

## HABITUAL ABORTION

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Repetitive spontaneous abortion is a distressing problem for both the patient and the physician. The understandable desire of the patient for active intervention, and the response of the physician to that desire, can have unfortunate consequences, best exemplified by the use of diethylstilbestrol for prevention of abortion. The formulation of a rational approach to the diagnostic investigation and the treatment of habitual abortion is hampered, however, by lack of agreement on its definition. In many studies of habitual abortion, women with two consecutive abortions are included, while other studies use a definition of three or more consecutive abortions. Moreover, many reports include women with a live-born child in addition to the abortions. Goldzieher<sup>1</sup> has pointed out that the latter group has a better prognosis than the group of women who have experienced only abortion. Another fundamental problem is confusion over the expectation for a successful pregnancy in a woman who is defined as a habitual aborter. Depending on the authority cited, a woman who has had three consecutive abortions without a live birth may have a 20% or an 80% chance for a live birth in her next pregnancy.<sup>2-5</sup> Studies on the efficacy of many forms of treatment have utilized the 20% expectation as a means of showing the value of their therapy, which often raised the success rate to 60% to 80%.<sup>6</sup> This review initially concerns itself with the question of abortion probability and then considers critically a number of the possible causes of habitual abortion and their treatment. The focus is on first-trimester abortion, and for that reason cervical incompetence is not considered. Many of the studies cited, however, do include pregnancy wastage up to the 5th or 6th month in their abortion groups.

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## INCIDENCE OF HABITUAL ABORTION

In the same 1938 volume of the *Journal of Obstetrics and Gynaecology of the British Empire*, which contained articles by McIndoe on vaginal reconstruction and by Sheehen on postpartum pituitary necrosis, Malpas<sup>2</sup> suggested that spontaneous abortion was due to either nonrecurrent or recurrent causes. Women who had abortions because of recurrent causes could be expected to lose every pregnancy. On the basis of theoretical formulations derived from data published by Whitehouse,<sup>7</sup> Malpas<sup>2</sup> suggested that the general incidence of abortion was 18% and that of every 100 pregnant women approximately 17 would abort for random causes and approximately 1 because of a recurrent cause. Malpas calculated that following three successive abortions a woman had only a 27% chance to achieve a term pregnancy. Eastman<sup>3</sup> modified the percentages of abortions due to nonrecurrent and recurrent causes and produced equally pessimistic predictions on the spontaneous cure of habitual abortion.

The figures published by Malpas<sup>2</sup> and Eastman<sup>3</sup> were accepted by many physicians.<sup>6</sup> On the other hand, Goldzieher<sup>1</sup> and Goldzieher and Benigno<sup>4</sup> noted the fallacy of using the theoretical estimates of Malpas<sup>2</sup> and Eastman<sup>3</sup> of what should happen as the control for tests of the efficacy of various medications. An equally invalid control was the previous obstetric history of the patients. Even if a woman has had two or three consecutive abortions it cannot be assumed that her chance of abortion in a subsequent pregnancy will be 100%. Furthermore, a number of authors produced clinical studies suggesting that the spontaneous cure rate after three successive abortions was substantially higher than the predictions of Malpas and Eastman. Evaluation of these clinical studies in terms of defining the

risk factors for successive abortions is made difficult by the inclusion of women with both two and three successive abortions and by the frequent use of therapeutic agents.

The study by Bevis,<sup>8</sup> for example, has been cited in the literature<sup>4</sup> as evidence for the high cure rate obtained with only psychologic support. However, the original paper indicates that, of the 32 patients, 2 were given thyroid and 8 were given progestational agents. Similarly, in a study by Speert,<sup>9</sup> 66 women with three consecutive abortions experienced only seven abortions in their next pregnancy. Approximately 25% received hormones, including thyroid, diethylstilbestrol, and progesterone. Schoeneck,<sup>10</sup> in a small group of nine patients who had aborted in their first three pregnancies, found that none aborted in their fourth pregnancy. In a survey of the literature, King<sup>11</sup> noted that 61% of pregnancies went to term after two consecutive abortions. In a similar survey, Goldzieher and Benigno<sup>4</sup> found that after three consecutive abortions 76% of women had a successful pregnancy. Warburton and Fraser<sup>12</sup> indicated that the risk of subsequent abortion was only 26% following three consecutive abortions, and in a subsequent publication<sup>13</sup> they quoted a number of other studies which seemed to bear out their relatively optimistic estimates. One reservation concerning their patient group is that the women were interviewed during a successful pregnancy which followed their abortions. It is possible that this group differs from women who will never have a successful pregnancy. The figures of Warburton and Fraser<sup>12</sup> were later modified to a 32% risk of abortion after three abortions, 26% after two abortions, and 24% risk after one abortion<sup>13</sup>; they have largely supplanted the Malpas and Eastman formulations in more recent writings on habitual abortion.

This more sanguine view has not gone uncontested. James<sup>14</sup> reviewed information obtained by the Kinsey group and found that, of 29 women who had had two consecutive abortions, 16 had a third abortion. James has also postulated that there are two groups of women, one of which is at high risk for abortion and has a higher recurrence rate. In another study, 7 of 12 women who had had three consecutive abortions suffered a fourth abortion.<sup>15</sup> A similar loss (47%) was reported in 30 women by Poland et al.<sup>16</sup> In none of these studies is it stated whether the women received drug therapy. The variation in control figures makes it imperative that all studies of treatment of habitual abortion include their own controls, and

not compare their experimental groups with controls of other studies or with the theoretical formulations of Malpas and Eastman.

At this time there exists no prospective study, starting prior to pregnancy, of the reproductive potential of women who have had three consecutive abortions and who receive no treatment. There is evidence that women who have a spontaneous abortion are at somewhat greater risk for a subsequent abortion, but the extent of that risk after three consecutive abortions has not been defined.

#### HORMONE ABNORMALITIES

*Thyroid.* Jones and Delfs<sup>17</sup> found lowered thyroid function in 63.5% of women diagnosed as habitual aborters. The testing in that series, published in 1951, consisted of recording the basal metabolism rate and obtaining blood cholesterol values. More recent work is summarized in the monograph by Burrow,<sup>18</sup> and only minimally suggestive evidence is available that hypothyroidism may play a role in abortion.

*Progesterone.* The major thrust of investigations of the role of progesterone deficiency in habitual abortion has been in two areas. The first was to implicate low pregnanediol levels in pregnancy as a cause for abortion and, as a corollary, to treat with exogenous progesterone or progestins. This approach has been shown to be fruitless, and the results are elaborated in detail below. The second approach, undertaken only in very limited studies, has been to diagnose the insufficient effect of progesterone on the endometrium during the luteal phase of the menstrual cycle (inadequate luteal phase) and to initiate treatment with exogenous hormone a few days after ovulation.

The former approach is exemplified by the study of Reifenstein,<sup>6</sup> who found therapeutic value in the use of 17 $\alpha$ -hydroxyprogesterone 17-N-caproate in the treatment of pregnancies which occurred subsequent to two or three consecutive abortions. This study used the Malpas figures as controls and it has been justifiably criticized for this methodologic failure. In contrast, Shearman and Garrett<sup>19</sup> found no increase in salvage when the same drug was used in cases where the pregnanediol level was below normal or where there was a decrease in pregnanediol excretion of more than 2.5 ng/24 hours from one week to the next, before the 12th week of pregnancy. This study included women with two or more consecutive abortions. Goldzieher<sup>20</sup> used similar criteria for

inclusion in a double-blind study of the effects of oral medroxyprogesterone acetate on pregnancy salvage. There was no advantage of the active drug compared with the placebo. This study and that of Shearman and Garrett<sup>19</sup> indicated that habitual aborters with a low pregnanediol excretion have a spontaneous salvage rate approximating 80%. Goldzieher calculated that 1078 habitual aborters separated into test and control groups would be required to prove the value of an agent which would raise the salvage rate from 80% to 90%. Further evidence of the lack of benefit of the use of hormones in prevention of the recurrence of abortion comes from the work of Kloppe and Macnaughton,<sup>21</sup> who studied the effects of a cyclopentenol ether of progesterone. The placebo group achieved a 64% salvage rate and the gestagen group a 56% salvage rate. In another report,<sup>22</sup> dydrogesterone or a placebo was given to pregnant women who had ferning of their cervical mucus in early pregnancy. The overall salvage rate was 85%, and there was no difference between the hormone and the placebo groups.

These studies on the use of progestational agents were restricted to pregnancies that were already diagnosed and well established. It is possible that those patients at greatest risk may have lost their pregnancies before they could be entered in these studies. An argument has been advanced, therefore, that hormone deficiency, specifically progesterone deficiency, must be corrected prior to implantation in order to prevent recurrent abortion. Jones and Delfs<sup>17</sup> utilized this type of preimplantation therapy with progesterone, but because a number of other preparations, e.g., thyroid and vitamin E, were also used, it is not possible to assess the value of progesterone treatment. In a later publication which included the cases reported by Jones and Delfs,<sup>17</sup> Jones<sup>23</sup> stated that, of 120 women with pregnancy wastage, 34 had inadequate luteal phases and with treatment 31 had live-born children. Endometrial biopsy was used to make the diagnosis of inadequate luteal phase, which was defined as an endometrium which was 3 or more days behind dates as determined by the onset of the subsequent menstrual period. Treatment consisted of progesterone delivered by vaginal suppositories or by daily intramuscular injection. An isolated inadequate luteal phase is not an unusual finding in infertile couples and an abnormality must be demonstrated in at least two cycles to establish the diagnosis.<sup>24</sup> By utilizing endometrial biopsy,

Botella Llusia<sup>25</sup> found that 38% of women with three or more consecutive abortions had a poorly developed secretory endometrium, compared with only 6% of infertile women. Grant et al.<sup>26</sup> used endometrial biopsy to establish the presence of an inadequate luteal phase in 60% of women with two or more consecutive abortions. This group had been selected for study because the women had poor basal body temperature charts. Treatment with 10 mg of ethisterone or norethisterone daily for 10 days starting approximately at the time of ovulation was followed by 66 term pregnancies in 79 women (84%). Treatment starting later in pregnancy resulted in a 71% salvage rate.

The diagnosis of inadequate luteal phase by measurement of serum progesterone has been made difficult by lack of agreement on normal values. Abraham et al.<sup>27</sup> suggested that if three values during the luteal phase totaled 15 ng/ml or greater a diagnosis of inadequate luteal phase was precluded. Jones<sup>23</sup> has made the diagnosis by biopsy in women who had higher values. A recent study compared endometrial biopsy, serum progesterone levels, and onset of the next menstrual period.<sup>28</sup> There was a better correlation between progesterone levels and the onset of the subsequent menstrual period than between the biopsy and the onset of menses.

Two recent studies dealt with serum progesterone levels in women who had had three consecutive abortions. One study indicated that 10 such women had abnormally low levels of progesterone during the luteal phase,<sup>29</sup> and all 10 women subsequently aborted again. The authors neglected to indicate how the women were selected for the study, although all were said to have progestational deficiency on biopsy. The second study found that six habitual aborters had a mid-luteal serum progesterone concentration of greater than 4 ng/ml, and five had full-term pregnancies.<sup>30</sup> The fate of the sixth woman was not specified. Four other women did not become pregnant again and three of them had progesterone values below 4 ng/ml. Interestingly, there were no subsequent abortions in this study.

The use of medroxyprogesterone acetate (Provera) following ovulation has been a popular but unsubstantiated treatment of real or imagined inadequate luteal phase. This drug, when given in high dosages, depresses progesterone levels and this effect should give some pause to its prescribers.<sup>31</sup> Moreover, the use of hormones in pregnancy without substantial evidence of benefit is no longer admissible. The evidence that prenatal

exposure to female sex hormones may be teratogenic is strong enough to prohibit the use of such drugs.<sup>32-34</sup>

Diethylstilbestrol had been used in the past as therapy for abortion. There was no justification for its use, and this was pointed out in 1953, many years before it was eventually abandoned.<sup>35</sup> The unfortunate consequences of that therapy are still being seen in the offspring of treated mothers.

In summary, the studies to date are not sufficiently controlled to determine whether progesterone therapy prior to the missed menstrual period is of value in habitual aborters who are diagnosed as having an inadequate luteal phase. The use of other hormones starting before or after the missed menstrual period can only be condemned.

#### MALE FACTOR

Joël<sup>36</sup> suggested that habitual abortion may be secondary to a decreased DNA content of sperm. Although this is an interesting concept, it has received little support.

Sperm seem to be filtered at the level of the cervix, which provides a barrier to the entry of morphologically abnormal sperm into the uterus. Therefore, the evaluation of sperm in cases of habitual abortion, from the standpoint of shape and form, would seem to be an unproductive procedure.

Joël<sup>36</sup> reported that habitual abortion could be associated with sperm counts above 250 million/ml. MacLeod and Gold<sup>37</sup> also found a tendency toward higher counts in couples who had had three consecutive abortions. Surprisingly, sperm motility was better in this group than that in a group which had had three consecutive normal pregnancies. At present the role, if any, of the male in habitual abortion is unknown.

#### DIABETES AND OTHER DISEASES

It is almost reflex for the physician to order a glucose tolerance test when he is faced with the problem of habitual abortion. Despite an occasional case report,<sup>38</sup> there seems to be no evidence that diabetes is a cause of habitual abortion. For that reason we see no value in the routine ordering of glucose tolerance tests. Similarly, syphilis has not been implicated in recurrent first-trimester abortion, and a serology study need not be routine in the diagnosis of this problem. Bacteriuria is often sought, but its connection with abortion has not been established.

Systemic lupus erythematosus is associated with an increased rate of abortion after the clinical onset of the disease.<sup>39</sup> In one study, when patients with lupus became symptomatic the abortion rate rose to over 40%.<sup>40</sup>

#### IMMUNOLOGY

The fetus contains antigens which are foreign to the mother, and classic immunologic theory would suggest that the fetus should be rejected in a manner similar to that of a skin graft from a donor. The ability of the fetus to avoid rejection has stimulated a great deal of study which has been reviewed by Beer and Billingham.<sup>41</sup> One of the many theories concerning the success of the fetus as an allograft hypothesizes that circulating antibody (blocking antibody) raised in response to paternal antigens provides protection against attack by maternal lymphocytes. Rocklin and co-workers<sup>42</sup> showed that a lymphocyte reaction to paternal antigens was present both in women with three or more consecutive abortions and in normal multiparous women. The women with a history of habitual abortion lacked appreciable levels of blocking factor, which was found, however, in the serum of normal multiparous women. This stimulating finding requires corroboration in a larger series. An earlier study which showed that women with a history of recurrent abortion rejected skin grafts from their husbands in an accelerated fashion<sup>43</sup> could be consistent with the "blocking antibody" hypothesis.

#### ANOMALIES OF THE REPRODUCTIVE TRACT

Midline fusion and canalization of the Müllerian ducts are requisites for normal uterine and vaginal development. Failure of either of these processes, totally or in part, is thought to occur in 1 of every 700 women. The double uterus and its variants, reflecting failure of midline fusion or resorption of septa, have long been recognized as factors in pregnancy wastage. However, the association is not clear-cut. A majority of women with recognized anomalies of the uterus will have successful pregnancies. In addition, in all likelihood there are many women with unrecognized anomalies who do not undergo medical scrutiny because they do not have problems referable to the abnormality. Even those who have pregnancy wastage can at times achieve subsequent success without surgical intervention. Jones and Wheelless<sup>44</sup> reported on 18 women who had had one

or two abortions and an additional 9 patients who had had three abortions, all of whom had a diagnosed uterine anomaly and hormone deficiency, who eventually produced at least one living child following treatment with progesterone and, in some cases, thyroid. Twenty-two patients did not respond to this medical management. Although this study indicates that a double uterus can be consistent with satisfactory reproductive performance, it is also true that reproductive failure may be caused by uterine malformations. A hysterosalpingogram should be obtained if a woman has two or more consecutive abortions or has repeated premature births. A bicornuate uterus, a septate uterus, or a single uterine horn can contribute to early pregnancy wastage. In a series reported by Jones,<sup>45</sup> the abortion rate was 33.8% with a bicornuate uterus, 22.2% with a septate uterus, and 34.6% with a single uterine horn. However, the numbers in each group were small. Significant improvements in pregnancy salvage have been reported following use of Strassman metroplasty<sup>46</sup> or a variety of techniques for removal of a uterine septum. Good descriptions of the surgical procedures are provided in the atlas of Kistner and Patton.<sup>47</sup> These authors, as well as Jones and Wheelless,<sup>44</sup> emphasize the need for investigating renal anomalies in all women found to have genital malformations. In the series of Jones,<sup>45</sup> 5.3% of women with genital anomalies also had an abnormal renal structure. In the subgroup of cases with vaginal agenesis the renal anomaly rate was close to 50%.<sup>48</sup> An equally high rate is seen in the presence of uteri derived from a single Müllerian duct.

Both uterine myomas and intrauterine adhesions have been implicated in habitual abortion.<sup>49</sup> In one report myomas were found in 18% of women with two or more abortions.<sup>50</sup>

#### INFECTION

*Toxoplasma gondii* can invade the placenta and be transmitted to the fetus. While some authors have implicated this parasite as a cause of habitual abortion, more recent work suggests that it is not a significant factor. Kimball et al.<sup>51</sup> found that the dye test for *Toxoplasma* antibodies was positive in 31.0% of women with no history of abortion, in 38.5% of women with sporadic abortion, and in 32.9% of women with habitual abortion. Similarly, Southern<sup>52</sup> reported that 5 of 25 women (20%) with a history of two or more successive abortions had positive dye tests as compared with 10 of 47 controls (21.3%).

*Listeria monocytogenes* can cause abortion in animals. However, in one study of 554 cases of abortion in women (including 74 of habitual abortion) there was no evidence bacteriologically or serologically of *Listeria* infection.<sup>53</sup>

In a report from Atlanta, herpesvirus infection in the first 20 weeks of pregnancy was associated with a 34% abortion rate as compared with 10.6% in the controls.<sup>54</sup> The role of this virus, if any, in habitual abortion has not been established. The same is true of cytomegaloviruses.

*Chlamydia trachomatis* is one of the most common sexually transmitted pathogens and there is new evidence that implicates the organism in salpingitis.<sup>55</sup> Studies in our laboratory<sup>56</sup> have shown that *Chlamydia* can also infect the mouse trophoblast in vitro. However, only an isolated report by Schacter<sup>57</sup> exists to indicate that *Chlamydia* can be cultured from human abortuses. One of the strains of *Chlamydia* cultured from those abortuses was shown to cause abortion in cattle.<sup>58</sup> Because it is commonly found in the cervix, it is doubtful whether the culture of *Chlamydia* from that area in women with habitual abortion will provide evidence of an etiologic role for this organism. Culture from aborted products of conception also are suspect because the tissue traverses the cervix, which may be infected.

Mycoplasma is commonly found in the vagina and cervix. In the first trimester of pregnancy, T-strain mycoplasma is found in the cervixes of 58% of women, and *Mycoplasma hominis* in 19%.<sup>59</sup> Caspi et al.<sup>60</sup> cultured mycoplasma from the products of conception of 31% of spontaneous abortions, but only 5% of specimens from therapeutic abortions were culture-positive. In another report, the cultures of four of five habitual aborters were positive for mycoplasma.<sup>61</sup> These five women, as well as a sixth woman whose cervix was not cultured, were treated with Declomycin. If the culture-negative woman is excluded, the results in subsequent pregnancies were two term pregnancies, one fetal death at 38 weeks associated with toxemia, one premature delivery at 34 weeks, and one abortion. Inexplicably, the authors did not specify which of these results occurred in the woman whose cervix was not cultured. In addition to this omission and the small numbers of cases, the authors compared their results with the previous reproductive histories of these patients as evidence of therapeutic success. As noted earlier, such a comparison is not valid.

Fraser and Taylor-Robinson<sup>62</sup> demonstrated that incubation of *M. pulmonis* with mouse sperm resulted in a decrease in both fertilization rates and embryo development. The adverse effects were not seen with *M. fermentans*. At this time the relationship of mycoplasma to habitual abortion remains to be determined.

#### PSYCHOLOGIC FACTORS

Mann<sup>63</sup> felt that there was a distinct psychologic orientation of women who suffered repeated pregnancy loss. In his view they came from homes in which the mother was dominant and the father was ineffective. Mann's description of the psychodynamics of habitual abortion is devoid of control material. More impressive studies are those by Tupper and Weil<sup>64</sup> and James.<sup>65</sup> The study group consisted of 38 women (24 had had children) who had had three consecutive abortions and who were again pregnant. The authors stated that these women fell into two main personality groups: (1) the basically immature woman who cannot accept the responsibility of motherhood and (2) the independent woman who yearns for the rewards of the male world and who "feels that maternity, the greatest reward of the female world, is much less satisfying." These interpretations of the female psyche, written in 1962 and 1963, indicate perhaps more about the authors than about their patients. Treatment consisted largely of a weekly interview with a psychiatrist and access to the psychiatrist by telephone at other times. In addition, sexual relations were prohibited during the first 3 to 4 months of pregnancy (no rationale for the proscription is given). There were also rare prescriptions of small doses of pentobarbital or meprobamate. Hormones were never given.

Nineteen of the couples received only an initial evaluation and then returned, because of geographic or other unspecified conditions, to their own family physicians for prenatal care. Of the 19 women in this group, 13 had another spontaneous abortion, compared with only 2 of 19 in the group receiving psychotherapy (a statistically significant difference). The two groups seemed comparable in terms of number of previous abortions, age, education, length of marriage, and occupation. Ten of the experimental group and thirteen of the controls had had children. An unanswered question is whether sexual abstinence was also advised in the control group. This study by Tupper and Weil<sup>64</sup> is deserving of corrobora-

tion. It may be difficult, however, to accomplish that goal because few habitual aborters will be content to be in an untreated control group.

#### GENETIC FACTORS

There are a number of genetic etiologies for recurrent abortion. Just as there are inherited single-gene defects that cause early childhood deaths (i.e., Tay-Sachs disease or tuberous sclerosis) or that cause late in utero demise (i.e., hypophosphatasia or  $\alpha$ -thalassemia), there are probably single-gene defects that cause early embryonic death and spontaneous abortion. It is unlikely that we will ever have an impressive list of such disorders, since the product of an early abortion is rarely studied biochemically and such studies would represent "blind guesswork" on the part of the investigators.

The cause of the majority of early spontaneous abortions is a chromosomal anomaly in the conceptus. With the introduction of improved tissue culture and karyotyping techniques it has become apparent that 50% to 60% of first-trimester abortions are chromosomally abnormal.<sup>66-68</sup> The most common aneuploidies fall into three classes. In most studies, trisomy accounts for 50% to 60% of the chromosomally abnormal abortuses, monosomy X for 15% to 25%, and polyploidy for 20% to 25%. If the clinically recognizable spontaneous abortion incidence is 15% of conceptions and 50% to 60% of these are chromosomally abnormal, then 7.5% to 10% of all conceptions are aneuploid. This calculation is supported by a study of first-trimester induced abortions demonstrating a 7.3% rate of chromosome anomalies in 300 abortuses.<sup>69</sup> In considering patients with recurrent abortion the question arises as to whether having one chromosomally abnormal spontaneous abortion increases the risk of a chromosome abnormality, and therefore a second spontaneous abortion, in the next pregnancy. Boué and Boué<sup>70</sup> have reported karyotypes of two consecutive abortuses in 43 women. There was a correlation between the normal or abnormal character of the two specimens. If the first abortus was chromosomally normal then the second abortus had a 50% chance of being chromosomally abnormal. However, if the first abortus was chromosomally abnormal then there was an 80% chance that the second abortus was also chromosomally abnormal. This means that some couples who have recurrent, chromosomally abnormal conceptions—almost all of which will result in spontaneous abortions—

present with a complaint of recurrent abortions. If this situation were diagnosed by karyotyping successive abortuses, it would be untreatable but would suggest that amniocentesis for prenatal diagnosis be performed if the woman carries a pregnancy to the second trimester.

In addition to numerical aberrations, chromosomes can undergo structural aberrations. "Translocation" describes the situation in which a fragment of one chromosome becomes attached to the broken end of another. A reciprocal translocation involves two chromosomes in a mutual exchange of broken-off fragments. A Robertsonian translocation is a special category of reciprocal translocation involving two acrocentric chromosomes in which breakage occurs close to the centromere in the short arm of one chromosome and in the long arm of the other. One of the resulting chromosomes is extremely small and is lost in subsequent mitotic divisions. An individual carrying a balanced reciprocal translocation in which essentially no genetic material has been lost will be phenotypically normal but may have reproductive problems. Depending upon the type of meiotic segregation the involved chromosomes undergo, the zygote may be (1) normal, (2) a balanced translocation carrier like its parent, (3) trisomic for part of a chromosome, or (4) monosomic for part of a chromosome. These last two conditions will almost always lead to spontaneous abortion.

The influence of balanced translocation states on the abortion rate can be studied by measuring the reproductive fitness of carriers or by ascertaining the incidence of balanced translocation carriers among couples with recurrent abortions. By using the former method, Jacobs et al.<sup>71</sup> found a significant reduction in reproductive fitness in carriers of balanced translocations owing to a reduction in live births and an increase in fetal deaths. They found similar results for D/D Robertsonian translocation carriers, although Hamerton<sup>72</sup> had not found any increase in the frequency of spontaneous abortions for such individuals. Neither study found a reduction in reproductive fitness for D/G translocation carriers.

The karyotypes of couples with two or more spontaneous abortions yield a 2.78% (43/1544) incidence of individuals who are balanced reciprocal translocation carriers.<sup>73-78</sup> This 5% rate of "positive" results for a given couple can be increased by altering the indication for karyotyping. Byrd et al.<sup>76</sup> found a 3.4% translocation carrier incidence among individuals with two or

more spontaneous abortions, but a 13.6% translocation carrier rate in individuals with a history of abortion plus fetal malformation. The recent introduction of chromosome-banding techniques has allowed recognition of smaller, more subtle, translocations. The incidence of balanced translocation carriers among individuals with two spontaneous abortions studied with these methods has been somewhat higher (i.e., 4.76%; 4 of 84). Some reports have quoted higher rates of "positive" results by including chromosomal variations such as pericentric inversions, large satellites on acrocentric chromosomes, or long Y chromosomes.<sup>73, 78</sup> These are normal variants found in the general population and should not be implicated as an etiology for recurrent abortions without detailed population studies. In view of the above data on balanced translocation carriers, a chromosome study, including banding, is appropriate for a couple with three or more spontaneous abortions.

#### SUMMARY

Given the many uncertainties raised by this review, what is a rational approach to the investigation of spontaneous abortion? If the woman has had only one abortion, then reassurance is in order with some discussion of the protective effects of abortion against the birth of chromosomally abnormal children. After two consecutive abortions, most couples will want some investigation of the problem. Currently, only chromosomal abnormalities and uterine malformations can be definitely implicated in the etiology of habitual abortion. It would be reasonable to obtain a karyotype and a hysteroqram in cases involving two consecutive abortions. Because of the expense and the probability that there is at least a 50% to 60% rate of spontaneous cure after two abortions, we restrict karyotyping to couples who have had three or more consecutive abortions. Karyotyping is also done if, in addition to one or two abortions, the couple has also had a child with congenital malformations. If at any time a fetus or abortus is karyotyped and found to have a translocation, parental karyotyping should be obtained. If an abortus is found to be trisomic, future pregnancies are at increased risk of also being trisomic, and consideration should be given to amniocentesis for prenatal diagnosis.<sup>79</sup>

Most physicians would feel uncomfortable with such a minimal investigation. Further studies



may be justified by the realization that information is not available to prove or to disprove other factors as causes of habitual abortion. Therefore, it might be reasonable to obtain thyroid function tests, serum progesterone determinations (using the criteria of Abraham et al.<sup>27</sup> for interpretation) or possibly endometrial biopsies, cervical culture for herpesvirus, and an antinuclear antibody test as a screen for lupus erythematosus.

Tests for mycoplasma and *Chlamydia* are probably only of value when obtained as part of research protocols. Similarly, immunologic studies are at present available only in research situations.

Lastly, psychologic support in the form of frequent visits, sympathetic counseling, and ready access should be a part of the care of couples with habitual abortion.

*Note Added in Proof:* Stray-Pedersen et al. (Am J Obstet Gynecol 130:307, 1978) have reported significantly higher colonization of the endometrium with T-mycoplasma in women with a history of habitual abortion as compared with normal fertile women.

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