Premature separation of the normally implanted placenta

Robert R. Morris
University of Nebraska Medical Center

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PREMATURE SEPARATION OF THE
NORMALLY IMPLANTED PLACENTA

BY ROBERT E. MORRIS

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INTRODUCTION

Premature separation of the normally implanted placenta is a subject which, although not one of the most common complications of pregnancy, is by no means rare. The purpose of this paper is to present a review of the subject as it has been discussed in the literature, presenting the condition in its most spectacular form, that of abruptio placenta, and then proceeding to discuss the more quiet and less dangerous forms, ranging all the way from abortion and miscarriage in the early months of pregnancy to the more benign forms of abruptio placenta in the later months.

During the past few years a great deal of new work has been done on the etiological and therapeutic considerations of premature separation of the placenta and its related subjects, abortion and miscarriage. The question of the relation of endocrine and vitamin factors to the production of such conditions has given rise to many controversial problems. Some men are firm believers on one side of the question and others radically oppose the new theories.

It is quite obvious that the final word has not been spoken regarding this controversial problem;
therefore it is not fitting that this paper should contain any foregone conclusions on the subject. Rather, I shall discuss both sides of the problem and attempt to present the prevailing ideas as to the usefulness, limitations, and applicability of the newer theories concerning premature separation of the normally implanted placenta.

Of course, during my review of the literature I have reached some definite ideas of my own. These ideas are expressed in the paper. However, it is not intended that they should be interpreted by the reader as dogmatic statements of truth and fact, because the truth regarding the subject of this paper has yet to be proven by further clinical and experimental evidence.
GENERAL CONSIDERATIONS

This paper has as its subject all forms of premature separation of the normally implanted placenta. By this it is meant to include not only the subject of abruptio placenta, which strictly speaking is hemorrhage occurring from premature separation of a normally implanted placenta taking place during the last three months of pregnancy, but also the earlier forms of premature separation arising prior to the period of fetal viability, which constitute the various forms of abortion and miscarriage.

By the term "normally implanted", it is meant to differentiate from placenta praevia, another condition which commonly gives rise to hemorrhage during pregnancy, and incidentally is a condition which is to be differentiated clinically from the subject of this paper. The forms of premature separation which occur in early pregnancy and constitute the abortion and miscarriage cases may or may not give rise to serious consequences. Abruptio placenta in later pregnancy may be only a minor complication of a normal labor, or it may be one of the gravest situations with which the obstetrician has to deal.

There is not a great deal of historical interest
in the subject of this paper. In 1775, Edward Rigby (54) first differentiated hemorrhage arising from separation of the normally situated placenta from that arising from placenta praevia. The former he called "accidental", the latter, "unavoidable" hemorrhage. The term accidental hemorrhage has persisted though open to criticism. R. W. Holmes (31), in 1901, suggested the term "ablatio placenta". DeLee (14) has suggested the term abruptio placenta.

Abruptio of the placenta means a sudden, forcible breaking off of the organ from its normal site, and in reality is an abortion at or near term. Holmes (32) stated that the condition of premature detachment of the normally situated placenta is one which has been given insufficient attention by obstetricians; that its frequency has been greatly underestimated; its mortality judged too high, and that its treatment is a moot question. This statement was made as early as 1901.

As to the incidence of premature separation of the normally implanted placenta, the figures given by various authorities are extremely variable. It ranges from 0.18 per cent by Kraul (39) to 1.06 per cent by Cragin and Goethals (25), or even 2.8 per cent by Laird (2). Shute (56) states that either
there is great variation of incidence in various parts of the world or there is variation of opinion as to what should be classified in this pathologic group, and also says that the latter explanation is probably correct.

Many cases are undoubtedly overlooked, since all placentas are not examined minutely; moreover there is a lack of adequate literature on the symptoms and signs which characterize early or mild degrees of abruptio placenta. As a result, only the most startling and striking cases are ever recognized as such. To illustrate this fact, in 750 placentas from consecutive deliveries by Goodall (26) in Montreal, it was found that 600 bore evidence of some hemorrhagic lesion. Only eleven of these cases had bled from the vagina during gestation, but early symptoms of the patients were localized uterine tenderness and sacral backache.

Beavers (5) has also shown that the incidence of abruptio placenta varies remarkably in clinics throughout the states. In his review, he reports seven such cases out of 1,000 deliveries by Broadhead, while the New York Lying-In Hospital had no cases in 10,000 deliveries. Mitchell (48) states that contrary to a widespread belief, accidental hemorrhage
is more frequent than placenta praevia. The separation may vary from the slightest to complete ablation of the placenta. Vaux (67) of the Philadelphia Lying-In Hospital reviewed his cases from July 1, 1934 to July 1, 1936. Out of a total of 2,952 obstetrical cases, 133 or 4.5 per cent were late bleeding cases. 129 out of this group were registered while four were emergency cases. Five were associated with trauma and eight with toxemia. Out of these 133 cases, bleeding in 13 of them was ascertained to be due to placenta praevia while premature separation accounted for seven, and 113 cases were of undetermined origin. In the series of premature separation cases, 85.7 per cent were registered and 17.2 per cent were emergency cases. From this we may assume that in the 113 cases that were of undetermined origin the bleeding could easily have been due to premature separation, and that this would markedly increase the incidence figures for this type of pathology.

As to the subject of abortion, it has been estimated that 700,000 abortions occur annually in the United States. This figure includes all types of abortion which come under three chief heads: criminal, spontaneous, and therapeutic. This paper
deals only with the spontaneous type, of which the Children's Bureau Maternal Mortality Statistics gives an incidence of 37 per cent of the total.

As has already been stated, the incidence of premature separation is extremely variable. Absolute figures are difficult to elicit because of the difference of opinion as to what should be classified in this pathologic group, and because of the inadequate information on symptoms and signs which characterize less striking cases.
ETIOLOGY

Many causes have been stated as being etiological factors in the condition of premature separation of the normally implanted placenta. Formerly, separation of the placenta in its usual site was attributed to trauma, emotion, or a peculiar laxity of the uterine vessels. Other causes which have been mentioned frequently are albuminuria, toxemia, chronic nephritis, hypertension, torsion of the uterus, a short cord, subinvolution, chronic endometritis, and multiparity. In 1918, Morse (50) put forth the idea that excessive rotation of the uterus interfered with the circulation and brought on premature separation. Multiparity has been given as a factor by many authors, but Davis and McGee at Chicago Lying-In Hospital give a series of cases (13) in which it was found that 36 per cent of all premature separations occur in primiparas, so these authors conclude that parity plays but a small role in the causation of this condition.

Hofbauer (30), in 1926 blamed histamine intoxication as a cause, but Davis and McGee (13) collected blood from the uterus of a case of uteroplacental apoplexy and were able to find no trace of histamine.
In 1928, Browne (7) attributed the condition to chronic nephritis. He produced a chronic nephritis in experimental animals by the injection of sodium oxalate or uranium nitrate, then by injecting bacillus pyocyaneus he was able to produce premature separation of the placenta and placental infarction. He attributed this separation to failure of the kidneys to excrete poisons from the circulation.

Winter (73), in 1884, observed an intimate relationship between the toxemias of pregnancy and the development of abruptio placenta. Since that time, more and more clinical and experimental evidence has accumulated to bear out this association. Williams (72) found 33 cases of toxemia in a series of 57 cases, an incidence of 57.8 per cent; Kraul (39) found an incidence of 33.3 per cent; Bartholomew (3) found toxemia in 55 per cent of his cases; and Fitzgibbon (20) gives his findings as 82 per cent of cases associated with toxemia. Some evidence of toxemia was found in 56 per cent of the series of Davis and McGee (13).

Since there is such a frequent association between the toxemias and premature separation, it seems that this is more than mere coincidence. There must be some intimate relationship between
the toxemias of pregnancy and the development of abruptio placentae. However, if toxemia were the primary etiological factor in its causation we would expect premature separation to be associated with the most serious of the pregnancy toxemias--eclampsia. However, the condition of eclampsia is an exception, since we seldom find premature separation of the placenta in eclamptic patients or in a toxemia that is the result of chronic nephritis. Harrar found abruptio placentae in only 1 per cent of 650 cases of eclampsia (29); Goethals in only 4.7 per cent of his cases (25); and Wilson in 8.7 per cent (71). Williams found chronic nephritis in two out of 57 cases (72); Frankl and Hiess in two out of 37 cases (23); Davis and McGee in 9.6 per cent of their cases, (13), and they admit that this finding is distinctly opposed to their clinical suppositions, since they have always feared the development of this serious complication in patients who had an old history of kidney disease. They suggest that perhaps the infarction and fibrosis of the placenta found in patients with chronic nephritis has led to the belief that the mechanism of abruptio would be favored.

Most recent work on the etiological factor concerned with premature separation of the normally
implanted placenta has had to do with the relation of vitamin E deficiency to the pathological condition. Extensive work has been done on this subject, but as yet there remains a great deal of doubt in the minds of many obstetricians as to the value of vitamin E in preventing abortion, miscarriage, and abruptio placenta. The controversial problem of this paper is largely concerned with this phase of the subject, and in the following pages I will present the prevailing ideas on the subject after reviewing the experimental and clinical evidence that has been given regarding vitamin E as an etiologic and therapeutic factor in these conditions.

To establish a basis for this discussion, it is first necessary to mention some of the pathological physiology involved. In the phenomenon called nidation, the fertilized ovum comes to rest within the uterus on the endometrium and burrows into that endometrium. The villi which develop in its decidua basalis are surrounded by a layer of trophoblast and studies of very early embryos indicate that the trophoblast is the active agent in eroding into the uterine walls. Kearns (37), in 1934, demonstrated the activity of this trophoblastic layer.

Mall (41), in 1917, suggested that spontaneous
abortion developed when the environment of the trophoblast was unsuitable, when, in short, maternal resistance to such invasion was too great. He believed that faulty implantation of the ovum was due to maternal rather than to ovular defect. Flexner (21) found that the maternal blood-serum has anti-proteolytic powers, therefore it is obvious that the ability of the placental villi to erode their way into the uterine mucosa has limits. It has been demonstrated that the decidua itself contains factors able to neutralize the proteolytic power of young placental villi.

Evans and Bishop, in 1921 (17, 18), having been previously concerned with the precise mechanism of the estrous cycle in the rat, began to study dietary influence on the ovulatory rhythm and on the various steps in the physiology of reproduction. They found that on supposedly complete dietaries, and with both growth and external appearance normal, animals would also exhibit normal estrous cycles and would breed, ovulate and conceive, yet be unable to experience a normalestation through the invariable occurrence of fetal death. On further investigation, it was found that the animals were deficient in vitamin E. When these rats were fed wheat germ oil, a rich source of
vitamin E, the normal gestation took place.

Shute (60), in studying all types of cases of premature interruption of pregnancy on the basis of anti-proteolytic substance, developed a simple laboratory test for detecting evidence of anti-proteolytic activity in the maternal blood serum. In this experimental work a commercial preparation of trypsin was used, because for many reasons the proteolytic ferment of the trophoblast more nearly resembles trypsin than erepsin. Shute (61) also gave evidence for the belief that a substance closely resembling estrin is the factor in the maternal blood serum responsible for resistance to proteolysis in many cases of spontaneous abortion, and that the concentration of availability of this anti-proteolytic principle is greater in the placentas of women whose pregnancies terminate prematurely than in more mature placentas.

In his experiments on proteolysis, Shute (60, 62) found that seventy-three per cent of 44 spontaneously aborting women had blood serum showing a characteristic type of resistance to the proteolytic action of commercial trypsin, while eight per cent or less of 128 normal pregnancies and self-induced abortions presented the same phenomenon. Shute also found that evidences
of deficiency of vitamin E seem to be intimately associated with the clinical signs and symptoms of abruptio placentae as well as with the cases of early miscarriage and abortion. 82 cases of abruptio placentae were tested, 78 per cent of which showed relative vitamin E deficiency and therefore an excess of blood estrogenic substance. Of the 82 cases, only 31 were of the severe classical type—of these 31 cases, 81 per cent revealed vitamin E deficiency.

Watson and Tew (69) have shown that female rats fed on an E-free diet developed in two to four months the classical evidences of E-deficiency, manifest by the habit of resorbing their fetuses. At the same time, the blood serum of these E-deficient rats revealed the presence in their sera of this antiproteolytic power, whereas only 5 per cent of a group of 20 rats given vitamin E or fed on approximately normal diets, or on E-deficiency diets for too short a time to become E-free, or normally fed male rats, revealed such power. This work has been checked and found to be correct by Shute (59).

From the above work, the theory has been put forth by Shute (60, 62) that the action of vitamin E is largely through its antagonism to estrogenic substances in the blood. He believes that vitamin
E in the pregnant woman acts by neutralizing estrogenic substance, which, when present in excess, resists the intrusion of the placental villi into the uterine wall. He attempts to explain in this way the fundamental mechanism of abortion, miscarriage, premature labor, and abruptio placentae.

There is a good deal of clinical evidence which seems to bear out the theory that vitamin E deficiency is an etiologic factor in the production of premature separation. It has been shown by Shute (58) that there is a definite seasonal rhythm in the incidence of premature interruption of pregnancy and in abruptio placentae, and the conception of deformed fetuses in particular. All these pathologic conditions were observed by him to appear more frequently from January to June each year and more infrequently from July to December, and were found to have some relation to deficiency of vitamin E in his experience. Shute also observes that in his experiments on rats, it has taken from two to four months, and usually four, to render the animals sufficiently defective in vitamin E to cause spontaneous resorption of their fetuses. He draws the conclusion that if the E-deficiency in the diet were less marked we would have an approximate analogy to the observations made on human females.
The latter from November onward eat progressively less green food and drink milk whose origin is further and further removed from green fodder.

As will be mentioned later in the paper, wheat germ oil is a rich source of vitamin E and therefore is used to supply this vitamin in the case of deficiencies. In using this oil to treat women with precarious pregnancies, Shute (56) has observed that more and more is required to preserve the pregnancy during the months from January to June each year. In many instances, he has had to triple the dose. He draws the conclusion that women who become pregnant before November begin to display an increasing tendency to terminate their pregnancies prematurely during the time from February to June, and he claims that the reason for this is the E-deficient diet that is eaten during those winter months. Therefore, the seasonal incidence in premature interruption of pregnancy and abruptio placenta is explained by Shute as being due to the greater availability of vitamin E in the green diets of summer and early autumn and the E-deficient diets of winter and early spring.

McGinn and Harer (45) in an article published in 1935 hinted at the same type of etiological factor as that given by Shute. In their words—"All writers
stress traumatism, endometritis, diseases of the ovum, emotional states, and toxemia. It is quite possible that we must look to the early development of the placenta for the real underlying cause. This embryologic factor may quite possibly be a paucity of anchoring villi, so that the placenta is from the very beginning only loosely attached to the decidua basalis. Such a placenta, particularly when subjected to the additional pathologic changes that so frequently accompany late gestational toxemia, would naturally be expected to separate from its uterine attachment—unquestionably, a placenta that is the site of large infarcts is less firmly attached to the decidua than is a normal non-infarcted placenta."

That pathological changes in the utero-placental union play a role in the causation of premature separation has been brought out in the work of McKelvey (46) at the University of Minnesota. Through his experimental data, he has information which demonstrates gross disturbances in the maternal vascular system in normal pregnancy. His work shows that lesions of the arterioles of the upper part of the decidua basalis frequently occur in a normal pregnancy. These changes include the laying down of a
fibrinoid material in the wall of the vessel, dilatation and aneurysmal dilatation. A series of these changes may be traced from mild lesions to rupture of the vessel with the production of miniature or clinical premature separation of the normally implanted placenta. McKelvey shows that premature separation of the normally implanted placenta is an extension of changes in the arterioles probably present in every human placenta. One of these factors is the arteriolar dilatation associated with the modified arteriovenous aneurysm effect of the intervillous space.

In summarizing this discussion of etiology, it may be said that in the past numerous causes have been stated as etiological factors in the condition of premature separation of the normally implanted placenta. In the light of more recent discoveries, it would appear that these causes are merely associated conditions and perhaps predisposing factors. The most commonly associated condition with premature separation is some form of toxemia; chronic nephritis and eclamptic toxemias are exceptions to this and are rarely associated with premature separations.

The prevailing views on the subject favor the
idea that premature separations are due to some underlying cause other than trauma, toxemia, emotion, etc., but when these conditions are superimposed upon the underlying cause the tendency to a premature separation is enhanced. This underlying cause manifests itself pathologically early in pregnancy in the human female by a resistance on the part of the decidua basalis to the lytic action of the trophoblast of the ovum with a resulting faulty implantation. In the later months of pregnancy, all mature placentas undergo certain degenerative changes which are most marked in the arterioles of the decidua basalis. If the underlying factor of premature separation is present, these changes become so extensive that the arterioles rupture and blood is extravasated into the intervillous space producing the typical mild or severe abruptio placenta.

If we are to take the evidence as presented by Shute, it would appear that the underlying factor mentioned above consists of vitamin E deficiency with a consequent preponderance of anti-proteolytic estrogenic substance. The evidence in favor of this is quite convincing in view of the fact that such deficiency is found by laboratory tests in the greater percentage of women showing spontaneous abortion and
abruptio placenta, and in rats which are unable to undergo gestation; and in the fact that women who are habitual aborters or who have mild degrees of premature separation are carried to term by the administration of vitamin E.

On the other hand, there are strong arguments against the views of Shute and his supporters. For example, it seems a strange occurrence that vitamin E deficiency should be manifest in rats by the habit of resorbing their fetuses, while in the human female it is manifest in the early part of pregnancy by poor nidation or faulty implantation of the ovum, and in the later months of pregnancy by extensive degenerative arteriolar changes in the placenta. If we are to accept Shute's view, these three different types of manifestation of vitamin E deficiency and consequent estrogenic excess must be correlated. This is the same as saying that the factor which causes rats to resorb their young is the same factor which causes the human decidua to resist nidation. Although such a statement seems far fetched, clinical evidence is presented which shows that E-deficient rats that resorb their fetuses do not do so when saturated with vitamin E; likewise, human premature separation is prevented by adequate vitamin E administration.
Therefore, assuming that premature separations of the normally implanted placenta are due to some underlying factor, with or without the association of other predisposing causes, I am inclined to believe that vitamin E plays some role in the causation of this condition. The question of whether it is entirely responsible or whether some other factor enters in will be answered only after further research and clinical reports.

The part of the problem which we, in the end, are interested in is whether or not vitamin E deficiency as the underlying etiological factor will be of value in the prophylaxis and treatment of premature separation. A bulk of evidence is presented which indicates that it is of value, although this value is within certain limits. This phase of the subject is more thoroughly stressed in the section on treatment.
PATHOLOGY

In any case of premature separation of the placenta, the pathological process begins in the decidua basalis. The classical work which has been done on this subject is that of McKelvey who reported upon the findings in the arterioles of the decidua basalis in normal and abnormal pregnancies (46). His work was inspired by the fact that it has been recognized that the vascular system of pregnancy demonstrates gross disturbances, the mechanism of which is not understood, nor is there a proved explanation why this disturbance extends to the degree of the production of a pathologic state in a minority of individuals and does not extend in the majority of cases.

In conducting his work, McKelvey obtained material from sections of placentas, the portion of the arteriole studied being that above the musculature. The material was collected over a period of years by setting aside the routine sections of the placentas which showed vessels. The original material was taken as far away as possible from the margin of the placenta and any sections which showed evidence characteristic of the marginal portion of the placenta
were discarded. Only occasional attempts were made to specifically obtain sections through vessels. Fetal vessels entering the decidua were excluded from the study. These retain their muscular walls in contradistinction to the maternal arterioles where formed walls are almost always absent. The fetal vessels pass through this area with surprisingly little change, while the maternal vessels are grossly affected. Because of the level at which the vessels were studied, it was found impossible to differentiate veins from arteries in most cases. In the vast majority of the vessels found there was great dilatation of the lumen and the vessel wall contained no structures to allow such a differentiation.

From the study of these many sections of placental tissue, Mckelvey demonstrated clearly that the vessels of the decidua basalis, which are apparently arterioles, are damaged in normal pregnancy (46). The arterioles which conduct blood to the intervillous space show extensive coiling in the decidua basalis; therefore, many cross sections of the same vessel are to be seen in a single section. In the vast majority there is no evidence of a muscular media or an adventitia, and the wall is composed solely of decidua, chorionic cells, a mixture of these in various stages
of degeneration or a peculiar hyaline acellular, ground-substance material which has been called fibrinoid and which stains densely pink with eosin. The wall of the arteriole, then, does not have the supporting structures usual to the arteriole elsewhere.

The majority of vessels in the decidua basalis show advanced degrees of replacement of the cellular surrounding structures by the peculiar fibrinoid material. This fibrinoid material has a concentric distribution which is unmistakable. It forms rings of varying thickness about the vessel lumen. It may have a well-defined margin against the surrounding cells, but most often connects directly with a similar substance just beneath the intervillous space. This material in the vessel wall gives the impression of being solid substance. Fibrils are not seen. The surrounding cells may show no evidence of degeneration.

Other vessels in the surrounding area appear to be diffusely infiltrated by a plasma-like material which invades peripherally and destroys the enmeshed chorionic or decidual cells. This seems to decrease in concentration and necrotizing influence as it proceeds further from the vessel. The endothelium
of the vessel is most often absent in the vessels of the decidua basalis at term. The greater degree of change in the vessel wall, the less endothelium is seen. Occasionally, areas of round cell infiltration or massive necrosis of the decidua are seen. These are not typical of the lesion.

That the fibrinoid material is not an efficient structure is manifested in the great dilatation of the lumen and the appearance of aneurysmal dilatations with breaking up of the wall at that point. Microscopically it is seen that the lumina of the vessels are very large, and that this dilatation does not represent a physiologic response seems evident from the character of the vessel wall and from the fact that aneurysmal dilatations of portions of the circumference with splitting of the fibrinoid material into separated layers occurs frequently. All degrees of this dilatation are seen until premature separation of the placenta occurs when enormous dilatation may be demonstrated. These lesions are not limited to pregnancy at term.

The dilatation of the apparently weakened vessel is a dangerous process and the question of its mechanism arises. It occurs in the absence of an increased systemic pressure. McKelvey (46) states that it is
possible that it represents a response to normal pressure in a weakened vessel. One other explanation is suggested as a likely cause by Burwell and his coworkers (8, 9). They draw attention to the fact that the intervillous space is a modified arteriovenous fistula. No capillaries are interposed between the arterial and venous circulations. That this arteriovenous fistula effect is modified is shown by the absence of sudden elevations of the systemic pressure at delivery when the fistula is removed. Many other changes in pregnancy as increased blood volume, the placental bruit, and increased venous pressure in the lower extremities are suggestively similar to those occurring in clinical and experimental arteriovenous fistulae. In the presence of an arteriovenous fistula there is a readily understandable dilatation of adjacent veins. Halsted (28) pointed out that there was also a dilatation of the proximal artery. The mechanism of this is unexplained. The similarity of the result here and in the vessels of the decidua basalis was pointed out by Burwell (8), and while it is not proved there is an inclination to accept this as a likely relationship. No exact morphologic studies of the vessels in the region of an experimental or clinical arteriovenous fistula can be
found in the literature so that nothing can be said of the relationship between the modified arteriovenous fistula and the deposition of the fibrinoid material in the arteriolar walls.

From the information given in the foregoing paragraphs we see that the pathological process of premature separation occurs in the arterioles of the decidua basalis, where there appears to be a series of changes which begin with replacement of the wall and endothelium by fibrinoid. Gradually, dilatation of the lumen and extension of the fibrinoid with increase in the coiling of the vessel lead to rupture. Blood is extruded. Depending upon the amount of this hemorrhage, varying degrees of premature separation occur. The smallest of these produces a condition described as miniature premature separation. This produces no clinical symptoms. It offers the best material for the study of the mechanism of premature separation, because in the larger separations there is too much tissue destruction to provide good study material. Larger hemorrhages lead to clinical premature separation.

In discussing the clinical pathologic entity of premature separation, Davis and McGee (13) point out that the bleeding causes a decidual splitting and
the development of a retroplacental hematoma. In some cases there develops a hematoma in the placenta itself. The extent of the process may become limited and we have a partial separation, or it may continue to extend until the entire placenta has been separated off the uterine wall. If the process occurs in labor it may be aided by the tumultuous uterine contractions.

The retroplacental bleeding may be limited to the uterine cavity by the placenta, the membranes, or a tightly engaged presenting part, and it will be entirely concealed. It may rupture through the membranes and into the amniotic cavity and still be concealed, or it may extend to the margin of the placenta, dissect the membranes off the uterine wall and appear externally.

Uteroplacental apoplexy presents an entirely different pathological picture. This type of pathology was first described by Couvelaire (11) and extensively studied by Essen-Moeller and Williams (72). Grossly, the uterus, the tubes, and the ovaries and often the broad ligaments present a bluish, purplish, mottled appearance. This characteristic discoloration may extend to the entire peritoneum lining the pelvis and the lower abdomen in the fatal cases. Sometimes
dark free blood is found in the peritoneal cavity having oozed through the fimbriated ends of the tubes or through tears in the serosal surfaces of the uterus and adnexa. The organ is flabby and stretched, having lost the power of contractility. The cut surface is wet and presents a bluish or purplish mottled appearance most marked in the outer and inner layers of the uterine wall.

Microscopically, there is present an extensive intramuscular hemorrhage which has infiltrated the muscle bundles and dissociated the muscle fibers so that they have lost their integrity and their contractility. The process is most marked in the inner and outer layers of the uterine wall, but the hemorrhagic extravasations can extend to the adnexa, the broad ligaments, and retroperitoneally. Here and there in the muscle tissue, there is present a marked edema. In advanced cases this appears to be more than a simple edema, but there is apparently present an actual solution of much of the cytoplasm of the muscle cells. Many of the small vessels show a marked increase in size and number of the endothelial cells lining their walls. The nuclei often appear swollen and hydropic. The cytoplasm is found to be rounded and vacuolated. In some of the small
vessels there is a network of homogeneous eosin staining material which does not seem to be fibrin but apparently represents cytoplasm of the vacuolated endothelial cells. In the larger vessels these changes are less marked but the endothelium is distinctly swollen. The whole process suggests the action of some lytic agent which affects both vascular endothelium and muscle cells in the same way.
SYMPTOMS, SIGNS, AND DIAGNOSIS

There is lacking in the literature an adequate description of the signs and symptoms which characterize early or mild degrees of abruptio placenta. Goodall (26) reported a series of 600 cases where a diagnosis of premature separation had been made after delivery by the finding of evidence of some hemorrhagic lesion on the placenta. In this series, the most frequently encountered and significant sign was the gradual appearance of a restricted palm-sized area of true uterine tenderness, accompanied by a steady sacral backache. Occasionally these features were soon followed by the occurrence of labor pains, violent fetal movements, and uterine hemorrhage of any grade of severity, or there was a gradual elevation of blood pressure, accompanied by edema of the extremities, rapid gain of body weight, and even albuminuria, indicating an early toxemia of pregnancy.

Davis and McGee (13) state that the mild type or the partial separation of the placenta usually occurs near the end of labor. The patient may have had a normal course, when suddenly the pains become much harder, last longer, and the interval between pains becomes shorter. These tetanic contractions
are often associated with some rigidity and tenderness of the uterus. There usually appears some external bleeding, and occasionally the passage of a small clot. On auscultation of the fetal heart one finds evidences of fetal asphyxia demonstrated by an irregularity in rhythm or a decrease in rate. The violent character of the labor usually terminates it rapidly, but if this does not occur, all the findings may become more pronounced. The fetal heart tones may entirely disappear if the infant cannot be rapidly rescued. A sudden change in the character of the labor, hemorrhages, evidences of fetal distress, and the finding of old blood clots in the uterus and partially attached to the placenta make the diagnosis of a partial abruptio placenta.

Richardson (53) states that stormy as it may be, there is probably no condition in obstetrics which is so ceremonious in its course as ablatio placenta. He believes that the event pursues a definite and methodical progression of incidents, which occur in an identical sequence without regard to the time factor involved, whether it be five minutes or five hours. This sequence as indicated by Richardson may be given as follows:

1. Hemorrhage (or separation).
2. Placental separation with increasing hemorrhage (both progression).
3. Decreased oxygenation and increased fetal carbon dioxide retention.
4. Fetal embarrassment with compensatory acceleration of fetal heart rate.
5. Fetal heart compensation to maximum tolerance.
6. Asphyxia with decreasing fetal heart rate.
7. Placental separation, complete either before or after.
8. Fetal death, quiet or violent.

Richardson (53) puts great significance on the fetal heart rate from the standpoint of diagnosis and prognosis. He claims that the placental separation disturbs the oxygen-carbon dioxide exchange which accelerates the fetal heart rate, and the amount of acceleration of the fetal heart rate bears a definite relationship to the area of placental detachment.

Complete abruptio placenta presents an entirely different clinical picture. According to Davis and McGee (13), who agree with most other authorities,
it occurs most often before the onset of labor, in fact, any time in the last trimester of pregnancy. There are no prodromal manifestations before one or the other of the most common symptoms occur. The onset may be dramatic with sudden excruciating pain in the lower abdomen; it may be ushered in by hemorrhage from the vagina and along with this there may be a rapidly developing picture of shock out of all proportion to the amount of hemorrhage visible; there may be a development of tenderness and rigidity of the uterus or an increase in uterine motility; or the uterus may change in size and shape due to the accumulation of blood within its cavity.

When there is an onset with pain in the lower abdomen, it is usually a continuous pain with little or no relief, the patient writhing and rolling. Then again, in some cases there is a mild, dull ache in the abdomen which is peculiarly sensitive. The pain may become more marked as the hours pass and often labor sets in to mask the true picture. The moderate abdominal discomfort is said to be associated with a very slow accumulation of blood in the uterus. The rapid distention of the uterus causes stretching of the peritoneum and the intense pain.

Bleeding may be of two types, external or inter-
nal. In the internal or concealed type the bleeding occurs behind the placenta or it is concealed in the uterine cavity by the presenting part or the free placenta acting as a tampon for the lower uterine segment. Mitchell (48) states that the outstanding sign in the internal variety is rigidity of the uterus. Increase in size or alteration in shape of the uterus may be noticed. The fetal outlines can no longer be felt nor the fetal heart sounds heard. The patient’s expression is anxious, she is restless and the signs of shock appear.

In the external or revealed variety, the bleeding is usually the first sign noticed, then follow signs of hemorrhage, pallor, rapidity of the pulse, fainting, and air hunger. On abdominal examination, the uterus is a little altered in consistency or size, but there is not the normal relaxation after a contraction. The cervix will usually admit a finger, and on palpating the lower uterine segment no placenta will be felt; thus placenta praevia may be excluded.

Davis and McGee (13) draw an axiom in which they state that the amount of external bleeding is no index of the amount of blood the circulation has lost. This truth is even more apparent in cases of uteroplacental apoplexy. Here, the blood not only accumu-
lates in the uterine cavity, but it extravasates and infiltrates into the uterine musculature, underneath the serosa, between the leaves of the broad ligaments and retroperitoneally. As the condition becomes more and more grave, it can be said that the patient is bleeding to death within her own tissues. Systemic signs of hemorrhage soon develop. The patient becomes more and more anemic. The mucous membranes become pale and washed out in appearance. The pulse rate mounts, the quality becoming progressively poorer. The blood pressure slowly falls. The patient's skin becomes cold and clammy. The woman also complains of weakness, faintness, dizziness, and occasionally becomes stuporous. The point should be made clear that many of these symptoms and findings occur late in patients with sudden and extensive hemorrhage, often too late to institute proper measures if one awaits their development. Davis and McGee (13) draw another axiom: that one must recognize the progressive hemorrhage early, be it relatively concealed into the patient's own tissues, or external, so that timely measures can be instituted.

The ligneous consistency of the uterus is present in only a portion of cases. Davis and McGee (13) had 112 cases of partial abruptio placentae of which
13.4 per cent showed this sign; 164 cases of total abruptio placenta of which 29.2 per cent showed the sign. When this marked, board-like rigidity of the uterus is present, it is pathognomonic of the underlying pathology, for very few conditions can simulate it. On the other hand, some of the patients present a soft uterus of a peculiar doughy consistency with moderate or little tenderness. This doughy, boggy sensation is given to the uterus by the accumulation of soft blood clots within its cavity.

The condition of abruptio placenta is to be differentiated from placenta praevia and from ruptured uterus. Matthews (**) offers the following as a guide to differential diagnosis between placenta praevia and abruptio placenta: In abruptio placenta the onset is sudden with severe pain, while in placenta praevia the onset is sudden but painless. In abruptio placenta the hemorrhage is either concealed or apparent, but in placenta praevia, the hemorrhage is always apparent. Hemorrhage in abruptio is usually severe from the beginning; in placenta praevia the hemorrhage is apt to be mild at first, later becoming more severe. In abruptio there is usually an associated cause such as trauma or toxemia; in placenta praevia there is no apparent cause for the
onset of painless bleeding. In abruptio, the fetal heart is frequently absent; in placenta praevia the fetal heart is heard. In abruptio, the uterus is tense and tender, but in placenta praevia it has a normal "feel". On vaginal examination, the placenta is palpable at the cervix in a placenta praevia, but in abruptio placenta it is not palpable.

Differentiating abruptio placenta from rupture of the uterus, Matthews (43) states that in rupture of the uterus there are no uterine contractions, the uterus is small and is pushed to one side by a second tumor, the child. No presenting part is felt in the vagina, and the rent in the uterus is often palpable.
TREATMENT

The treatment of premature separation of the placenta resolves itself into two categories: first, the treatment of the early abortions and miscarriages, and the milder forms of abruptio placenta; second, treatment of the more severe and grave forms of abruptio placenta. As to the type of treatment used, there are two general divisions, one including medical measures, the other including obstetrical and surgical measures. There is necessarily a good deal of over-lapping of these two types of treatment, and it is impossible to classify individuals in such a way that one particular type of treatment may be used on a patient without considering the other type. In general, however, the more severe forms of abruptio placenta require obstetrical or surgical treatment, while medical treatment is used for the miniature forms of premature separation and in the early abortions and miscarriages. Although this distinction is by no means universal, it will be well to keep it in mind during the ensuing discussion.

Considering first the obstetrical and surgical management of the severe forms of abruptio placenta, there seems to be two schools of thought regarding
the method of handling such a case. One group prefers more conservative measures; another group resorts to radical methods.

The greatest proponent of the conservative methods is Dr. F. C. Irving of Boston Lying-In Hospital. Dr. Irving (34) divides his cases into two groups: those with internal hemorrhage and those with external hemorrhage. His treatment is administered according to the type of hemorrhage which the patient shows. In his series, out of 234 cases, 170 patients delivered normally, by low forceps, or by the breech. In every instance delivery took place only after full dilatation of the cervix, and there were no deaths. Labor was allowed to progress without interference.

If bleeding occurred before the onset of labor, contractions were induced in some instances by rupture of the membranes or by metreعراض. Dr. Irving states that bleeding which is entirely concealed is an exception. In all but two of his 119 cases of internal hemorrhage, there was visible bleeding at some time. 69 cases of internal hemorrhage were delivered by Cesarean section. The death rate was 14.5 per cent maternal. 34 were treated by conservative measures with a 2.9 per cent mortality. Pelvic operative delivery had a death rate of 19.7 per cent.
Dr. Irving (34) makes the conclusion that conservative measures give a better prognosis for the mother in both types of premature separation of the placenta. As regards the infant, if it be alive, the advantage is with Caesarean section, but the prognosis for the mother is not so good if section is performed.

In discussing the conservative methods, Dr. Wm. E. Studdiford Jr. (34) states that he believes those patients with partial placental separation should be treated conservatively. The slight degree of placental separation present in most of these patients is evident by the fact that many living infants result in cases of operative delivery. The fetal death rate, according to Dr. Studdiford, is probably increased by allowing these patients to deliver spontaneously, since the degree of placental separation may increase during this process. The maternal death rate should not be much above normal expectation. On the other hand, he claims that Caesarean section must inevitably lead to greater maternal risk. In the severe type of case which is often characterized by complete placental separation and by hemorrhagic infiltration of the myometrium, Dr. Studdiford states that it has always seemed best to
allow these patients to deliver spontaneously if possible, however, certain cases present such obstacles to rapid delivery that it seems best to handle them by Caesarean section. Occasionally, due to a functionless myometrium, hysterectomy may even be indicated.

Through his clinical experience, Dr. Norris W. Vaux (67) of Philadelphia has separated all cases of suspected premature separation into two groups:

1. Those cases with mild frank bleeding whose general condition and that of the infant in utero has not yet become affected by blood loss.

2. Those cases which undoubtedly have concealed or frank hemorrhage sufficient to produce shock and collapse from blood loss. This is frequently seen in emergency cases, when the placenta has become completely detached and intrauterine fetal suffocation has occurred.

The first group given above, according to Dr. Vaux (67), should be treated conservatively for at least a time. In the second group, immediately we should direct treatment towards combating the shock
and collapse, then follow this by prompt radical surgery. Dr. Vaux states that to those who feel that the conservative method of treating hemorrhage in the last trimester of pregnancy is the best way to meet this complication, in his opinion the radical method of delivery, in the end, is more conservative. Although the fetal mortality may be high in both, the maternal mortality is distinctly benefitted by the radical method of procedure.

Mitchell (48) offers a good summary in the general methods of handling a given case of premature separation. He states that early diagnosis is essential, since time is of such importance. Preparation for intravenous injection or blood transfusion should begin at once whether they appear necessary or not. If possible, a suitable donor should be in readiness as soon as the bleeding is arrested. The mother's welfare is the prime consideration, since the fetal mortality in any type is high, and in uteroplacental apoplexy reaches 100 per cent. In this type, blood is forced between the uterine muscle fibers, the uterus is paralyzed, and even after being emptied may be powerless to retract. In such a case death ensues from post-partum hemorrhage unless the organ is removed. The treatment may be obstetrical or sur-
sical. Each has its place, but the decision which to adopt should be reached early. At first, surgical measures such as Caesarean section or hysterectomy would seem preferable, but since the patient is usually in shock, since labor has usually begun, and since the condition is much more frequent in multiparas, obstetrical measures give on the whole better results.

The two ends sought in treatment are lessening of shock and relief of tension. The former is obtained by rest, warmth, quiet, and the use of morphine; the latter by rupture of the membranes. If labor is not progressing rapidly, pitocin in 2 minim doses, and the application of a snug binder will bring on pains. After the uterus is empty, an intravenous injection of 5 per cent glucose in normal saline should be given, or in severe cases, a blood transfusion. The simplicity of these measures makes them applicable to home cases. Plugging the vagina increases tension and is apt to cause infection. The Vorhees bag is open to the same objections although it may hasten dilatation of the cervix. Version and manual dilatation of the cervix should not be employed.

Harvey B. Matthews (43) of the Long Island N. Y. College of Medicine believes that a case of premature
separation should never be kept in the home for delivery if she can possibly be admitted to a hospital. Once the diagnosis is made, delivery must be accomplished. Matthews states that the methods by which the pregnancy shall be terminated depend upon:

1. The condition of the cervix
2. The size of the pelvis
3. The size and position of the fetus
4. The contractility of the uterus

Matthews (43) believes that if the patient is a multipara with a soft, partially dilatable cervix, rupture of the membranes and a firm abdominal binder usually are all that need be done. Morphine should be given to help combat the shock as well as to accelerate dilatation of the cervix. In addition, a few applications of nasal pituitrin, given every 30 minutes until uterine contractions are improved and maintained is often of very great benefit. In the primiparous patient, the problem is still more difficult. If the cervix is partially dilated and is still further dilatable, rupture of the membranes with insertion of a hydrostatic bag plus vaginal pack will usually control further bleeding and labor will progress until delivery can be accomplished.
with the least trauma to the cervix. Version and breech extraction, and forceps delivery are very dangerous, due to added shock superimposed upon a patient already suffering from hemorrhage and shock.

Matthews (43) holds that indications for Caesarean section in this condition are all those conditions in which methods of vaginal delivery are unwarranted. As Dr. Whitridge Williams (72) has shown, even after delivery is accomplished the uterus often fails to contract because of the profuse widespread hemorrhage infiltrating into its musculature. There is paralysis of the uterine muscle and post-partum hemorrhage is almost sure to occur. If this cannot be controlled, hysterectomy must be performed.

R. F. Miller (47) of Ann Arbor, Mich. also brings out the fact that in cases of uterine apoplexy, the damage may be so great as to prevent uterine contractions and necessitate hysterectomy. He maintains, however, that moderate uterine apoplexy is not incompatible with contraction, and judgement must, therefore, be exercised in evaluating these cases when treated by Caesarean section. Abnormal discoloration of the uterus alone is insufficient reason for hysterectomy.
Frank (22) believes that Caesarean section is considered by most obstetricians to be the treatment of choice for ablatio placenta. In some cases this operation must be supplemented by removal of the uterus, as has been mentioned above. Frank claims that where the hysterectomy is done at the time of the section because of hemorrhagic infiltration of the uterine musculature, the dangers are not especially great. Occasionally, however, at the time of Caesarean section, the surgeon feels that the uterus is contracting satisfactorily, and yet the sequellae promptly show that this is not the case. It requires considerable judgement and courage to subject the patient to an immediate secondary operation to save her life.

After the foregoing discussion of the ideas of various men as to whether one should employ conservative or radical measures in handling a case of abruptio placenta, it is difficult to draw any hard and fast rules as to which method to use. So many factors come into play that one must treat each patient as an individual problem, rather than trying to place her in one definite class and applying treatment that has been set aside for that class only. It seems that, in any event, any patient
with symptoms and signs of abruptio placenta should be immediately hospitalized if possible. After hospitalization, further study must be made to ascertain whether or not the bleeding is of mild or severe variety.

Richardson (53) stresses that an early diagnosis is imperative and that we must not sit by the patient, watching every change. He states that an early diagnosis of abruptio placenta is best arrived at by directing earnest attention toward the fetal condition, and upon arriving at a positive diagnosis, unless delivery is imminent, resorting to immediate action. According to Richardson, the action we will take must be governed by the progress of labor, the condition of the cervix, and the descent of the head, but all of these in consideration of the condition of the baby as well as the mother, for anything directed toward saving the baby will by initiated earlier than if our symptom complex is based entirely upon maternal signs and symptoms.

Davis and McGee (13) are open minded upon the subject of treatment and it is their belief that patients should be individualized and treated according to the method which seems indicated by the symptoms and signs of the moment. The following para-
graphs agree with the conclusions I have reached after reviewing both the conservative and radical methods of treatment, and they are taken largely from the writings of the above authors.

In the partial separations, or the mild cases which most often occur in a labor which is frequently accentuated by abnormally strong uterine contractions, conservative treatment may be used and the labor allowed to terminate as near spontaneously as possible. One should carefully follow the patient's condition, noting the amount of bleeding, the possibility of concealed hemorrhage, the character of the labor pains, the blood pressure, and the state of the fetus. Gradual increasing asphyxia on the part of the baby characterized by an increasing irregularity of rhythm or slowing of the fetal heart rate may mean an increase in the extent of the separation. If the membranes are intact they should be ruptured to make internal bleeding less likely, to facilitate the labor, and to permit a closer adaptation of the uterus about the baby, thereby decreasing the possibility of hemorrhage. Tumultuous pains can be temporized by administering some anesthesia with pains, such as ethylene and oxygen. As soon as the labor can be terminated with safety to the mother and to
the baby this should be done by the most conservative means. Forceps delivery or version and extraction may be the operation of choice. Immediately on the birth of the baby, the mother should receive a cubic centimeter of pituitrin. One need not hesitate to terminate the third stage promptly by a manual removal of the placenta if the hemorrhage becomes at all alarming.

In the complete separations or the grave cases of abruptio placenta, the treatment must necessarily become somewhat more radical. This is probably the most dangerous condition threatening the life of the pregnant woman and the decision as to what is the best plan in an individual case will often tax the most experienced operator. The life of the mother depends on the proper course to be followed. The patient should be carefully studied to determine whether we are dealing with a simple separation of the placenta or a serious uteroplacental apoplexy.

If the patient is in labor and is making normal progress, conservative measures may suffice. Rupture of the bag of waters, the temporary dislodgement of the presenting part to rule out the possibility of concealed hemorrhage, and a tight abdominal binder of the Beck or Spanish Windlass type may be all that
is necessary. The baby is most often dead and needs no consideration. Small doses of pituitrin intramuscularly may hasten the labor and lessen the bleeding. As soon as there is sufficient dilatation to deliver the baby, the labor may be most expeditiously terminated by forceps, version and extraction, or craniotomy, depending upon the existing conditions.

In the patients who are not in labor, the fulminating cases who enter in shock, the patients in whom labor does not progress satisfactorily and rapidly, in the patients in whom a toxemic uteroplacental apoplexy can be diagnosed, abdominal delivery offers the best results in the hands of those experienced to do major surgery provided proper facilities are at hand. A rapid Cesarean section, preferably the low cervical type, or laparotrhachelotomy, and if at all possible under local anesthesia, terminates the labor most rapidly and satisfactorily. The advisability of a hysterectomy will depend on the ability of the uterine musculature to contract down and control the bleeding. Whenever there is any doubt as to this ability on the part of the uterus to take hold of the situation, it had better be sacrificed. While it is not always necessary to do a hysterectomy in all cases of uteroplacental apoplexy, it is
very often necessary.

Timely treatment is most important in the severe forms of separation. To wait until a patient is exsanguinated and then decide on radical surgery is not fair to the patient or to the method of delivery. The diagnosis of the gravity of the situation must be made early and the treatment instituted immediately. Every surgeon knows that to operate upon patients in shock is bad practice. Patients who enter in shock must be rapidly prepared before radical surgery is resorted to. Blood transfusions, glucose and saline intravenously and subcutaneously, and morphine will bring the patient out of shock and improve her operative risk. Local anesthesia is the least harmful of all the anesthetics. If hysterectomy is decided upon, the broad ligaments can be rapidly clamped while the transfusion is taking place, and the remainder of the operation can proceed more slowly.

The above discussion has dealt with the obstetrical and surgical management of the moderate and severe forms of abruptio placentae. The work done in recent years on the efficacy of using vitamin therapy in the treatment of abortion, miscarriage, and mild
abruptio placenta leads to the next discussion—the medical treatment by the use of wheat germ oil or vitamin E. In approaching this problem it is realized that it is of controversial nature as to whether it should or should not be used. Many feel that its use is objectionable, others feel that it is a valuable therapeutic agent for carrying pregnancies to term which would otherwise terminate in abortion, miscarriage, or go on to severe abruptio placenta with fetal death and grave maternal prognosis. It is impossible for me to draw any conclusions on this controversial problem because eminent authorities are still unsettled as to the efficacy of the use of vitamin E. I shall attempt to give a review of the ideas of a few of these authorities on the subject and their arguments for and against this type of therapy. A solution of the problem at present is in the hands of the individual practitioner who must draw his conclusions from results in his own cases.

On the subject of abortion and miscarriage, Shute (59) recognizes that in view of the very high percentage of pregnancies in both America and Europe which terminate prematurely, whether by act of nature or human intervention, it would appear that the
greater proportion of these abortions are natural, because the success of widely known abortifacient medicines taken orally are known by the whole profession to be inert. This suggests that abortion was impending when these drugs were taken and that their success was largely a triumph of coincidence. If we were to admit that even one-tenth of conceptions were in danger of premature spontaneous interruption, the widespread use of wheat germ oil early in gestation might seem to be justified. If we include in this indication for its use, the beneficial effects achieved by it in the prophylaxis and therapy of abruptio placenta, and if that complication of pregnancy occurs as commonly as Goodall (27) and others believe, then there is some reason to advise the use of vitamin E therapy in every pregnancy. Shute has treated miscarriages and abortions and has prevented miscarriage in 91 per cent and abortion in 83 per cent of the group of patients treated. He gives his therapeutic success as 89 per cent.

The results of treatment of abruptio placenta, according to Shute (56), are encouraging. However, he states that those patients first seen when placental detachment is already complete or nearly
complete offer little excuse for anything but the classical measures used for such an emergency. Shute indicates that his therapy with vitamin E may be used when there is a close search made for true uterine tenderness during pregnancy, combined with an early test of the blood serum for the presence of specific hormone-vitamin imbalance. In the less severe cases, when properly and adequately saturated and kept saturated with vitamin E (as determined by clinical evidence and repeated tests of the serums), they have not progressed to a severe stage of placental detachment with death of the fetus (56). In approximately twenty hours, an adequate massive dose of eight to twelve drams of bulk wheat germ oil has completely abolished the characteristic circumscribed area of uterine tenderness. The accompanying severe sacral backache and uterine cramps have subsided as rapidly. When uterine hemorrhage has been present, it has responded promptly as well. Within the first day of treatment, the patients have remarked that their indescribable subjective discomfort has disappeared. Stopping the oil therapy has often been followed by a recurrence of uterine tenderness and bleeding, which in turn, have disappeared on further vitamin E therapy. No case
recognized early and treated adequately has gone on to the severe classical type, in Shute's experience (56).

Shute (56) claims that best results have been obtained in women who showed little or no evidence of an associated toxemia. However, when toxemia was detected early, at the first rise of blood pressure beyond the accepted critical level, at the first continued excessive gain of weight or appearance of edema, at the first mild albuminuria or in patients in whom by abdominal palpation the fetus seemed unusually small in consideration of the duration of gestation or was surrounded by some excess of amniotic fluid, wheat germ oil therapy was immediately beneficial. The blood pressures, both systolic and diastolic returned to normal levels and were maintained there as long as the patient remained saturated with wheat germ oil. Albuminuria ceased and the unusual rate of weight gain was diminished, or the patient might even lose weight. Edema decreased, sometimes with frequency and polyuria, and all this without the use of salt-restriction, bed rest, or other standard measures. Some of these small fetuses seemed suddenly to increase in size in an amazing way.
However, in women in whom the evidences of toxemia were of some duration, the beneficial results of the wheat germ oil therapy, at least as far as it concerned the signs of toxemia, were scarcely discernible; but such of these cases as displayed deficiency of vitamin E (or excess of estrogenic substance) in the blood serum did not go on to true eclampsia. The placentas adhered sufficiently well to enable induction and labor to proceed safely for mother and child.

Holmes (31), in 1923, divided the toxemias of late pregnancy into those which went on to eclampsia and those ending as ablatio placenta. Shute (56) has found only eight cases of eclampsia which showed vitamin E deficiency and excess of estrogenic substance; similarly Brickenbach and Fromme (6) found no increase in the blood folliculin content in four eclamptic patients. The Smiths (14) found that the blood and placentas of eclamptic patients are characterized by a low estrin and an excess of the antagonistic anterior pituitary gonadotropic hormone.

Holmes (31), Baird (2), Davis and McGee (13), and others have pointed out that abruptio placenta is only rarely associated with eclampsia or eclampsism. LeLorier (40) found only two cases of eclampsia in
association with 31 cases of retroplacental hematoma.

From the above evidence, Shute (56) suspects that the late toxemias of pregnancy may prove to be divisible into two main groups, those deficient in vitamin E and displaying an excess of estrogenic substance in the blood, and a very much smaller group with adequate vitamin E and characterized by an excessive secretion of prolact. The former are cases in which abruptio placenta is actual or impending, the latter are cases in which true eclampsia is actual or impending. The use of vitamin E therapy in the cases of toxemia with impending abruptio, therefore, is indicated to benefit both the abruptio and the toxemia.

In contrast to the successes of vitamin E therapy, it is reported (59) that there is a considerable percentage of cases, ranging from 28 to 31 per cent, in which vitamin E therapy has appeared to be inadequate. Failure with this mode of therapy according to Shute (59) is to be ascribed to inadequate dosage, personal idiosyncrasies leading to inadequate assimilation, associated hypothyroidism, failure to allow for seasonal depletion of the body depots of vitamin E, rancid oil which has been kept
at too high a temperature or allowed to deteriorate with age. Shute believes that if these factors are corrected, many of the failures with wheat germ oil therapy will disappear and the failures will constitute less than 15 per cent. Vogt-Kollér (63) in his series of 23 cases reported that 73 per cent of the patients went to term and 87 per cent delivered viable children. Watson and Tew (69) in 53 cases reported 72 per cent success. Currie (12) reported 86 per cent of his 35 cases carried successfully to term. Shute (59) emphasized the fact that many cases may not be due to proteolytic substance in the blood at all, but to other factors, such as infection, trauma, sperm abnormality, etc., and that in these cases the rationale of wheat germ therapy is not well founded.

Some writers have condemned wheat germ oil therapy because of its effect upon congenital anomalies. It has long been recognized that many spontaneous abortions and miscarriages are associated with developmental anomalies of the fetus. This was best illustrated in the extensive studies of Mall and Meyer (42). Beckwith Whitehouse (70) mentioned two instances of deformed infants born at term after abor-
tion had been averted. Moench (49) states that it is often not worth while to try to save the products of gestation which nature is trying to get rid of on account of the chance that the child will show developmental defects at birth. Bacon said he had delayed an abortion in two or three instances in which a monster had been delivered at term (42). Nageotte-Wilcouchewitch (52) reported two examples of threatened abortions which were carried to term only to produce idiots, and two threatened miscarriages which when carried to term or near term produced respectively an infant with a malformed chest and one with a congenital scoliosis. Kane (36) among thirty-six living children whose mothers were habitual aborters, found that five were congenitally defective, and thought that the prevention of abortion in the early months of pregnancy merely prevented nature's elimination of the unfit. He suggested that fetal anomalies might be due to hormonal deficiency. Some people may feel, therefore, that the prevention of abortion and miscarriage by means of adequate wheat germ oil therapy is a misdirected effort.

There are, however, reports which take the opposite side of the argument. Falls (19) using progesterone therapy was able to carry 83 per cent
of his group of 41 cases of threatened or habitual abortion to viability. All that were carried to term were normal, but two of his failures were cases in which abnormal fetuses were expelled. Currie (12) carried 21 cases of habitual abortion to term with wheat germ oil therapy and notes that one of these died of a "structural deformity of the throat". Whitehouse (70) mentions a woman delivered prematurely of a spina bifida in her second pregnancy, who was carried to term in her third pregnancy by means of wheat germ oil. The normal baby delivered in this third pregnancy was born with a dimple over the lower spine. Neither Vogt-Moller (68), Juhasz-Schaffer (35), nor Watson and Tew (69) have reported fetal anomalies in the infants brought to term by them under the influence of wheat germ oil. Of the 29 cases of threatened abortion or miscarriage carried to term on wheat germ oil by Shute (59), one infant developed soon after birth a mild type of spasticity of the legs which has persisted. This patient had no oil until the fifth month. Another woman, who was first seen at the fourth month with so much amniotic fluid that the fundus uteri was at the level usual for a six month pregnancy, was
given wheat germ oil at the fifth month, carried thus for two months, then x-rayed. As a deformed child was detected, labor was induced and a fetus with craniorachischisis was delivered.

Shute (59) brings out the fact that the primary desire in the problem of treating habitual abortion with wheat germ oil is to discover the potential anomaly before at least the twelfth week of pregnancy and institute treatment while the fetus is still plastic. One can hope that the correction is at least theoretically possible. One can often detect spontaneous abortion before it develops by means of Shute's test for a disturbance of the relation between vitamin E and estrogenic substance in the blood serum. In experimenting on this equilibrium, Shute tested a large number of blood samples taken in the first trimester of pregnancy, especially from women who had had anomalous fetuses previously. Five women who later delivered deformed infants showed estrogenic excess and deficiency of vitamin E in their blood sera. Six out of eight of defective pregnancies first tested in the second trimester showed the same result. Shute concludes from this that where such a disturbance in the relation of
vitamin E to estrogentic substance is found, one may suspect, at least, that the fetus is deformed. Lacomber (44) and Byerly and his coworkers (10) in their studies strongly suggested that vitamin E is a factor in producing fetal deformity. That vitamin $B_1$ is also a factor appears from the report of Slonaker (63), and that estrogentic substance is involved is indicated by Kozelka and Gallagher (38).

No one can yet answer the question as to what wheat germ oil, rich in both vitamins E and $B_1$, will accomplish if given very early in pregnancy. Murphy (51) has pointed out that when there is one defective child, the next child has twenty-four times as much chance of being deformed as a child chosen at random in the general population. He took a consecutive series of 275 families, each known to have possessed a congenitally malformed or defective child, and also one or more subsequent members, and interviewed them with regard to the outcome of all conceptions of the mothers. Thirty-four, or approximately 12.4 per cent of all the families, gave rise to one or more additional congenital malformed members. Among 431 conceptions that followed the birth of a malformed child, 331, or 76.8 per cent, ended in the
birth of a full term, normally developed offspring. The remaining 100, or approximately one in four of the subsequent conceptions, ended in forty-three (ten per cent) congenitally malformed children, forty-two miscarriages (including abortions), nine premature births, and six stillbirths.

In families having one congenitally malformed child, a second one was born once in 8.9 births, whereas in the general population a congenitally malformed infant appeared only once in every 213 births. From this study it is concluded that offspring presenting congenital malformations which are serious enough to warrant being recorded on death certificates are approximately 24 times as likely to occur in families possessing a congenitally malformed child as in the population at large.

From the foregoing discussion of congenital deformities and their relation to vitamin E, we may end by saying that it is far from being a settled question as to whether or not the carrying of a pregnancy to term that tries to abort early will or will not result in a well formed baby. There is evidence given in both directions. It seems that enough evidence has been put forth to give hope that if treatment is begun early enough, the result
will have a good chance at a favorable outcome. On the other hand, in case treatment is begun too late a date in pregnancy, it might result in carrying the woman on to term only to deliver a congenital anomaly. This is at least an approach to the problem of congenital anomalies in the human being. It offers some hope and indicates a fertile field for further study. At present it is impossible to say definitely whether or not vitamin E therapy is justified in cases of abortion and miscarriage, due to the fact that a deformed fetus may be carried on to term. The problem must, for the present, remain in the judgement of the individual practitioner.

Another possible objection to wheat germ oil therapy might arise from the report of Rowntree (55) on the sarcogenic properties of crude ether-extracted wheat germ oil in rats. In the patients treated by Shute (56) with wheat germ oil, only one out of 127 receiving the ether-extracted oil developed malignancy. She revealed chorionepitheliomatous change in what was grossly an hydatid mole found ten months after the termination of a pregnancy in which she had been given an ether-extracted wheat germ oil in small doses for the final six weeks. Rowntree's
report suggests a certain species specificity in the rat for his oil-produced tumor. He and his colleagues did not find such tumors produced with cold-pressed wheat germ oil. Moreover, they found the tumors developed in the susceptible species only upon administration of oil containing sediment and when the oil was given in doses enormously greater in proportion to weight than have ever been fed to human beings. As rancidity, which rapidly destroys vitamin E, did not affect the carcogentic power of their oil, it appears that the vitamin itself cannot be blamed for the production of the neoplasms.

In the clinical administration of wheat germ oil, there seems to be no general agreement about the dosage of it required by patients of various clinical types. Early in the experimental work on the subject, Evans and his coworkers (16) determined the minimal single dose of the oil which would protect an E-free rat from resorbing or aborting its young. Juhasz-Schaffer (35), Sure (66), and Gierhake (24) have similarly estimated this rat dose using various oils and concentrates. However, such estimates have relatively little value in deciding upon the dosage to be administered to human patients.
according to Shute (57). The first workers (68) in the clinical field, in most cases, used two to three drams as the daily dose from the time treatment was begun. No precautions as to storage or the variations in individual requirement were urged in their reports.

Shute (57) states that sufficient wheat germ oil should be given to render the blood serum of the patient under consideration digestible by a dilute trypsin solution under the precise conditions of the test elaborated by him (60). He found that many women threatening to abort would not do so if given a single massive dose of the oil, supplemented by smaller daily doses thereafter. The usual initial dose required was six drams or more, and within twenty hours of its administration the anti-proteolytic factor disappeared from the blood stream. Its disappearance from the serum coincided with the disappearance of symptoms and signs of premature separation. The method suggested by Shute is to administer within the first twenty-four hours of therapy, three doses each of four drams of wheat germ oil and to follow this with one dram of oil each day.
Bacharach (1) has pointed out that it is very doubtful if there can be a standard preparation or unit of vitamin E, for no biologic standardization is possible. Also, as Shute (57) emphasizes, there is variation in the capacities of different individuals to assimilate the various known vitamins, and therefore the dosage is variable with different individuals. The dosage also varies with the individual requirements, the quality of the oil used, and the stage of the pregnancy.
PROGNOSIS

No definite statements can be made regarding the prognosis in cases of premature separation of the placenta. In the words of Holmes (33), "Ablatio is one of the cataclysms of the child-bearing woman. Probably more is gained by a prompt diagnosis and aggressive treatment than is lost by the severity of symptoms. Procrastination is largely responsible for the maternal and fetal mortality."

So many factors enter into the discussion of this subject that one must consider the outlook from the standpoint of the patient as a whole rather than from just the standpoint of the pathology involved. In general, the prognosis in severe cases is dependent upon two main factors: the severity of the separation and the hemorrhage and the time which elapses from the onset of the condition until adequate treatment is instituted. This statement applies only to the mother in the majority of cases; in all cases of complete separation of the placenta the fetus is dead.

Various authors cite a maternal mortality which ranges from about 13 up to 50 per cent, with a fetal
mortality ranging from 20 to 85 per cent (53). Irving (34) states that the maternal death rate in premature separation of the normally implanted placenta is increased if the hemorrhage is internal; that is, retained within the uterine cavity, or if there coexists a toxic state, such as preeclampsia, eclampsia, or nephritis. Retention of blood within the uterus more often is associated with fatal outcome than the presence of toxemia.

In discussing the role of internal hemorrhage and toxemia in determining mortality, Irving (34) gives the following examples. In a series of 353 cases of his, 224 had no associated toxemia, and the maternal death rate was eight out of this group, or 3.5 per cent. In 129 cases showing toxemia, there were ten deaths, with a 7.7 per cent mortality. 234 out of the total 353 cases showed external hemorrhage; out of this group, there were four deaths with a 1.7 per cent mortality. In 119 cases of internal hemorrhage, there were 14 deaths, for a mortality of 11.8 per cent.

In Irving's series (34) there were 237 infants out of the cases of external hemorrhage. 34 or 14.3 per cent were dead in utero when their mothers
were admitted to the hospital. Forty others, although alive in the uterus were under four pounds when born. In one-third of cases, salvage of the infant was either impossible or unlikely.

Vaux (67) in correlating the fetal mortality to the types of bleeding gives the information that in his experience, placenta praevia bleeding has been associated with 23.0 per cent mortality; premature separation of the normally implanted placenta with 57.1 per cent fetal mortality.

Matthews (43) states that the fetal mortality for severe abruptio placenta is 95 to 100 per cent. The maternal mortality in his experience is about 50 per cent. In the milder cases, the maternal mortality and morbidity is not much higher than in normal cases.

The most logical attitude taken in regard to prognosis in premature separation seems to be that of Richardson (53). It is his belief that the prognosis is considerably more grave when the physician is content to sit by the patient, watching every change. In his opinion, it is the fetus that should be closely watched, and he states that the early diagnosis is made when earnest attention is
directed toward the fetal condition. This opinion is based upon the supposition that anything directed toward saving the baby will be initiated earlier than if our symptom complex is based entirely upon maternal symptoms and signs.

If action is taken upon the condition of the fetal heart tones and not after they are gone; if action is not deferred until the uterus is ligneous; if efforts are directed to saving the baby, the efforts in behalf of the mother will be more effectual. This is true since the earliest sign that can be observed referable to the fetus is an acceleration in fetal heart tones, which will come more often than not before the evidence of hemorrhage, and this, in turn, will be a true indication of the progress of the conditions.
BIBLIOGRAPHY

1. Bacharach, A. L.
   Vitamin E
   Manufacturing Chemist 7: 395, 1936

2. Baird, D.
   Maternal Mortality in Hospital Review of
   999 Fatal Cases in Glasgow Royal Maternity
   Hospital During Ten Years, 1925 - 1934
   Lancet 1: 295, 1936

3. Bartholomew, R. A.
   Premature Separation of the Placenta
   Am. J. Obst. & Gynec. 18: 813, 1929

   The Placenta As A Modified Arteriovenous
   Fistula
   Am. J. M. Sc. 195: 1, 1938

5. Beavers, H.
   Abruptio Placenta
   Texas State J. Med. 33: 28 - 32, 1937

6. Erickenbach, W., and Fromme, H.
   (See Shute, 56)
   Klin. Woehnschr. 1: 496, 1935

7. Browne, F. J.
   Further Experimental Observations on Etiology,
   Accidental Hemorrhage and Placental Infarct

8. Burwell, C. Sidney
   The Placenta As A Modified Arteriovenous
   Fistula, Considered In Relation To The
   Circulatory Adjustments To Pregnancy
   Am. J. M. Sc. 195: 1, 1938

9. Burwell, C. Sidney, Strayhorn, W. D., Flickinger, D.,
   Corlette, M. B., Bowerman, E. P., Kennedy, J. A.
   Circulation During Pregnancy
   Arch. Int. Med. 62: 979, 1938
   A New Nutritional Disease of the Chick Embryo

11. Couvelaire, A.
   (See Mitchell, 48)
   Ann. de gynec. et d'obst. 8: 1911, 1912

12. Currie, D. W.
   Vitamin Treatment of Habitual Abortion

   Abruptio Placenta
   Surg. Gynec. & Obst. 53: 768 – 779, 1931

14. DeLee, Joseph B.
    Principles and Practice of Obstetrics, p. 479
    Philadelphia and London
    W. A. Saunders Company, 1936

15. Essen-Moeller (See Williams, 72)
    L'hémorragie retroplacentaire
    Arch. mens. d'obst. et gynec. 4: 145, 1915

16. Evans, H. M.
    Vitamin E
    J. A. M. A. 99: 469, 1932

17. Evans, H. M., and Bishop, Katherine S.
    On the Relations Between Fertility and Nutrition
    Journal Metabolic Research 1: 319, Feb. 1922

18. Evans, H. M., and Bishop, Katherine S.
    The Ovulation Rhythm in the Rat on Inadequate Nutritional Regimes
    Journal Metabolic Research 1: 335, March 1922
Effect of Progestin and Estrogenic Substance on Human Uterine Contractions  
J. A. M. A. 106: 271, 1936

20. Fitzgibbon, G.  
Revised Conception of Antepartum Accidental Hemorrhage  
J. Obst. & Gynaec. Brit. Emp. 82: 2, 1926

Antitryptic Titre in Pregnancy  

22. Frank, C. H.  
Ablatio Placenta Treated by Caesarean Section Followed by Hysterectomy  
Am. J. Obst. & Gynec. 33: 512 - 514, 1937

23. Frankl, O., and Hiess V. (See Davis and McGee, 13)  
Premature Separation of Normally Implanted Placenta  
Arch. f. Gynak.

24. Gierhake, G. (See Schute, 57)  
Experimenteller Beitrag zur Vitamin E- Frage  
Arch. f. Gynak. 156: 348, 1933

25. Goethals, T. R.  
Premature Separation of Placenta and Statistical Review  
Am. J. Obst. & Gynec. 15: 627, 1928

26. Goodall, J. R.  
Toxemia of Pregnancy, A Clinical and Pathological Study  
J. A. M. A. 105: 2122, 1935

27. Goodall, J. R.  
Toxemia of Pregnancy  
28. Halsted, W. S.
   (Quoted by McKelvey, 46)
   Proc. Nat. Acad. Sc. 5: 76, 1919

29. Harrar, J. A.
   Accidental Hemorrhage
   Bull. Lying-In Hosp. N. Y. 11:
   151, 1917

30. Hofbauer, J.
   Experimental Studies on Toxemias of
   Pregnancy
   Am. J. Obst. & Gynec. 12: 2, 1926

31. Holmes, R. W.
   Uteroplacental Apoplexy and Ablatio
   Placentae
   Am. J. Obst. & Gynec. 6: 517, 1923

32. Holmes, R. W.
   Ablatio Placentae
   Am. J. Obst. & Dis. Women and Child
   44: 753, 1901

33. Holmes, R. W.
   Gynecology and Obstetrics, p. 31
   Hagerstown, Md.
   W. F. Prior Co., Inc.

34. Irving, F. C.
   The Conservative Treatment of Premature
   Separation of The Normally Implanted Pla-
   centa
   Am. J. Obst. & Gynec. 34: 881 - 889,
   1937

35. Juhasz-Schaffer, A.
   (See Shute, 59)
   Ergebn. d. inn. Med. u. Kindirh. 45:
   129, 1933

36. Kane, H. F.
   Progesterone In Combating Habitual Abortion
   Am. J. Obst. & Gynec. 32: 110, 1936

37. Kearns, F. J.
   The Anatomy and Histology of Placental
   Circulation
   Am. J. Obst. & Gynec. 27: 840, 1934
38. Kozelka, A. W., and Gallagher, T. F.
   Effect of Male Hormone Extracts, Theelin, and Theelol on the Chick Embryo

39. Kraul, L. (See Davis and McGee, 13)
   Premature Separation of the Placenta, 27 Cases

40. LeLorier, V.
   (See Schute, 56)

41. Hall, F. F.
   Placental Circulation

42. Hall, F. F., and Meyer, A. W.
   Contrib. to Embryology No. 56
   Carnegie Inst. of Washington 12: 1926

43. Matthews, H. B.
   Hemorrhage During Pregnancy

44. Macomber, D.
   Studies of Reproduction in the Rat
   New England M. J. 209: 1277, 1933

45. McGlinn, J. A. and Harer, W. B.
   The Treatment of Abruptio Placentae
   Am. J. Obst. & Gynec. 30: 226, 1935

46. McKelvey, J. L.
   Vascular Lesions in the Decidua Basalis
   Am. J. Obst. & Gynec. 38: 815 - 823, 1939

47. Miller, N. F.
   Bloody Complications in Obstetrics

48. Mitchell, R.
   Abruptio Placenta
49. Moench, G. L.
   A Consideration of Some of the Aspects of Sterility
   Am. J. Obst. & Gynec. 32: 406, 1936

50. Morse, A. H.
   Premature Separation of the Placenta
   Surg. Gynec. & Obst. 26: 133, 1918

51. Murphy, D. P.
   Congenital Defects
   J. A. M. A. 106: 456, 1936

52. Nageotte-Wilcouchewitch, M. (See Schute, 59)
   Influence Teratogenique des Menaces D'Avortement
   La Presse Medicale 2: 2079, 1937

53. Richardson, G. C.
   The Significance of Fetal Heart Tones in Ablatio Placentae
   Am. J. Obst. & Gynec. 32: 429, 1936

54. Rigby, E. (See Mitchell, 48)
   An Essay on Uterine Hemorrhage
   Sixth Edition, 1776

55. Rowntree, L. G., Steinberg, E. S., Dorrance, G. M., and Ciccone, E. F.
   Sarcoma in Rats From The Ingestion of a Crude Wheat Germ Oil Made By Ether Extraction
   Am. J. Cancer 31: 359, 1937

56. Shute, E. V.
   The Early Diagnosis of Abruptio Placenta and Its Treatment with Wheat Germ Oil
   Am. J. Obst. & Gynec. 33: 429 - 436, 1937

57. Shute, E. V.
   Wheat Germ Oil Therapy -- Dosage, Idiosyncrasy
   Am. J. Obst. & Gynec. 35: 249, 1938

58. Shute, E. V.
   Preservation of Potency, Influence on Labor, and Seasonal Needs of Wheat Germ Oil
   Am. J. Obst. & Gynec. 35: 609 - 614, 1938
59. Shute, E. V.
Rat Experiments, Lactation, Clinical Uses, "Failures", and Effect Upon Congenital Anomalies of Wheat Germ Oil
Am. J. Obst. & Gynec. 35: 810 - 817, 1938

60. Shute, E. V.
Resistance to Proteolysis Found in the Blood Serum of Aborting Women

61. Shute, E. V.
Is Oestrin the Cause of the Resistance to Proteolysis Found in the Blood Serum of Aborting Women?

62. Shute, E. V.
Abruptio Placenta—Wheat Germ Oil Therapy
J. Obst. & Gynaec. Brit. Emp. 43: 74, 1936

63. Slonaker, J. R.
The Effect of Different Percents of Protein in the Diet
Am. J. Physiol. 96: 547, 1931

64. Smith, G. V. S., and Smith, O. W.
Evidence for the Placental Origin of the Excessive Erolan of Late Pregnancy Toxemia and Eclampsia
Surg. Gynec. & Obst. 61: 175, 1935

65. Sure, B.
Dietary Requirements for Reproduction
J. Biol. Chem. 74: 45, 1927

66. Sure, B.
Dietary Requirements for Reproduction
J. Biol. Chem. 63: 211, 1925

67. Vaux, N. W.
Vaginal Bleeding In the Last Trimester of Pregnancy
West Virginia M. J. 33: 485 - 491, 1937
68. Vogt-Moller, P.
Treatment of Habitual Abortion With Wheat Germ Oil
Lancet 2: 182, 1931

69. Watson, E. M. and Tew, W. P.
(Quoted by Schute, 59)
48: 189, 1935

70. Whitehouse, B. (See Robinson, A.)
Discussion of the Causes of Early Abortion and Sterility

71. Wilson, P.
Premature Detachment of the Placenta
Surg. Gynec. & Obst. 34: 57, 1922

72. Williams, W.
Obstetrics, Ed. V, p. 995
New York
D. Appleton & Co., 1930

73. Winter (See Davis and McGee, 13)
Zur Lehre von der vorzeitigen Placentaerlosung bei Nephritis
Ztschr. f. Gerburtsh. u. Gynack. 11: 398, 1885