Important factors in assessing the appropriate daily maintenance dose within the range of 50 to 175 mg. are the weight, age (apparent rather than real), general health, and renal function. The more robust, young, and less acutely ill patients require the largest doses, whilst the frail, elderly, and severely ill cases need the smallest maintenance doses. Any lowering of renal function will materially reduce the amount of phenylindanedione required.

Once the daily maintenance dose has been established, this dose can be continued for a prolonged period without any significant fluctuation in the prothrombin times. (With improvement in a severely ill patient's general condition, a small increase in the daily maintenance dose may sometimes be necessary.) This uniform action of phenylindanedione means that in most cases, once the daily maintenance dose has been established, prothrombin estimations are necessary only twice or, at the most, three times a week. (In patients on prolonged therapy, prothrombin estimations weekly or less often are usually enough.)

No toxic effects from phenylindanedione were encountered in this series. In a small series of seven cases reported previously, the giving of much larger doses than those required to maintain an adequate therapeutic prothrombin level resulted in haemorrhage in one case only and no other toxic reactions. This haemorrhage and the severe prothrombin deficiency seen in the other six cases were quickly controlled within eight to twenty hours by vitamin K₁ given orally.

The total daily dose of phenylindanedione in each case was given in two divided amounts, morning and evening. In most cases it turns the urine a pinkish-orange colour.

I wish to thank Charles E. Frosst and Co. (Canada) for the initial supplies of phenylindanedione ("danilone") and also Evans Medical Supplies Ltd. for additional amounts of the drug ("dindevan"). I also wish to express my gratitude to Dr. E. Lozinski, of Charles E. Frosst and Co., for his help and advice.

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Robert James Graves, who died on March 20, 1853, is best remembered to-day for his accurate account of exophthalmic goitre (1835). Although earlier descriptions of the condition were given by Flajani (1802) and Parry (1815), it is best known in Britain as "Graves's disease." He was one of the founders of the Park Street School of Medicine in Dublin. While physician to the Meath Hospital he introduced Continental methods of clinical teaching with good effect. Graves qualified in 1818 and then studied in London and on the Continent. When he was in Austria his fluency in languages led him to be taken for a German spy and he was imprisoned for ten days. During a journey from Genoa to Sicily the ship in which he was travelling ran into a storm and the crew threatened to abandon ship. Graves seized an axe and smashed the ship's boat; he then assumed command and repaired the pumps with leather from his own boots. Graves contributed many papers to medical literature. His *Clinical Lectures on the Practice of Medicine*, 1848, is considered his best work.

TREATMENT OF NAUSEA AND VOMITING OF PREGNANCY WITH ANTIHISTAMINES

BY

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During the past few years good results have been reported from the use of antihistamine preparations in nausea and vomiting of pregnancy. Dougray (1949) recorded 94 cases thus treated, with 83% cured, and Carliner *et al.* (1949) reported on 43 patients treated with dimenhydrinate ("dramamine"), with 72% cured. At St. Andrew's Hospital during the past three years a large proportion of patients complaining of nausea and vomiting in pregnancy were freed from these symptoms by taking an antihistamine preparation. So successful was this treatment that it was extended to patients who complained mainly of heartburn, with equally gratifying results. After some months it was decided to make a clinical trial, treating one group of patients with an active antihistamine preparation and another group with an inert preparation.

Method

Although all patients were questioned as a routine on vomiting in pregnancy, only those who specifically complained were treated. Cases were divided into three groups: severe vomiting, in which vomiting occurred at frequent intervals during the day or caused the patient a good deal of distress; occasional vomiting, in which vomiting was not frequent and regular and did not unduly distress the patient; and cases in which heartburn and nausea were the predominant symptoms. No attempt at clinical assessment was made, apart from excluding any obvious non-obstetric cause of vomiting, and the patient's own statement was the guide to the group in which she was placed. As the element of suggestion plays a part in the treatment of these patients, and some patients will respond to any form of therapy, it was decided to include only those who had already received some other form of treatment without improving.

Two antihistamine preparations were used, both in tablet form: mepyramine maleate ("anthisan"), 100 mg., and promethazine-8-chlorotheophyllinate ("avomine"), 25 mg. They appeared to be equally effective. The control tablets contained lactose only, and were identical in size and shape, and almost identical in colour with the active tablets. Patients were divided into two groups of 60; one group was treated with antihistamine tablets and the other group with the inert tablets. The tablets were collected from the hospital dispensary and enough for three days' treatment were given. Patients were instructed to take a tablet at night before retiring. This routine was altered occasionally for those whose symptoms were particularly troublesome at a set time—for example, after the evening meal or after getting into bed at night. These patients were instructed to take the tablet about two hours before the expected time of onset of the symptoms.

Patients were seen five days later at the antenatal clinic. Those who were free from symptoms while taking the tablets were classified as cured; others were classified as improved or unchanged. The short period of three days for treatment was chosen because experience had shown that patients who were going to benefit by the treatment did so almost immediately. There was also the additional factor that by giving a short course of treatment and by

seeing the patients soon afterwards there was less risk of their forgetting the facts or becoming confused about details.

Results

Of the 60 patients who were treated with an active antihistamine preparation, 47 reported themselves as cured and six as improved. Thus 88% were either cured or improved by the treatment. In the control group, three patients regarded themselves as cured and four as improved, a total of 10%. Table I shows that no case of severe vomiting

TABLE I.—Results of Treatment

Treatment	No. of Cases	No. Cured	No. Improved	No Change
<i>Severe Vomiting</i>				
Antihistamine ..	31	25	2	4
Inert tablet ..	33	—	—	33
<i>Moderate Vomiting</i>				
Antihistamine ..	17	12	3	2
Inert tablet ..	16	2	4	10
<i>Nausea and Heartburn</i>				
Antihistamine ..	12	10	1	1
Inert tablet ..	11	1	—	10

was affected by an inert preparation, and that it was in the cases of moderate vomiting that the inert tablets had most effect.

Most of the patients in the control series were subsequently treated with antihistamines, when they showed a higher proportion of cured and improved (Table II). Thus

TABLE II.—Control Cases Subsequently Treated with Antihistamines

No. of Cases	No. Cured	No. Improved	No Change
50	43	3	4

out of 50 of these patients treated 86% were cured, 6% were improved, and only 8% showed no change. With this group, however, other factors may have affected the results. These patients were being treated at a somewhat later stage in pregnancy, and it was possible that time was effecting a cure. Also, as the antihistamine tablets they subsequently received were of a brighter colour than the inert tablets, they may well have deduced that they were receiving a more potent preparation, and so the factor of suggestion may have influenced the results.

In most cases three days' treatment was insufficient to effect a permanent cure, and it was necessary to continue treatment for at least a fortnight, and sometimes for four weeks. No other treatment was given and no dietary restrictions were imposed. No adverse effects were noted from even a prolonged course, although occasionally some patients complained of drowsiness.

Comment

The causes of nausea and vomiting in pregnancy are not known, and it is therefore a matter of speculation why the antihistamines give relief. Finch (1938) suggested that nausea and vomiting of pregnancy are due to an allergic tendency, and that the patient had become sensitized to some secretion of her own corpus luteum. He carried out intradermal tests with corpus luteum extract and found that the reaction produced was in direct proportion to the degree of nausea and vomiting present. Kapeller-Adler and Adler (1943) have shown that there is an increased histamine production by the body in pregnancy. They suggest that, whereas in normal pregnancies the serum is able to inactivate histamine, in cases of hyperemesis gravidarum and mild pre-eclampsia the serum has lost this power and

in consequence there is an excess of histamine in the body, and it is this excess which is responsible for the disturbed gastric function.

These theories offer some explanation for the mode of action of the antihistamines. On the other hand, it is well recognized that most of the drugs used for their antihistamine properties have some depressant action on the central nervous system, and it is possible that they exert their influence by lowering the sensitivity of the vomiting centre.

Some of the patients who did not respond to treatment improved after the dosage was increased or when a more powerful form of antihistamine such as promethazine hydrochloride, 25 mg. twice daily, was given. This confirms Dougray's experience, although he found it necessary to give a higher dosage.

A number of patients had a recurrence of symptoms in the latter weeks of pregnancy, and these were all successfully treated with antihistamines. It is occasionally taught that vomiting late in pregnancy is of serious significance, but in the absence of any evidence of pre-eclampsia this is not so.

Summary

A number of patients suffering from gastric disturbances in pregnancy were treated with antihistamine preparations and an equal number were given an inert preparation. The results showed that a high proportion of patients obtained relief with the antihistamines and only a small proportion were relieved with the inert preparation.

My thanks are due to Messrs. May and Baker for a generous supply of avomine tablets and for supplying the inert tablets.

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ACUTE NITROBENZENE POISONING WITH TRANSIENT AMINO-ACIDURIA

BY

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Many cases of nitrobenzene poisoning have been recorded. The majority of these have been due to accidental ingestion, contact, or inhalation, especially in industry. The case reported here was the result of a deliberate attempt at suicide and showed the usual characteristic manifestations of methaemoglobinaemia. There was also a marked transient amino-aciduria.

Case Report

A married woman aged 24, living apart from her husband and 4-year-old son, became depressed and decided to commit suicide. At 11 a.m. she swallowed "about half a bottle" of a bee mixture, which was clearly labelled as a poison. So far as could be ascertained later, she drank about 1 oz. (28 ml.) of this mixture, which contains nitrobenzene (or oil of mirbane) 2 parts, safrol oil 1 part, and petrol 2 parts. Therefore she may have swallowed almost 200 minims (12 ml.) of nitrobenzene.

She found the taste of the mixture most unpleasant and noted a burning sensation in her mouth. Half an hour