RECENT ADVANCES IN OBSTETRICS

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IF we review the vast amount of research that has been carried out in obstetrics during recent years, wath are the major advances that have resulted? Which advances promise to become a permanent part of our armamentarum? More particularly, which appear to be of the greatest practical value? It is my purpose in this presentation to review with you four such advances.

1. **Inmunologic Tests for Pregnancy.** Almost 40 years have now elapsed since the introduction of the Aschheim-Zondek test for pregnancy; and if we look back over the major achievements in our specialty during the first half on the century, this was surely one of the greatest. (Klin Wschr. 6: 1322, 1927). Meanwhile, many other endocrine tests have been devised based on the same general principle, the differences lying chiefly in the animal used for assay. These various tests have made it possible to diagnose pregnancy much earlier than can be done by physical examination and when performed six weeks or more after the last menstrual period, those in routine clinical use are about 95 per cent accurate. Their two main disadvantages are (a) the long waiting period before an answer is given and (b) the bother and expense of maintaining an animal colony.

The recent introduction of immunological methods for the diagnosis of pregnancy represents the first major advance in this area since the advent of the original Aschheim-Zondek test. This new type of test eliminates the two main disadvantages of the bioassay methods and appears to be just as accurate.

This immunologic test is based on an antigen-antibody reaction in which human chorionic gonadotrophin is the antigen; and the antiserum is obtained from rabbits immunized againts this antigen. In other words, human chorionic gonadotrophin is injected into rabbits. This produces antibodies to this hormone in the serum of the rabbits. When this serum or anti-serum is then mixed with erythrocytes coated with chorionic gonadotrophin, the erythrocytes agglutinate. This is true unless, prior to the mixing of the anti-serum with the erythrocytes, it is added to pregnancy urine. In that case the chorionic gonadotrophin in the pregnancy urine unites with the antibodies in the added serum and uses it all up. Therefore, when now added to erythrocytes coated

with chorionic gonadotrophin, it does not cause agglutination since there are no active antibodies left to do so. This absence of agglutination is a positive test for pregnancy. If, however, the urine examined does not contain chorionic gonadotrophin, the antibodies are not used up and so will subsequently agglutinate the red cells. This is a negative test. So-called "latex" particles coated with chorionic gonadotrophin have also been used instead of red cells.

Immunologic tests of this kind have now been compared with the standard tests such as the toad or Hogben test in many studies. The agreement has been excellent in general, but there is some tendency for the immunologic tests to give occasional false positives. It is believed that changing the dilutions of the urine now employed may reduce this source of error.

In sum, the evidence indicates that the immunologic tests are approximately as accurate as the Hobgen test, are simple to carry out and are much more rapid. It is too soon to predict that the immunologic procedures will displace the older tests, but they may possibly do so.

2. **Methotrexate in Choriocarcinoma.** The next advance I should like to discuss is one of the most dramatic in the history of obstetrics and also in the history of malignant disease, namely, the value of chemotherapy with methotrexate in the treatment of choriocarcinoma.

It used to be said that the survival of any patient suffering from choriocarcinoma was ipso facto evidence that the original diagnosis was incorrect, that the case was not one of choriocarcinoma because, if so, the patient would certainly have died. Although not strictly true, this hopeless attitude toward choriocarcinoma in the past was close to the truth. For example, among 103 patients with metastatic choriocarcinoma recorded in the Mathieu Registry, there were only 6 five-year survivals as reported by Brewer and his associates (Am. J. Obst. & Gynec. 81: 574, 1961).

With the administration of methotrexate this 95 per cent death rate has been reduced to 50 per cent. Many clinics throughout the world have reported such a figure; for example, let us consider the data of Hertz who is entitled to immense credit for introducing this therapeutic agent. In 63 women with metastatic choriocarcinoma who were treated with methotrexate, 30 or 47 per cent were alive and showed no evidence of the disease five years later (Am. J. Obst. & Gynec. 82: 631, 1961). In evaluating these results, it must be remembered that all the patients had metastases. In 52 per cent, or in the great majority, these were pulmonary. Similar results habe been reported from Hong Kong, Taiwan, the Philippines, as well as in other medical centers including several in Latin America.

But the significance of this reduction in death rate in choriocarcinoma by methotrexate extends beyond this one disease. If this particular form of malignancy can be arrested by chemotherapy, there is reason to hope that, in

the course of time, ohter chemicals may be discovered that will yield similar results in other forms of cancer, in breast, uterine, and gastric cancer. A vast amount of research is now being directed to this problem.

3. **Management of Fetal Death before Labor.** When a fetus in utero dies berofe the onset of labor, several weeks may elapse before its expulsion. This is a difficult period for all concerned, including the obstetrician, since the patient, her husband and the entire family often insist that the dead fetus be delivered at once. A few years ago about all the obstetrician could do was to counsel patience and wait because, when the fetus has been dead several weeks, the initiation of labor by mechanical means or with oxytocin is likely to be difficult.

Thanks to the work of several European obstetricians, it is now known that labor can be induced regularly and safely by means of injecting certain hypertonic solutions into the amniotic sac. Either a 20 per cent sodium chloride solution or a 50 per cent glucose solution may be used. In the case of the glucose solution, the following technique is used. As you know, when the fetus is dead, the amniotic fluid is thick, scanty and discolored. Therefore, after the injection of local anesthesia, a Nº 14 cannula and trocar are inserted into the uterus in the midline between the symphysis and umbilicus, care being taken to avoid the bladder which should be emptied beforehand. After removal of the trocar a catheter with an internal diameter of 1 mm. and an external diameter of 2 mm. is introduced. Then 200 cc. of amniotic fluid is removed and 200 cc. of the 50 per cent glucose injected.

In 22 patients reported by Wood and his associates of London, labor started within 3 to 85 hours after the injection. The interval exceeded 48 hours in only 3 cases. Labor was less than 13 hours in all cases. Other reports are equally good.

In addition to cases of fetal death, this method is also useful in cases of anencephalus. The mechanism by which hypertonic solutions initiate labor is not completely clear, but it is probably due to the suppression of the manufacture of progesterone by the placenta.

4. **Management of Rh Immunization.** Provided that the mother is known to be immunized, as shown by antibody titers, the question is: when should labor be induced so that the baby will not be badly damaged and yet be mature enough to survive? Despite the exercise of the best judgment, it is possible to be wrong in these cases in two ways. On one hand, while waiting for the baby to grow a little bigger, fetal death may occur in an infant quite large enough to survive. On the other hand, in some cases, you may perform induction of labor at an early date only to deliver an **unaffected** baby who dies of prematurity. In both instances, the infant might have been saved if some test had been available which would show whether the baby

was being severely affected by maternal antibodies, moderately affected, or not affected at all. As for maternal antibody titers, when these are zero, the outlook is good; but if antibodies are present, their amount is not a reliable index of the amount of fetal damage present. Therefore a more reliable test is needed to determine the condition of the fetus.

The color of the amniotic fluid, obtained by amniocentesis, is now being used extensively for this purpose. The basis of this test is the parallelism which exists between the bilirubin content of amniotic fluid and fetal anemia. This parallelism is well established (Lancet, 2: 443, 1950; idem, 1: 395, 1952; J. Obst. & Gyn. Brit. Emp. 60: 244, 1953; idem, 63: 68, 1956). With a little experience, even the gross color of the amniotic fluid is helpful, that is, how deeply yellow it is. But a much more accurate estimate of the amount of bilirubin present can be made by the spectrophotometric analysis of the fluid. Limitations of time prevent a detailed consideration of the spectrophotometric technique, but this is set forth in extenso in the articles by Liley of Aukland, New Zealand, and of Freda of New York City (Amer. J. Obst. & Gyn. 82: 1359, 1961.

Any biochemical laboratory should be able to perform this test. At best, of course, it is just a helpful adjunct; but when correlated with other data it is often helpful.

Several other advances might also be discussed, but from the viewpoint of their practical usefulness, it seems to me that these four are particularly outstanding.