Management of the Pregnant Diabetic

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INTRODUCTION

Among the 140,665 deliveries at the Providence Lying-In Hospital in the thirty-one year period 1927-1957, 169 diabetic women were observed in 273 pregnancies. Weeding out abortions, dubious diagnoses and cases delivered elsewhere, there remain 251 viable pregnancies on which this study is based.

Although this is the fifth largest obstetrical service in the country, the mechanics of organization and physician-patient relationship are comparable to any large community hospital not directly connected with a teaching center. In the management of the pregnant diabetic, we experience certain disadvantages common to all such institutions:

1. Local industrialization and the prevalence of prepaid insurance coverage have created a progressive shift from clinic to private patient status. About seven eighths of our current clientele is private. This is a closed-staff hospital, but because of its size the staff is large. Consequently in the last ten-year period, only about one fifth of the diabetics were the clinic's responsibility. The ninety-three private deliveries were conducted by twenty-six different obstetricians, and forty-three internists and general practitioners participated in their medical management. This *lack of uniformity of control* is in marked contrast to the teaching hospital, where a select group personally supervises most of the diabetics.

2. Limitation of funds induces patient resistance to the long periods of hospitalization desirable in the last trimester.

3. Most important to remember, the community obstetrical service is obliged to accept emergency cases and miscellaneous drifters, infrequently seen in specialized centers. This has a devastating effect on fetal loss statistics.

Our problems are those of the majority of hospitals, but size permits accumulation of a large body of material in a shorter time. A review of our experience might be informative, in seeking the areas where results may be improved.

In light of modern knowledge, it may seem primitive to revert to discussion of such fundamentals as ketosis and toxemia. Yet these continue to be major causes of fetal death. A refreshingly candid appraisal from the Johns Hopkins Hospital[1] showed that one half of the fetal loss occurred in utero, three quarters of it in women under poor diabetic control; and 18.8 per cent of the total fetal loss was associated with significant degrees of toxemia. Among 119 diabetics in a Belfast, Ireland, clinic[2] there were seven instances of coma, with 71.4 per cent loss, and nineteen cases of pre-eclampsia, with 25.2 per cent wastage. This could be expanded into a large bibliography of error in simple medical care, by no means always the responsibility of the obstetrician, and often the fault of the patient herself.

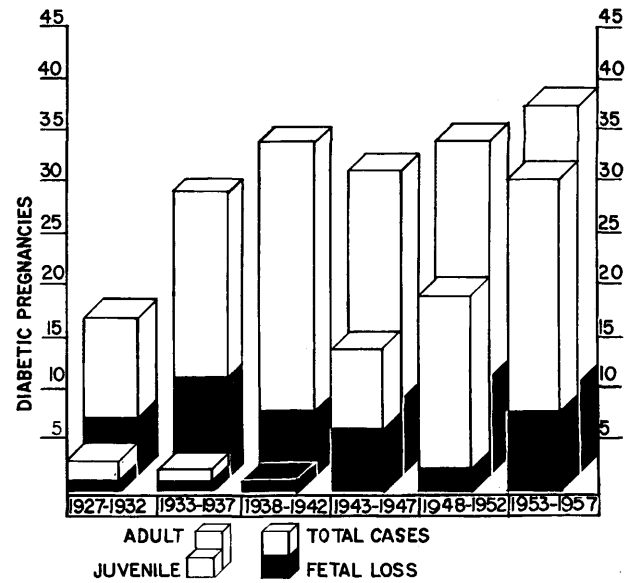

FIG. 1. Five-year periods—type of patients and fetal loss.

DEFINITION OF TERMS

In this study no distinction is made between "old" and "new" series, nor between clinic and private patients.

Unless otherwise specified, the entire viable fetal loss among diabetic patients during thirty-one years is counted. This includes intra-uterine death known to have occurred before acceptance of the case. It also includes infants leaving this hospital alive to die elsewhere, within two weeks, of congenital anomaly.

From the Providence Lying-In Hospital, Providence, Rhode Island.

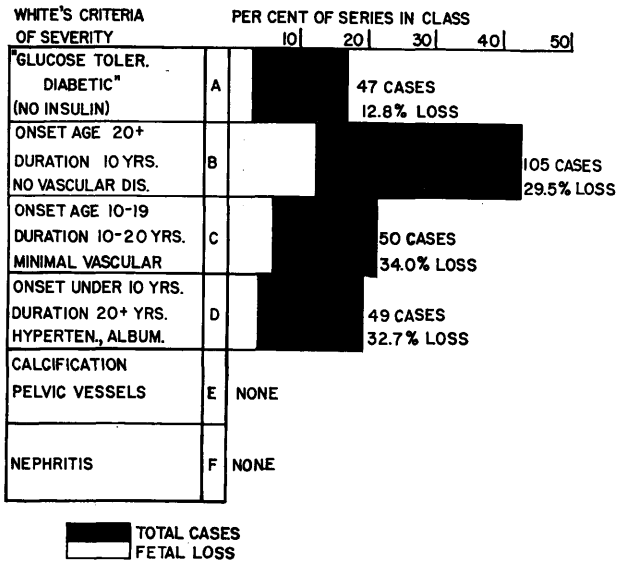

FIG. 2. Distribution and fetal loss by White's classification.

White's original criterion[3] of 960 gm. (2 lb., 2 oz.) for viability is still used, although we[4] regard this as an unrealistically low level. If, as in some reports, the standard is raised to 1,500 gm. (3 lb., 5 oz.),[5] or to about twenty-eight weeks,[6,7] the basic fetal survival here recorded would improve by 5 per cent across the board.

White's classification of severity[3,8] is followed for uniformity, although we do not concur in all its details.[9] The salient features of age of onset and duration of disease involved in this scheme are indicated in figure 2.

"Juvenile" denotes a diabetic diagnosed before age twenty; "adult" or "older women" acquired the disease afterwards. This is the basic metabolic background of the individual. The status at any given pregnancy is further clarified by specifying a disease span of "less than ten years" or of "ten-year" duration.

There is no desire to make the fetal salvage look good. This unvarnished account of rather mediocre results seeks the answer to two questions: What kind of diabetic women lose their babies; and under what circumstances? Statistics are a tool to pin-point trouble spots where corrective measures may be intelligently applied.

POTENTIALLY DANGEROUS CASES

The profession has been thoroughly alerted to the hazards of pregnancy in the juvenile diabetic. With attention focused in that direction, there is a tendency to overlook certain other areas of fetal loss.

1. *Fetal loss in older women.* There is a rising incidence of juvenile cases by five-year periods (figure 1). Despite the increasing number of these young women, there is a striking improvement in their fetal salvage. The perinatal loss in juvenile diabetes in the last ten years is less than half that of the preceding period. On the other hand, although the proportion of adult cases is diminishing, their fetal loss remains constant at about 25 per cent.

2. *Loss in mild diabetes.* When severity is graded by White's classification (figure 2), the fetal loss is 13 per cent in Class A and 30 per cent in Class B. This is a tragic waste in these relatively mild diabetics. Too much of it results from failure to establish the diagnosis until the patient is in serious condition, or from regarding the known mild diabetic too lightly. There is increasing emphasis in the recent literature[10-13] on prompt detection and active management of diabetes unmasked by the current pregnancy.

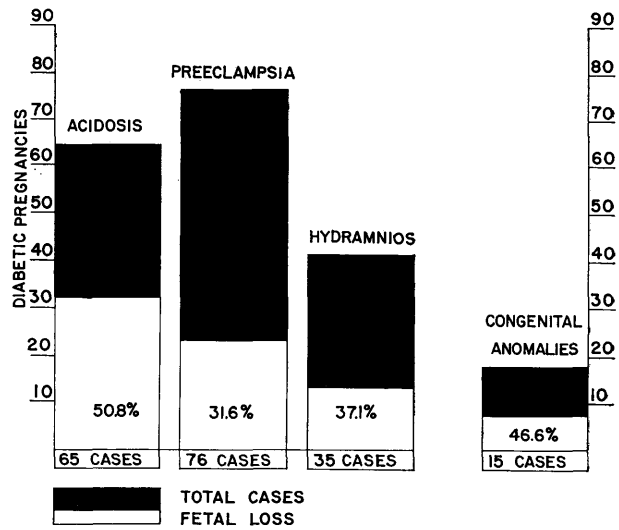

FIG. 3. "The Killers"—complications associated with a high fetal loss.

3. *The role of age and multiparity.* Age and parity influence both the course of the diabetic process itself and the general outcome of pregnancy in these women.

On the first of these points the pattern is familiar: progressively large infants, transient glycosuria, then an abnormal glucose tolerance, and finally frank diabetes. This sequence needs no elaboration.

The role of age and parity in the over-all outcome of the diabetic pregnancy itself is more difficult to evaluate. Results must be assessed on fetal loss; and this picture is obscured by such extraneous complications as toxemia, congenital anomaly, and obstetrical accidents. These are common to all diabetics; they are frequently compounded; and over most of them we have little or no control.

The one complication over which we can exert some effective restraint is acidosis. The types of break in control comprising categories 1-3, figure 4, are considered to be "preventable." If this preventable acidosis could be eliminated, the remaining fetal loss would represent the assorted hazards that beset all diabetics, regardless of age or duration. In the following discussion deaths attributable to "preventable" acidosis have been deleted from the "corrected" computations. When this residual fetal wastage is examined on the basis of age of onset and longevity of disease, some interesting data are elicited:

FIGURE 4

Acidosis—causes and fetal loss

Cause of break in control	Cases	Per cent all acidosis	Fetal loss No.	Fetal loss Per cent
1. Unco-operative patient	21	32.3	13	61.9
2. Inadequate medical supervision	11	16.9	8	72.7
3. Undiagnosed until in acidosis	5	7.7	3	60.0
4. Intercurrent infection	18	27.7	5	27.7
5. "Brittle" diabetic under competent medical management	10	15.4	4	40.0
Total acidosis	65	100.0	33	50.8

The preventable acidosis in categories 1, 2, and 3 represents 56.9 per cent of all acidosis, and is associated with 34.3 per cent of the gross fetal loss in diabetes.

1. *Age versus duration.* The corrected fetal loss in juvenile diabetes is 10 per cent in girls of less than ten years' duration, and goes to 17 per cent in ten-year cases. It is 17 per cent in adult diabetics with short-term disease, rising to 50 per cent in the ten-year patients. In other words, (a) there is a significant increase in fetal wastage in long-standing diabetes; and (b) this is most striking in the older age group of patients.

2. *Variations within the same class of severity.* The same question can be approached from another direction, by comparing the performance of the different types of women who fall by definition into the same severity classification. White's heterogeneous Class D is a good example, since it includes three groups with widely divergent age and metabolic characteristics:

a. First are the dramatic juveniles, all of more than ten years' duration, and most with a high insulin requirement. Their average age was 26.5, and only six were thirty years or older. The gross fetal loss was 16.6 per cent, corrected to 8.3 per cent.

b. Next come the older women with essential hypertension, only two of whom were ten-year diabetics. The average age of those who required insulin was 36.8 years. The age of mothers with dead infants was roughly equal to those whose offspring survived. The gross and the corrected fetal loss here was *more than three times as great* as that of the juveniles in the same class.

c. Last is the handful of essential hypertensives with diabetes so mild as to require no insulin. Their average age was also 36.8. It may be only a sampling error that their gross and corrected fetal loss was *greater* than that of their insulin-treated contemporaries.

This is tenuous evidence, based on a small series of cases. It does not correlate with the concept of severity postulated by White, who places the weight of emphasis on the juvenile diabetics. Nevertheless, the inference is that although parity, duration of disease, and level of insulin demand all sway the result, advancing maternal age is perhaps the determining factor in the over-all outcome of pregnancy in the diabetic.

There is no desire to minimize the serious problems presented by the juvenile patient. We simply emphasize that appreciable fetal salvage may be achieved by more meticulous attention to the older women, many of them mild diabetics of short duration and with low insulin requirement, and some of them even undiagnosed at the outset of pregnancy.

MAJOR COMPLICATIONS

Three clinically detectable physiological complications are associated with the great majority of fetal deaths (figure 3). They may not be the immediate cause of exitus, but they play an important part in the chain of events leading to the intra-uterine death, or to the onset of labor or the manner of delivery resulting in neonatal demise.

1. In the presence of acidosis the fetal loss is 51 per cent.

2. Among all cases of pre-eclampsia 32 per cent of the infants died.

3. Where hydramnios was recorded the wastage was 37 per cent.

4. Congenital anomaly must be mentioned here, although it is seldom detected prior to birth, because it has been so publicized. Our incidence of malformations was three times that of the general population; but this was still a small number, and only half were incompatible with life. Congenital anomaly was not responsible for an important segment of the fetal loss.

ACIDOSIS

Significant ketoacidosis occurred in one quarter of our cases, with deplorable results (figure 4). "Preventable" breaks in control due to unco-operative patients, inadequate medical supervision, and undiagnosed diabetes comprised 57 per cent of all acidosis encountered, and accounted for one third of the gross fetal loss. We are not alone in this regard. Pedowitz and Shlevin[14] report 28.7 per cent acidosis, contributing to two thirds of the perinatal loss, which could "be explained in large measure by poor patient co-operation." This peculiar negativism is characteristic of the emotional make-up of many diabetics.

As preventable acidosis is reduced, the importance of intercurrent infection comes to the fore. Commonest pitfalls are gastrointestinal upsets, urinary infections, and respiratory conditions, in that order. Five of the seven episodes of coma seen in six patients were from these causes. Each woman must be impressed with the danger of even the simplest sources of temperature and fluid loss.

The time of appearance and the lethal effect of acidosis are quite uniform. There were three instances in the nonviable pregnancies, and acidosis was undoubtedly the reason for fetal death in two late abortions. Half of the severe ketosis and two thirds of the coma occurred before thirty-six weeks. The fetal wastage was about 50 per cent both before and after this time point.

This problem points up the flaw in division of responsibility between internist and obstetrician. These crises often arise when the medical member of the team is unavailable. The obstetrician who accepts a diabetic must have a sound working knowledge of the management of precoma.

The other side of the metabolic coin should be mentioned. Really severe insulin reactions occurred only three times, all before thirty-six weeks. One infant succumbed at the time; of the two who survived the immediate insult, one died weeks later of other causes.

TOXEMIA

Pre-eclampsia is the next most important complication, appearing in one third of the series (figure 5). The fetal loss was 22 per cent in mild toxemia, and double that in the severe type. One third of all hypertensives developed superimposed pre-eclampsia, with a 54 per cent wastage. These figures do not include twenty-one cases of otherwise uncomplicated essential hypertension, a not innocuous condition in which 24 per cent of the infants died. There was one case of eclampsia, with fetal survival.

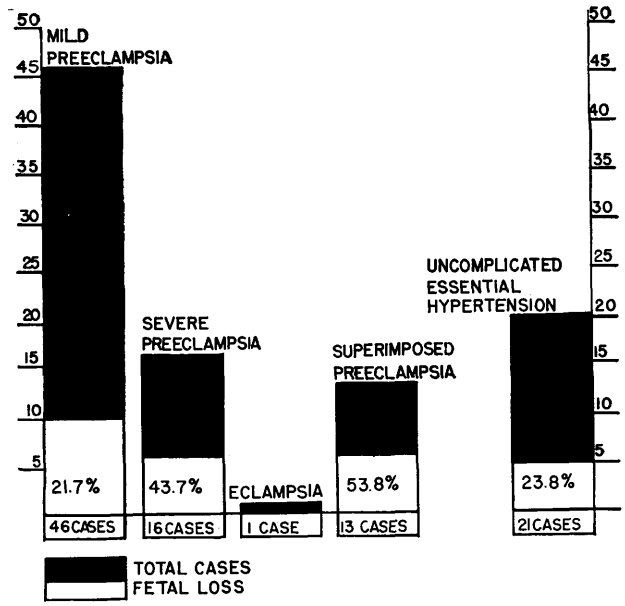

FIG. 5. Toxemia—types and fetal loss.

Management of toxemia is much more difficult than in the normal woman. The diabetic has an inherent tendency to accumulate fluid in all possible bodily water storage spaces, including the uterus. To this little-understood phenomenon is ascribed an endocrine etiology. That this edema is a precursor to pre-eclampsia is evidenced by the consistently high toxemia rate among the diabetics of clinics with excellent results in their other patients.

Water imbalance has been combated without notable success in several ways: (1) Traditional regimes of fluid and sodium ion restriction. (2) Employment of various diuretics, including the sugar and magnesium concentrates, ammonium chloride, mercurial agents, and anhydrase inhibitors. (3) New preparations combining hypotensive and diuretic properties have some promise. (4) One argument advanced for sex hormone therapy is that the method reduces the incidence of toxemia. (5) Drainage of hydramnios has been performed in some clinics.

Instead of the usual porky, edematous, diabetic infant, the products of toxic mothers, especially in essential hypertension, may be underweight. Their fragility is in rough proportion to the period of exposure to the pre-eclampsia. A short attempt at stabilization may be desirable, but it is unwise to temporize with toxemia. Even though the pressure improves, continued intra-uterine existence jeopardizes the fetus.

HYDRAMNIOS

Knowledge of the causes and physiology of hydramnios is meager. It probably occurs to some degree in all diabetics, but is hard to measure quantitatively. As previously suggested, it accompanies profound metabolic disturbance more frequently than it does congenital malformation. Further, there is more than an accidental relationship between the appearance of hydramnios and the development of fetal edema leading to hydrops. Gross distention may be considered a valid indication to terminate pregnancy.

Decompression of the uterus by tapping is still in the experimental stage. The rationale of merely reducing intra-uterine tension in hope of prolonging pregnancy is debatable. The point is what happens to the fetus, whose exposure to the abnormal chemical and physiological environment producing the hydramnios is thus artificially prolonged. Final evaluation will depend on the experience with these infants.

PHILOSOPHY OF MANAGEMENT

The closest internist-obstetrician integration is essential. Our ideas on management are crystallizing along the following lines:

1. *Diabetic control.* All observers agree that *control of the diabetes is of prime importance.* The internist is responsible for prevention of acidosis. Just how rigidly to keep the patient sugar-free is a controversial subject not germane to this review.

2. *Prevention of toxemia.* During the second and early third trimesters the principal function of the obstetrician is to avert toxemia. The final answer to this formidable assignment could be an effective double-acting drug: diuretic to control edema and minimize pre-eclampsia; hypotensive to reduce essential arteriolar spasm, which in turn would diminish superimposed pre-eclampsia.

3. *Female sex hormones.* Hormone therapy is alleged to confer a number of benefits. About 10 per cent of our cases were so treated. One third of these were relatively mild diabetics, the rest severe by any standard. The results did not encourage continuation of the method. In all, twenty-four women received hormones and 227 did not. The only significant difference was a section rate three times as high in the hormone group, because early termination was part of the regime in vogue. The incidence of acidosis and of toxemia, and the fetal loss, were virtually the same in both groups.

4. *Time of delivery.* Approaching term, the big question is how much longer the pregnancy may safely continue. Much has been said about late intra-uterine death, implying a mysterious phenomenon which strikes without warning in the last month. It has been attributed to hormonal imbalance, placental senescence, and other hypothetical causes, none of them adequately verified. The "interventionist" school recommends early termination to forestall this disaster. This seems to offer an easy solution to a difficult problem, but the entire concept is open to doubt.

a. The so-called "senescent placenta" of diabetes is not an established entity, either by clinical observation or by pathological study.

b. Death in utero occurs infrequently without some demonstrable metabolic, anatomical, or obstetrical reason. Only seven of our forty-eight stillbirths could be classified as "unexplained."

c. *Mandatory early delivery.* The thirty-sixth week is repeatedly designated the critical point at which diabetic pregnancies must end, because thereafter things rapidly go wrong. This theory does not seem to stand the test of practice. Interference so early only too often converts a small but living fetus into a premature neonatal death statistic.

Clayton[15] reports 201 cases from London. Termination was usually at thirty-six weeks, involving a section rate of 67 per cent. The fetal mortality was 28 per cent, including twenty-one stillbirths and thirty neonatal deaths. Autopsy showed atelectasis or hyaline membrane disease in 76.6 per cent of the latter.

Louw and Sinclair[16] in Cape Town, South Africa, regard it "a reasonable procedure to interrupt pregnancy soon after the thirty-sixth week." Their perinatal loss in ninety booked cases was seven stillbirths and seven neonatal deaths.

White's group is the best-known American exponent of early delivery. The Boston hospital accommodating most of its patients segregates the statistics in a "Joslin Clinic" column. The last annual report[17] lists seventy-seven infants in seventy-five deliveries. Subtracting nine abortions, the section rate in sixty-six viable pregnancies was 56 per cent. The fruit of this effort was eight stillbirths and thirteen neonatal deaths, a viable fetal loss of 30.9 per cent.

All this is epitomized by Waters' crisp remark[18] that "the fetal loss due to bad timing is just about as high as that from deferred interference." It inspires little confidence in the philosophy that the tribulations of diabetic pregnancy are conveniently solved by early delivery. There is a discernible trend for shrewd observers[19-20] to edge up closer towards term.

We can not subscribe to the belief that intra-uterine death, of itself, takes a sharp upswing after thirty-six

FIGURE 6

Causes of fetal death

Principal cause	Under thirty-six weeks			Thirty-six weeks and over			Total	
	Stillbirth	Neonatal	Total	Stillbirth	Neonatal	Total	No.	Per cent
Acidosis major cause	10	2	12	9	—	9	21	30.0
Toxemia major cause	4	2	6	7	1	8	14	20.0
Congenital anomaly	2	1	3	2	2	4	7	10.0
Prolapsed cord, cord around neck, etc.	3	—	3	1	—	1	4	5.7
Traumatic vaginal delivery	—	—	—	3	—	3	3	4.3
Prematurity (under 2,250 gm. or 5 lb.)	—	8*	8	—	—	—	8	11.4
Atelectasis, hyaline membr., pulm. edema, etc.	—	2	2	—	4	4	6	8.6
"Unexplained" intra-uterine death	4	—	4	3	—	3	7	10.0
Total	23	15	38	25	7	32	70	100.0

*One pair of premature twins counted as a unit.

weeks. Most stillbirths are only secondary reflections of crises in maternal physiology. There were more fetal deaths in our series before thirty-six weeks than after. If the wastage in very small infants produced by spontaneous premature labor is excluded, the loss from all other causes was almost exactly the same in the two groups. With this correction, the incidence of intra-uterine death was 76.7 per cent before and 78.1 per cent from thirty-six weeks on; and the principal reason for these deaths was acidosis and/or toxemia in 60.9 and 64.0 per cent respectively (figure 6).

This bolsters our conviction that there is no happy target date at which pregnancy must automatically be terminated. Although these infants may be handicapped by the maternal metabolic environment and compromised by their own edema, they are entitled to as much maturity as can be obtained for them. Little is gained by interference *unless and until* there arise such complications as instability of control, pre-eclampsia, or hydramnios. If and when this happens, prompt action is in order.

5. *Method of delivery.* The need for intervention brings the final decision of what method to employ. This should depend on the usual considerations of parity, cervical preparedness, and the size and position of the fetus. Of equal importance is evaluation of the ability of mother and infant to withstand a period of stress and trauma. In many instances, including most breech presentations, abdominal delivery will be indicated. Also a policy of carrying as close to term as practicable will result in more large babies, with a corresponding increase of cesareans for disproportion.

We have no antipathy to increasing the section rate in areas that prove constructive. Our current incidence is about 25 per cent, and it will rise as more juvenile diabetics and their repeat operations collect. Published reports, however, are not convincing that rates in excess of 65 per cent can be justified by the salvage achieved.

Nor must we forget that when diabetes itself is the indication for primary section, the girl is condemned to surgery for the rest of her reproductive career. We had one multipara and two primiparas go into spontaneous labor while awaiting section for very acceptable indications; one primipara has had a subsequent normal vaginal delivery; all the infants are alive. This is a saving of four planned operations which proved in retrospect to be unnecessary.

CONCLUSION

Headway in improving fetal salvage in diabetes seems painfully slow. The loss over a thirty-one year span was 28 per cent, and remains close to 25 per cent in recent periods. Much of this loss occurs among the older women and milder cases who should do better. Too much of it stems from small but costly slips in diabetic control and from debatable obstetrical judgment. We believe that improved fetal salvage will come about, not by emptying the uterus earlier or by doing more cesareans,

but largely as the result of more meticulous attention to control of diabetes and a more effective attack on toxemia.

SUMMARIO IN INTERLINGUA

Regime De Gravidas Diabetic

Progresso in salvar vitas fetal in casos de diabete es penosemente lente. Pro un periodo de trenta-un annos, le perdita amontava a 28 pro cento, e pro periodos recente ille valor remane proxime a 25 pro cento. Un grande parte de iste perdita interessa feminas de etates plus avantiate e con diabete comparativemente pauco sever. Isto non deberea esser. Le causa es troppo frequentemente un micre (sed costose) error in le control del diabete o un dubitose judicamento obstetric. Nos opina que progresso in salvar vitas fetal va esser effectuate non per vacuar le utero plus precocemente o per interprender un plus grande numero de sectiones cesaree sed primarimente in consequentia de un plus meticulose attention al detalios del control de diabete e de un plus efficace attacco super le menacia toxemic.

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The first clinical and experimental observations that formed the background for the utilization of certain sulfonamide derivatives in the treatment of diabetes were made during the first half of 1942. At that time, M. Janbon and his co-workers of the Infectious Disease Clinic at the Medical School of Montpellier, were investigating the therapeutic effects of the isopropylthiodiazole derivative of sulfanilamide (2254 R.P.) in typhoid fever. They found that this drug produced in some patients, especially those who were undernourished, symptoms and signs resembling hypoglycemia. Some patients had great neurological disturbances, and died. The chemical data revealed low values for blood sugar. The intravenous injection of glucose tended to alleviate the symptoms in some individuals, but in others it was not helpful. Janbon presented this problem to us and asked for our advice.

Some months earlier we had completed an experimental study with Hedon and Heymann of the irreversible neurological lesions produced in the dog by large doses of Protamine Zinc insulin. It occurred to me that there might be a parallelism between the effects of 2254 R.P. and of Protamine Zinc insulin. This was, of course, a tentative idea, and it was necessary to submit it to experimental test.

Auguste Loubatiéres, in *Annals of the New York Academy of Sciences,* Vol. 71, p. 4.