Diagnostic Pregnancy Tests in Patients Treated with Tranquillizers

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Early diagnosis of pregnancy is often important and occasionally extremely difficult, especially in subjects with mental disorders. Fear of pregnancy after sexual intercourse may result from or be the cause of amenorrhoea, and in either case may lead to severe anxiety or more serious psychological illness. Delusions of pregnancy, with or without signs of pseudopregnancy, are not uncommon, and are a further source of confusion.

Diagnosis of pregnancy may be impossible by physical examination alone for the first few weeks after conception, and speed may be important if serious psychiatric breakdown is to be prevented or therapeutic abortion contemplated. In these cases, therefore, reliance may be placed upon laboratory pregnancy tests. In the past these depended upon the detection of increased chorionic gonadotrophic activity in urine or blood by animal inoculation. The value of such biological tests in the early recognition of both normal and abnormal pregnancies is well established, but all have proved unreliable in patients with psychiatric disorders (Hilbert, 1958 ; Hodgson, 1959 ; Brillhart, 1959 ; Russo and Souza, 1961 ; unpublished observations), especially during treatment with tranquillizers —for example, phenothiazines—when up to 75% of tests yield false-positive results (Foxworthy and Lehman, 1957). The introduction of an immunological test for pregnancy (Wide and Gemzell, 1960) differing in principle from previous pregnancy tests offered new hope of early and accurate diagnosis without the necessity for interrupting tranquillizer therapy as had formerly been advocated (Brillhart, 1959).

A trial of three commercial pregnancy tests in psychiatric patients receiving phenothiazines was begun in 1962. A preliminary account has already appeared (Marks and Shackcloth, 1963).

Materials and Methods

Preliminary investigations were carried out on 55 chronic hospital in-patients receiving various tranquillizers in moderate-to-large amounts, and who were known not to be pregnant. "Early morning" urine specimens were examined by each of the three different commercially available immunological pregnancy tests (Ortho pregnancy test, Pregnosticon, Prepuerin) according to the manufacturers' instructions, and by the Hogben test.

The preliminary investigations indicated that interference with the immunological pregnancy tests by tranquillizing drugs was slight or not at all, and clinicians using the laboratory's diagnostic facilities were advised that it was no longer necessary to discontinue drug therapy for 48 hours before making the test. A trial was carried out on 324 patients in psychiatric hospitals in the area, with the same three commercial preparations as before, except that Gravindex was substituted for the Ortho test soon after the trial began. "Early morning" urine specimens were examined, but where the urine was more than eight hours old, was contaminated with blood or bacteria, or had a specific gravity of less than 1010 a further specimen was requested.

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In reporting the result it was pointed out that a negative result was inconclusive if less than 38 days had elapsed since the last menstrual period.

Requests for follow-up information, including details of drug therapy at the time of the test, were sent three to six months after the original report. Replies were received in respect of 241 patients.

Results

In the preliminary investigation negative results were obtained with all three immunological tests in each of the 55 non-pregnant hospital patients. The Hogben test was negative in 54 and falsely positive in one—an 18-year-old mentally subnormal woman receiving 300 mg. of chlorpromazine a day.

Of 241 patients in the main trial for whom follow-up data were available 158 were correctly reported as non-pregnant and 79 as pregnant, of whom 17 underwent therapeutic abortion. Three patients were incorrectly reported as pregnant, and in one case there was some uncertainty whether the woman had procured an illegal abortion. No case was incorrectly reported as non-pregnant.

The ages of the pregnant and non-pregnant group showed similar distributions, but there were larger numbers of non-pregnant patients at both extremes of the child-bearing period (Table I).

TABLE I.—*Age Distribution of 237 Patients Undergoing Diagnostic Urine Pregnancy Tests*

Age:	11–15	16–20	21–30	31–40	41–50	51–60	Unknown
Pregnant ..	0	11	35	20	6	0	7
Non-pregnant	3	25	58	34	14	3	21

Most patients (77%) were receiving one or more psychotropic drugs. Chlorpromazine was the commonest, being given alone or in combination to more than half the patients. Doses were usually between 300 and 400 mg./day, but ranged from 100 to 1,200 mg. day. The type and amount of drugs received by pregnant and non-pregnant subjects (Table II) were similar.

TABLE II.—*Drug Therapy in Patients Undergoing Diagnostic Urine Pregnancy Tests*

	None	1 Drug	2 Drugs	3 Drugs	4 Drugs	5 Drugs
Pregnant ..	25	27	22	3	0	1
Non-pregnant ..	33	64	36	19	3	2

The results of three different immunological tests agreed in the majority of cases but were discordant in 16 (Table III). All the patients in this group for whom information is available were receiving one or more psychotropic drugs.

The commonest cause for requesting a diagnostic urine pregnancy test was amenorrhoea of from 5 to 150 weeks' duration, but in a substantial proportion (10%) of the cases (Table IV) menstruation had occurred less than 35 days earlier, when the patient's fear or delusion of pregnancy, rather than

evidence of it, was the reason for making the request. It was perhaps not so remarkable that all of the tests carried out under these circumstances were negative as that none of the patients was in fact pregnant.

TABLE III.—*Discrepant Results Obtained with Three Different Immunological Urine Pregnancy Tests*

	Age	Gravindex	Pregnosticon	Prepuerin	Drugs: mg./day	Comment
			11 *Patients Correctly Reported as Not Pregnant*			
1	21	Negative	Positive	Negative	Thioridazine, 200 mg.	
2	33	,,	,,	,,	Chlorpromazine, 15 mg.	
3	27	,,	,,	,,	Chlorpromazine, 150 mg.	
4	36	Positive	Negative	,,	Trifluoperazine, 15 mg. Orphenadrine, 100 mg.	
5	28	Doubtful	,,	,,	Trifluoperazine, 15 mg. Isocarboxazide, 20 mg.	
6	31	Positive	,,	,,	Chlorpromazine, 1,200 mg.	All 3 tests negative 2 months earlier
7	44	Negative	Positive	,,	Unknown	Pregnosticon still positive after dilution 1 : 2
8	34	,,	,,	,,	Promazine, 300 mg.	
9	23	Positive	Doubtful	,,	Chlorpromazine, 150 mg.	All 3 tests negative 6 days later
10	30	Positive*	Negative	,,	Chlorpromazine, 300 mg.	All 3 tests negative 5 days later
11	27	Positive*	,,	,,	Chlorpromazine, 300 mg. Phenelzine, 45 mg.	
			3 *Patients Correctly Reported as Pregnant*			
12	24	Negative	Positive	Positive	Unknown	
13	42	Positive	Negative	,,	Imipramine, 150 mg.	
14	32	Negative	Positive	,,	Chlordiazepoxide, 10 mg.	Urine specimen contaminated with staphylococci
			3 *Patients Incorrectly Reported as Pregnant*			
15	—	Not done	Positive	Positive	Chlorpromazine, 300 mg.	
16	23	Positive	,,	Doubtful	Thioridazine, 200 mg.	
17	33	Not done	,,	Not done	Primidone	

* Ortho pregnancy test.

TABLE IV.—*Interval Between Last Menstrual Period and Pregnancy Test*

Weeks:	3	4	5	5–7	8–10	10	Unknown
Pregnant ..	0	0	0	11	15	32	21
Not pregnant	7	4	6	38	19	21	63

False Positives

In one subject, incorrectly reported as pregnant, the error lay in the interpretation of the results rather than in technique. In two cases urine pregnancy tests were unequivocally positive, but confirmation of pregnancy was not obtained. Though spontaneous abortion occurring soon after the test and masquerading as a "normal" period could not be excluded, it seemed unlikely. The first patient was a 32-year-old woman being treated with 300 mg. of chlorpromazine a day for an affective disorder following an incestuous relationship with her brother. Though a second pregnancy test (type unknown) carried out elsewhere was reported as positive, her subsequent menstrual history was normal. The second patient was a 33-year-old mentally subnormal woman with three months' amenorrhoea who admitted to sexual intercourse on several occasions before and during that time. A Pregnosticon pregnancy test was reported as positive (the other two tests were not carried out), but shortly afterwards the patient menstruated. The loss was smaller and of shorter duration than usual. A second pregnancy test 10 days later was negative. The next two periods were scantier than usual, but gynaecological examination revealed no evidence of missed or incomplete abortion, and menstruation subsequently returned to normal without further treatment.

Discussion

Immunological urine tests for pregnancy have gained wide acceptance in obstetric and general practice. Their chief advantages over biological pregnancy tests are their ready availability, ease of performance, and greater sensitivity, enabling earlier detection of trophoblastic tissue, which is of especial importance in ectopic pregnancies. A major disadvantage is their tendency to yield false-positive results, which are claimed to be exceedingly rare with the best of the biological techniques (Hobson, 1963).

The situation is somewhat different in psychiatric patients treated with phenothiazines, when most, but not all (Batrinos *et al.*, 1961 ; Bueno, 1962), authors report such a high incidence of false-positive pregnancy tests by traditional biological methods as to make them virtually useless (Foxworthy and Lehman, 1957 ; Hilbert, 1958 ; Hodgson, 1959 ; Brillhart, 1959).

The cause of false-positive pregnancy tests in phenothiazine-treated patients is unknown. They are not due to early, but non-viable, pregnancies which end in spontaneous abortion, since they are as common in men and post-menopausal women as in women of reproductive age. Nor are they due to a direct effect upon the test animal of unchanged drug excreted in the urine. The excretion by the patient of a drug metabolite with gonadotrophic activity for the test animal is possible but unlikely. A more plausible explanation is that under the influence of certain psychotropic drugs—especially in psycho-sexually deranged subjects—there is increased production and excretion of an endogenous gonadotrophic substance with immunological properties similar to human chorionic gonadotrophin (H.C.G.) (Barnett, 1963).

In the past it was assumed that increased secretion of pituitary follicle-stimulating hormone (F.S.H.) might account both for some of the clinical side-effects of phenothiazines and the high incidence of false-positive pregnancy tests, but both Batrinos *et al.* (1962) and Ciprut *et al.* (1962), failed to find consistent changes in F.S.H. excretion in women during treatment with phenothiazines despite obvious clinical side-effects in some cases. Furthermore, F.S.H. does not cross-react with anti-H.C.G. and would not be expected to produce false-positive immunological pregnancy tests even if its excretion were increased. Pituitary luteinizing hormone (L.H. ; I.C.S.H.), on the other hand, cross-reacts (Butt *et al.*, 1961) with anti-H.C.G., suggesting that its increased secretion might be responsible for false-positive pregnancy tests by both biological and immunological techniques. Support for this suggestion comes from observations by Sulman and Winnik (1956) that, in man, chlorpromazine causes a measurable non-sustained increase in urinary L.H. activity.

The practical implications of the present study are that pregnancy can be diagnosed in phenothiazine-treated subjects with a high degree of certainty, provided a suitable immunological technique is used. While this requirement was best met in the present study by Prepuerin (Table III), it would appear advisable, where accuracy is of paramount importance, to use at least two different tests and to investigate further those patients in whom the results are discrepant.

Summary

Urinary pregnancy tests with three commercially available immunological preparations were carried out on 324 patients, the majority of whom were receiving phenothiazine or other psychotropic drugs. Follow-up data were available on 241. Of these, 79 were correctly reported as pregnant and 158 as non-pregnant. Three were incorrectly reported as pregnant, and in one the evidence was inconclusive. Discrepant results were obtained in 16 patients. The most reliable results were obtained with Prepuerin, but it is recommended that at least

two different kinds of test should be used routinely in patients receiving phenothiazine treatment.

Increased production and excretion of pituitary luteinizing hormone is suggested as the possible cause of false-positive immunological and biological pregnancy tests in phenothiazine-treated subjects.

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Low-protein Purine-free Diet in Treatment of Acute Leukaemia in Children: Preliminary Communication

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When considering the clinical symptoms accompanying responses or resistance to therapy in acute leukaemia of children our attention was drawn to the behaviour of the liver. Cases with symptoms of hepatic dysfunction manifested by low pre-albumin and albumin levels, raised gamma-globulin, and low plasma cholesterol levels, persisting or developing in the course of treatment, were found to have a bad prognosis (Halikowski *et al.*, 1965; Mejbaum-Katzenellenbogen *et al.*, 1965).

In 26 cases of acute leukaemia in children treated by standard methods (1962–4) negative correlation was found between the size of the liver (in centimetres below the costal margin) at the beginning of treatment and the survival time (Fig. 1).

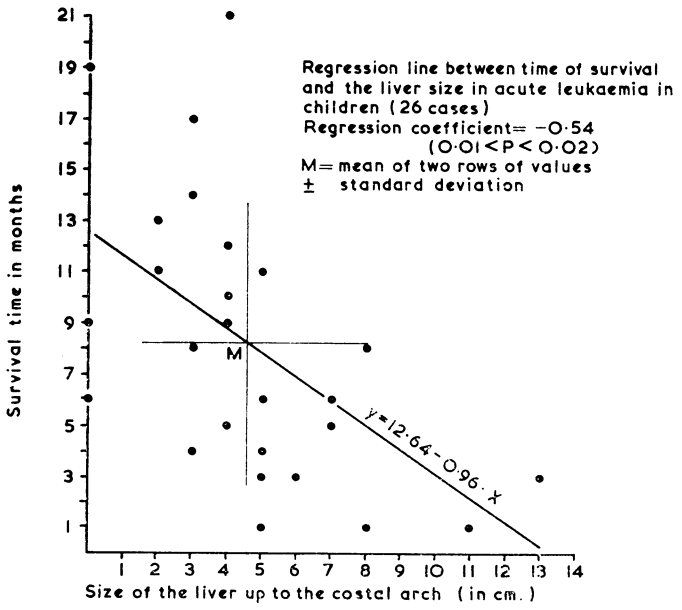

FIG. 1

Working Hypothesis

The hypothesis was proposed that response to treatment might be dependent on hepatic function. One of the disorders connected with hepatic dysfunction may consist in enzymatic block of the metabolic processes involved in syntheses occurring in the bone-marrow.

In acute leukaemia the outstanding feature of the clinical picture is bone-marrow insufficiency with aplastic symptoms. Low erythroblastosis, absence of normal development of the bone-marrow granulocytes, and pancytopenia in the peripheral blood are regularly met with. This raises the question whether these changes are not an expression of the basic lesion in acute leukaemia, while proliferation of pathologic cells is secondary.

The hypothesis of enzymatic blocking has already been proposed by Haddow (1954) and Osgood (1957).

In various countries the incidence of leukaemia and consumption of animal protein seem to be correlated. Statistical data tend to show a rise in the incidence of leukaemia in the higher income groups. This seems to be true not only in special population groups but also in different countries. It is widely known and generally accepted that protein consumption (especially animal protein) is a good indicator of the standard of living. The greater incidence of leukaemia in countries with a high protein consumption may be fortuitous, or it may be connected with a third factor or be due to a variety of causes. In the latter case high protein consumption, the content of certain amino-acids, or other factors associated with high protein consumption (purines) may be responsible.

The hypothesis of the part played by the liver in the disease, as well as the above-mentioned epidemiological observations, seems to make acceptable the possibility that some sort of "narrow throat" in metabolic pathways may, with other factors, be characteristic of a pre-leukaemic state. When excessive loading with the substrate occurs the full picture of the disease may develop.

As a result of a reduced supply of substrate, low-protein purine-free diet may diminish the effects of enzymatic block and thus act as a factor in the maintenance or resumption of normal development of bone-marrow cells.

Clinical Trials with Low-protein Purine-free Diet

On the basis of this working hypothesis low-protein purine-free diet has since October 1964 been introduced as an adjunct to the routine therapy of acute leukaemia in children.

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