PREGNANCY DIAGNOSIS STATION.

REPORT ON FIRST YEAR'S WORKING.

BY

F. A. E. CREW, M.D., D.Sc., Ph.D.,
DIRECTOR, ANIMAL BREEDING RESEARCH DEPARTMENT, UNIVERSITY
OF EDINBURGH.

Introduction.

A LITTLE more than a year ago my colleague Dr. B. P. Wiesner convinced me that for several reasons it was desirable to examine on a large scale the pregnancy diagnosis test of Zondek and Aschheim. Out of this suggestion emerged the Pregnancy Diagnosis Station, the conduct of which has very largely been in hands of Dr. E. M. Robertson, working under the supervision of Dr. Wiesner.

The station, attached to the Animal Breeding Research Department, was opened a year ago. At that time a certain amount of work had been done on the accuracy and applicability of the Aschheim and Zondek reaction (A.Z.R.), but this work was almost entirely restricted to experimental material, and to cases selected in various respects. At the station, however, the test had to be applied under routine conditions and on unselected cases. It was intended that, should the results prove favourable, the work of the station would continue so as to make its services available for hospitals and practitioners. It is obvious to everybody who knows the technique of the test that it has to be carried out at some selected centre where the keeping of animals on a sufficient scale is possible; it cannot be carried out anywhere and everywhere.

The station has had to deal with a considerable number of specimens sent in for diagnosis from hospitals and doctors in all parts of Great Britain and Ireland. It cannot yet be decided what actual percentage of the cases was diagnosed correctly, since the findings of the station have to be controlled by clinical diagnosis performed by the doctor, and such control information has to be communicated to the station by him. In many cases this confirmation has not yet been received, and so a full account cannot be given. However, this report at the end of the first year may fulfil a double purpose by conveying an impression of the preliminary results, and by explaining certain limits of the test as well as sources of misunderstanding.

The Test.

Aschheim and Zondek have fully described their technique, and more recently Allen and Dickens published a full account of the test. The method of carrying out the test at the Pregnancy Diagnosis Station corresponds almost exactly to the Aschheim and Zondek technique, except that naked-eye detection of blood points in the ovaries is relied upon entirely, and the third pituitary reaction of Zondek and Aschheim is neglected. Microscopic examination is not found necessary, because a minimum positive reaction produces an easily recognized blood point formation. If, however, the blood points are small and sunk in the ovary, and at the same time corpora lutea formation is marked, the blood points may be distinguished by holding the ovary up to the light, when they appear darker than the densest of the corpora lutea. Some investigators when in doubt press the ovary in glycerin between two cover-slips and examine under a lens. For this test, as the results show, the naked-eye technique is not less accurate than the microscopic. By abandoning microscopic examination the whole procedure is made simple and rapid. However, if there is any doubt as to the presence of blood points, a fresh specimen of urine is obtained, where possible, and the test is repeated.

In order that no mistakes may arise during the handling of specimens, and that the recording be as accurate as possible, a special record book is used. Each sample on arrival at the station is at once filtered into a numbered bottle, and any particulars regarding the specimen are entered in the record book, opposite the corresponding number. For each entry in the book there are two pages. The first of these is so printed and perforated that from it are available two numbered labels, one for the urine container and one for the mouse cage; a record card for filing; a "result" letter; a "follow-up" letter; and an

injection record card. All entries are duplicated on to the second page, which remains in the book. As soon as the results become available the "result" letter is sent off to the "sender"—at the latest within six days of the arrival of the specimen (the test actually takes about 100 hours). In an attempt to supply a result in very urgent cases, certain experiments have led to the adoption of an emergency test. It was found that by using larger doses of urine a result could be obtained within sixty hours. In cases of great urgency such a procedure is adopted, but a control test with the standard method is also carried out. If the emergency test turns out to be positive, then a positive result is returned at once; a negative result, however, is withheld until the second test is completed. Such a modification had been suggested by the originators of the test.

The station requires that two ounces of fresh morning urine, in a sterile container strong enough to withstand the dangers of transport, be sent along with a few notes on the case, giving the name, age, parity, date of the last menstrual period, menstrual history, history of any severe constitutional disturbances, and also such information as will supply a reason for sending the urine within twenty-eight days of the last menstrual period.

Limitations and "Errors."

It has been found that in about 1 per cent. of cases the sample of urine kills the experimental animals, and so no result is forthcoming. In these cases, where possible, second and third specimens are tested, generally without success. The cause of death of the mice seems to be different for different specimens of urine. The prevention of bacterial action or the elimination of toxic elements has not been practised in the station, because, so far, no simple method for doing so has been devised. There is not, so far, a sufficiency of clinical detail or of data from the examination of such urines to allow of an opinion being formed as to the nature of the toxicity. It is hoped that before long a solution to this problem will eliminate one source of weakness in the test.

On account of the nature of the organization of the station, errors arising from the human element are reduced to a minimum and can be neglected. Two factors which must contribute to the error are (1) unsuitable conditions of the urine—for example, dilution; if not a morning specimen the urine may be insufficiently concentrated to give a positive result; this is unusual; (2) lack of complete and accurate control of results.

It must be pointed out that as far as the station is concerned the control is entirely in the hands of the "sender" of the specimens, and for the following reasons cannot be as reliable as it would be were the test carried out on a purely experimental basis: (1) the doctor has to depend on the uninitiated patient for many clinical details, information about, and description of, abortions, etc.; (2) microscopical examination of pathological specimens is not always possible. For an adequate control both these items are necessary in many cases.

The Results.

In all, 840 cases have been dealt with from the inception of the station up to the end of January, 1930. In 10 cases the urine was insufficient in amount, or lost in transit, and therefore no test was possible. Thus 830 tests have been carried out, but in 24 cases "no result" had to be returned on account of the toxicity of the urine causing the death of the test animals. Of 806 cases diagnosed at the station the report only deals with the 460 about which control information has so far been received. It is obvious that of necessity such information is generally some months in arrears, hence the comparatively small number of controlled cases.

Diagnosed at the station as:

Positive	226
Negative	174

These have been controlled thus:

Correct	446
Incorrect	14

It is at once seen that with the 14 (so-called) cases of incorrect diagnosis the results show an error of 3.04 per cent. However, this figure, having been influenced by various factors, only represents an apparent error, and so provides a misleading impression of the value of the test.

In order to judge this value correctly it is necessary to discuss certain limitations of the test and to analyse the factors which have adversely affected the results.

Examination of Results.

As this biological test for pregnancy is of recent origin and quite unique, it is natural that some time must elapse before practitioners become familiar with it and with the principles involved, and thus realize the importance of sending case-notes to the station. Only scanty—if any—notes have been received, and the classification and analysis of cases has frequently been difficult. However, an examination of the results has been attempted. A short discussion of the basis of the test will make for a clearer understanding of these results.

It will be remembered that the A.Z.R. is based on the occurrence in the urine of large amounts of at least one gonadotrope hormone which normally (that is, outside pregnancy) is only found in the anterior lobe of the hypophysis. During pregnancy it is apparently produced by, and certainly found in, the placenta; and in associated conditions, such as hydatidiform mole, it is also produced in large quantities. The presence of large amounts of this substance in the urine is therefore not necessarily a sign of the presence of a foetus. However, its production in large amounts, in conditions unassociated with pregnancy, is apparently rare. Thus the term "pregnancy" is used, in communications from the station, qualified by the words "does exist" or "does not exist," according to whether the test shows a positive or negative result. Of course, one could refuse with some justification the term "pregnancy" in certain cases if one defines pregnancy as the time during which an ovum is actually developing in the maternal organism. A positive A.Z.R. is a sign that the body contains at the time highly active sources of those hormones, such as the placenta or its derivatives, or some other abnormally active tissue. The test has been proved to show a positive reaction in cases of retained adherent fractions of the placenta, incomplete abortion, hydatidiform mole, and chorion epithelioma. The test is also positive for a few days after normal parturition and complete abortion. On the other hand, the presence of an inactive (dead) placenta is not associated with the production of this hormone, and so the presence of a dead foetus and placenta does not lead to a positive result.

The distribution of positive and negative results among the 14 so-called incorrect diagnoses was as follows:

No.	A.Z.R.	Doctor.
13	...	+
1	...	+

Details of these cases are seen below in tabular form.

No.	Test	Dr.	Details.	Remarks.
5	-	+	Six months' amenorrhoea. Abdomen 3 months pregnant. No P.V. Doctor suggests missed abortion	? Dead ovum.
10	-	+	60 days after L.M.P. (last menstrual period) Later diagnosed as missed abortion	Dead ovum.
12	-	+	Macerated foetus delivered at 12 hours after urine taken	Dead ovum.
13	-	+	Same as 12	
2	-	+	No details	
11	-	+	No details	
14	-	+	No details	
8	-	+	60 days after L.M.P.	
9	-	+	36 days after L.M.P.	
6	-	+	45 days' amenorrhoea. Miscarried 1 month later	? Deficiency causing miscarriage.
7	-	+	41 days after L.M.P. 2 years ago had 1 ovary removed and both tubes excluded. Abortion 15 days after time of test	? Deficiency causing abortion.
3	-	+	Lactating. Baby 8 months. Repeated 2 months later. Positive	Lactating. ? Pregnancy came later.
4	-	+	43 days after L.M.P. Repeated 3 months later. Positive	
1	+	-	No menstrual irregularity. Breasts active. Young girl. Repeated 3 weeks later. Negative	? Endocrine disturbance.

The above table reveals that 5, 10, 12, and 13 were cases in which, at the time of taking the urine, the foetus was dead and the pregnancy ended.

Cases 2, 11, and 14 cannot be discussed, as no details of the histories were supplied.

Apparently the results given in Cases 8 and 9 were incorrect, but here again details of the subsequent course of each case are lacking, and so the station is left in doubt. Case 1 seems to have been mis-diagnosed, as the doctor attending the case says that there was no possibility of an abortion having taken place between the time of test 1 and test 2. It is to be noted that Case 1 is the only one where a positive result was questioned.

Cases 6 and 7 are associated with premature interruption of pregnancy some short time after the test was found negative. Recent findings show that the pregnant state and the maintenance thereof is necessarily associated with a great production of the hormones mentioned above, and it follows that if the production is insufficient then the pregnancy comes to an end. This seems to be exemplified in Cases 6 and 7, the negative result meaning that there is not sufficient hormone in the urine to affect the mouse ovary, and this deficiency in the maternal organism is such that pregnancy cannot go on. Thus abortion is precipitated.

It seems obvious from the details of the table that, of the 14 cases labelled incorrect, at least 4 cases (5, 10, 12, and 13) were so designated by the "sender" through a misunderstanding of the test. These cases were probably correctly diagnosed in so far as the test detects the presence of active products of conception. This means that the apparent percentage error of 3.04 is reduced to a real error of 2.2 per cent., and, were details available of Cases 2, 8, 11, and 14, this figure might be still further reduced.

Special Analyses.

The average age of pregnancy diagnosed was 69 days; 78 cases were within sixty days of the last menstrual period, and of these 2 were within nineteen days of the last menstrual period, and 2 within eight days of the first lapsed menstrual period. In 6 cases the history was more definite, and of these 5 were within forty days, and 1 within twenty-eight days, of the last coitus. It was also known in these cases that menstruation had been regular up to the time of that coitus.

In order that an idea may be formed as to the type of case in which the Aschheim and Zondek test is sought notes on a few cases are given.

Correct Negative Diagnosis.

(C. 4.) Married, aged 34; diminution of menses but no actual cessation. ? Two months pregnant or menopause.

(C. 5.) Unmarried; forty-seven days since last menstrual period; patient stout, breasts enlarged, uterus retroverted, cervix soft, some morning sickness. ? Pregnancy or menopause.

(G. 2.) Married; forty-seven days since last menstrual period; last baby six months ago.

(I. Z. 0.) Single, aged 22; sixty-two days since last menstrual period.

(I. Z. 9.) Married, aged 33; operation for ruptured ovarian cyst, uterus large. ? Pregnant.

(I. D. 4.) Married, aged 36; one hundred and ten days since last menstrual period; 3-para; patient very neurætic and convinced she is pregnant; has had several slight "shows."

(3. F. 2.) Married, aged 42; one hundred and fifty days since last menstrual period; 2-para; breasts enlarged; patient very stout and no fundus felt. ? Menopause or pregnancy.

(4. E. 8.) Married, aged 44; fifty-three days since last menstrual period; 1-para; menstrual history previously regular. Uterus contains a fibroid which might require surgical treatment.

(4. H. 8.) Married, aged 46; seventy days since last menstrual period; 3-para; uterus enlarged by one or more fibroids, but one part resembles the pregnant uterus in softness and size.

(0. K.) Married; some sickness for three to four months; swelling in the pelvis; said she felt foetal movements; no amenorrhoea, A.Z.R. negative, and abdomen opened and tuberculous mass found.

Correct Positive Results.

(I. 9.) Single, aged 22; sixty-two days since last menstrual period; patient becoming stout; question of pregnancy difficult to settle.

(I. E. I.) Married; seventy-seven days since last menstrual period; 2-para. Lost child five months ago. Is vomiting frequently and losing weight.

- (1. F. 0.) Married; forty-one days since last menstrual period; 3-para; sickness with enlargement of the breasts; not to be relied upon as patient wishes to become pregnant.
- (2. E. 4.) Married, aged 25; fifty-six days since last menstrual period; 1-para. ? Retroverted gravid uterus.
- (2. F. 7.) Married; sixty days since last menstrual period; has chronic salpingo-oophoritis; doctor thinks pregnancy unlikely.
- (2. I. 6.) Married, aged 40; seventy days since last menstrual period; 2-para; uterus abnormally enlarged. ? Fibroids or fibroids and pregnancy.
- (3. E.) Married; fifty days since last menstrual period; severe phthisis.
- (3. E. 2.) Married, aged 24; seventy-four days since last menstrual period; very severe vomiting. ? Hyperemesis.
- (5. C. 4.) Regular menstruation up to the time of operation for haemorrhoids; since operation (three months) had amenorrhoea. ? Pregnancy.
- (5. I. 1.) Single; fifty-six days since last menstrual period; had previously long period of amenorrhoea—up to ten weeks.

The test shows an error of 2.2 per cent. It has been suggested that this figure is not exceeded in the ordinary run of practice with the usual clinical methods. That may be so, but from the type of case sent for diagnosis it is fairly obvious that the station deals with cases which normally form the small percentage not easily diagnosed by purely clinical methods.

The biological importance of the test was obvious from the beginning, and it was for the station to show whether it could be applied on a practical basis, and at the same time maintain sufficiency and accuracy. Experience in working the station for one year shows that the test is quite capable of practical application under suitably organized conditions, and it is hoped that the report demonstrates that the test, if so applied, is a valuable diagnostic aid.

Conclusion.

The work of the station will be continued. During this first experimental year the fees were kept as low as possible, but it was found that the expenses were not covered, and a deficit was incurred. It has now been decided, therefore, that the fees will have to be increased as from March 7th. For private practitioners the fee will now be 10s. for each diagnosis; for hospitals and infirmaries 3s. It is hoped that the expenses will thus be covered and that a further increase will be avoided.

England and Wales.

Birmingham General Hospital.

THE 150th anniversary of the opening of the General Hospital, Birmingham, which occurred last year, was commemorated by a special service in the chapel, and subsequently by a choral service in the cathedral church of St. Philip. At the anniversary dinner in October members of the medical staff were the guests of the senior physician and senior surgeon. In the report for 1929 the executive board expresses the hope that it may be possible to start building the new hospitals centre at an early date. The scheme was outlined in the *British Medical Journal* of February 8th (p. 255). Co-operation with the Queen's Hospital has been strengthened by the interchange of liaison officers between the medical committees of the two institutions. The wards and casualty departments in course of erection on St. Mary's site are expected to be ready for occupation in the autumn. This extension has reduced the annual income of the hospital by over £2,000. As a result of a broadcast appeal in the early part of the year 600 mg. of radium were purchased by the hospital, which has now over thirty beds available for the radium treatment of cancer. Progress in this department was recognized by the National Radium Commission in selecting the General Hospital as a centre for treatment and research. The experiment of receiving paying patients is reported to have been entirely successful. In-patients during the year numbered 7,057, a decrease of 407. Out-patients increased from 55,003 to 57,838. In the social service department 134 children were helped in various ways. A convalescent home has recently been opened for children under 3 years of age. According to the forty-

fourth annual report of the Jaffray Branch Hospital, 368 patients were treated in 1929, 65 less than in the previous year. The number of beds is now sixty-five, which includes four cots.

Council Hospital Accommodation in London.

Under the Local Government Act there have passed under the direction of the Central Public Health Committee of the London County Council eleven fever hospitals (6,771 beds) hitherto directed by the Metropolitan Asylums Board; three "river hospitals" at Dartford (1,898 beds) for fever and small-pox; one hospital for ophthalmia neonatorum, marasmus, and zymotic enteritis (60 beds); two institutions for venereal diseases (103 beds); nine institutions for tuberculosis (2,057 beds); two for sane epileptics (705 beds); and five for children (1,992 beds). In addition, thirty Poor Law hospitals and infirmaries (17,022 beds), hitherto directed by boards of guardians, have come under the committee's control. To the Mental Hospitals Committee there have been transferred from the Metropolitan Asylums Board five hospitals or colonies (10,387 beds). In addition to the provision made for the treatment of sick persons in what have hitherto been known as Poor Law Hospitals, there is accommodation for sick persons in institutions which provide also for the able-bodied poor. The Central Public Health Committee finds the questions involved in the separation of the able-bodied poor from the sick, especially in view of the varying degrees of sickness, very difficult of settlement. It is thought desirable that two types of hospital should be recognized, one for the acute sick (including patients under continuous medical or surgical treatment, maternity patients, and mental patients), and the other for the chronic sick (including patients under institutional treatment because they are suffering from some chronic disease, and also aged and infirm persons requiring medical and nursing attention). Careful consideration has led to the belief that the present accommodation for the acute sick may be inadequate for future needs. In the institutions which now come under the Council's control there is what is described as a heterogeneous mass of chronic sick and aged and infirm persons, and it is not easy to define the degree of infirmity or disability in this group which places a person technically among the "sick." There can be no clear line of demarcation between the healthy aged and the infirm aged, the one gradually passing into the other; although the borderline case may not be technically "sick," it requires as much medical and nursing care as many serious maladies. The committee feels that there can be no doubt that a hospital standard of care and attention should be applied to all persons suffering from chronic disease and also to the aged and infirm. It is therefore proposed to allocate twelve institutions comprising 9,061 beds, for the chronic sick—namely, the Fulham, Hammer-smith, Kensington, Holborn, St. Pancras, Shoreditch, City of London, Hackney, Stepney, Camberwell, Greenwich, and Lambeth institutions. The accommodation controlled by the Central Public Health Committee and that controlled by the Central Public Assistance Committee here overlap. A certain amount of accommodation for "healthy" cases remains in hospitals under the direction of the former, and for chronic sick cases in institutions under the direction of the latter, but it is stated that time will be necessary for reorganization and re-classification, and that the present allocation must be regarded as provisional only.

Royal Free Hospital.

At the annual court of governors of the Royal Free Hospital, on March 25th, under the chairmanship of Lord Riddell, the American Ambassador paid a tribute to the humanitarian work of the hospital. Its policy, he said, considered the actual needs of every person requiring treatment, whatever his status or race. He also referred to the service the hospital had rendered to Americans in London. Most of the matters discussed in the 102nd annual report have already been mentioned in these columns. The foundation stone of the Eastman dental clinic was laid by the Prince of Wales last April, and the building is expected to be ready in May. Arrangements