
≥13-weeks gestation	22.2	26.1	2.2	3.0
Patients without pre-existing complications, by procedure				
Suction*	4.2	6.1	0.4	0.6
D&C*	6.0	8.2	0.5	0.8
Saline*	23.4	27.2	1.7	2.4
Hysterotomy	33.4	32.9	6.7	6.9
Hysterectomy	49.9	50.9	14.3	15.6
Patients without complications or sterilization				
<12-weeks gestation	4.2	6.2	0.4	0.6
≥13-weeks gestation	20.6	26.0	1.6	2.1
Patients with pre-existing complications, without sterilization				
<12-weeks gestation	12.7	17.1	1.4	2.0
≥13-weeks gestation	29.9	35.1	4.6	6.7
Patients without pre-existing complications, with sterilization				
<12-weeks gestation	25.9	28.0	6.1	7.2
≥13-weeks gestation	35.8	35.4	8.2	8.0
Patients with pre-existing complications and sterilization				
<12-weeks gestation	43.0	46.2	14.9	17.1
≥13-weeks gestation	56.5	60.4	13.8	17.4

*From Tietze and Dawson, 1973.

*Without tubal sterilization.

*With tubal sterilization.

Discussion of Paper by Ory

To reemphasize a point made by Dr. Ory concerning abortion, particular attention should be given to health effects of multiple variables, the effect of time (length of gestation), and the relationship of the two to each other as they affect abortion-related mortality and morbidity. The following data are taken from a study by the Institute of Medicine, *Legalized Abortion and the Public Health*, which was published in May 1975 (Institute of Medicine, 1975).

Table 3 examines abortion and the variables of preexisting disease, no preexisting disease, associated sterilization, no associated sterilization, and relates these variables to gestational age of greater than 13 weeks or less than 12 weeks. The best outcome was achieved in patients who had no preexisting disease, no associated sterilization procedure, and were less than 12-weeks pregnant. The opposite is true for poorest outcome, i.e., patients had preexisting disease, associated sterilization procedure, and were more than 13-weeks pregnant.

Table 4 shows an increasing mortality and morbidity with advancing pregnancy, by weekly increments. It also depicts the decreased morbidity and mortality that are associated with suction procedures and

TABLE 4 Reported Deaths Associated with Legal Abortion in the United States, by Weeks of Gestation and Method of Abortion, 1972 and 1973*

Length of Gestation and Abortion Method	Number of Abortions	Number of Deaths	Mortality Ratio (Deaths per 100,000 Abortions)
Weeks of gestation*			
< 8	421,896	2	0.5
9-10	361,885	6	1.7
11-12	212,981	9	4.2
13-15	87,573	6	6.9
≥16 or more	118,228	19	16.1
Method of abortion			
Suction/D&C	1,065,338	17	1.6
Saline	123,684	19	15.4
Hysterotomy/hysterectomy	8,161	5	61.3
Other	5,380	1	18.6

*From U.S. Department of Health, Education, and Welfare, 1978.

*Distribution of abortions based on gestation of pregnancy known for 449,709 abortions reported during 1972 (77% of the total for that year) and for 453,535 abortions reported for 1973 (74% of the total for that year).

in increased mortality and morbidity with surgical procedures. Figure 1 illustrates this increasing mortality with advancing fetal age.

Legalized abortion is rather new to the American scene. Consequently, some long-term complications are unresolved. I will close, therefore, by simply listing these long-term complications, which are associated with legalized abortion, and offering Dr. Ory and others a challenge to help us formulate a better understanding of these entities which are sterility, prematurity, spontaneous abortion, ectopic pregnancy, Rh isoimmunization, specific effects on teenagers, and psychological sequelae. The World Health Organization has already begun to seek some of these answers in a structured manner. I hope that the Family Planning Evaluation Division will also play a pivotal role in the process.

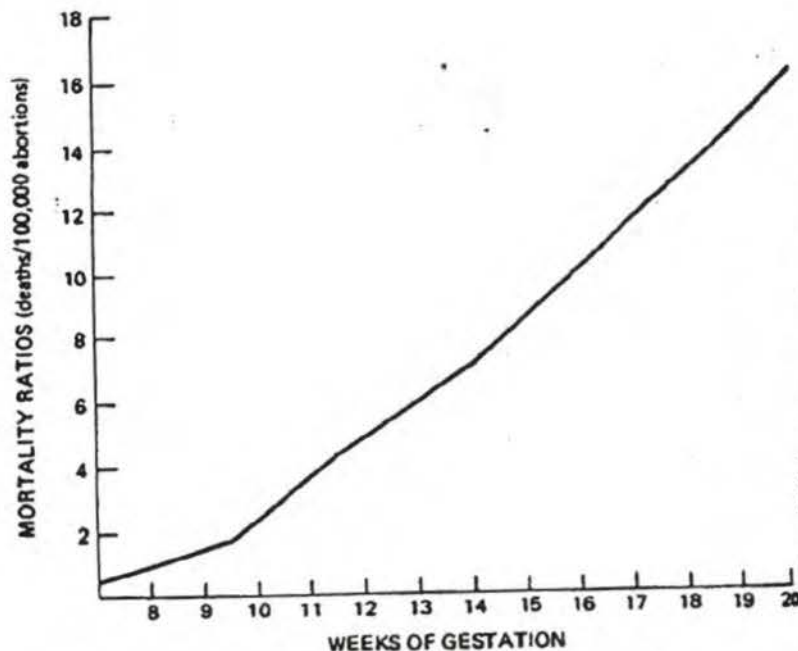


FIGURE 1 Abortion mortality ratios by weeks of gestation, United States, combined 1972-1973 data. From Institute of Medicine, 1975.

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Contraception:

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hemoglobin SS on the basis of its relative insolubility in organic buffers. Hemoglobin electrophoresis permits the identification of hemoglobins S, F, C, A₂, and A in their relative proportions. On the basis of the patient's negative past history, one may assume that she does not have sickle cell anemia (SS disease), but could well have sickle cell trait (AS), hemoglobin SC disease, or sickle cell beta-thalassemia disease.

If the hemoglobin electrophoresis pattern is one of sickle cell trait, only two problems appear to be of special concern in pregnancy. The first is an increased incidence of bacteriuria, both symptomatic and asymptomatic, which may be identified by appropriate urinary screening techniques and treated with antibacterial therapy as indicated. The second problem relates to the unlikely possibility that the offspring may inherit sickle cell anemia if the father also carries the S hemoglobin gene. Since, at present, prenatal diagnosis of sickle cell anemia can be accomplished only by fetoscopy and fetal blood sampling, neither of which is readily available in ordinary practice, the management of this contingency will probably be limited to counseling about risks.

Hemoglobin SC disease and sickle cell beta-thalassemia disease have similar but unpredictable courses during pregnancy. Both tend to be symptomatic only during pregnancy and are associated with bone marrow infarction, with intense bone and joint pain, and sometimes with pulmonary embolism of necrotic bone marrow. Patients with these diseases can have a course in pregnancy similar to that of sickle cell anemia itself, and should be managed accordingly.

The ordinary management of a patient with a potentially dangerous sickle cell disorder should include careful monitoring for infection, intrauterine growth retardation, onset of premature labor, and impending fetal death in late pregnancy. In order to anticipate and, if possible, prevent the occurrence of crises with bone marrow and pulmonary infarction, it is essential to monitor the patient's level of S hemoglobin. There is no satisfactory test for this purpose, although the sodium metabisulfite test and serial hemoglobin electrophoresis determinations may be useful.

The level of S hemoglobin below which crises can be averted varies from patient to patient and depends to some extent on which other hemoglobins are available (F, A₂, A, or C). I favor maintaining the hemoglobin of a pregnant patient at a level of 10 g/100 ml or greater,

using partial exchange transfusions of packed cells to ensure that the patient's circulating blood has a sufficient portion of nonsickling cells (as in cells from banked blood containing hemoglobin A) to minimize the in vivo sickling phenomenon.

Patients with sickle cell anemia hemoglobin SC disease or sickle cell beta-thalassemia disease deserve careful counseling with regard to the increased risk they face with each pregnancy. They should be encouraged to consider permanent sterilization procedures.

EXCLUSIVE REVIEW

Henry V. Foster, Jr., MD, FACOG: Professor and Chairman, Department of Obstetrics and Gynecology, Meharry Medical College, Nashville, Tenn.



The proper management of any patient with a positive sickle cell screening test cannot be planned until a more definitive diagnosis of the specific hemoglobinopathy is made. However, even before obtaining hemoglobin electrophoresis, several reasonable presumptions can be made, based on the historical data presented.

The fact that the patient has been asymptomatic for her entire life points very strongly away from a homozygous form of hemoglobinopathy, eg, sickle cell (SS) disease. There is only a very slight likelihood that she may be doubly heterozygous for sickle cell-hemoglobin C (SC) disease. Patients with SC disease tend to do moderately well in the nonpregnant state, but they often have splenomegaly. Also, occasionally, a patient with S beta-thalassemia will present as this patient does. Here the hemoglobin electrophoresis will point to the thalassemia diagnosis by revealing greater than 3.2% hemoglobin A₂.

In view of her history, this patient's hemoglobin electrophoresis probably will reveal AS hemoglobin, or sickle cell trait. Should this be the case, blood for hemoglobin electrophoresis should be obtained from the father and genetic counseling should be provided.

With one exception, pregnancy management and perinatal outcome are essentially the same for patients with sickle cell trait as for the general obstetrical population. Sickle cell trait patients have been found to have a two- to three-fold increased incidence of kidney infection. Accordingly, a sterile urine sample should be obtained initially and culture and sensitivity studies performed.

All patients with positive cultures (approximately 20% to 25%) should be treated for a minimum of 14 to 21 days with ampicillin, 500 mg four times a day. Cultures should then be repeated. If the cultures are negative, the patient should be treated with liberal oral fluid intake and a mild urinary analgesic such as

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phenazopyridine hydrochloric acid, 200 mg twice a day, throughout the remainder of the pregnancy. Ampicillin therapy may be reinstituted if indicated. The normal onset of labor can be awaited in these patients, and labor and delivery can be managed normally. Intervention is indicated only for obstetrical considerations.

Lastly, screening for sickle cell hemoglobin is essential in all patients of African and Mediterranean descent. However, if possible, this screening should be done with hemoglobin electrophoresis rather than other types of screening tests. Hemoglobin C (except C_{Harlem}) does not sickle. Hence, the heterozygous patient with AC hemoglobin who is asymptomatic would be missed if hemoglobin electrophoresis were not used. Should the father possess sickle trait, the patient would have a 25% chance of delivering an infant affected with SC hemoglobinopathy. This genetic possibility should be determined and the information made available to the patient as early as possible.

CONSULTING EDITOR'S COMMENT

Sickle cell and hemoglobin SC diseases are hemoglobinopathies almost unique to the black race—the largest minority population in the United States. Approximately 8% of black patients are SA heterozygotes

with sickle cell trait, and 2% are heterozygotes for hemoglobin C disease. About 1 in every 2,000 black women of reproductive age is SS homozygous with sickle cell disease; 1 in 2,400 has hemoglobin SC disease. The incidence of sickle cell disease is considerably less than that which would be anticipated from theoretical calculations. It must be assumed that death in childhood and infertility in affected women cause an attrition, reducing the number of women with sickle cell disease who become pregnant.

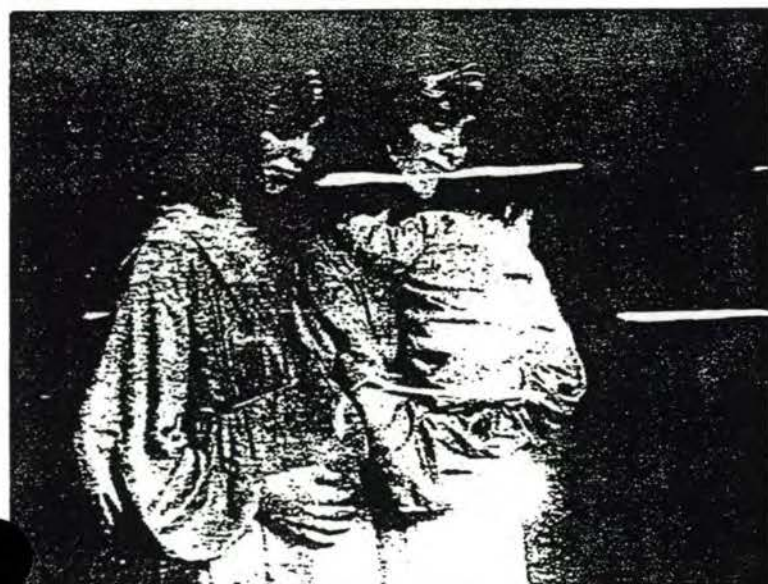
The large population at risk of sickle cell disease and other hemoglobinopathies, the severe impact of these diseases upon pregnancy, and the well-known exacerbation of the diseases in pregnancy make this a critical, though rare, area of obstetric practice. The genetic implication of reproduction between heterozygote carriers upon the newborn is also of concern to the obstetrician.

Like the theoretical patient used to introduce this discussion, a totally asymptomatic woman who is found to have a positive sickle cell screen in early pregnancy is most unlikely to have sickle cell disease. All of the respondents agree that it is most unusual for a homozygous patient to be detected for the first time in pregnancy, although this may occur occasionally. Patients with sickle cell disease are usually symptomatic long before reproductive age. However, double heterozygotes with sickle cell beta-thalassemia or,

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more rarely, sickle-hereditary persistence of fetal hemoglobin (S-HPFH), may be anemic but asymptomatic and first found by sickle cell screen. Such patients have a much higher percentage of hemoglobin S than is found in heterozygotes with SA trait.

The risk in pregnancy of any of the variants of sickle cell anemia mandates the routine screening of all black patients as they enter prenatal care. This is particularly important for clinics serving large black populations, but it is also true in private practice. Reports from the less developed countries in Africa indicate that a high maternal mortality with sickle cell hemoglobin or hemoglobin SC disease still persists; however, in this country, a series of recent reports have indicated gratifying progress and no maternal deaths. Nonetheless, all reports of patients with hemoglobinopathy indicate a high pregnancy attrition by abortion and perinatal death. These confirm the continued risk to the fetus due to chronically low hemoglobin accentuated by repeated crises that tend to be much more common during pregnancy.

As stressed by Dr Foster, concerns about the pregnant patient must also be extended to the fetus. When a mother is found to have sickle trait, the father must also be screened. If both parents have the trait, the statistical risk of the child's having the disease or trait is obvious. Recently, there has been increasing attention directed toward the prenatal diagnosis of homozygous sickle cell disease. Until now, this diagnosis has been possible only by sampling fetal blood, a technique that requires skill and equipment available only in a few centers in the United States and which, by its invasive nature, carries risk to the fetus. Recent work has raised the hope that the disease may be recognized by studying DNA from uncultured fetal cells of the amniotic fluid.* If this method proves reliable, a significant step in prenatal diagnosis and counseling will have been achieved.

Jan Schneider, MD

*Kan YW, Dozy AM: Antenatal diagnosis of sickle-cell anemia by DNA analysis of amniotic-fluid cells. *Lancet*, Oct 28, 1978.

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Pictured at left is Jan Schneider, MD, Chairman, Obstetrics and Gynecology, The Medical College of Pennsylvania, Philadelphia. As Consulting Editor for **OB WORLD**, Dr Schneider selects the problem to be discussed in each issue of the newsletter and the academician who provides an in-depth review of the problem.

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Consensus development conferences held at the National Institutes of Health bring together biomedical-research scientists, practicing physicians, consumers, and others as appropriate in efforts to reach agreements on the efficacy and safety of developments in medical technology.

The report below summarizes conclusions reached at a conference held at the National Institutes of Health on 23-24 April 1979 and sponsored by the National Heart, Lung, and Blood Institute; it was prepared by the conference's four consensus development groups and is signed by the conference cochairmen.

Transfusion Therapy in Pregnant Patients with Sickle-Cell Disease: A National Institutes of Health Consensus Development Conference

FOUR CONSENSUS GROUPS met in Bethesda, Maryland, on 23 and 24 April 1979 to consider whether there is sufficient evidence about prophylactic transfusion therapy to advocate its use for treatment of pregnant patients with sickle-cell disease. The work groups focused on four subject areas: need for further research, clinical research approaches, perinatal considerations, and sociomedical issues. Each group developed conclusions on its own subject.

Work Group I: Need for Further Research

Further research in transfusion therapy for pregnant patients with sickle-cell disease is needed, but the question must be approached systematically.

In transfusion therapy, pregnant patients with sickle-cell disease are divided into two general major groups for management. Patients in the first group are treated symptomatically, but most of them do receive blood components; blood transfusions are used whenever they are judged to be needed but are not given prophylactically. Patients in the second group are treated with prophylactic blood transfusions, used to raise hemoglobin (Hb) levels and hematocrit values and to suppress Hb S-containing cells, while replacing them with Hb A cells. Other patients in this second group are managed with exchange transfusions.

The following question was posed: Have positive effects of prophylactic transfusion therapy for pregnant patients with sickle-cell disease been satisfactorily proved? The consensus of the group is that the value of this type of transfusion therapy has not been proved. Although most studies of transfusion therapy have examined effects on maternal infection, toxemia, jaundice, anemia, sickle-cell crisis and hospitalization, and on fetal growth retardation, perinatal mortality, and premature delivery, there is no consensus as to whether these are affected by transfusion. The reasons for lack of evidence adequate to prove or refute the value of transfusion therapy are sever-

al: The problems associated with sickle-cell disease and pregnancy are not well defined, previously reported data are retrospective, there are no controls for data on pregnancies in patients with sickle-cell disease, data on patients are not comparable among institutions, and pathophysiologic mechanisms leading to poor outcome in patients with sickle-cell disease are not understood.

The problems of the pregnant patient with sickle-cell disease must be defined before attempts are made to solve them. Which variables to study and modify must be ascertained before the best outcome for both mother and infant can be sought. Because some of the patients seem to be at low risk, a method must be found to decide which mothers need, and which do not need, transfusion therapy.

Studies of pregnant patients with sickle-cell disease may shed light on reasons for intrauterine growth retardation, on reasons for fetal stress and distress and on how they should be managed, and on the importance of various indices in ascertaining degree of risk for individual patients.

Because the positive effects of transfusion therapy have been neither proved nor refuted, a task force for study design should be formed. The task force would develop a protocol for a prospective randomized study to ascertain the benefits and risks of transfusions. To provide for an adequate data base, the National Cooperative Study of the Clinical Course of Sickle Cell Disease should be expanded to include additional perinatal information decided upon by a task force. Further input should come from interested perinatal centers. The National Cooperative Study, concerned with the "natural history" of sickle-cell disease, has already been funded by the National Institutes of Health (NIH) for 5 years and involves 15 medical centers and 23 hospitals.

Other aspects of management are not well established. Both the effect of this clinical problem on the lay population and the decisions of the patient with sickle-cell disease regarding future pregnancies should be carefully considered.

Work Group II: Approaches to Clinical Research

Further research is needed to define the relation between outcome and transfusion therapy during pregnancy. This research must be prospective and randomized if it is to be definitive. Because no one hospital or city has a sufficient patient population to do such a study within a reasonable interval, a national cooperative multicenter approach should be used. The study should be integrated with the ongoing natural history study. To be well conducted, such an expensive and extensive task must be given priority; organized through mechanisms of the National Heart, Lung, and Blood Institute; and adequately funded.

Patients should not be excluded from the study on the basis of genotype, but criteria must be developed for those who will be included. For example, is the patient's history helpful in case selection. Should patients with

sickle B+ thalassemia and patients with hemoglobin F levels of 10% or more be included in the study?

Data must be accumulated to ascertain more fully the risks of transfusion, and methods must be defined for minimizing transfusion risks. Follow-up data must be collected, with careful collaboration among obstetricians, hematologists, pediatricians, pathologists, and blood-banking personnel. Blood-typing and processing requirements must be carefully defined.

Patients should be randomized to "transfusion" or "no-transfusion" therapy prospectively after they have given informed consent; patients randomized to no-transfusion therapy may be transfused, however, for specifically defined indications.

Data collection must start as early in pregnancy as possible, and benefits and timing must be determined by the study design analysis group. After initial therapy, high hemoglobin S levels must be monitored frequently and an upper limit defined (possibly from data from the natural history study), which, when exceeded, warrants repeat transfusion. Hemoglobin levels not to be exceeded must be defined.

Work Group III: Perinatal Considerations

Perinatal considerations for transfusion therapy in patients with sickle-cell disease should include three questions:

1. How should the clinical course of patients be monitored?
2. What are the challenges of intrapartum management?
3. What is the approach to infant follow-up?

A detailed series of clinical and laboratory procedures could be used to follow patients through the antepartum, intrapartum, and postpartum periods to establish a data base. If complete data are gathered during pregnancy, they might yield important retrospective information from which prospective therapeutic guidelines could be developed.

Regardless of the specific guidelines followed for pregnant patients with sickle-cell disease, medical care should be provided in a tertiary center, with a joint effort among obstetricians, hematologists, and pediatricians. It should involve awareness of the clinical course of the disease during pregnancy as well as therapeutic modalities that may modify the course and outcome of pregnancy. Infants born to patients with sickle-cell disease, who may or may not have had transfusion therapy during pregnancy, should be followed for a minimum of 2 years.

Because the value of the detailed list of procedures prepared by the work group has not been documented by appropriate study, the list should not be considered at

this time as recommendations for patient management.

Work Group IV: Sociomedical Issues

Present data are insufficient to advocate a large-scale nationwide policy of transfusion therapy or to reach definitive conclusions about ethical considerations. Nevertheless, a study to ascertain (within 1 to 2 years) in a limited number of centers the value of therapeutic, versus prophylactic, transfusion in management should be undertaken. Such a study is justified by the present marked differences in opinion on the value of various treatment modalities.

Any study design must consider psychologic considerations, including patient and physician levels of awareness and knowledge, and must allow for prejudice or feelings concerning fear of transfusion, possible intimidation from the community regarding transfusion needle marks (confused with addiction), pressure on family for repeated blood donations, convenience factors favoring time of transfusion for physician or patient, overprotectiveness by patient's family, and possible "addiction" of patient to transfusion. Economic, geographic, and educational data relating to patient and physician must be considered, and continual updating of information about the progress of the study for all concerned must be planned. Counseling should be available both before and after conception. Information about the value of amniocentesis in selected instances should be made available to patients. Any study design should take all psychosocial aspects into account.

Access to the study must be available to all patients who wish to become involved, but they should not be coerced. Informed consent should be obtained from all participants. Innovative methods, such as audiovisual presentations with subsequent question-and-answer sessions, should be developed to avoid coercion of patients. Patient feedback mechanisms to test levels of comprehension need to be developed. Paramedical personnel may need to be included.

Funding for patient care in such a study should be through private or public means and not by grant support. Analysis of data and reporting can be related to NIH support, but funding for patient care cannot.

The presence of hemoglobin-SS, SC, or sickle thalassemia, which constitute sickle-cell disease, should not be the sole justification for either abortion or sterilization. The procedures should be done on the basis of medical indications or patient desire, or both. The medical and legal communities need to be apprised of this consensus. (JOHN C. MORRISON, M.D.; *University of Tennessee, Memphis*; and HENRY FOSTER, M.D.; *Meharry Medical College, Nashville, Tennessee*; cochairmen for the consensus meeting)

Reproductive Performance in Women with Sex Chromosome Mosaicism

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Among chromosomal analyses performed in 23 couples with a history of 2 or more spontaneous abortions, 5 women had mosaicism of the sex chromosomes, 46,XX/47,XXX, but all the men had normal 46,XY chromosomal complements. A review of the literature revealed that 75% of the fetuses of mothers with sex chromosome mosaicism were abnormal. Fifty percent of these pregnancies ended in abortion and one third of the infants exhibited a chromosomal or physical abnormality. The possible effect of sex chromosome mosaicism on outcome of pregnancy is emphasized.

In general, 15% of all clinically recognized pregnancies terminate in abortion,^{1,2} and approximately 50% of aborted fetuses are chromosomally abnormal. Some of these chromosomal aberrations can be traced to balanced translocations in the parents, resulting in unbalanced gametes. Although chromosomal aberrations in couples with recurrent spontaneous abortion have been reported frequently,³⁻¹⁰ it has been demonstrated only recently that mosaicism of the sex chromosomes is also of paramount importance in regard to fetal wastage.¹¹⁻²² In this study the authors have attempted to assess the importance of sex chromosome mosaicism in couples with a history of unsuccessful pregnancies.

Materials and Methods

Chromosome analyses of peripheral blood were carried out in 23 couples referred to the genetic counseling program of Meharry Medical College because of a history of 2 or more spontaneous abortions, stillbirths, or neonatal deaths. Lymphocyte cultures were per-

formed according to conventional methods. Q- and R-banding techniques were employed in all cases to detect structural defects in chromosomal complements. When indicated, chromosome studies were also performed on skin fibroblast cell cultures. An average of 55 cells were analyzed for chromosome counts.

Results

Five women were found to have mosaicism of the sex chromosomes, and all males had normal 46,XY chromosomes.

A 32-year-old highly educated woman had had 3 abortions and had borne 1 normal daughter. Sixty percent of cultured lymphocytes showed 47,XXX chromosomes, and the remaining cells contained a normal set of chromosomes.

A 29-year-old woman with no physical or mental abnormalities had a history of multiple abortions, and 1 of her stillborn infants had an imperforate anus and deformed hands. Chromosome analysis of lymphocytes revealed 95% cells with 47,XXX and 5% normal 46,XX chromosomes.

A 30-year-old woman had oligomenorrhea. The clitoris was enlarged. Her chin was hirsute, but there was no hair on her abdomen or legs. She had had 3 abortions. Chromosome analysis revealed 33% 47,XXX chromosomes; the remaining were normal 46,XX chromosomes.

A 38-year-old woman had had 3 abortions. She was physically and mentally normal. Of 35 lymphocytes analyzed, all but 1 had normal 46,XX chromosomes; 1 cell had 47,XXX chromosomes. Skin fibroblast culture revealed 40% of cells with 47,XXX chromosomes; the rest were normal 46,XX chromosomes.

A 28-year-old woman had had 4 abortions, 1 female child with Down syndrome who died after 1 year, and 1 normal 7-year-old daughter. She came to the authors for prenatal diagnosis. As a regular routine procedure,

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Table 1. Fetal Outcome for Women with Mosaicism of Sex Chromosomes

Maternal mosaicism	Case no. (reference)	History		Abnormal children	
		Normal children	Abortions	No.	Defect
46,XX/47,XXX					
	1 (34)	1	2	1	47,XXY
	2 (34)	0	1	1	46,XX/47,XXX
	3 (12)	4	2	1	47,XXY
	4 (21)	0	1	1	46,XY/47,XXX
	5 (11)	3	1	1	47,XXY
	6 (13)	2	2	1	47,XXY
	7 (20)	1	1	1	47,XXY
	8 (22)	0	0	1	48,XXYY
	9 (18)	4	2	1	46,XX/92,XXYY
	10 (PS)	1	3	0	
	11 (PS)	0	4	0	
	12 (PS)	0	3	0	
	13 (PS)	0	3	0	
	14 (PS)	2	4	1	47,XY,*21
Total		18	29	10	
45,X/46,XX					
	15 (36)	1	1	0	
	16 (17)	0	4	1	Down syndrome
	17 (37)	1	0	0	
	18 (38)	2	0	0	
	19 (35)	0	0	3	CNS defects
	20 (39)	0	1	0	
	21 (40)	1	3	1	45,X/46,XX
Total		5	9	5	
45,X/46,XX/47,XXX					
	22 (41)	0	0	1	45,X/46,XX
	23 (41)	0	0	2	Twins: 45,X and 45,X/46,XX/47,XXX
	24 (14)	0	1	1	45,X/46,XY
	25 (14)	0	0	1	46,XX*
	26 (1)	1	0	0	
	27 (16)	0	1	0	
	28 (28)	1	0	1	47,XY,*21
	29 (29)	0	3	0	
	30 (15)	1	3	2	47,XY,*21 and a leukemic child
	31 (15)	0	2	0	
Total		3	10	8	
Total		26	48	23	

CNS = central nervous system; PS = present study.

* With congenital heart defects.

chromosome analyses from blood were performed on her, her husband, and their daughter. Husband and daughter had normal 46,XY and 46,XX chromosome complements, respectively. The patient's chromosome analysis revealed 75 lymphocytic cells of which 64 cells were 46,XX and 11 cells were 47,XXX. Amniotic fluid cell culture revealed 46,XY chromosomal complements. At term the woman delivered a healthy 3.18-kg male infant.

Previously the authors reported a case of a diploid and tetraploid mosaic child born to a mother who her-

self had a mosaic karyotype of 46,XX/47,XXX. Ninety-one percent of the cells were 47,XXX and 9% were 46,XX. She had had 2 abortions and 4 normal children.¹⁸

Discussion

Sex chromosome aneuploidy has been found to occur in older women.^{23, 24} Court-Brown²⁵ noted a 5% incidence of cells with 45,X in the general female population after age 55. In the present cases, all women

were younger than 35 years of age and had a higher percentage of mosaicism. According to Bochkov et al²⁶ and Nielsen,²⁷ if more than 5 cells with identical chromosome abnormalities are found among 23 cells analyzed, a mosaic is established above the 25% level with 95% probability. These reports indicate that in all 5 women studied, the 46,XX/47,XXX sex chromosome represented true mosaicism rather than age effects.

Mosaicism is due to nondisjunction or anaphase lag of a chromosome after zygote formation. If the zygote initially had 46,XX chromosomes, the nondisjunction of an X chromosome would produce a mosaicism of 46,XX/45,X/47,XXX, or, with the loss of 45,X cell line, it would be 46,XX/47,XXX only. Mosaicism of 45,X/46,XX would be produced by an anaphase lag of an X chromosome in a normal zygote with 46,XX. An anaphase lag of a chromosome in a zygote with 47,XXX would produce a mosaicism of 46,XX/47,XXX in the fetus.

Five women with sex chromosome mosaicism and a history of spontaneous abortions were found to have normal as well as abnormal children with chromosomal defects (Table 1). Review of the literature revealed that 31 mothers with sex chromosome mosaicism conceived 96 times, and about three fourths of the fetuses were abnormal. Abortions occurred in 50%, and one fourth had genetic or other congenital abnormalities. It has also been reported that women having sex chromosome mosaicism have borne children with Down syndrome as well as with sex chromosome aneuploidy and mosaicism.^{13, 17, 28} This may indicate that a woman with mosaicism might be at greater risk of bearing an abnormal child than would nonmosaic parents. An ideal way to examine the relationship between fetal loss and sex chromosome mosaicism in the parents would be to monitor the chromosomes of their spontaneous abortuses. The most plausible explanation of abortion in trisomy X mosaic mothers is 1) the presence of a gene or genes for nondisjunction or an anaphase lag, which would produce abortuses with monosomy or trisomy, or 2) primary nondisjunction, which would produce an aneuploid nonviable zygote. Kim et al²⁹ previously reported a case of mosaicism in a man with 46,XX/47,XXY whose wife had had 3 spontaneous abortions and had borne a trisomy 21 child.

It has been estimated that approximately 52 to 60% of all fetuses aborted spontaneously are chromosomally abnormal.^{30,31} Approximately 15.5% have monosomy X and 52.6% have autosomal trisomy. In aborted fetuses trisomy X occurs rarely—less than 1%. The overall frequency of major chromosome disorders in couples with repeated abortions is 2.6%, of which

translocations are the most frequent type (2%); sex chromosome mosaicism occurred in 0.32%.³ In comparison, the frequency of sex chromosome mosaicism in the newborn population is 0.04%.^{27, 32, 33} Thus there is an eightfold increase in the frequency of sex chromosome mosaicism in women with fetal wastage in comparison to those with liveborn infants.

It may therefore be concluded that a chromosome analysis should be done routinely in every couple with a history of recurrent abortion or unexplained fetal wastage. Large numbers of cells should be analyzed for chromosome count to detect the presence of mosaicism. If possible, more than 1 source should be utilized for chromosome analysis, such as skin fibroblasts, lymphocytes, and gonadal tissues, if available. Precise genetic counseling must also be given to couples in whom abnormal karyotypes have been identified by new banding techniques. It should be recommended that subsequent pregnancies be monitored by amniocentesis in such cases so that abortion can be made available for genetically abnormal fetuses when found.

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FETUS, PLACENTA, AND NEWBORN

Amniotic fluid lipids in sickle cell disease

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Amniotic fluid of sickle cell disease patients past the thirty-seventh week of pregnancy contained 63.4%, 71.7%, and 48.6% less total lipids, total nonpolar lipids, and total phospholipids, respectively, as compared with amniotic fluid of normal patients. No remarkable variation in the composition of nonpolar lipids was noticed between the two groups. However, the phospholipid composition was significantly varied. For example, the percentage amounts of choline glycerophospholipids (lecithin) was low and the percentage amounts of other phospholipids was high in sickle cell pregnancy as compared with normal pregnancy. Furthermore, increased levels of polyunsaturated fatty acids and fluorescent lipid pigments were found in amniotic fluids of sickle cell patients. (AM. J. OBSTET. GYNECOL. 136:211, 1980.)

IN AN earlier study,¹ we reported the detailed composition of lipids of human amniotic fluids in normal pregnancy. This study and studies conducted by others²⁻⁴ confirm that lipids are normal constituents of amniotic fluids and increase progressively with gestational age. Nelson³ reported that total lipid, total phospholipid, and choline glycerophospholipid (lecithin) levels in amniotic fluids decrease in abnormal pregnancies associated with pre-eclampsia. Pomerance and co-workers,⁴ on the other hand, failed to find any significant variation in the content of phospholipids and triglycerides in amniotic fluid between normal and such abnormal pregnancies. Gluck and Kulovich⁵ re-

ported that abnormalities of pregnancy associated with maternal sickle cell disease accelerate fetal pulmonary maturation. They also indicated that most maternal conditions associated with accelerated maturation of fetal lung development also are associated with significant fetal and neonatal deaths. To our knowledge, nothing is known about the regulatory mechanism involved in the acceleration of fetal pulmonary maturation in maternal sickle cell disease. The present study reports the first comprehensive composition study of amniotic fluid lipids in maternal sickle cell disease.

Material and methods

Ten milliliters of amniotic fluid was obtained at 38 to 40 weeks' gestation from each of four normal subjects and four patients with sickle cell disease. The fluid was collected by either transabdominal or vaginal amniocentesis, and only specimens free of gross blood were used. Lipids were extracted, separated into various lipid classes by thin-layer chromatography (TLC), and quantitated by gravimetric and charring-transmission densitometric methods as described earlier.¹ A preparative silica gel TLC,⁶ using the solvent systems of Mangold and Malins,⁷ and Parker and Peterson,⁸ was done to isolate individual nonpolar and phospholipid

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Table I. Composition of human amniotic fluid lipids

Components	Normal	Sickle cell disease
Total lipids	42.14 $\pm$ 2.81*	15.41 $\pm$ 1.12
Total nonpolar lipids	30.41 $\pm$ 1.35	8.60 $\pm$ 0.82
Total polar lipids†	11.73 $\pm$ 1.25	6.81 $\pm$ 0.81
Total phospholipids	10.70 $\pm$ 0.91	5.50 $\pm$ 0.45
Fluorescence value‡	0.00	0.79 $\pm$ 0.08

*Values in milligrams per 100 ml of amniotic fluid $\pm$ SD of 4 analyses.

†Composed of phospholipids, cerebroside, and prostaglandins.

‡Fluorescence values are expressed relative to a quinine sulfate standard (1 μ g/ml in 0.1N H₂SO₄) which had a fluorescence intensity of 90 units when the meter multiplier in the spectrophotofluorometer was set at 0.3.

Table II. Percentage composition of nonpolar lipids

Parameters	Normal	Sickle cell disease
Hydrocarbons	7.58 $\pm$ 0.28*	6.60 $\pm$ 0.24
Cholesterol esters	22.52 $\pm$ 1.85	23.44 $\pm$ 1.02
Ether lipids	1.28 $\pm$ 0.01	1.32 $\pm$ 0.00
Triglycerides	31.17 $\pm$ 1.09	30.72 $\pm$ 1.05
Free fatty acids	15.81 $\pm$ 0.42	16.23 $\pm$ 0.61
Free cholesterol	16.07 $\pm$ 0.65	17.39 $\pm$ 0.28
Diglycerides	3.58 $\pm$ 0.01	3.00 $\pm$ 0.00
Monoglycerides	1.93 $\pm$ 0.01	1.83 $\pm$ 0.00

*Mean $\pm$ SD of 4 analyses.

Table III. Percentage composition of phospholipids

Parameters	Normal	Sickle cell disease
Ethanolamine glycerophospholipids	11.51 $\pm$ 0.62*	25.49 $\pm$ 0.71
Serine glycerophospholipids	7.99 $\pm$ 0.28	17.51 $\pm$ 0.58
Inositol glycerophospholipids	4.41 $\pm$ 0.12	8.89 $\pm$ 0.29
Choline glycerophospholipids	67.79 $\pm$ 2.52	30.49 $\pm$ 1.28
Sphingomyelins	8.11 $\pm$ 0.26	15.12 $\pm$ 0.73
Lysocholine glycerophospholipids	0.19 $\pm$ 0.00	2.50 $\pm$ 0.01

*Mean (% of total phospholipids) $\pm$ SD of 4 analyses.

classes, respectively. The quantity of free and total cholesterol in the total lipid solution was determined by adopting the procedure of Courchain and associates.¹¹ Glycerides (tri-, di-, and mono-) and free fatty acids isolated from the TLC plates were assayed by the methods of Van Handel and Zilversmit¹² and Novak,¹³ respectively. The quantity of total phospholipids in the total lipid solution, and individual phospholipids isolated from TLC plates, was determined by measuring the amount of phosphorus.¹⁴ The acyl group composition of individual lipid classes was determined by gas-liquid chromatography of their fatty acid esters¹⁵ according to the conditions described earlier.¹ For

fluorescence analysis, lipid extracts of amniotic fluid were prepared according to the method described by Fletcher and associates.¹⁶ Fluorescent measurements of these extracts were made with an Aminco-Bowman Spectrophotofluorometer. Quinine sulfate at a concentration of 1 μ g/ml of 0.1N H₂SO₄ was used as a standard for fluorescence intensity and wavelength calibration.

Results

Data on the composition of lipids at term are shown in Table I. It is noted that the percentage amount of both nonpolar and polar lipids are low in patients with sickle cell disease (S-S) as compared with normal patients. Lipid extracts from amniotic fluid of sickle cell patients showed fluorescence excitation and emission maxima at the 450 nm and 345 nm regions, respectively. These were absent in normal patients. Phospholipids were the major components of polar lipids in both cases. Cerebrosides and prostaglandins (E₂) were the minor polar lipid components detected in both groups. The amounts of cerebroside and prostaglandins were not measured. Table II shows the percentage composition of nonpolar lipids in normal and sickle cell pregnancy. No remarkable variation in the percentage composition of nonpolar lipids was noted between the two groups. In order of predominance, triglycerides, cholesterol esters, free cholesterol, fatty acids, and hydrocarbons were the major nonpolar lipids in both groups. Diglycerides, monoglycerides, and ether lipids were the minor components. Table III shows the percentage composition of phospholipids in normal and sickle cell pregnancy. It is observed that whereas the percentage amounts of choline glycerophospholipids were significantly low in sickle cell pregnancy, the percentage amounts of other phospholipids were high in sickle cell pregnancy as compared with normal pregnancy. In order of predominance, choline glycerophospholipids, ethanolamine glycerophospholipids, sphingomyelins, serine glycerophospholipids, and inositol glycerophospholipids were the major phospholipids in both groups. Lysocholine glycerophospholipids were present only in trace amounts in normal pregnancies, whereas amniotic fluid of sickle cell patients contained significantly high amounts of this lipid as compared with normal patients. Data on the acyl group composition of cholesterol esters, triglycerides, and free fatty acids are shown in Table IV. Palmitoyl (16:0), palmitoleoyl (16:1), stearoyl (18:0), and oleoyl (18:1) were the major acyl groups in cholesterol esters in both groups. The 16:0/16:1 ratio of cholesterol esters was high in sickle cell patients as compared with normal patients. The percentage amounts of 18:0, 18:1, 18:3, 20:4, 22:0, and

Table IV. Acyl group composition of nonpolar lipids

Acyl group	Normal			Sickle cell disease		
	Cholesterol esters	Triglycerides	Free fatty acids	Cholesterol esters	Triglycerides	Free fatty acids
12:0*	1.1 ± 0.1†	1.9 ± 0.2	0.2 ± 0.1	0.9 ± 0.1	1.3 ± 0.3	2.1 ± 0.3
14:0	4.4 ± 0.5	1.8 ± 0.1	2.2 ± 0.3	3.8 ± 0.7	7.5 ± 1.1	6.5 ± 1.2
14:1	2.6 ± 0.2	1.6 ± 0.2	0.2 ± 0.1	1.1 ± 0.2	1.2 ± 0.1	1.0 ± 0.2
15:0	2.0 ± 0.3	1.3 ± 0.1	0.6 ± 0.2	1.8 ± 0.4	0.9 ± 0.1	1.0 ± 0.3
15:1	1.8 ± 0.2	1.3 ± 0.1	0.3 ± 0.1	1.6 ± 0.5	1.4 ± 0.3	0.6 ± 0.1
16:0	30.5 ± 1.3	25.2 ± 1.1	26.6 ± 1.9	20.7 ± 1.2	20.8 ± 1.8	20.6 ± 1.3
16:1	10.9 ± 0.7	5.1 ± 1.1	5.7 ± 0.8	4.6 ± 1.3	3.2 ± 0.3	3.2 ± 0.4
17:0	3.2 ± 0.2	0.9 ± 0.1	0.6 ± 0.2	1.8 ± 0.6	0.8 ± 0.1	1.3 ± 0.4
17:1	2.1 ± 0.1	1.0 ± 0.1	0.3 ± 0.1	1.6 ± 0.5	1.2 ± 0.1	1.5 ± 0.3
18:0	4.1 ± 0.4	12.2 ± 1.2	15.6 ± 1.3	10.6 ± 0.9	10.8 ± 0.5	13.2 ± 1.1
18:1	24.2 ± 1.9	37.8 ± 1.8	42.3 ± 1.9	31.2 ± 1.7	30.3 ± 1.7	32.8 ± 2.5
18:2	0.6 ± 0.1	0.9 ± 0.1	1.2 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.2 ± 0.1
18:3	0.8 ± 0.1	0.9 ± 0.2	0.6 ± 0.1	3.8 ± 0.1	3.6 ± 0.7	2.3 ± 0.5
20:0	2.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	1.1 ± 0.1	0.6 ± 0.1	1.8 ± 0.3
20:4	2.8 ± 0.3	2.4 ± 0.7	0.8 ± 0.1	4.2 ± 0.1	4.9 ± 0.7	4.5 ± 1.1
22:0	2.9 ± 0.5	2.5 ± 0.2	0.6 ± 0.2	4.4 ± 0.1	5.5 ± 0.5	2.1 ± 0.6
22:5	2.4 ± 0.5	0.6 ± 0.1	0.4 ± 0.1	4.3 ± 0.1	3.8 ± 0.3	2.2 ± 0.4
24:0	1.5 ± 0.2	1.4 ± 0.1	1.6 ± 0.3	1.6 ± 0.1	1.3 ± 0.4	2.1 ± 0.3

*Number of carbon atoms: number of double bonds.

†Each value is the mean (weight % of total fatty acids) ± SD of 4 analyses.

Table V. Acyl group composition of phospholipids

Acyl group	Normal		Sickle cell disease	
	Choline glycerophospholipids	Sphingomyelins	Choline glycerophospholipids	Sphingomyelins
12:0*	1.5 ± 0.1†	2.1 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
14:0	4.1 ± 0.2	4.6 ± 0.2	4.6 ± 1.0	2.5 ± 0.1
14:1	0.5 ± 0.1	1.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1
15:0	1.0 ± 0.1	1.6 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
15:1	0.8 ± 0.1	1.4 ± 0.2	0.5 ± 0.1	0.4 ± 0.1
16:0	49.6 ± 2.3	32.5 ± 1.5	22.3 ± 1.9	21.3 ± 1.8
16:1	5.6 ± 0.9	5.2 ± 0.4	8.3 ± 1.1	4.4 ± 0.1
17:0	0.8 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	2.9 ± 0.1
17:1	0.5 ± 0.1	0.6 ± 0.1	10.8 ± 1.1	0.6 ± 0.1
18:0	6.5 ± 0.9	7.9 ± 0.6	21.2 ± 1.3	12.8 ± 1.5
18:1	12.5 ± 1.3	24.3 ± 1.5	3.9 ± 0.6	32.5 ± 1.1
18:2	3.6 ± 0.1	1.9 ± 0.2	4.8 ± 1.5	4.3 ± 0.1
18:3	0.9 ± 0.1	1.5 ± 0.1	1.8 ± 0.4	4.8 ± 1.0
20:0	1.4 ± 0.2	0.5 ± 0.1	0.9 ± 0.2	1.0 ± 0.1
20:4	6.5 ± 1.3	3.6 ± 0.2	10.3 ± 1.1	5.3 ± 1.4
22:0	0.8 ± 0.1	1.5 ± 0.2	0.9 ± 0.1	0.5 ± 0.1
22:5	0.6 ± 0.1	2.2 ± 0.3	4.2 ± 1.2	3.1 ± 1.3
24:0	2.8 ± 0.5	5.8 ± 0.5	2.5 ± 0.4	2.2 ± 0.3

*Number of carbon atoms: number of double bonds.

†Each value is the mean (weight % of total fatty acids) ± SD of 4 analyses.

acyl groups in cholesterol esters were high in sickle cell pregnancy as compared with normal pregnancy. Palmitoyl, palmitoleoyl, stearoyl, and oleoyl were the major acyl groups in triglycerides in both groups. The percentage amounts of 14:0, 18:3, 20:4, 22:0, and 22:5 were high in triglycerides in sickle cell pregnancy as compared with normal pregnancy. The percentage amounts of 16:0 and 18:1 acyl groups in triglycerides were low in sickle cell pregnancy as compared with normal pregnancy. Palmitoyl, stearoyl, and oleoyl were

the major acyl groups in the free fatty acid fraction of both groups. The percentage amounts of 12:0, 14:0, 18:3, 20:4, 22:0, and 22:5 in free fatty acids were high in the sickle cell group as compared with normal group. The percentage amounts of 16:0 and 18:1 in free fatty acids were low in sickle cell pregnancy as compared with normal pregnancy. Data on the acyl group composition of choline glycerophospholipids (lecithin) and sphingomyelins are shown in Table V. Myristoyl, palmitoyl, palmitoleoyl, stearoyl, oleoyl,

linoleoyl, and arachidonoyl were the major acyl groups of lecithin in both cases. It is observed that whereas the percentage amounts of 16:0 in lecithin were significantly low in sickle cell pregnancy as compared with normal pregnancy, the percentage amounts of 16:1, 18:0, 18:1, 20:4, and 22:5 in lecithin were high in sickle cell patients as compared with normal patients. Myristoyl, palmitoyl, stearoyl, oleoyl, linoleoyl, arachidonoyl, docosapentaenoyl, and lignoceroyl (24:0) were the major acyl groups in sphingomyelin. The percentage amounts of 16:0 acyl group in sphingomyelin were low in sickle cell pregnancy as compared with normal pregnancy whereas the percentage amounts of 17:1, 18:0, 18:1, 18:3, 20:4, and 22:5 were high in sickle cell patients as compared with normal patients.

Comment

Amniotic fluids of sickle cell patients contained 63.4%, 71.7%, and 48.6% less total lipids, total nonpolar lipids, and total phospholipids, respectively, as compared with amniotic fluids of normal patients. Thus it is observed that in sickle cell pregnancy, nonpolar lipids are lost in higher amounts than are phospholipids. It is not known at this time whether the excessive loss of nonpolar lipids, such as triglycerides in amniotic fluids of sickle cell patients, is attributable to the excessive utilization of the storage lipids as a source of energy by the fetus. It is known that various esterified fatty acids in amniotic fluids arise in the fetus.⁶ It has also been reported that in several abnormal pregnancies (prematurity, respiratory distress syndrome, hyaline membrane disease, anencephaly with polyhydramnios) the lipid values of amniotic fluids are reduced.

Increased levels of fluorescent lipid pigments were found in amniotic fluids of sickle cell patients. Increased levels of fluorescent lipid pigments have also been found in sickled erythrocytes.¹⁷ Peroxidation of unsaturated lipids has been related to the occurrence of fluorescence pigments in sickled erythrocytes. It is not known at this time whether there is an increased peroxidation of amniotic fluid lipids in sickle cell patients. It is to be noted, however, that polyunsaturated fatty acid levels in amniotic fluid are high in sickle cell patients as compared with normal patients, and unsaturated lipids are susceptible to oxidation.

There was no remarkable variation in the composition of nonpolar lipids between normal and sickle cell

patients. Each component of nonpolar lipids was reduced approximately 70% in sickle cell patients compared with normal patients. The free fatty content of amniotic fluids is rather high, perhaps because of the lapse of time between collection and extraction.¹⁸ However, the existence of high amount free fatty acids in amniotic fluids has been reported earlier.^{1, 19}

The composition of phospholipids was significantly varied between normal and sickle cell patients. Sickle cell patients contained 48.6% less total phospholipids than did normal patients. This reduction of total phospholipids is attributed mostly to the loss of lecithin. Sickle cell patients contained 76.9% less lecithin in amniotic fluids as compared with normal patients. There was no significant change in the absolute amount of inositol glycerophospholipids and sphingomyelins. However, sickle cell patients contained 14%, 11.4%, and 84.6% more ethanolamine glycerophospholipids, serine glycerophospholipids, and choline glycerophospholipids, respectively, as compared with normal patients. Lysocholine glycerophospholipids were present only in trace amounts in normal patients. The physiologic significance of the increased ethanolamine glycerophospholipids and serine glycerophospholipids in amniotic fluids is not known at this time. However, it is known that these two lipids are responsible for the thromboplastic activity of platelets.²⁰ It is possible that there is a relationship between blood clotting, sickle cell disease, and increased amniotic fluid ethanolamine glycerophospholipids and serine glycerophospholipids. The increase in choline glycerophospholipids in the amniotic fluid of sickle cell patients may be associated with damage to either the fetal or alveolar membranes. It has been reported that there is a significant decrease in lecithin in the lungs of infants dying of hyaline membrane disease,^{21, 22} and also it is thought that fetal lungs contribute to the formation of amniotic fluids.²³⁻²⁵ There it seems possible that abnormal amniotic fluid phospholipid patterns in sickle cell pregnancy might be associated with a high incidence of neonatal death. Further studies are needed to understand the mechanism involved in the decreased synthesis of lung surfactant lecithin.

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ORIGINAL COMMUNICATIONS

INTERVAL MINI-LAPAROTOMY: AN ALTERNATIVE TO LAPAROSCOPIC STERILIZATION?

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The author compares the contraindications, complications, and outcomes of laparoscopic and interval mini-laparotomy sterilization procedures. A review of a major series is presented.

Clearly, with the world's burgeoning population growth and its resultant effect on our natural resources, it is necessary to continue our efforts to refine and develop better techniques that will assure needed fertility regulation. Particularly, these contraceptive techniques must have broad applicability to developing nations and indeed an applicability to those less affluent enclaves within our own so-called developed nations. Hence, these new techniques must not require sophisticated health care delivery systems and obviously must offer safety, effectiveness, and economy. The development of laparoscopic techniques for female sterilization represents a step in this direction. This procedure can be conducted on an outpatient basis under local anesthesia. The operating time is relatively short and the postoperative recovery period normally is brief. The focus of this presentation, therefore, will be to consider whether or not the mini-laparotomy sterilization procedure achieves these ideals better and with fewer complications than does laparoscopy.

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EQUIPMENT AND SURGICAL TECHNIQUES

A brief review of the equipment required and the surgical techniques involved is necessary before attempting to compare the advantages and disadvantages of the two procedures. The operative equipment needed for laparoscopic surgery is rather extensive and includes an insufflator, fiber optics, light source, and laparoscopic surgical instruments, ie, Verres needle, valved cannula, trocars, laparoscope, coagulation forceps, scissors, aspirator, and coagulation unit. The mini-laparotomy procedure requires only some specialized form of instrument to elevate the uterus, such as a valved uterine cannula or, even better, the ballooned uterine elevator as recommended by Hasson.¹

The basic steps in the technique for laparoscopy include the establishment of a pneumoperitoneum, the introduction of the laparoscope preceded by the use of a trocar, and the electrocoagulation of the oviducts or use of the spring-clip method or Silastic bands or rings.

The technique for the mini-laparotomy procedure is simple and can be performed either with general, conduction, or local anesthesia. The patient is placed in the lithotomy position with an indwelling Foley catheter in place and either a uterine cannula or ballooned uterine elevator is placed in the uterine cavity for mobilization. The abdomen is entered utilizing a transverse suprapubic incision just above the hairline usually 2.5 to 3 cm in maximal length. The uterus is elevated to approximate the anterior abdominal wall and rotated in either direction thereby bringing the fal-

TABLE 1. INTERVAL MINI-LAPAROTOMY VS LAPAROSCOPIC STERILIZATION—COMPLICATIONS

	Total No. of Procedures	Uterine Perforation		Bladder Injury		Intestinal Injury		Bleeding		Infections		Deaths	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Laparoscopic													
Corson-Bolognese ⁴	1,545	9	0.58	1	0.06	3	0.19	1	0.06	9	.58		
Georgy, et al ¹⁸	800			2	0.25								
Peterson-Behrman ¹⁹	186					1	0.53	5	2.6	0	0.0		
Thompson-Wheless ⁸	3,600					11	0.30						
Chan-Pevan ²⁰	142							2	1.4				
AAGL (1972-1974) ²	185,000											28	.015
Mini-Laparotomy													
Ramathibodi ¹⁰	2,786	9	0.32	5	0.32	13	0.11	10	0.36	26	.93	0	0

loper tubes into view. Babcock clamps are used to "walk" the tubes in a lateral direction until the fimbriated ends are identified. From this point on, a simple Pomeroy procedure is conducted.

CONTRAINDICATIONS

In considering contraindications, only those entities uncommon to the other procedure will be discussed, ie, unilateral contraindications. First, there are no distinct contraindications for the mini-laparotomy procedure that are unique and thus do not apply to laparoscopy. To the contrary, there are three clear contraindications and two relative contraindications existing exclusively for laparoscopy. These are cardiorespiratory decompensation, sickle hemoglobinopathy, and hernias. Relative contraindications are peritonitis and intestinal obstruction; however, the latter two conditions would by and large obviate elective sterilization.

On the other hand, cardiorespiratory decompensation constitutes a contraindication to laparoscopic procedures—even those conducted under local anesthesia. Because of the relatively high fixed position of the diaphragm created by the pneumoperitoneum, lung aeration is further compromised. And, in 90 percent of laparoscopic procedures conducted in this country, carbon dioxide is the gas utilized; hence, varying degrees of hypercarbia develop, further reducing adequate tissue oxygenation.²

For the same reasons listed above, laparoscopy

is contraindicated in patients with sickle hemoglobinopathies including sickle cell trait. Both reduced oxygen tension and decreased pH promotes sickling of the defective erythrocytes.

Most authorities consider abdominal hernia formation, especially hiatus hernias, as a barrier to laparoscopy.³ These weakened areas are particularly susceptible to the increased intra-abdominal pressure created by the pneumoperitoneum. Some, however, question the justification for inclusion of non-hiatal hernias.⁴

COMPLICATIONS

As with contraindications, there are some complications that are unilateral and apply only to laparoscopy, primarily because of unique characteristics inherent in creating the pneumoperitoneum. Hypercarbia results after the insufflation of carbon dioxide.⁵ The elevated pCO₂ has been shown to be the result of carbon dioxide absorption from the peritoneal surface, and not simply due to improper ventilation during anesthesia.⁶

Air embolism, pneumothorax, and mediastinal emphysema are all complications secondary to the establishment of the pneumoperitoneum. Air (CO₂) when placed anywhere other than the peritoneal cavity is potentially dangerous. Such misadventures occur when carbon dioxide is introduced into a major vessel or into the subcutaneous or retroperitoneal spaces.

Accidental burns associated with laparoscopy may affect the patient or operator.⁷ Electrocoagulation burns to the patient may affect the patient's

TABLE 2. INTERVAL MINI-LAPAROTOMY VS LAPAROSCOPIC STERILIZATION—SUBSEQUENT PREGNANCIES

	Total No. of Procedures	No. of Pregnancies	%
Laparoscopic			
Corson-Bolognese ⁴	1,545	3	0.19
Peterson-Behrman ¹⁹	186	1	0.53
Thompson-Wheeler ⁸	4,200	31	0.73
AAGL (1972-1974) ²	185,000	300	0.16
Mini-Laparotomy			
Ramathibodi ¹⁰	2,786	?	?
Garb ¹⁵	5,477	22	0.4
Tietze ¹⁶	20,000	34	0.17

skin, anterior abdominal wall, or any of the intra-abdominal viscera. Most often such burns are caused by faulty equipment, poor surgical technique, or both.

Inadvertent perforation can occur while establishing the pneumoperitoneum or introducing the trocar, and rarely even by the laparoscope itself. Structures that are most often injured are the intestines, omentum, urinary bladder, and larger blood vessels.^{4,8}

Complications that have been described thus far are those which occur primarily as a result of the unique characteristics associated with establishing the pneumoperitoneum. However, there are some complications mutually common to mini-laparotomy and hence a basis exists for comparison. In making these comparisons, the author is fully aware that no well-structured prospective study between interval laparoscopic sterilization and mini-laparotomy has been conducted. To the author's knowledge, there are no standardized definitions to assure uniformity in reporting. This study compares the outcomes of several laparoscopic studies with one large mini-laparotomy study.^{9,10}

COMPARISON OF OUTCOMES

Table 1 compares uterine perforation, bladder injury, and intestinal injury. Uterine perforation occurred almost twice as often with laparoscopy. Most uterine perforations, occurring using the balloon uterine elevator, happen when catheters of improper internal diameters were used.¹¹

Bladder injuries sustained during mini-laparotomy were more frequent in one and less frequent than in another laparoscopic study. Intestinal injuries were less frequent with mini-laparotomy than with all three laparoscopy series.

Table 1 compares bleeding, infections, and deaths. Bleeding occurred more often with mini-laparotomy in one study and less often in another than with the laparoscopic approach.

Infections seen with mini-laparotomy occurred more frequently than in any of the laparoscopic studies. The Ramathibodi study, however, subdivided infections into grossly infected (two cases) and skin inflammation (24 cases). Also, 466 cases (16 percent) of the 2,786 procedures from this study were conducted in outpatient centers in rural Thailand by nonphysicians.

An extensively compiled study by the American Association of Gynecologic Laparoscopists (185,000 procedures) revealed a mortality rate of 15 deaths per 100,000 procedures for the three-year period 1972-1974.² However, when these figures are reviewed by individual year, there is a trend toward an annual decline in the mortality rate: 1972—24/100,000, 1973—13/100,000, and 1974—8.5/100,000 procedures. No mortality figures were alluded to in either of Osathanondh's studies.^{9,10} The mortality rate for surgical oviduct ligation and resection is probably near five deaths per 100,000 procedures as reported by Child.¹²

There are some who acknowledge a significantly higher subsequent pregnancy rate with laparoscopy and, hence, are unsure of the justifi-

cation of this procedure.¹³ Here again, a prospective study comparing these two parameters has not been conducted. In Table 2, the subsequent pregnancy rate from five laparoscopy studies is reviewed. The pregnancy rate in these studies ranged from a low of 0.16 percent to a high of 2.8 percent, in a study using the spring clip exclusively. There is no specified time period or cutoff point by which pregnancy in these studies was measured. The question of subsequent pregnancies did not appear in either of the Ramathibodi studies.^{9,10} However, Garb reported 22 pregnancies in 5,477 Pomeroy procedures, yielding an overall pregnancy rate of 0.4 percent.¹⁵ Based on ten major studies from three continents, Tietze found 34 failures occurred with 20,000 surgical sterilizations (0.17 percent).¹⁶ In these studies, no distinction was made as to the time of the procedure, ie, postpartum or during the interval state.

Another factor for consideration is the required operating time for the two procedures. Such a comparison has been made of 60 operations, 30 by laparoscopy and 30 by mini-laparotomy. The median and mean operating time for mini-laparotomy was 23 minutes and 29 minutes, respectively. And for laparoscopy the time was 20 and 21 minutes, respectively.¹⁷

It is difficult, if not impossible, to accurately measure the economic difference between the two procedures; however, without doubt, the special training and equipment required for laparoscopy require an increased financial output. Possibly with the exception of the cervical cannula or ballooned uterine elevator all units now conducting surgery have the basic equipment necessary to perform mini-laparotomy surgery. On the other hand, an average reasonable cost for complete laparoscopic equipment is approximately \$4,500. This includes fiber optics, a light source, insufflator, and numerous operative accessories. However, any busy service will require a minimum of two completely interchangeable units or an initial capital outlay of approximately \$9,000 per hospital.

SUMMARY

Some crude comparisons between laparoscopy and mini-laparotomy have been made. As often occurs when firm data are lacking, more questions are raised than are answered. All who provide sterilization services to women should have open

minds and remain flexible, and hopefully time and a few well-structured prospective studies will provide some firm answers.

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EFFECT OF MERCURY COMPOUNDS ON CHOLINEACETYL TRANSFERASE¹
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ABSTRACT

Methylmercury poisoning exhibits prominent signs and symptoms of the central nervous system. In an attempt to study the mechanism of toxicity, mercuric chloride (HgCl_2) and methylmercury chloride (CH_3HgCl) were given orally by gavage and through drinking water to male albino rats. Rats were sacrificed at appropriate time and brain and diaphragm were analyzed for cholineacetyltransferase (ChAT) activity, and also examined histopathologically. Both HgCl_2 and CH_3HgCl given orally by gavage significantly inhibited ChAT activity which was dose related. CH_3HgCl produced greater inhibition than HgCl_2 . CH_3HgCl through drinking water also significantly inhibited brain ChAT, however rats did not drink water containing HgCl_2 . Both HgCl_2 and CH_3HgCl also inhibited ChAT when incubated *in vitro* with rat brain homogenates. Histopathological studies revealed neural degeneration and necrosis in the cerebrum of rats treated with these mercurials. These results indicate the possible involvement of cholinergic system during mercury intoxication.

The clinical signs and symptoms associated with methyl mercury poisoning have been well documented since the Minamata Bay outbreak in Japan (1,2). Although a syndrome of mercurial intoxication can be brought about by either inorganic or organic compounds, neurological damage is more severe in organic intoxication (3). The early symptoms are reported to be peripheral neuropathy, paresthesia and fatigue. Impairment of memory and inability to concentrate, indicate that central nervous system is involved (4). Due to high affinity of mercuric ions towards the sulfhydryl (-SH) and disulfide (S-S) groups, the biochemical basis for the toxicological effects of mercury is generally sought through mercury sulfur interactions (5). Choline acetyl transferase (ChAT) a key enzyme for the synthesis of acetylcholine (ACh) has sulfhydryl groups (6). Erdina *et al* (7) found a decreased cortical ACh in mercury exposed animals. The purpose of this investigation is to study the effect of mercurials on ChAT, with a view to explore the biochemical mechanism of mercury intoxication.

MATERIALS AND METHODS

Mercuric chloride (HgCl_2) was obtained from Merck & Co. Inc. Rahway

¹A preliminary report of this work was presented at the annual meeting of American Society of Pharmacology and Experimental Therapeutics, Portland, Oregon, August, 1979.

²To whom inquiries should be directed

E.J. and methyl mercury chloride (CH_3HgCl) was obtained from Alfa Inorganics, Beverly, Massachusetts and were dissolved in physiological saline. Male albino sprague dawley rats (Harlan Industries Inc., Cumberland, Indiana) kept at *ad-libitum* diet and free access to water were used in this study. One group of three animals was used for each experiment. HgCl_2 and CH_3HgCl at dosages of 2 mg/kg and 10 mg/kg were given orally by gavage to individual groups of rats, Monday through Friday for 4 weeks and control group was receiving an equivalent amount of saline. HgCl_2 and CH_3HgCl was also given in drinking water at a concentration of 10 $\mu\text{g}/\text{ml}$ and 50 $\mu\text{g}/\text{ml}$ and control group was given drinking water (tap). Animals were sacrificed at appropriate time (as indicated under the results) by decapitation; brain and diaphragm were taken out, washed, blotted and homogenized in phosphate buffer (pH 7.4, 0.5M) containing NaCN (0.02 M) and EDTA (0.005 M). Ten percent brain and diaphragm homogenates were used for ChAT assay. ChAT was assayed by measuring the formation of ^{14}C ACh from ^{14}C Acetyl CoA and choline using the methods reported by Harbison, Dwivedi and Evans (8). For *in vitro* studies, HgCl_2 and CH_3HgCl were dissolved in distilled water at different concentrations and were added to the incubation medium with phosphate buffer.

Histopathology: Brain tissue was fixed in 10 percent neutral buffered formalin and embedded in paraffin, sectioned and stained with hematoxylin and eosin (H&E) and observed microscopically for histopathological changes. Brain tissue taken from animals treated with HgCl_2 and CH_3HgCl , as well as normal (control) rat were used in this study.

Statistical Evaluation: Statistical comparison between sample means was made by the two tailed group student's T test. The level of significance in all cases was considered at $P < 0.05$.

RESULTS AND DISCUSSION

The effect of HgCl_2 and CH_3HgCl on rat brain and diaphragm ChAT is shown in Table 1.

As is evident from this Table, both HgCl_2 and CH_3HgCl significantly inhibited brain ChAT activity ($P < 0.05$), which is also dose related. However, CH_3HgCl produced greater inhibition than HgCl_2 at both dosages studied. Both HgCl_2 and CH_3HgCl inhibited rat diaphragm ChAT, CH_3HgCl produced higher inhibition at a lower dosage of 2 mg/kg than a higher dosage of 10 mg/kg. In studies using drinking water, animals refused to drink HgCl_2 in water; therefore, we could not get any data for the effect of HgCl_2 on ChAT through drinking water. As is evident from Table 2, CH_3HgCl given through drinking water significantly inhibited brain ChAT activity ($P < 0.05$). Both HgCl_2 and CH_3HgCl also inhibited rat brain ChAT when incubated *in vitro*. CH_3HgCl produced a 96% inhibition and HgCl_2 produced a 67% inhibition of ChAT activity at a final concentration of $1 \times 10^{-4}\text{M}$.

Histopathological studies revealed neural degeneration and cerebral necrosis in HgCl_2 and CH_3HgCl treated rats.

A significant decrease in the ChAT activity of rat brain and diaphragm

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TABLE 1

EFFECT OF $HgCl_2$ and CH_3HgCl GIVEN ORALLY MONDAY-FRIDAY FOR FOUR CONSECUTIVE WEEKS ON RAT BRAIN AND DIAPHRAGM CHOLINE ACETYL TRANSFERASE.

TREATMENT	DOSAGE	ChAT ACTIVITY	
		$\times 10^{-9}$ MOLES ACh SYNTHESIZED/g/HR*	
		DIAPHRAGM	BRAIN
CONTROL	-	521.3 $\pm$ 16.5	961.2 $\pm$ 38.6
$HgCl_2$	2mg/kg	270.6 $\pm$ 10.2 (48)**	663.2 $\pm$ 12.1(31)**
$HgCl_2$	10mg/kg	505.5 $\pm$ 14.3 (03)	389.3 $\pm$ 6.9(59)**
CH_3HgCl	2mg/kg	123.9 $\pm$ 7.1 (76)**	597.4 $\pm$ 14.2(38)**
CH_3HgCl	10mg/kg	326.8 $\pm$ 8.9 (37)**	318.6 $\pm$ 9.8(67)**

*Each value represents mean $\pm$ standard error, which is derived from three separate animals and assay from each animal was done in duplicate. Experimental conditions are as described in text. Figures in parenthesis represent percent inhibition. **Significant inhibition $P < 0.05$.

TABLE 2

EFFECT OF CH_3HgCl GIVEN IN DRINKING WATER ON RAT BRAIN CHOLINE ACETYL TRANSFERASE ACTIVITY.

TREATMENT	DOSAGE	$\times 10^{-9}$ MOLES ACh SYNTHESIZED/g/HR*		
		TIME OF SACRIFICE		
		5 DAYS	10 DAYS	20 DAYS
CONTROL	-	887.2 $\pm$ 62.1	795.8 $\pm$ 18.8	889.6 $\pm$ 19.7
CH_3HgCl	10 μ g/ml	686.8 $\pm$ 38.4 (17)**	648.6 $\pm$ 8.1 (22)**	596.8 $\pm$ 74.9 (28)**
CH_3HgCl	50 μ g/ml	611.8 $\pm$ 17.3 (26)**	479.9 $\pm$ 11.5 (42)**	678.7 $\pm$ 15.9 (20)**

*Each value represents mean $\pm$ SE, which is derived from three animals and each assay was done in duplicate. Experimental conditions are described in text. Figures in parenthesis represent percent inhibition. **Significant inhibition $P < 0.05$.

In $HgCl_2$ and CH_3HgCl treated animals could be explained by the interaction of mercurials with sulfhydryl group present of ChAT (5,6). In diaphragm tissue, a higher inhibition of ChAT activity was noted at the lower dosages of 2 mg/kg than 10 mg/kg of $HgCl_2$ and CH_3HgCl . Similar results were also observed during cadmium induced immunopathological changes in rats (9,10). This might be due to a protective mechanism which is only mimicked by a higher dose of mercury, which induces the biosynthesis of metallothionein (11). However, further studies are needed to confirm the existence of the above mechanism in dosages being used in our study. Interestingly however, a similar pattern is not observed in the brain tissues. Von Burg and Landry (12) has reported that methyl mercury is capable of inhibiting rat phrenic nerve muscular contraction of the isolated hemidiaphragm preparations and explained the observed inhibition due to an action on the disulfide bond, believed to be present on the cholinergic receptor. Irdina et al., (6) observed that methyl mercury, produced a decreased cortical ACh in the absence of changes in acetyl cholinesterase (AChE) activity and explained the

suppression of biosynthesis of this neurohormone, possibly due to impaired supply of acetyl-CoA from mitochondria. Our results indicate a decreased ChAT activity after mercurial exposure which could be responsible for the decreased levels of ACh. ChAT inhibition observed *in vitro* suggests the possible interaction with thiol group present on ChAT, which is responsible for decreased ChAT activity and decreased ACh synthesis. Therefore, in addition to the action on the cholinergic receptor, these mercurials also inactivate the enzyme involved in the synthesis of ACh and all these actions put together may be responsible for neurotoxicity. However, further studies are needed to fully evaluate the effect of these mercurials on the complete cholinergic system and other neurotransmitters and the enzymes involved in their pathway to get a clear picture of the biochemical basis of mercury intoxication.

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Henry W. Foster, Jr., MD

Managing sickle cell anemia in pregnant patients

The basic approach consists of blood and fluid replacement, and close observation. Prophylactic partial exchange transfusions, performed at about 24 weeks gestation, may help prevent or at least decrease the frequency and severity of symptoms. Genetic counseling is essential, as is choosing the right contraceptive after delivery.

Few conditions are associated with greater maternal morbidity and mortality, and fetal wastage, than is sickle cell disease in the pregnant patient. The current maternal mortality figure is imprecise, but has been reported as high as 10%.¹ Fetal wastage, including abortion and perinatal loss, may range between 40% and 60%. Treatment plans must be directed toward alleviating the symptoms of this genetically acquired incurable disease.

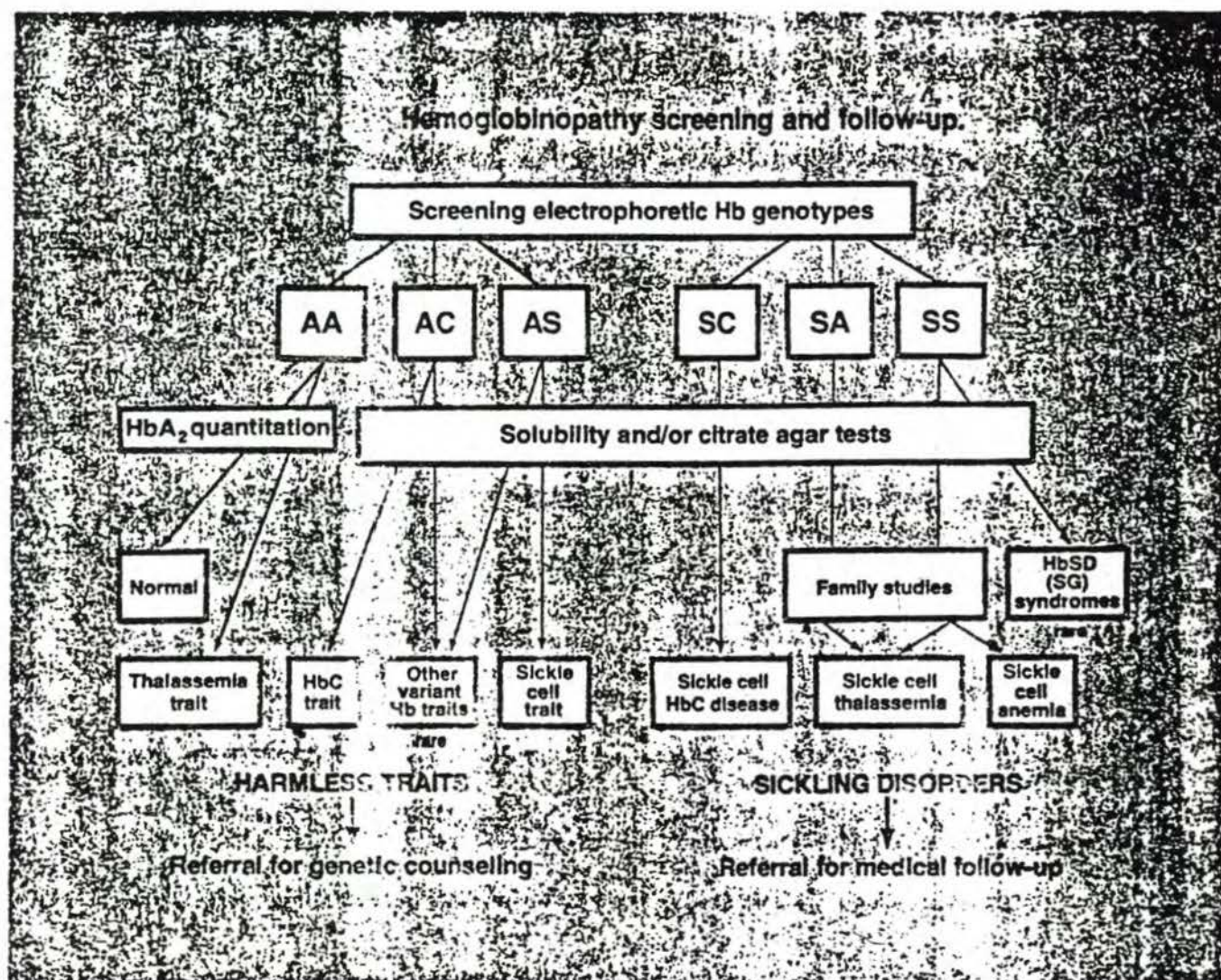
The altered hemoglobin molecule characteristic of the disease, seen primarily in individuals of African descent, probably occurred as a spontaneous mutation in response to the malaria parasite *Plasmodium falciparum*. The mutation affords protection by denying the malaria parasite the necessary concentrations of oxygen within the erythrocytes. But while this Mendelian trait—thought to be an autosomal recessive—protects against one disease state, it produces a new set of abnormal clinical manifestations.

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The molecular alteration that distinguishes hemoglobin S (HbS) from normal hemoglobin A (HbA) appears to be almost inconsequential. A minor change in the sequence of only two of the hemoglobin molecule's 574 amino acids significantly affects the oxygen-carrying capacity and survival time of the red blood cells. Normally, the hemoglobin molecule consists of four polypeptide chains, two alpha chains (containing 141 amino acids), and two beta chains (containing 146 amino acids). The substitution of the single amino acid valine for glutamic acid at a specific site in each beta chain (sixth position from the N-terminus) distinguishes HbS from HbA. Sickle cell hemoglobin C disease (HbC) involves the substitution of lysine for glutamic acid at the same position.

More than 150 abnormal hemoglobins have been identified, but the vast majority produce no clinical manifestations. The five hemoglobinopathies seen most often in Afro-Americans involve HbS and HbC. The homozygous HbSS and the doubly heterozygous HbSC and HbSThal (thalassemia) hemoglobinopathies

SICKLE CELL AND PREGNANCY



are associated with the greatest maternal morbidity and mortality and fetal wastage. The approximate incidence of the various hemoglobinopathies in black Americans are as follows: sickle cell trait, HbAS, 1 in 12; hemoglobin AC, 1 in 60; sickle cell anemia, HbSS, 1 in 600; sickle cell hemoglobin C disease, HbSC, 1 in 850; and sickle cell β thalassemia, HbS β Thal, 1 in 1,600. Hemoglobin C disease, HbCC, the sixth most common hemoglobinopathy, which affects 1 in 4,400 black Americans, has no significant adverse effect on morbidity and mortality either for mother or for fetus.

Need for screening and counseling

Because of the trait's wide prevalence among people of African descent, pregnant patients must be accurately and consistently screened. The need to identify those with the homozygous and doubly heterozygous forms (associated with extreme maternal and fetal mortality and morbidity) is obvious. However, it is also important to identify other, less dramatic, forms. Patients who carry only the trait for abnormal hemoglobin, though they are usually asymptomatic, can produce children with sickle cell disease if the father has the disease

or carries the trait. An awareness of the possibility of sickle cell disease in the newborn alerts the parents and the pediatrician and affords an opportunity to diminish the impact of early life-threatening complications.

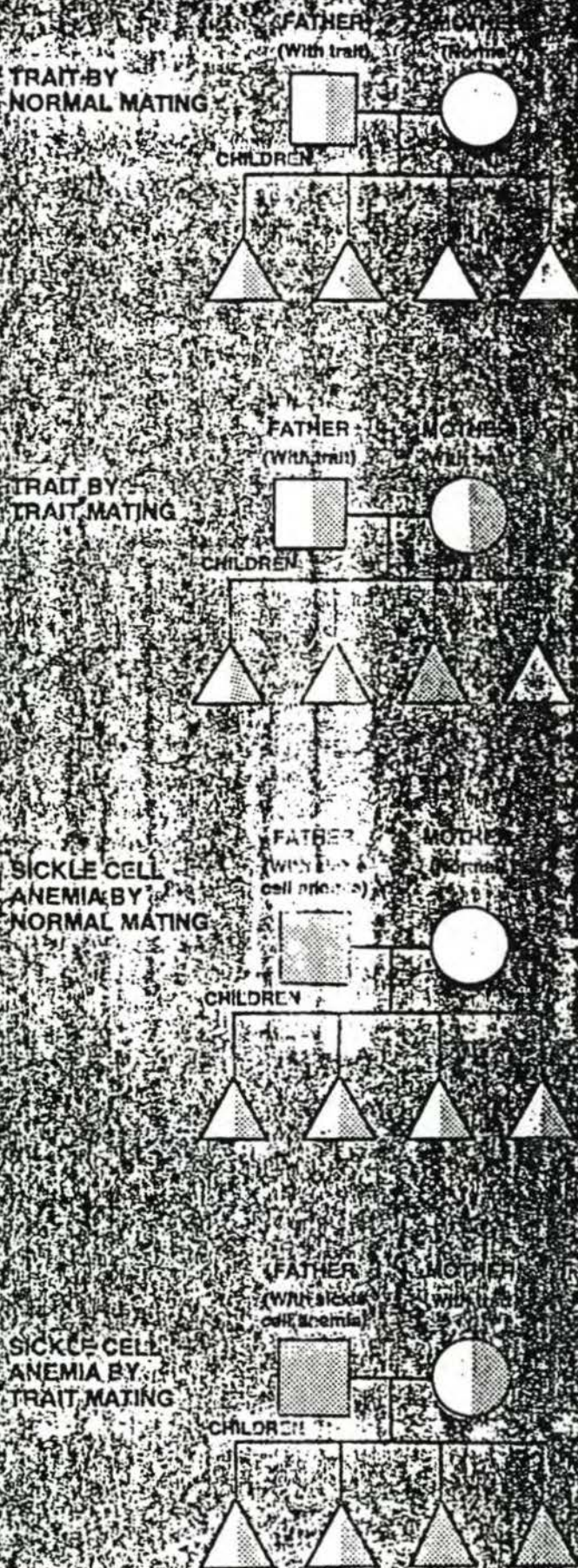
Proper screening for abnormal hemoglobins is best accomplished by electrophoresis followed by solubility testing. These tests—once considered sophisticated—can be obtained through almost any clinical laboratory and are cost-effective when you consider the prevalence of the abnormal hemoglobin. The cost (in Nashville) is \$20. There is, of course, no need to repeat the test in subsequent pregnancies.

The so-called sickle prep test, which uses sodium metabisulfite to promote sickling by reducing oxygen tension, is inadequate because of its inability to detect hemoglobin C (except C-Harlem). Even when this test is positive, hemoglobin electrophoresis must be done to distinguish trait from disease. Solubility testing after electrophoresis helps identify many rare hemoglobin variants that have the same electrophoretic mobility as hemoglobin S. When results are unclear, sophisticated confirmatory tests become necessary (Fig. 1).

Proper counseling of pregnant patients is essential to provide education and reassurance, as is referral to a specialist when solubility testing or eye or kidney complications make that necessary. Audiovisual material is useful in explaining the genetic implications of the disease. Genotype charts, which display percentage inheritance odds, are particularly helpful (Fig. 2).

The most frequent serious risk is the trait-by-trait (HbAS/HbAS) mating; it carries a 25% chance of producing a child with the disease state (HbSS). Sickle cell disease in pregnancy carries a significant risk, and patients must be so advised. Once parents have a clear understanding of this complicated problem, however, they can be reassured. To minimize guilt feelings, it is helpful to explain the possibility that sickle hemoglobin evolved as protection against malaria. When patients with sickle cell disease (HbSS) receive exemplary care, the maternal mortality should not exceed 3%.² The decision to risk pregnancy is

Fig. 2 Genetics of sickle cell disease



Epifoam™ (hydrocortisone acetate 1%)

Before prescribing, see complete product information of which the following is a brief summary:

Description: A topical steroid foam containing hydrocortisone acetate 1% in a base of pramoxine HCl, propylene glycol, cetyl alcohol, PEG-100 stearate, glyceryl stearate, laureth-23, polyoxyl-40 stearate, methylparaben, propylparaben, triethanolamine or hydrochloric acid to adjust pH, purified water, propellant (inert), butane and propane.

Contraindications: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Precautions: If irritation develops, the product should be discontinued and appropriate therapy instituted.

In the presence of an infection, the use of appropriate antifungal or antibacterial agents should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

If extensive areas are treated or if the occlusive technique is used, the possibility exists of increased systemic absorption of the corticosteroid and suitable precautions should be taken particularly in children and infants.

Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not absolutely been established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids, in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

This product is not for ophthalmic use.

Adverse Reactions: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

Dosage and Administration: Apply to affected areas 3 or 4 times daily. Transfer the medication to a pad and apply gently, or apply the foam directly.

How Supplied: In aerosol container of 10 gm.

SICKLE CELL AND PREGNANCY

therefore a viable option. For patients who choose not to take this risk, the option of elective abortion must be available.

Several ways to determine the sickle genotype of the fetus before birth are currently being explored. The two basic procedures being studied involve fetal blood sampling through the fetoscope,^{3,4} and endonuclease gene mapping, using DNA from uncultured amniotic fluid cells obtained by amniocentesis.⁵

Patients found to have a sickle cell trait should have urine cultures and sensitivity studies, because they are 2.5 times as likely to have urinary tract infection (UTI) as is the general obstetric population. Those with positive cultures should be treated with appropriate antibiotics for 3 weeks, recultured, and—if results are negative—maintained on methenamine mandelate (Mandelamine, Manese, Mandacon).

One retrospective study reports an increased incidence of premature rupture of membranes in patients with sickle cell trait.⁶ However, no other report of this phenomenon has appeared.

Clinical management

In pregnancy, symptoms produced by the disease are usually related to acute attacks, known as crises. Our fundamental approach has been to treat them with analgesics, blood and fluid replacement, and antibiotics.

For many years, maternal replacement transfusions have been used in crises. The purpose is to maintain hemoglobin levels in the 7- to 9-gm range.^{7,8} Many centers, including our own, have recently begun to use partial exchange transfusions prophylactically rather than therapeutically in crises.⁹ We seek consanguineous members of the family who have no sickle hemoglobin for these exchange transfusions, to reduce the chances of atypical antibodies.

Prophylactic transfusions raise hemoglobin and hematocrit levels while suppressing HbS-containing cells and replacing them with HbA-containing cells. However, transfusions raise the possibility of hepatitis, transfusion reaction, and volume and iron overload. More-

SICKLE CELL AND PREGNANCY

over, the benefits of such therapy have not yet been proven, because no controlled prospective randomized evaluation has been conducted. The National Heart, Lung and Blood Institute recently sponsored a consensus development conference on this subject.^{10,11} Participants concluded that the risk-benefit ratio needs further prospective evaluation over the next 3 to 5 years.

Antepartum care. At our institution, we perform the following tests at the initial visit: hemoglobin electrophoresis, hemogram, blood group and type, reticulocyte count, erythrocyte sedimentation rate, Pap smear, GC smear, venereal disease reaction level, rubella titer, tine test, liver profile, and urinalysis with culture and sensitivity studies. Urinary tract infection is reported to occur ten times more often in patients with sickle cell disease than in the general obstetric population. At least 25% of untreated patients develop UTI. Twice that number have positive urine cultures and we treat them with antibiotics for 3 weeks, reculture them and, if the results are negative, maintain them on methenamine mandelate.

All patients receive supplemental prenatal vitamins containing iron and folic acid. The diet should be high protein/low fat and provide 35 calories per kilogram of ideal body weight. Salt restriction and diuretics are contraindicated, even though as many as 22% of these women may develop toxemia of pregnancy. Patients should be seen at 2-week intervals. Infection, threatened abortion, toxemia, abruptio placentae, and thrombophlebitis can all precipitate a crisis.

At approximately 24 weeks gestation, we hospitalize our sickle cell disease patients for prophylactic partial exchange transfusion, using the protocol on page 31. During hospitalization, we measure biparietal diameters by ultrasound to help establish fetal age.

In these patients, fetal lung maturation seems to be accelerated. We conduct oxytocin stress tests weekly on an outpatient basis from the 37th week of gestation until labor. If the test is positive, we terminate the pregnancy by cesarean section. Labor is induced and elec-

Motrin[®] (ibuprofen)

effective relief of mild to moderate menstrual pain...

Motrin[®] Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain.

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis, acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting AD REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcer drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in vision have been reported. If these develop, discontinue Motrin and the patient have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug Interactions: Aspirin: Used concomitantly may decrease Motrin blood levels. Coumarin: Bleeding has been reported in patients taking Motrin and coumarin. Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea, epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, at cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness, headache, nervousness. **Dermatologic:** Rash (including maculopurpuric type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema. Fluid retention generally responds promptly to drug discontinuation.

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous lesions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin, hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Fever, serum sickness, lupus erythematosus syndrome.** **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied if acidic and excreted in the urine, so alkaline diuresis may be beneficial.

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tronically monitored in all patients beyond 41 weeks gestation.

Labor and delivery. Labor, whether it is spontaneous or induced, should be managed much the same as labor in cardiac patients. Oversedation should be avoided and oxygen administered. Epidural anesthesia obviates the need for narcotics. We use median episiotomy and low forceps to shorten the second stage of labor.

Fluid replacement during labor, a critical factor in these patients, is easily mismanaged. Sick cell disease patients frequently fall into negative fluid balance. Most have impaired renal concentration capacity and thus excrete excessive quantities of urine. And, as do most patients in labor, they lose their appetites, which results in impaired fluid and food intake. IV fluid intake should include ample amounts of water/dextrose solutions and adequate electrolyte replacement. These patients tend to have metabolic acidosis, which can be corrected with lactate or bicarbonate solutions and the effects monitored with serum electrolytes.

Postpartum management. During the postpartum period, the patient must be carefully monitored for signs of infection and crisis. Catheterization should be avoided if possible and broad spectrum antibiotics administered for at least 96 hours into the postpartum period. Congestive heart failure occurs frequently in the postpartum period and digitalis should be administered, if necessary.

Hemoglobin electrophoresis should be carried out on cord blood samples. Hemoglobins S and C can be identified at birth, even though the major portion of the newborn's hemoglobin is of fetal type. An early diagnosis of sickle cell disease should alert the parents and the pediatrician to watch for signs and symptoms of painful or life-threatening complications. Prompt treatment can minimize their effect.

The postpartum period is also a convenient time to give the mother the rather recently developed polyvalent pneumococcal vaccine. This vaccine, indicated for all patients with sickle cell disease, should not be administered

Guide for prophylactic partial exchange transfusion

1. Determine Hct, HbA, type and X-match, bilirubin, reticulocyte count, LDH, urine hemoglobin.
2. Infuse 300 ml of normal saline (5 ml/min).
3. Phlebotomize 500 ml blood in the opposite arm (10 ml/min).
4. Transfuse 2 units of packed cells (buffy-coat-poor washed red cells) (5 ml/min).
5. Repeat steps 2, 3, and 4.
6. Determine Hct and HbA by quantitative hemoglobin electrophoresis 12 hours later (therapeutic objective: HbA > 70%, Hct > 35%).
7. Repeat step 1 monthly thereafter.
8. Repeat steps 2, 3, and 4 if:
 - (a) Hb A is < 30% or Hct is < 25%;
 - (b) crisis occurs;
 - (c) labor ensues;
 - (d) surgery becomes necessary.

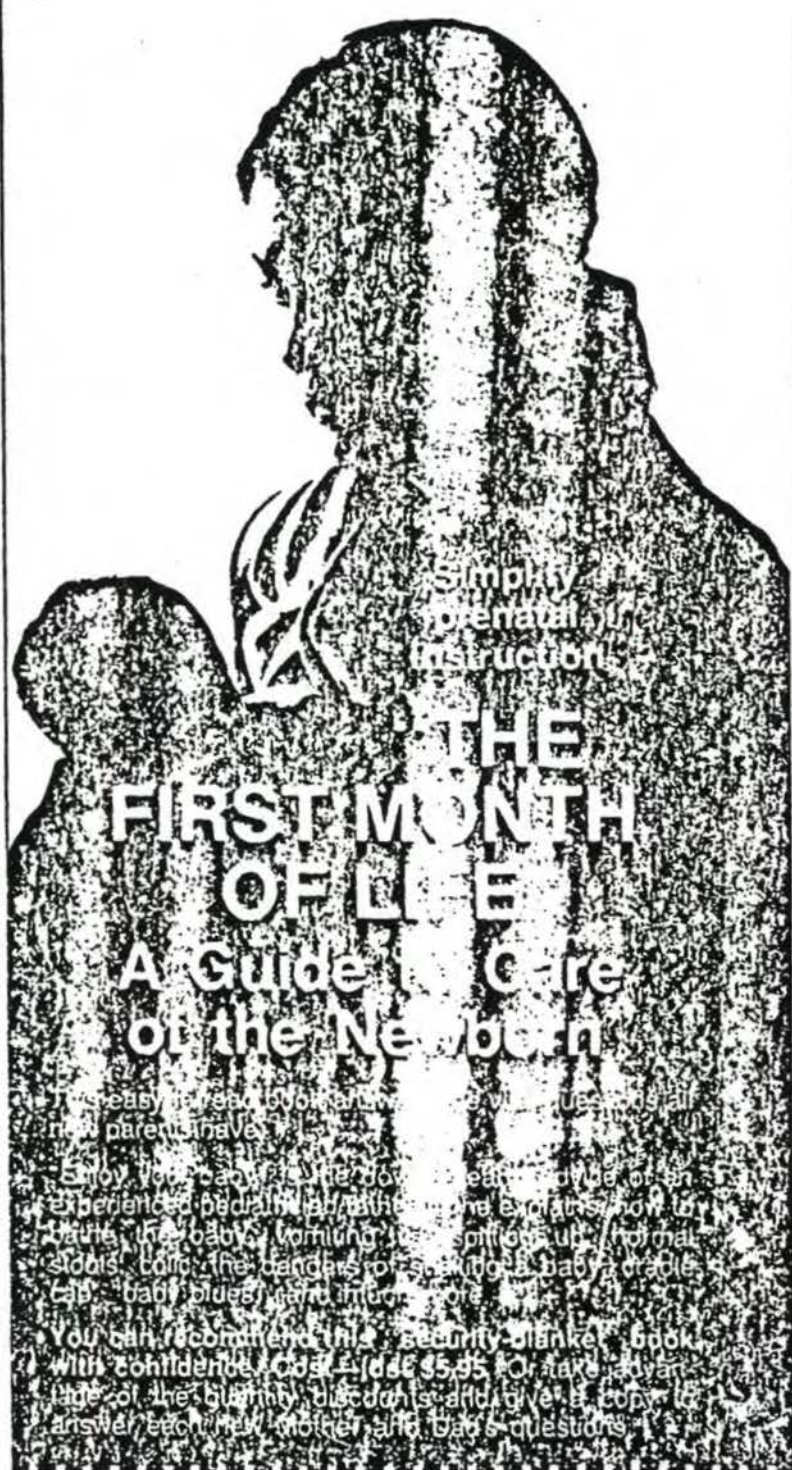
during pregnancy. Revaccination is recommended at 3-year intervals.

When crises occur

Managing sickle cell disease crises in pregnant patients differs little from procedures employed with nonpregnant patients. Most crises are of the vaso-occlusive type and produce intense pain. Aplastic (aregenerative) crises are only about a fifth as common and acute sequestration crises are mostly confined to childhood. The basic components of crisis management include analgesics, partial exchange transfusion, IV fluid and electrolyte replacement, oxygen administration, and elimination of infection. However, one must keep in mind that the signs and symptoms of crisis can be virtually indistinguishable from those of an acute abdominal condition. Appendicitis and ectopic pregnancy must always be ruled out.

What contraceptive is best?

Providing effective and safe contraception to the patient with sickle cell disease is difficult. The most effective agents, oral contraceptives, are contraindicated—at least theoretically—because they increase blood coagulability, thus lowering the threshold for crises. Incidence of thromboembolic disorders, nor-



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SICKLE CELL AND PREGNANCY

mally greater in these patients, is further increased by the pill. The estrogen component of the estrogen-progestin preparation is probably the major offender. Thus, a progestin-only pill seems a wise choice. IUDs are not recommended because of risk of endometritis, which can progress to a more generalized pelvic infection, pelvic peritonitis and, ultimately, precipitate a crisis. Usually, I prefer to use the barrier contraceptives, with the option of therapeutic abortion when contraception fails.

Many sickle cell disease patients who have had a successful pregnancy choose sterilization. It should be performed after the 6-week postpartum period, with either regional or local anesthesia. Laparoscopic sterilization is not recommended; this procedure compromises lung aeration because of the relatively high, fixed position of the diaphragm. Carbon dioxide, used in 90% of laparoscopic procedures done in the US, causes hypercarbia which further promotes sickling.¹²

The vast accumulation of knowledge over the past 20 years has greatly increased our understanding of the sickle cell disease process. As we learn more about genetic counseling, pregnancy management, and contraceptive technique, we can expect continued improvement in maternal and fetal outcomes.

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Contraceptives in Sickle Cell Disease

HENRY W. FOSTER, JR., MD,* Nashville, Tenn

ABSTRACT: Choosing the proper method of contraception for patients with sickle cell disease is an empiric exercise. In this manuscript, the commonly used contraceptive methods are examined for their risk-benefit ratio. However, because of its extensive use and effectiveness, steroid contraception is examined in greatest depth. Physiologic and pathologic changes induced by oral steroid contraceptives are evaluated, and their potential effects on patients with sickle cell disease are considered. Physiologic alterations evaluated are carbohydrate metabolism, blood lipid levels, hepatic function, thyroid function, and pigment changes. Pathologic changes reviewed are hypertension, thromboembolic phenomena, myocardial infarction, amenorrhea, and emotional changes. The choice of sterilization procedures is also considered for these patients.

THE PROVISION of contraceptives for female patients with homozygous and doubly heterozygous sickle hemoglobinopathies is an unsettled and challenging issue. Computer search of the world's literature over a most recent 40-month period yielded but a single article devoted exclusively to contraception and sickle cell hemoglobinopathies.¹ For the sickle cell disease patient who has successfully negotiated a pregnancy, the contraceptive question is often settled by the patient's choice of a sterilization procedure. However, for those who do not choose this method and for nulligravida patients, the difficult decision remains. Lack of definitive data on this subject has made the provision of contraception to patients with sickle cell disease an empiric exercise.

At the onset, it should be emphasized that contraceptive management of patients with sickle cell trait is no different from that of the normal population. Hence, comments contained here are applicable only to patients with sickle cell disease.

Contraceptive methods can be grouped into the following six broad categories: (1) steroid contraception, (2) intrauterine devices, (3) barrier methods, (4) timing methods, (5) sterilization, and (6) abortion. Although some discussion will be afforded each of these methods, the greater portion of time will be devoted to the more effective method of steroid contraception since it is clearly this method that presents the most controversy.

The most widely used form of hormonal contraception is the combination pill containing synthetic progestins and estrogens. Pills containing progestin only are used on a very limited basis, as is the long-acting intra-muscular medroxyprogesterone acetate (Depo-

Provera). Although not a steroid, diethylstilbestrol (DES) under special circumstances has a contraceptive applicability. There is no consensus as to whether sickle cell disease constitutes an absolute or relative contraindication to the use of steroid contraception, but there are few, if any, who do not suspect some increased risk factor. Given this lack of definitive data upon which to make this judgment, it appears logical to review the known physiologic and pathologic changes induced by steroid hormones. Having done this, coupled with an understanding of the natural history of sickle cell disease, one should be in a better position to make a reasonable judgment as to the contraceptive role, if any, of steroid hormone in patients with sickle cell disease.

Physiologic alterations in carbohydrate metabolism, blood lipids, hepatic function, thyroid function, and pigmentation may result from oral steroid contraception. The combination oral contraceptives have been shown to increase fasting blood glucose in 10% to 25% of normal patients. Theoretically, this could place sickle cell patients at some increased risk of infection. Progestins alone have no known adverse effect on carbohydrate metabolism.

Plasma levels of triglycerides and phospholipids have been found to rise in patients using combination oral contraceptives. The mechanism by which this occurs is unknown, but may relate to increased hepatic production. Ordinarily, there are no known long-term effects, but patients with established hypertriglyceridemia become worse and thus more prone to acute vascular accidents.

Some patients using oral contraceptives have an increase in SGOT and alkaline phosphatase levels. Moreover, marked liver impairment is one of the absolute contraindications to steroid usage. This has particular relevance for patients with sickle cell disease.

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given their chronic hemolysis which predisposes them to cholelithiasis.

Although there is some alteration in results of thyroid function tests similar to those seen in normal pregnancy (ie. increased thyroid-binding globulin leading to increased PBI, increased T_4 , and decreased T_3 uptake), the free thyroxine index and thyroid function remain normal.

The physiologic increase in pigmentation seen in approximately one third of pill users is of no clinical consequence.

Pathologic alterations also attributable to combination steroid contraceptives are (1) hypertension, (2) thromboembolic phenomena, (3) myocardial infarction, (4) amenorrhea, and (5) emotional lability and depression. It is this category of alterations that understandably causes us greatest concern in all patients when prescribing steroid contraceptives.

Over the past decade there have been many reports showing a relationship between the estrogen component of the pill and hypertension. The incidence is usually in the neighborhood of 15% to 20%, with about 5% of the patients reaching dangerously high blood pressure levels. Both the systolic and diastolic pressures increase, and both normotensive and previously hypertensive patients can be affected. The mechanism of action is not known but probably is by way of the direct action of estrogen on the juxtaglomerular cells. The hypertension is thought to be of the renin-dependent type, since there is an increase in renin and renin substrate. Although not an absolute contraindication, this feature of the estrogen-containing pill most certainly would be of significant concern in a patient with sickle cell disease.

Thromboembolism constitutes a most serious untoward effect of the birth control pill. Current data show a sevenfold increase in the risk of death from thromboembolic disease for oral contraceptive users over nonpregnant nonusers, the increase in the risk of death being 15 per million and 2 per million respectively. A previous history of deep vein thrombosis is a contraindication to use of the pill, and it is believed by

some that sickle cell disease also constitutes a contraindication to the use of estrogen.² The increased coagulability seen in patients with sickle cell disease appears to add a modifying risk factor that may make the pill unacceptable. Although the effect of sickle cell disease as a modifying risk factor in pill users has not been established, it is interesting to note the effect of other similar modifying factors as presented by the Center for Disease Control's Epidemiologic Studies Branch, Family Planning Evaluation Division, Bureau of Epidemiology.

Examined in the Table is the risk of complications in oral contraceptive users with a specified risk factor(s) compared to normal contraceptive users without a risk factor(s). Severe hypertension in patients taking oral contraceptives increases the risk of thrombotic stroke by just over 13-fold and the risk of hemorrhagic stroke just over 25-fold. The modifying risk factor of cigarette smoking (not controlled for age) also increases the risk, but to a lesser extent than severe hypertension. It could therefore be assumed that sickle cell disease, too, can be viewed as an increased risk factor with respect to use of oral steroid contraceptives.

An increased incidence of myocardial infarction seems to occur only in women who have passed 40 years of age and then only in those who have other coexisting risk factors, eg. hypertension, obesity, and smoking. This consideration, therefore, should be of no great significance for the patient with sickle cell disease or any other patient, since most practitioners do not prescribe oral contraceptives in this age group.

The pathologic alterations of amenorrhea and emotional lability after use of the pill have no known special significance for patients with sickle cell disease.

Because of the thromboembolic phenomenon caused by combination oral contraceptives and because of the increased incidence of thromboembolic disorders in sickle cell disease, the use of oral steroid contraceptives is considered relatively contraindicated in patients with sickle cell disease.

It is also believed that the use of DES as an after-the-fact contraceptive agent is contraindicated in patients with sickle cell disease for the same reasons stated in regard to the combination pill. Moreover, the equivalent dosage of estrogen required here is some 50 to 100 times that of the estrogen contained in the low-dose combination birth control pill.

Progestin-only contraceptives such as the mini pill and long-acting intramuscular progesterone have been suggested for patients with sickle cell disease. Theoretically, this estrogen-free medication should pose a lesser threat, but there are no good data that clearly exempt progestins as a causative or contributory factor to the thromboembolic phenomenon. Ad-

TABLE. Major Harmful Effects of Birth Control Pills (BCP): Modification of Those Effects by Other Factors*

Complication	Modifying Factor	Risk of Complication in BCP Users vs Non-BCP Users † Risk Factors
Thrombotic stroke	None	3.0:1
	Severe HCVDT	13.6:1
	Smoker, ≥1 pack/day	6.1:1
Hemorrhagic stroke	None	1.5:1
	Severe HCVDT	25.7:1
	Smoker, ≥1 pack/day	7.6:1

*From Ory HW: The health effects of fertility control. Presented at the National Academy of Sciences Symposium on Contraceptive Technology, May 16, 1978.

†Hypertensive cardiovascular disease.

ditionally, it has been suggested that the intermediate metabolism of progestins may involve conversion to estrogen.

The use of medroxyprogesterone acetate (Depo-Provera) for contraception in patients with sickle cell disease has been suggested, but the same questions previously raised remain unanswered. Moreover, because this agent is not approved in this country for contraceptive use, there are significant medicolegal implications. It would appear, therefore, that the use of DES and all steroid contraceptives, including the progestins, should probably be avoided.

What then is the role, if any, for the second most effective form of reversible contraception—the intrauterine device? Here, too, there seems to be no consensus among practitioners. Again, to make a judgment requires an evaluation of the known complications associated with IUDs. The two complications that bear the greatest relevance to patients with sickle cell disease are infection and excessive hemorrhage. Irrespective of the technic used for insertion, bacteria are introduced into the uterine cavity, and although the bacterial count usually decreases after a few weeks, it has been suggested that endometritis persists. Moreover, most serious complications from IUDs, including death (0.3 to 1.0 per 100,000 IUD users per year) and sepsis,³ are related to infection. Because of the known adverse effect of infection on the patient with sickle cell disease, this feature, it seems, renders IUD inappropriate for them.

IUDs tend also to increase the incidence of both menorrhagia and metrorrhagia; hence the adverse effects of excessive bleeding on sickle cell disease present another reason why the IUD probably is best not used in these patients.

The complications of expulsion, perforation, and ectopic pregnancy take on greater significance when the patient has sickle cell disease. This is particularly true for perforation and ectopic pregnancy, where infection and the need for surgery become likely.

Since contraceptive effectiveness and safety bear inverse relationships to each other, we are now left to consider the less effective but safer barrier methods of contraception. Condoms, diaphragms, foams, and jellies are acceptable forms of contraception in well motivated patients. With adequate patient education, the barrier contraception recommended for patients with sickle cell disease is a spermicidal jelly containing nonoxonyl-9, used preferably with a diaphragm. In addition, the patient is taught how to calculate her probable day of ovulation; at this time her sex partner is advised to use a condom in addition to her jelly and the diaphragm. The condom should be added during the three days before, the three days after, and on the calculated date of likely ovulation. Although this contraceptive approach may appear complex, with

adequate education patient compliance can be often achieved in these usually highly motivated patients. Nevertheless, therapeutic abortion is an option that must be made available to patients who fail with this contraceptive approach.⁴

In the strictest sense, sterilization should not be considered a form of contraception because of its irreversibility. It is, however, a form of fertility control very often chosen by these patients and hence warrants comment. With the current popularity of laparoscopic sterilization, it should be emphasized that this procedure compromises to some degree lung aeration, because of the relatively high fixed position of the diaphragm. Further, in 90% of the laparoscopic procedures conducted in this country, carbon dioxide is used to establish the pneumoperitoneum, which results in hypercarbia.⁵ The elevated PCO_2 and lowered pH have been shown to be the result of carbon dioxide absorption from the peritoneal surface and not necessarily due to improper ventilation during anesthesia.⁶ It is well known that hypercarbia, decreased pH, and decreased oxygenation all predispose patients with sickle cell disease to crises. For this reason, it is believed that laparoscopic sterilization should not be used in these patients. As an alternative, the interval "mini lap" sterilization procedure, using local anesthesia, is recommended.

The use of abortion solely as a form of contraception, though acceptable in some parts of Europe, has not become prevalent in the United States. Clearly this would not be ideal in sickle cell disease. This method would necessitate an operative procedure through 16 weeks' gestation, and thereafter termination procedures would require the use of prostaglandins or hypertonic saline infusions, with their inherent risk of complications and possible subsequent abdominal surgery.

Of the six broad methods of fertility control discussed—steroids, IUDs, barrier methods, timing methods, sterilization, and abortion—effectiveness versus safety is the basis upon which choices must be made. Because steroids, IUDs, and abortions probably carry too great a risk and because sterilization is inappropriate if reversibility is a consideration, barrier methods combined with timing probably offer the best balance between safety and effectiveness.

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GUEST EDITORIAL

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Medical and Social Barriers To the Health Of Urban Infants

No potential killer or cripple is more fundamental than one which makes for a compromised beginning. A newborn infant whose birth weight is substantially below established norms is at significant risk of neonatal death; when it survives it bears the risk of physical and intellectual impairment.^{1,2}

Notably, those factors which contribute to an increased incidence of low birth weight infants are disproportionately higher among urban inner-city dwellers, in particular among black women. It has been estimated that 14 percent of non-white newborns weigh less than 2,500 grams.⁴ This figure is seven percent for white newborns.

The quality of human reproduction closely parallels future productivity and the quality of life. Accordingly, we must clearly understand the complex dynamics which underlie the threat of neonatal mortality and promote the utilization of suitable systems of health care delivery which will minimize this threat.

Poor health care outcomes derive from both medical and social factors—essentially from a failure to link health needs with medical services. This concept is depicted in Figure 1. Here, unmet needs for mothers and infants are caused by barriers to the health care system. When describing these barriers, sociologists often use the terms "attitudinal" and "organizational" barriers. Attitudinal barriers prevent individuals from becoming motivated to seek needed health services, and organizational barriers prevent motivated individuals from utilizing them. The extent to which these barriers are operative is reflected in the quality of health care outcome.

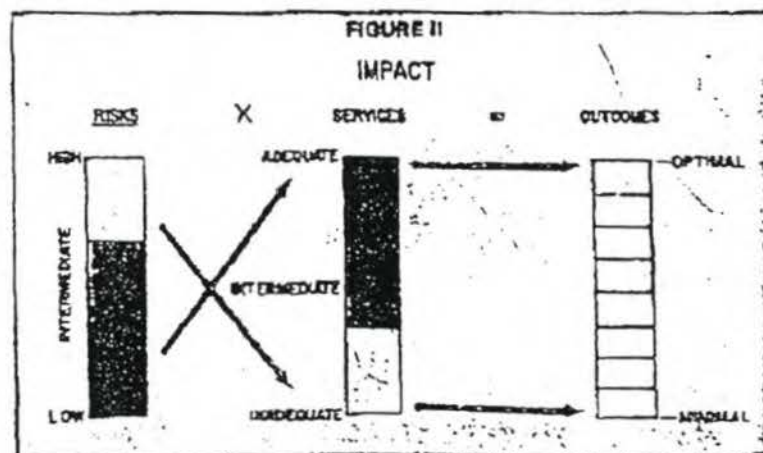
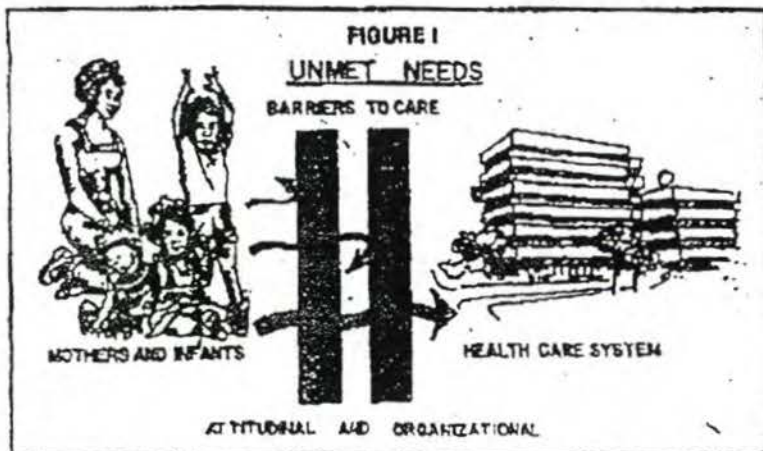
Infant birth weight is one of the significant measurable perinatal outcome parameters. The two major variables which impact most upon this outcome are patient risks and services provided

(see Figure II). Patients at low risk who receive adequate services, generally have the best health care outcome. Reciprocally, those at high risk who receive inadequate care generally do very poorly—an occurrence which too often characterizes our urban inner-city population.

Attitudinal and organizational barriers adversely affect patient risk and quality of services. Patient risk factors

are usually measured in terms of social risks and medical risks. Social risks involve such factors as age, marital status, income, educational attainment, etc. Medical risks are conveniently subdivided in obstetric and non-obstetric risks. Examples of non-obstetric risks are anemia, diabetes, overweight and underweight. Obstetric risks are such entities as cephalopelvic disproportion, abruptio placentae, premature rupture of the membranes, etc. It should be noted that within a given pregnancy or within a short period of time, significant measurable improvement is possible in reducing medical risks. Such is not the case with most social risks; they are much more resistant to change over a short period of time. A pregnant 13-year-old patient, for example, can be no older than 14 years when she delivers that pregnancy. Similarly, no substantial improvement in educational attainment during a single pregnancy is likely. However, these rather discouraging insights notwithstanding, knowledge as to the

Continued on page 13



PROFESSIONAL OPPORTUNITIES

GRANTS TO RESEARCHERS FOR STUDIES OF STRATEGIES TO PROMOTE HEALTHY LIFESTYLES

The National Center for Health Services Research has announced availability of grants to researchers for studies on specific strategies to improve health through promotion of healthy lifestyles and prevention of injury and disease. Of particular interest are studies relating to economic, political and social aspects of prevention, health education and delivery of health services. Eligible for awards are academic institutions, agencies of state or local government, non-profit organizations and individuals.

COMMUNITY SURVEILLANCE FOR CORONARY HEART DISEASE

The National Heart, Lung and Blood Institute of the National Institutes of Health is soliciting proposals relating to designing, planning and conducting a one-year pilot study of a surveillance system for cardiovascular disease, including coronary heart disease and other chronic diseases. The purpose of the surveillance is to monitor, in geographically circumscribed communities in various regions of the nation, such factors as concurrent trends in incidence of first and recurrent myocardial infarctions and cardiac deaths over time, and total mortality and morbidity resulting from cancer, stroke, diabetes, chronic lung diseases and other related factors. Requests for copies of RFP #1-2 should be sent to Mr. Robert Bess, Contracting Officer, Epidemiology Branch, DHVD, NHLBI, Federal Bldg., Room 200, 7550 Wisconsin Avenue, Bethesda, Maryland 20205. The deadline for receiving proposals is March 24, 1981.

MIRNING SCHOLARSHIPS

The National Student Nurses' Association will award a total of \$48,200 in scholarships to 43 students of nursing in 1981. Applications for the scholarships may be obtained from NSNA, Ten Columbus Circle, New York, N.Y. 10019.

GRANTS FOR DISSERTATION RESEARCH SUPPORT, 1981

The National Center for Health Services Research has announced availability of grant support for research projects undertaken in conjunction with preparation of dissertations. Students are eligible to apply for grants if they are enrolled in an accredited doctoral degree program in the social, medical, management or health sciences and intend to conduct or are conducting dissertation research on the organization, delivery, financing, or quality of health care services. All requirements for the doctoral degree other than the dissertation must be completed by the time of the grant award. Grants to support dissertation research range up to \$20,000 in total direct costs. Applications for the July, 1981 awards must be submitted on or before April 1, 1981. Request application form PHS-394 from Chief, Grants Review Branch (Dissertation), National Center for Health Services Research, Room 7-50A, Center Building, 3700 East-West Highway, Hyattsville, Md., 20772.

HUMAN MILK BANKING STUDIES

The Clinical Nutrition and Early Development Branch, Center for Research for Mothers and Children, of the National Institute of Child Health and Human Development is soliciting proposals entitled "Human Milk Banking Studies." Notice of this program points out "studies on those maternal variables which may influence the composition of colostrum and milk would greatly increase understanding of metabolic demands and tolerances of the infant who is at risk because of premature birth and low birth weight." Proposals are being solicited in five areas: (1) maternal nutritional status, diet, and post-partum weight changes (this could include food preferences and taboos); (2) infective agents; (3) drugs and medications; (4) environmental factors (this could include occupational exposures); (5) maternal behavioral factors (this could include infant feeding practices and patterns as well as maternal sociocultural factors). Proposals are also being solicited for studies that adapt existing methods and/or develop new methods for processing human milk. Emphasis will be on procedures that assure the retention of the greatest degree of biological function of milk while rendering it safe for clinical use (both maternal and viral contamination should be considered).

The Request for Proposals, RFP No. NICHD-CRMC-81-1 will be issued on or about January 9, 1981. The closing date for receipt of proposals submitted under the RFP will be April 13, 1981. Copies of the RFP may be obtained by sending a written request to: Mr. Michael R. Mackenzie, Contracts Management Section, Office of Grants and Contracts, National Institute of Child Health and Human Development, Landow Building - Room 8C29, Bethesda, Maryland 20205.

Send a self-addressed label. A limited number of copies are available. Requests for the RFP must cite the RFP number referenced above.

GUEST EDITORIAL

Continued from page 8.

nature of social risks is essential for effective planning and health care delivery.

The other variable which impacts on health care outcome is quality of services. For obstetrical services to be viewed as adequate, the patient must be seen not only early in pregnancy, but also in an appropriate number of timely follow-up visits. Additionally, the mother and the newborn infant must be cared for in facilities where there is the sophistication appropriate for the level of care required.

Medical service risks are usually related to organizational barriers, e.g., lack of physical facilities, personnel, transportation, etc. All too often, these are noticeably and disproportionately deficient in the inner-city. Moreover, it must be fully appreciated that the mere presence of adequate physical facilities, personnel and equipment does not equate with adequate services if these elements are not connected with and utilized by those at need. If this linkage fails to occur, then indeed, the "system" becomes a non-system.

All who assume a responsibility for this segment of our population must marshal medical resources to reduce patient risks and make available better health services. Finally, however, it must also be understood that there is a limit to the extent of improvement in health care outcome that is possible without significantly improving access by the inner-city population to the economic, political and educational systems of this country.

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Phosphoenolpyruvate carboxykinase activity in human amniotic fluid

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Amniotic fluid samples obtained from normal pregnancies during gestation were used to quantitate the levels of phosphoenolpyruvate carboxykinase (PEPCK) activity. It is concluded that: (1) PEPCK activity was highest in the amniotic fluid cells of midtrimester pregnancies as compared to those of pregnancies close to term; (2) the activity of PEPCK seen in the amniotic fluid supernatant was about one fourth to one half of that seen in the amniotic cells; (3) the amniotic fluid supernatant PEPCK activity fluctuated very little during the entire gestation. (AM. J. OBSTET. GYNECOL. 139:939, 1981.)

RECENT ADVANCES in biochemical genetics have made possible the in utero detection of several metabolic disorders and many of them have been shown to be due to specific enzyme abnormalities. Since the initial discovery in 1961 of an enzyme deficiency in cultured fibroblasts, more than 110 metabolic disorders have been shown to be associated with a deficiency of a specific enzyme activity.^{1,2} Our long-range program is to develop suitable methods for prenatal diagnosis of disorders associated with carbohydrate metabolism. Congenital lactic acidosis has been associated with a deficiency of glucose-6-phosphatase,³ fructose-1,6-diphosphatase,⁴ and pyruvate carboxylase.⁵ Pyruvate carboxylase deficiency has been implicated in Leigh's syndrome⁶ and a deficiency of the extramitochondrial form of hepatic phosphoenolpyruvate carboxykinase (PEPCK) has been found in a case of persistent neonatal hypoglycemia.⁷ Since nothing is known about gluconeogenic enzymes in human amniotic fluid, we examined the enzymes involved in gluconeogenesis. One of the key enzymes of gluconeogenesis is PEPCK. Our attention is focused on that enzyme because of the

fact that complete absence or very low levels of activity of this enzyme have been found in livers of autopsy specimens of victims of sudden infant death syndrome.⁸ This paper reveals that the activity of PEPCK in human amniotic fluid is comparable to the reported values of the enzyme in cultured human fibroblasts.⁹⁻¹¹

Material and methods

Chemicals. NaH¹⁴CO₃ and Aquasol were purchased from New England Nuclear, Boston, Massachusetts. Other analytical enzymes and cofactors were purchased from Boehringer-Mannheim Corp., New York, New York. All other chemicals were of reagent grade and were obtained from readily available sources.

Collection of amniotic fluid. Amniotic fluid samples were obtained by transabdominal or direct amniocentesis at the time of cesarean section. The amniotic fluid was stored in the refrigerator or centrifuged at 3,000 rpm for 20 minutes at 4° C to separate the vernix caseosa, fetal squamous epithelial cells, and lanugo from the supernatant. The supernatant was aspirated into a clean test tube; the pellet containing the sedimented cells was suspended in 5.0 ml of 0.25M sucrose solution and centrifuged at the speed and time mentioned earlier. This procedure was repeated twice to remove any trapped supernatant from the pellet. The supernatant obtained in the two washes was aspirated and discarded. The washed pellet (containing the amniotic fluid cells) was suspended in a known volume of water (0.5 to 1.5 ml) and sonified for four 15-second intervals in a Branson Cell Disrupter, Model W 158, at a setting of 5 to release the enzyme from the cells. The sonified extract (amniotic fluid cells) and the superna-

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Table I. Specific activity of PEPCK in human amniotic fluid at different periods of gestation

Fraction of amniotic fluid	Enzyme activity (mU/preparation*)			
	Weeks of gestation			
	Group 1: 14-17 wk (n = 9)	Group 2: 18-23 wk (n = 15)	Group 3: 37-40 wk (n = 8)	Group 4: term labor (n = 4)
Amniotic fluid cells (devoid of supernatant)	10.08 ± 1.32 (93)	14.22 ± 1.47† (131)	5.55 ± 0.23‡ (51)	10.85 ± 1.05 (100)
Amniotic fluid supernatant (devoid of cells)	2.86 ± 0.37 (99)	2.64 ± 0.24 (92)	2.45 ± 0.28 (85)	2.88 ± 0.31 (100)

*Milliunits represent nanomoles of HCO₃ fixed per milligram of protein per minute. The values given are means ± SEM of 15 different samples as indicated; each sample was assayed in duplicate. Numbers in parentheses indicate the percentage activity, with the activity from term labor samples taken as 100.

†Significantly different (p < 0.05).

‡Significantly different (p < 0.01).

tant obtained were used immediately for enzyme assays. The patients were divided into four gestational groups: group 1, 14 to 17 weeks; group 2, 18 to 23 weeks; group 3, 37 to 40 weeks; and group 4, in labor at term. There were 9, 15, 8, and 4 samples, respectively, in each of the four groups.

PEPCK assay. All enzyme assays were conducted under conditions where enzyme activities were proportional to time and enzyme concentration. PEPCK was assayed at 37° C by a modification¹² of the method of Chang and Lane.¹³ The total reaction mixture was 1.0 ml. A 5-minute preincubation at 37° C of all the assay ingredients except the enzyme extract was performed. The reaction was started by the addition of the enzyme extract and incubated for an additional 20 minutes. The reaction was then stopped with 0.5 ml of a 10% solution of trichloroacetic acid and cooled. The tubes were centrifuged to sediment the precipitated proteins. The clear supernatant was removed and bubbled with carbon dioxide for 10 minutes to remove the unreacted (¹⁴C) bicarbonate used in the assay and 0.5 ml of the aliquot was added to 10.0 ml of Aquasol and counted in a Beckman Model LS-355 liquid scintillation spectrometer. Protein was determined by the method of Lowry and associates,¹⁴ with bovine serum albumin used as the standard.

Results

The variation in the activity of PEPCK in human amniotic fluid with gestational age is represented in Table I. The enzyme activity (specific) is expressed as nanomoles per milligram of amniotic fluid (cells or supernatant) protein per minute. A significant increase in PEPCK activity of the human amniotic fluid cells from 10.08 to 14.22 nmoles/mg of protein was observed during the increase of gestational age from 14 to 17 weeks to 18 to 23 weeks (Table I). However, this activity dropped down to 10.85 nmoles/mg of protein at term.

It can also be seen in the same table that PEPCK activity at 37 to 40 weeks of gestation was 5.55 nmoles/mg protein. In contrast to the PEPCK activity in amniotic fluid cells, the activity seen in the amniotic fluid supernatant fluctuated very little during the entire gestational period and varied from 2.45 to 2.88 nmoles/mg of protein.

The assays of PEPCK activity in amniotic fluid cells and the supernatant were linear with time and amount of added protein. Since PEPCK activity in the amniotic fluid supernatant was much less when compared to the activity in the amniotic fluid cells, a mixing and dilution experiment was conducted which indicated that the amniotic fluid cells contained no activator and the amniotic fluid supernatant had no inhibitor of PEPCK activity to influence each other. Mercaptopicolinic acid which suppressed the activity of rat liver PEPCK¹⁵ inhibited this enzyme in amniotic fluid by about 60%.

Comment

The specific activity of PEPCK in amniotic fluid cells increases with gestation, reaching a peak level at 18 to 23 weeks of gestation and decreasing at 37 to 40 weeks. The activity increases to 10.85 nmoles/mg of protein at term in labor, which is closer to the activity seen at 14 to 17 weeks of gestation. The PEPCK activities seen at 18 to 23 weeks or in term labor samples (P < 0.05 to 0.01). The reason for this variation in PEPCK activity is not clear. However, fluctuations in activities of various enzymes of human amniotic fluid are well documented.¹⁶ Since the percentage of viable cells in a sample of amniotic fluid varies widely, in future studies we plan to estimate the number of viable cells in each sample and study the gluconeogenic enzymes after culturing amniotic fluid cells.

It is known that the glucose concentration of amniotic fluid is much lower than that of the mater-

serum and that the concentration of glucose in amniotic fluid decreases greatly after the thirty-second week of gestation, as term approaches.¹⁹ The determination of whether this is related to the decline in PEPCK activity observed at 37 weeks (this work) will have to await further results on the existence of all four gluconeogenic enzymes in amniotic fluid (pyruvate carboxylase has been found recently in amniotic fluid*), and also the capacity of the amniotic fluid gluconeogenic enzymes to synthesize glucose. While the PEPCK activity of the amniotic fluid cells varies with gestation, the activity seen in the amniotic fluid supernatant is virtually constant during the entire period of gestation.

The specific activity of PEPCK in mammalian tissue is high in the liver and kidney,²⁰ which are the two major gluconeogenic tissues. Although appreciable activity of PEPCK is seen in the lung, adipose tissue, and brain,²¹⁻²³ the level of activity in the rat skin is barely

detectable.²⁴ PEPCK activity (nanomoles) has also been shown recently to be present in several lines of human cultured fibroblasts,⁹⁻¹¹ and the levels of activity seen in human amniotic fluid cells and supernatant are comparable to that seen in cultured fibroblasts. Having established the normal range of PEPCK activity in human amniotic fluid during various stages of gestation, we are now focusing our attention on obtaining some data on the levels of PEPCK activity in amniotic fluid of high-risk pregnancies (diabetes, hypertension, obese patients, neural tube defects, pregnancy with a crib death sibling) and studying the gluconeogenic enzymes of amniotic fluid cells in culture. To our knowledge this represents the first work to show the existence of PEPCK in human amniotic fluid.

We wish to acknowledge the assistance of all the staff members and residents of this department in obtaining the necessary amniotic fluid samples used in this work. 3-Mercaptopicolinic acid was a gift from Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

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PHOSPHOLIPASE A₂ ACTIVITY IN HUMAN AMNIOTIC FLUID.Rengachari Raghunathan*, Henry W. Foster* and Salil K. Das.
Moharri Med. Coll., Nashville, TN 37208

It has been clearly demonstrated that human parturition is initiated by the action of prostaglandins (E₂ and/or F_{2α}) on the myometrium. PG synthesis is in turn regulated by the enzymatic release of arachidonic acid from phospholipids. The enzyme which catalyzes the release of fatty acids from the 2-position of phospholipids is phospholipase A₂. Thus the critical question relating to the onset of human parturition revolves around the mechanism of action of phospholipase A₂. Though this enzyme has been shown to be present in several animal tissues, including fetal membranes, fetal chorion and uterine decidua, very little is known about the presence of this enzyme in human amniotic fluid. The present study reports data on phospholipase A₂ activity in human amniotic fluid. Amniotic fluids were obtained from pregnant women at 16-18 weeks of gestation and during term pregnancies and separated into cells and supernatant. Phospholipase A₂ activity was assayed using 1,2 dipalmitoyl-1-¹⁴C-phosphatidylcholine as substrate. The specific activity was expressed as nmoles substrate hydrolyzed per mg protein per min. The activity in both cells and supernatant increased almost 2-fold during gestational development. Also the activity in cells was 4 and 2-fold higher than that in supernatants of early and term pregnancies, respectively. (Supported by NIH Grant RR-08037)

3759

NEWLY INTERNALIZED EPIDERMAL GROWTH FACTOR AND LOW DENSITY LIPOPROTEIN LOCALIZED WITHIN A NON-LYSOSOMAL INTERMEDIATE VESICLE. Michael Merion* and William S. Sly.
Washington University School of Medicine, St. Louis, MO 63110.

Adsorptive endocytosis of Epidermal Growth Factor (EGF), and Low Density Lipoprotein (LDL) by human fibroblasts has been examined using a sequence of two Percoll gradients. Both ligands may be localized within 2-5 minutes at a modal density of 1.043 g/ml that is enriched in the enzymatic marker NADH

ENDOCYTOSIS (3758-3759)

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Important Advances in Clinical Medicine

Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in obstetrics and gynecology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 44 Gough Street, San Francisco, CA 94103

Exchange Transfusion in Pregnant Women With Sickle Cell Disease

THE FIRST published article suggesting that exchange transfusion might be used for prevention as well as treatment of sickle cell disease complicated by pregnancy appeared in 1963. This rather aggressive approach attempted to address the 10% maternal death rates being reported at that time and pregnancy wastage (abortion and perinatal death) that varied from 40% to 60%. Only in the past few years, however, has this modality achieved rather widespread use, which has been reinforced by recent reports suggesting an improvement in both maternal and fetal outcome. Prophylactic partial exchange transfusion (PPET) reduces the concentration of hemoglobin S by replacing it with hemoglobin A, which offers better tissue perfusion and oxygenation. Other possible advantages of this therapeutic approach include suppressed hemoglobin S erythropoiesis, an increased sense of well-being, reduced infections, reduced crises (both frequency and intensity) and improved perinatal outcome.

Despite these potentially positive factors, there are disadvantages to this approach—both real and theoretical; thus not all physicians are in accord with the recommendation for this procedure in pregnant women who have sickle cell disease. With prophylactic partial exchange transfusion, large numbers of blood cells are transfused and isosensitization remains a serious threat to patients. The other possible disadvantages include hepatitis, anaphylaxis, volume overload, hemochromatosis, premature labor and psychological dependence.

Risks are minimized by the use of washed, buffy coat-poor erythrocytes—which decreases the number of leukocytes, a very frequent cause of transfusion reactions. The risk of hepatitis is also lessened by using washed cells. Further, consanguineous donors who have no sickled hemoglobin should be used to reduce the chance of atypical antibody formation. The potential problem of iron overload seems more theoretic than real. With PPET, iron is also removed, albeit a smaller amount than that which is replaced. Women in addition are relatively protected by periodic blood loss associated with menstruation, iron loss to the fetus during pregnancy and the blood loss that attends parturition.

Most physicians thus far have used a manual method to conduct PPET, which, after hydration, involves the removal by phlebotomy of whole blood and the rather awkward replacement of packed cells containing hemoglobin A. The possibility of volume overload, although an infrequent occurrence, should not be overlooked. Moreover, with this manual method there is a permanent loss of a patient's endogenously produced plasma, platelets and leukocytes. More recently a transfusion technique known as automated erythrocytapheresis has been used. With this technique, a continuous flow system withdraws a measured volume of a patient's blood and selectively removes from it by differential centrifugation the hemoglobin S-containing erythrocytes. The patient's remaining plasma, platelets and leukocytes are returned to her circulation, along with an aliquot of hemoglobin A-containing donor erythrocytes.

As stated earlier, the risk-benefit ratio of this thera-

peutic approach is unclear and because of this a consensus development conference on this subject was convened in 1979 by the National Institutes of Health. I hope that the issues raised in this article can be answered through a randomized multicenter collaborative study such as that suggested by the consensus development conferees.

HENRY W. FOSTER, JR, MD

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The G Suit in the Management of Intra-abdominal Hemorrhage

ONE OF THE most effective therapeutic procedures available to an obstetrician-gynecologist for the control of intractable abdominal hemorrhage is the gravity (G) suit. The G suit is also known as the MAST suit (military antishock trousers) and the antishock suit. It was used extensively in the Vietnam War, allowing transport time to base hospitals of severe trauma casualties and thus saving many lives. It is also used extensively throughout the United States by paramedics when transporting a patient in shock to a hospital. The G suit consists of three inflatable chambers, one for each leg and one for the abdomen. Inflation of these chambers to a pressure of 10 to 20 mm of mercury creates a circumferential compression of the vessels in the abdomen and legs, which has two effects. First, it causes a shunting of blood from the legs and abdomen to the vital structures of the head and chest; it has been estimated that an autotransfusion of as much as 750 to 1,000 ml of blood can occur depending on a patient's size and blood volume. Second, the use of the G suit has a hemostatic effect by reducing the radius and the tension of vessel walls, allowing clot formation.

The G suit's application in obstetrics and gynecology is primarily in the treatment of hemorrhagic shock. There are many clinical situations in which its use is most appropriate. One of the most dramatic is in treating shock in a patient with a ruptured ectopic pregnancy. Patients in shock respond to application of the G suit with a rise in their blood pressure and a slowed pulse rate, thus allowing time to restore blood volume and to transfer the patient to the surgery for a definitive procedure.

Postoperative bleeding due to oozing and raw vascular beds that cannot be controlled by good surgical technique and packing can be very effectively controlled by using a G suit. Some examples would be for oozing after hysterectomy in patients with extensive adhesions due to chronic pelvic inflammatory disease or endometriosis; after cesarean section for placenta previa, especially when implantation has occurred at the site of a previous scar; uncontrolled venous bleed-

ing in a space of Retzius after suprapubic bladder neck suspensions, and after cesarean hysterectomy oozing due to the increased vascularity. By using the G suit in a prophylactic manner for 24 to 36 hours, the frequency of second operations and hematomas can be reduced.

Postpartum hemorrhage due to uterine atony may be effectively controlled by using the G suit. Patients aborting and those passing a hydatidiform mole who are hemorrhaging excessively and in shock respond to application of a G suit until definitive therapy can be implemented. Patients in septic shock without blood loss can be treated by the use of a G suit, which allows a team to implement all of the therapeutic modalities that are indicated and necessary. Patients with coagulopathies respond well to the G suit as a supporting modality.

The use of the G suit in many varied conditions that cause massive blood loss or shock has been extensively studied and reported. There are few contraindications for its use, the main ones being patients who have cerebral edema, pulmonary edema, congestive heart failure or bleeding above the diaphragm. The abdominal chamber should never be used for a pregnant patient.

Very few complications have been reported and the benefits can be lifesaving as well as reducing the amount of blood products needed and their associated complications.

JOHN E. GUNNING, MD

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Comparative Risks of Osteoporosis and Endometrial Cancer

CESSATION OF ovarian function and the associated drop in endogenous estrogen levels lead to a variety of estrogen deficiency conditions such as osteoporosis, vasomotor symptoms, urogenital tract atrophy and psychological changes. At the same time, the incidence of endometrial carcinoma—a disease known to be related to estrogen use or estrogen production—increases, though the overall incidence of this disease is small. Of all estrogen-dependent diseases that are more or less specific to menopause, osteoporosis and endometrial carcinoma carry the greatest morbidity and mortality.

Osteoporosis affects up to 25% of all white women 65 years of age and older. The clinical implications of this disease are manifold: It is estimated that after age 45 years, 1 million women in the United States each year suffer fractures—700,000 are due to osteoporosis and half of these could have been prevented. In 1979 there were about 125,000 cases of hip fracture in older women in the United States. The cost of medical treatment of these fractures could be as high as \$1 billion yearly and 15% of all women will die within three

Study of lipids in human amnion and chorion

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Most previous fetal membrane studies have focused primarily on their phospholipids as the precursors of arachidonic acid and the obligate precursors of prostaglandins E_2 and $F_{2\alpha}$, with little attention being afforded nonpolar lipids as another possible source. In this presentation, a special emphasis is placed on nonpolar lipids and their acyl group makeup. A substantial amount of acyl group (20:4) lipids was found. The implication of this finding could be that a nonpolar lipid source is necessary for the production of prostaglandins E_2 and $F_{2\alpha}$. (AM. J. OBSTET. GYNECOL. 149:670, 1984.)

During the past decade much information has been gathered on events involving human parturition. The amnion and chorion, the two major components of fetal membranes, although slightly adherent, are never intimately connected and are always easily separable, even at term. They play a dynamic role in the birth process by serving as a rich reservoir of phospholipids containing arachidonic acid, the obligate precursor of prostaglandins E_2 and $F_{2\alpha}$.^{1, 2} Prostaglandins occupy a key role in the initiation of the myometrial contractions that are necessary for labor.³

In view of the fact that fetal membranes are so actively involved in the process of parturition, it is evident that a comprehensive study of their basic chemical composition is essential. Although several studies have examined fetal membrane phospholipid content in laboring and nonlaboring patients, most have focused on phospholipids with little attention being afforded to the nonpolar lipids of the fetal membranes. This communication, therefore, quantifies the total postpartum lipid content of the amnion and the chorion measured separately in women who have undergone the spontaneous onset of labor. In this study a special focus is placed on the nonpolar lipids, triglycerides, free fatty acids, and cholesterol esters. Further, the acyl makeup of these three nonpolar lipids is presented.

Material and methods

Processing of fetal membranes. The placenta and its membranes were obtained at the time of spontaneous

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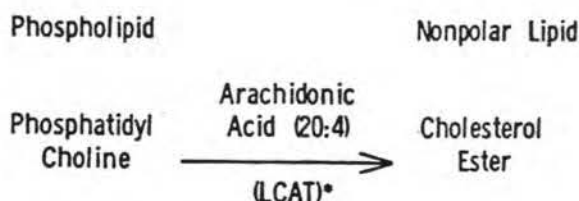


Fig. 1. The transfer of arachidonic acid (20:4) to the nonpolar lipid cholesterol ester. LCAT = Lecithin cholesterol acyltransferase.

Table I. Composition of human amnion and chorion lipids*

Components	Amnion	Chorion
Total lipids	470.0 ± 9.3	1530.2 ± 20.4
Total nonpolar lipids	319.6 ± 8.5	1042.1 ± 18.9
Cholesterol esters	43.7 ± 1.8	263.2 ± 7.5
Free cholesterol	71.4 ± 2.3	209.6 ± 6.8
Triglycerides	160.7 ± 2.9	416.2 ± 8.3
Free fatty acids	43.8 ± 2.1	153.0 ± 6.9
Total phospholipids	150.4 ± 5.3	488.1 ± 7.8
Phosphatidylethanolamine	19.0 ± 1.2	158.6 ± 3.4
Phosphatidylserine	7.2 ± 0.4	82.2 ± 2.9
Phosphatidylinositol	9.5 ± 0.3	100.5 ± 2.8
Phosphatidylcholine	69.6 ± 2.4	78.5 ± 2.1
Sphingomyelin	45.1 ± 2.1	68.3 ± 2.5

*Values are in milligrams per 100 gm of samples ± SD of eight analyses.

vaginal delivery of eight patients with uncomplicated gestations. The amnion and chorion were separated immediately after delivery with the use of Allis clamps and thumb forceps. The membranes were freed of blood by washing with normal saline. The specimens were immediately placed in clean glass containers and were frozen at -20° C. They were maintained frozen until analysis was performed within 1 week of the date of collection.

Analysis of lipids. Lipids were extracted, separated into various lipid classes by thin-layer chromatography, and quantitated by a gravimetric method as described

Table II. Composition of nonpolar lipids of amnion and chorion

Acyl group	Cholesterol esters		Triglycerides		Free fatty acids	
	Amnion	Chorion	Amnion	Chorion	Amnion	Chorion
12:0*	1.6 ± 0.1†	1.8 ± 0.3†	1.1 ± 0.1	1.1 ± 0.2	1.2 ± 0.0	1.2 ± 0.1
13:0	1.0 ± 0.1	1.1 ± 0.2	0.8 ± 0.1	0.7 ± 0.1	1.3 ± 0.1	1.4 ± 0.2
14:0	2.3 ± 0.1	2.2 ± 0.1	3.3 ± 0.4	3.2 ± 0.1	2.9 ± 0.2	2.7 ± 0.2
14:1	2.6 ± 0.3	2.8 ± 0.3	1.1 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	0.9 ± 0.2
16:0	39.9 ± 1.5	39.1 ± 2.2	40.9 ± 2.8	41.1 ± 1.9	43.5 ± 2.1	43.9 ± 2.3
16:1	3.9 ± 0.8	4.1 ± 0.4	2.9 ± 0.3	2.7 ± 0.1	3.1 ± 0.1	3.9 ± 0.4
17:0	0.6 ± 0.1	0.5 ± 0.1	0.9 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.1
17:1	11.5 ± 0.5	11.9 ± 0.8	1.4 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.3 ± 0.2
18:0	16.9 ± 1.1	16.3 ± 1.1	18.5 ± 1.2	18.9 ± 0.5	19.7 ± 0.8	18.9 ± 1.3
18:1	9.2 ± 0.0	9.9 ± 0.5	22.1 ± 0.8	21.9 ± 1.2	11.1 ± 1.1	10.9 ± 1.1
18:2	0.6 ± 0.1	0.5 ± 0.1	0.7 ± 0.1	0.9 ± 0.1	0.7 ± 0.1	0.9 ± 0.1
18:3	0.2 ± 0.0	0.3 ± 0.0	0.5 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.9 ± 0.1
20:0	0.8 ± 0.1	0.7 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	1.1 ± 0.2
20:1	0.6 ± 0.1	0.5 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	0.9 ± 0.1
20:4	5.6 ± 0.5	6.2 ± 0.5	1.8 ± 0.1	1.7 ± 0.2	1.4 ± 0.1	1.5 ± 0.2
22:0	0.5 ± 0.1	0.6 ± 0.1	1.1 ± 0.1	1.3 ± 0.1	8.1 ± 0.1	7.9 ± 0.1
24:0	2.2 ± 0.2	1.5 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	0.8 ± 0.1

*Ratio of the number of carbon atoms to the number of double bonds.

†Each value is the mean (weight percentage of total acyl groups) ± SD of eight analyses.

earlier.⁴ Preparative silica gel thin-layer chromatography,⁵ with the use of the solvent systems of Mangold and Malins⁶ and Parker and Peterson,⁷ was done to isolate individual nonpolar and phospholipid classes, respectively. The quantity of free and total cholesterol in the total lipid solution was determined by the use of the procedure of Chourchaine et al.⁸ Glycerides (triglycerides, diglycerides, and monoglycerides) and free fatty acids isolated from the thin-layer chromatography plates were analyzed by the methods of Van Handel and Zilversmit⁹ and Novak,¹⁰ respectively. The quantity of total phospholipids isolated from the thin-layer chromatography plates was determined by measuring the amount of phosphorus.¹¹ The acyl group composition of the individual lipid classes was determined by gas liquid chromatography of their fatty acid esters¹² according to the conditions described earlier.⁴

Results

Data on the composition of the lipids are shown in Table I. Triglycerides, cholesterol, cholesterol esters, and free fatty acids were the major nonpolar lipids, and phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylcholine, and sphingomyelin were the major phospholipids. The lipid composition of amnion differed from that of chorion. Chorion contained higher amounts of lipids than amnion. Phosphatidylethanolamine was the major phospholipid in chorion, whereas phosphatidylcholine was the major phospholipid in amnion. Data on the acyl group composition of cholesterol esters, triglycerides, and free fatty acids are shown in Table II. Palmitoyl

(16:0), stearoyl (18:0), and oleoyl (18:1) were the major acyl groups in the nonpolar lipids. In contrast to other nonpolar lipid classes, cholesterol esters of both chorion and amnion contained appreciably higher amounts of 17:1 and 20:4 acyl groups. Data on the acyl group composition of the individual phospholipids are shown in Tables IIIA and IIIB. The 16:0, 18:0, 18:1, and 20:4 acyl groups were the major components in lipids of both chorion and amnion. In contrast to other phospholipid classes, phosphatidylcholine of both chorion and amnion contained unusually higher amounts of the 17:1 acyl group. In general the acyl group composition of all lipids was identical in amnion and chorion.

Comment

Because the fetal membranes play such an important role in the birth process, we felt it would be useful to measure the lipid content of the amnion and chorion separately. Previous studies have always measured the contents of these structures together.

The significance of the fact that chorion contains higher amounts of lipids than the amnion is not completely clear. Perhaps this results from the anatomical relationship of the chorion to the decidua—they are in direct apposition. Also, it is likely that a portion of the decidua remains adherent to the chorion after being expelled from the uterine cavity. However, although a greater amount of lipid is present in the chorion, the acyl group composition of all lipids was essentially identical for the amnion and chorion. The most interesting observation resulting from the study is the

Table IIIA. Acyl group composition of phospholipids of human amnion and chorion

Acyl group	Phosphatidylethanolamine		Phosphatidylserine	
	Amnion	Chorion	Amnion	Chorion
12:0*	2.2 ± 0.1†	2.4 ± 0.2	1.9 ± 0.2	1.8 ± 0.2
13:0	1.0 ± 0.1	1.2 ± 0.1	0.8 ± 0.1	1.8 ± 0.1
14:0	4.3 ± 0.4	3.9 ± 0.1	3.7 ± 0.1	4.3 ± 0.1
14:1	1.2 ± 0.2	1.1 ± 0.1	1.6 ± 0.3	1.6 ± 0.1
16:0	34.6 ± 1.5	33.0 ± 1.8	32.5 ± 2.1	32.8 ± 2.9
16:1	4.9 ± 0.3	4.8 ± 0.3	4.9 ± 0.2	5.2 ± 0.4
17:0	2.4 ± 0.1	2.8 ± 0.3	2.7 ± 0.1	2.9 ± 0.1
17:1	3.3 ± 0.2	3.7 ± 0.2	3.8 ± 0.1	4.1 ± 0.1
18:0	10.8 ± 0.9	11.9 ± 1.1	12.2 ± 0.9	11.9 ± 0.8
18:1	17.4 ± 1.0	17.9 ± 1.3	18.9 ± 0.8	18.1 ± 1.1
18:2	2.9 ± 0.2	2.8 ± 0.3	2.8 ± 0.1	1.8 ± 0.3
18:3	1.7 ± 0.1	1.5 ± 0.1	1.6 ± 0.0	1.4 ± 0.2
20:0	1.1 ± 0.2	1.1 ± 0.1	1.0 ± 0.0	1.2 ± 0.1
20:1	1.4 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	1.6 ± 0.1
20:4	6.1 ± 0.1	5.9 ± 0.6	4.6 ± 0.4	4.7 ± 0.3
22:0	1.9 ± 0.1	2.2 ± 0.1	2.9 ± 0.2	2.8 ± 0.1
24:0	2.8 ± 0.2	2.1 ± 0.1	2.4 ± 0.2	1.9 ± 0.1
24:1	—	—	—	—

*Ratio of the number of carbon atoms to the number of double bonds.

†Each value is the mean (weight percentage of total acyl groups) ± SD of eight analyses.

Table IIIB. Acyl group composition of phospholipids of human amnion and chorion

Acyl group	Phosphatidylinositol		Phosphatidylcholine		Sphingomyelin	
	Amnion	Chorion	Amnion	Chorion	Amnion	Chorion
12:0*	1.8 ± 0.2†	1.6 ± 0.1	0.2 ± 0.0	0.3 ± 0.0	0.7 ± 0.0	0.8 ± 0.1
13:0	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.0	1.4 ± 0.1	1.3 ± 0.1	0.6 ± 0.0
14:0	2.5 ± 0.1	1.8 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	1.5 ± 0.1	1.6 ± 0.1
14:1	1.5 ± 0.1	1.8 ± 0.1	0.5 ± 0.0	0.7 ± 0.1	0.6 ± 0.0	0.6 ± 0.0
16:0	32.1 ± 2.6	30.3 ± 1.9	33.0 ± 1.3	34.6 ± 2.1	10.9 ± 0.1	11.1 ± 0.8
16:1	4.8 ± 0.3	2.9 ± 0.3	2.4 ± 0.1	2.2 ± 0.1	1.7 ± 0.1	1.4 ± 0.1
17:0	2.5 ± 0.1	2.1 ± 0.1	1.2 ± 0.0	1.6 ± 0.1	1.0 ± 0.0	0.6 ± 0.0
17:1	3.9 ± 0.1	2.9 ± 0.1	6.1 ± 0.1	5.9 ± 0.2	2.3 ± 0.1	0.3 ± 0.0
18:0	13.5 ± 1.1	12.4 ± 0.8	20.9 ± 1.1	19.5 ± 0.9	11.1 ± 0.9	11.2 ± 0.9
18:1	19.8 ± 1.1	26.6 ± 2.1	21.1 ± 1.1	20.2 ± 0.9	12.3 ± 1.1	12.9 ± 1.1
18:2	2.0 ± 0.3	1.4 ± 0.1	1.0 ± 0.1	0.8 ± 0.1	0.8 ± 0.0	0.8 ± 0.1
18:3	1.9 ± 0.1	1.5 ± 0.1	1.2 ± 0.0	1.6 ± 0.1	0.7 ± 0.1	0.6 ± 0.1
20:0	0.8 ± 0.1	0.8 ± 0.1	1.0 ± 0.0	0.9 ± 0.0	0.7 ± 0.1	0.6 ± 0.1
20:1	1.2 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.5 ± 0.0	0.6 ± 0.1
20:4	4.4 ± 0.1	4.9 ± 0.3	6.5 ± 0.2	6.9 ± 0.5	0.1 ± 0.0	0.1 ± 0.0
22:0	4.2 ± 0.1	4.5 ± 0.3	0.9 ± 0.1	1.6 ± 0.1	Trace	Trace
24:0	2.1 ± 0.1	2.5 ± 0.2	0.5 ± 0.1	0.3 ± 0.0	26.2 ± 2.1	28.1 ± 0.9
24:1	—	—	—	—	27.6 ± 1.7	28.1 ± 2.1

*Ratio of the number of carbon atoms to the number of double bonds.

†Each value is the mean (weight percentage of total acyl groups) ± SD of eight analyses.

finding of a substantial amount of the acyl group 20:4 as a component of cholesterol esters for both amnion and chorion. The implication of this finding could be that a nonpolar lipid source of additional arachidonic acid serves as an obligate precursor necessary for the production of prostaglandins F_{2a} and E_2 . This additional source of precursor was suggested earlier in a study with amniotic fluid by Das et al.⁴ It was reported that the arachidonic acid level in cholesterol esters increases with gestational advancement. Another theoretical possibility is that fetal membranes contain lecithin

cholesterol acyltransferase activity, and this enzyme plays a key role in maintaining an equilibrium between lecithin and cholesterol esters (see Fig. 1). Whenever these membranes do not have any immediate need of prostaglandin biosynthesis, some of the arachidonic acid from lecithin may be diverted to esterify cholesterol by lecithin cholesterol acyltransferase.

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