value of the 35–64-year-old male patients decreased from 236 mg. to 215 mg. per 100 ml. serum. This decrease was statistically highly significant.

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EARLY SYMPTOMS OF PRE-ECLAMPTIC TOXÆMIA

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IN previous work on pre-eclamptic toxæmia certain warning symptoms were noted well in advance of any signs (Dalton 1954). This finding has since been corroborated in the course of trials of the prophylactic value of progesterone. Patients between the 16th and 28th weeks of pregnancy were asked " Do you feel as well now as before you became pregnant? "; and the subsequent history of the pregnancy has been found to differ in those who said " yes " and those who said " no ".

At the antenatal clinic of the Obstetric Hospital, University College Hospital, London, between the years 1955 and 1958 the registrars put this question to 386 patients attending for routine examination at the 16th or 28th week (first series); and in 1958 I questioned 247 patients attending for examination at any time between the 16th and 28th weeks of pregnancy (second series). Patients who said that they felt less well than before their pregnancy were asked if this was due to nausea and vomiting, headaches, backaches, vertigo, fainting, paræsthesia, or lethargy. In the second series those with symptoms were also asked if they felt depressed, and in addition a note was made of those patients who felt better than usual.

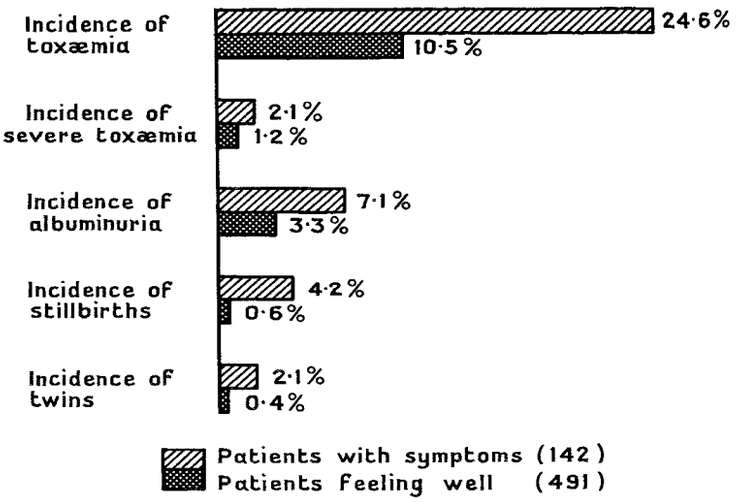
In this investigation pre-eclamptic toxæmia was diagnosed if a woman, previously free from hypertension and albuminuria, was found after the 28th week to have a blood-pressure of 140/90 mm. Hg or over, with œdema or with albumin in a catheter specimen.

Results

Of the 670 patients who were questioned 12 were excluded because antenatal care was not completed (abortion or cancelled booking) and 25 had a blood-pressure of at least 140/90 before the 28th week. Of the remaining 633, 491 (78%) said that they felt well and 142 (22%) had symptoms. The striking difference in the incidence of toxæmia in these two groups is shown in table I: of the women who had symptoms between the 16th and 28th week, one in every four developed toxæmia, compared with one in every ten who had felt well.

TABLE I—INCIDENCE OF TOXÆMIA

Patients	Series	Toxæmia	Normal	Total
With symptoms	1st	13 (25%)	38	51
	2nd	22 (24%)	69	91
	Total	35 (25%)	107	142
Feeling well	1st	34 (10%)	301	335
	2nd	18 (12%)	138	156
	Total	52 (11%)	439	491



Differences between patients with symptoms and those feeling well between the 16th and 28th weeks of pregnancy.

The figure shows that the patients with symptoms during the middle trimester also had double the incidence of a more severe grade of toxæmia (with a blood-pressure of at least 140/90 mm. Hg, and both œdema and albuminuria), double the incidence of albuminuria, a higher stillbirth-rate, and more twin pregnancies. The incidence of œdema was not significantly different (33% in patients with symptoms compared with 37% in patients feeling well).

TABLE II—SYMPTOMS IN THE MIDDLE TRIMESTER

—	Toxæmia	Normal
Nausea and vomiting (142 patients)	65%	71%
Headache (,, ,,)	35%	42%
Backache (,, ,,)	44%	51%
Lethargy (,, ,,)	88%	78%
Vertigo (,, ,,)	26%	20%
Fainting (,, ,,)	12%	9%
Paræsthesia (,, ,,)	46%	30%
Depression (91 patients)	52%	50%

In the second series 33 patients (13%) said they had felt better than usual since becoming pregnant. Of these 3 (9%) developed toxæmia, and 1 (3%) developed albuminuria; there were no stillbirths or twins and 13 patients (39%) developed œdema. Thus there was little difference between the patients who felt well and those whose wellbeing had actually improved with pregnancy.

142 women complained of symptoms, and little difference is apparent in the symptoms of those who afterwards developed toxæmia and those who did not (table II).

An analysis of the number of symptoms suggests that these women did not lightly complain; for 94% had at least two unrelated symptoms, 71% had three, and 48% had at least four. At another London maternity hospital, I found that 72% of 136 patients had three or more unrelated symptoms and 51% admitted to four or more (Dalton 1957).

In the second series some patients were interviewed more than once. Of 74 patients with symptoms on only one occasion, 20% developed toxæmia, whereas among the 17 whose symptoms persisted from one interview until

the next (a month later) 41% did so. The series was also analysed as regards the duration of pregnancy at the time of the interview; but no difference was found in the incidence of toxæmia among patients with symptoms and among those feeling well at the 4th, 5th, or 6th month of pregnancy.

Discussion

The presence of symptoms between the 16th and 28th weeks of pregnancy suggests that the factor responsible for pre-eclamptic toxæmia is already operating many weeks before the development of signs. Further it suggests that in any patient who has symptoms—even if there are no signs and no excessive gain in weight—prophylactic treatment of toxæmia should begin during the middle trimester. The similarity in type and distribution of symptoms among those patients afterwards developing toxæmia and in those whose pregnancies proceed normally suggests that the patients with continuing symptoms may have subclinical toxæmia.

Summary

In a series of 633 patients one in every four women with symptoms between the 16th and 28th weeks of pregnancy subsequently developed toxæmia, compared with one in every ten women who were feeling well during these middle months. Those with symptoms during the middle trimester also had a greater incidence of albuminuria, stillbirths, and twins. It is suggested that patients with symptoms during pregnancy should be treated with a toxæmic prophylactic regime even in the absence of signs or excessive weight gain.

It is a pleasure to express my thanks to Prof. W. C. W. Nixon for allowing me to carry out these trials in his hospital and to his registrars for their assistance, and to Prof. D. D. Reid for his statistical assistance.

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ANTITUBERCULOUS THERAPY COMBINED WITH ADRENAL STEROIDS IN THE TREATMENT OF PLEURAL EFFUSIONS

A CONTROLLED THERAPEUTIC TRIAL

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SEVERAL authors have reported favourably on the use of adrenal steroids combined with antituberculous drugs in the treatment of tuberculous pleural effusions (Sors and Trocmé 1954, James 1956, Aspin and O'Hara 1958), but as far as we are aware no controlled therapeutic trial has so far been carried out. Such a trial was designed to evaluate this method of treatment in African mine labourers employed in the goldmining industry of the Witwatersrand, among whom pleural effusions are relatively common.

In selecting cases for the trial we were faced with the difficulty that some medical officers concerned with the care of African mine labourers doubt whether tuberculosis is the major cause of pleurisy with effusion in this population. This view is based on the fact that it is unusual to isolate tubercle bacilli from the pleural fluid. Because of the extremely high incidence of pneumonia among these patients, some doctors are of the opinion that a substantial number of cases are postpneumonic in origin. Others consider that scurvy, which is not rare, may account for those effusions which are hæmorrhagic (approximately a third of the total). Nevertheless, we regard the majority of cases, including the hæmorrhagic ones, as tuberculous. This is supported by the high incidence of tuberculosis in these labourers, by the thoracoscopic findings (Fleishman et al. 1956), and by the follow-up study of Stott and Brass (1955). The diagnosis of tuberculous pleural effusion in the cases entering the trial was based, therefore, on evidence which, though presumptive, is generally regarded as sound. This evidence has been reviewed by Roper and Waring (1955).

It is for these reasons that the trial included four different methods of treatment—namely, ascorbic acid, penicillin, standard antituberculous therapy, and standard antituberculous therapy combined with adrenal steroids. It was hoped that the inclusion of groups receiving ascorbic acid and penicillin, while acting as bases from which to judge any improvement effected by the other two methods of treatment, would shed some light on the role of scurvy and of pneumonia in the pathogenesis of the cases studied.

Design of the Trial

From June 1, 1957, to September 26, 1958, all cases of pleural effusion which occurred among the African labourers employed by one group of mining companies were admitted to a central hospital as soon as the diagnosis was confirmed by X-ray examination of the chest and by aspirating 20 ml. of fluid from the pleural cavity. Referring medical officers were requested to limit the paracentesis to 20 ml. so that the possible beneficial effects of removing larger amounts were avoided. Although the disadvantages of examining so small a quantity of fluid were realised, it was nevertheless submitted to full examination including a culture and a biological test for tubercle bacilli.

On admission to the central hospital a full clinical examination was carried out and another X-ray film of the chest taken for confirmation. Patients showing evidence of pulmonary tuberculosis or of any pathology other than the effusion were rejected. In addition, a few cases with cervical or other adenopathy, abdominal masses, and vitamin deficiency were excluded. Consequently those admitted to the trial could be described as suffering from pleural effusion for which no obvious clinical or radiological cause was evident. A blood count, erythrocyte-sedimentation rate (E.S.R.) (Wintrobe), Mantoux skin test (Koch's old tuberculin 1/1000), and sputum examinations completed the initial investigations.

A panel of 5 doctors allotted a score to the effusion ranging from 1 to 4, depending upon whether it was judged to occupy $^1/_4$, $^1/_2$, $^3/_4$, or the whole of the hemithorax respectively. Occasionally it was found necessary to allot $^1/_2$ scores—e.g., $2^1/_2$. Minimal effusions were not accepted. Sealed instructions for treatment were previously prepared, and as each case was admitted to the trial a member of the hospital clerical staff drew one, so that the following four methods of treatment were allocated at random:

Treatment V. 500 mg. of ascorbic acid intramuscularly daily for the first 14 days only.

Treatment P. 300,000 units of procaine penicillin intramuscularly twice daily for the first 14 days only.

Treatment T. 1 g. of streptomycin sulphate intramuscularly daily for 8 weeks. 200 mg. of isoniazid three times daily for 8 weeks.