THE EPILEPTIC IN RELATION TO PREGNANCY*

BY

HELEN DIMSDALE, M.D., F.R.C.P.

*Neurologist, Royal Free Hospital; Assistant Physician,
Maida Vale Hospital for Nervous Diseases, London*

The modern management of epilepsy, which combines the use of improved anticonvulsants with a more sympathetic attitude towards the disability, encourages the epileptic to live a normal life in the community. Opportunities for the epileptic to marry are increased by the widening of their social contacts, and less emphasis is laid on the risk of direct inheritance of epileptic fits. Pregnancy in the epileptic is therefore likely to become a more common therapeutic problem, and it is important to know what treatment is necessary to control epileptic attacks during gestation.

What is the definition of epilepsy? Williams (1958) has suggested that a patient has epilepsy when the attacks recur without a demonstrable independent cause. General epilepsies consist of petit mal and grand mal, which, although so different in their clinical manifestations, are both forms of genetic epilepsy and show electroencephalographic (E.E.G.) similarities, in that the disturbances are symmetrical and synchronous in the hemispheres. Partial or focal epilepsy is characterized by a focal onset both in the clinical manifestation and in the E.E.G. features. Suter and Klingman (1957) found that focal E.E.G. abnormalities were present more commonly when attacks began with pregnancy than in patients who had a previous history of epilepsy and showed an increase of fits during pregnancy.

Burnett (1946) reviewed the statistics from the literature and stated that about a third of pregnant epileptics showed an increase of fits. The neurologist tends to see patients with gestational epilepsy or those whose epilepsy has increased in severity, and so has the impression that deterioration is the usual result. However, many patients get through a pregnancy without ill effect and occasionally amelioration results, perhaps due to better therapy. Curious case histories are on record in which a patient may have epileptic attacks when pregnant with a male child but not with a female. Endocrine factors have been postulated, but the cause is quite unknown. As might be expected, a patient with menstrual epilepsy, which indicates a sensitivity of the seizure threshold to metabolic changes, tends to have fits in pregnancy, and these may become more severe.

Deterioration in Pregnancy

The exacerbation of a previously unsuspected genetic epilepsy with menstrual manifestations is illustrated by the following case history.

A woman aged 22 suffered from severe dysmenorrhoea associated with a short episode of disturbance of consciousness which had been regarded as a form of faint. When pregnancy occurred it was hoped that it might

ultimately prove beneficial for her menstrual disorder. However, she developed major attacks when 22 weeks pregnant, the E.E.G. was characteristic of genetic epilepsy, and a family history of epilepsy was obtained. She was treated by rest, sedation with hydantoinate, and phenobarbitone or methylphenobarbitone, but she was still having two larval attacks weekly when discharged.

Reactivation of an Epileptogenic Focus

After a long period of complete freedom from epileptic attacks, or a single convulsive episode, there may be a recurrence of fits in pregnancy; so it is important to ask for a history of convulsions in the antenatal interview.

A woman aged 34 had a major fit at the age of 14. An uncomplicated pregnancy took place at the age of 26; then at the age of 30 she became pregnant again and developed frequent epileptic attacks. These were preceded by a mood of depression and were associated with an aura of vertigo and visceral disturbance with sweating and pallor, followed by an abrupt loss of consciousness resulting in injury on falling. An E.E.G. showed evidence of a right anterior temporal lobe focus. The attacks persisted after delivery, and the patient has become an epileptic; but whether the pregnancy had a significant effect in reactivating the focus is difficult to decide.

Gestational Epilepsy

Epilepsy may develop in a first or later pregnancy, and the attacks tend to be focal in clinical or E.E.G. manifestations.

A patient aged 41 started to have epileptic attacks during her fifth pregnancy, with a focal onset in the right arm. She was fully investigated to exclude a neoplastic or atrophic lesion, with negative results, and the attacks responded satisfactorily to phenobarbitone.

Fits appearing after a disturbance of consciousness at the time of delivery or in the puerperium may be associated with temporal-lobe attacks, and it is possible that the delivery has resulted in a vascular lesion of the temporal lobe.

A patient was unconscious for 24 hours after her first labour. At the age of 28 she developed attacks in which she felt nauseated, experienced hallucinations of taste, and tended to mutter over and over again, "I have been doing this for years and years." She would stand stiff and still and then have a period of post-epileptic automatism. An E.E.G. showed a generalized dysrhythmia with some fast activity in the left anterior temporal region. During her fourth pregnancy she was admitted with serial major attacks, which were controlled by the addition of phenytoin to her previous sedatives of methylphenobarbitone and phenobarbitone.

Another woman developed temporal-lobe epilepsy two weeks after the birth of her child. The attacks were preceded by a vision of a man in a white coat standing behind her, which she associated with her labour. It is well known that in temporal-lobe epilepsy an experience with an emotional content tends to be revisualized during the course of the attacks, as manifested in this patient.

Metabolic Aspects

The question arises, Which are the metabolic changes occurring in pregnancy likely to trigger off a liability to seizures? The effect of hydration on the epileptic is well known, and the vasopressin diagnostic test employs

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this sensitization of the cerebral mechanism as a test of epilepsy. Alteration of the pH of the blood towards alkalosis by hyperventilation is a usual technique employed in departments of electroencephalography to reveal abnormal rhythms. Convulsions may also occur as the result or reduction of the serum calcium, sodium, potassium, and magnesium. Klingman (1954) has shown that epileptic patients make a clinical improvement and show a more stable E.E.G. if treated with a moderately low sodium diet and sodium-binding ion-exchange resin to reduce any tendency to hydration.

To summarize, hydration, alkalosis, and reduction of the serum electrolytes are changes which result in seizures in the epileptic and are also changes associated with the pregnant state.

During pregnancy there is a gain in weight, which is in part due to extra water retained in the increased plasma volume and in the intracellular and extracellular tissues. An increase of about 20 to 24 lb. (9 to 11 kg.) is regarded as permissible, and some 10 lb. (4.5 kg.) of this is due to extra water retained. The increase of body fluid in normal pregnancy would favour cerebral instability and the appearance of attacks in the predisposed patient. Any uncontrolled weight gain might have serious implications, and studies on pregnant epileptic patients suggest that a rapid increase in weight usually precedes the appearance of more frequent epileptic seizures.

A reduction of CO₂ in the alveolar blood occurs as a feature of pregnancy with hyperventilation due to an increased sensitivity of the respiratory centres. Although a slight compensatory acidosis is usually maintained, loss of chloride through vomiting may favour an alkalosis. Oral sedatives also may be lost as a result of vomiting. The concentration of sodium, calcium, and magnesium ions tends to be slightly reduced in the serum in the pregnant state, although in the case of sodium the total body content is increased.

Aldosterone secretion is not infrequently increased in pregnancy, and is the hormonal factor which is important in regulating the degree of water and sodium retention and the excretion of potassium. Much work has been done on the significance of this hormone in water and salt retention in the toxæmias of pregnancy, but Barnes and Quilligan (1956) thought that there was no correlation between its level and the severity of the clinical state of the patient. They suggested that the increase in the hormone might be in response to the sodium restriction in the diet rather than a cause of sodium retention.

Status Epilepticus

Hormonal effects with retention of intracellular fluids triggering off the cerebral cortex are postulated as the cause of uncontrollable epileptic phenomena. Status epilepticus is a grave complication, and may develop at any time during pregnancy and labour, or after delivery. Usually an increasing number of major attacks which do not respond to sedation precede the onset of status, but uncontrollable fits may be the first intimation that the patient is dysrhythmic. The mortality is higher than that of eclampsia, from which it requires to be distinguished. The incidence is fortunately low. Klein *et al.* (1956) reported two cases, both fatal, among 52,000 deliveries at the Morrisana City Hospital, New York. Goodwin and Lawson (1947) recorded a recovery in the first trimester of

pregnancy, although fits continued for five days. Status epilepticus can be differentiated from eclamptic convulsions by the normal blood pressure and the lack of gross albuminuria and oedema, although there is not uncommonly some slight oedema of the dependent parts of the body before the appearance of the serial fits.

Abnormal Pregnancy

Toxaemia and Pre-eclampsia

Consideration of metabolic and genetic factors is helpful in understanding the close relationship between fits and toxæmia. Recent work on the aetiology of toxæmia has developed along two lines of investigation, both, however, resulting in the same conclusion, that the essential feature is a pressor factor as a common mechanism in the production of the eclamptic picture. McClure Browne (1957) stressed the importance of hypertension as a cause of placental ischaemia, and Morris (1957) found that exercise reduced the rate of the myometrial circulation as shown by sodium isotope clearance. Quantitative improvement of clearance follows rest, so his work confirmed the value of rest in the prevention of eclampsia. Sophian (1957) considered that renal ischaemia was the vital mechanism producing salt and water retention. He suggested that stretch of the uterine wall, which was most likely to occur in first or twin pregnancies activated a utero-renal reflex, resulting in ischaemia of the kidneys. The slowing of circulation in the kidneys produced oedema, increased protein in the urine, and ultimately hypertension.

Hereditary Factors

Burnett (1946) drew attention to the significance of constitutional factors in the relationship between epilepsy and eclampsia. He observed that epilepsy might be inaugurated by eclamptic convulsions and that there was a predisposition towards epilepsy among the relatives of an individual who had fits associated with toxæmia. Patients showed an unequal tendency to fits in eclampsia, although their metabolic disorder might be of equal severity and there appeared no constant relationship between the degree of toxæmia and the clinical manifestation of fits.

Rosenbaum and Maltby (1943) provided E.E.G. confirmation that a cerebral dysrhythmia was important in the production of convulsions, as E.E.G. abnormalities were present in 65% of eclamptics as against 10% in non-convulsive pre-eclamptic patients. The situation seems rather to resemble that of head injury, in that certain individuals exposed to a cerebral disturbance, whether traumatic or metabolic, develop fits if there is a hereditary or constitutional predisposition.

The trigger mechanism generally suggested in toxæmia of pregnancy is a combination of cerebral oedema and of cerebral vasoconstriction. The accepted mode of treatment in pre-eclamptic toxæmia aims at the prevention of increased blood pressure and oedema. The measures, which include rest, a diet with a high protein and low carbohydrate and fat content, and a reduction in salt intake, would also tend to suppress the occurrence of fits in the dysrhythmic subject.

Hypertension and Epilepsy in Pregnancy

Essential hypertension combined with toxæmia of pregnancy may precipitate the appearance of epilepsy.

One woman, at the age of 34, had seven eclamptic fits, associated with high blood pressure and renal dysfunction. Thirteen years later she still suffers from a severe hypertension with focal fits affecting the right side of the body, starting in the right foot, although her E.E.G. was to be correlated with epilepsy. An intravenous pyelogram showed an inactive kidney on the right and a dilute secretion on the left. Treatment with the usual sedatives and, more recently, hypotensive drugs, including mecamlamine, has resulted in a reduction in the number of fits, which formerly occurred many times a day. Here probably is an example of a patient with a basic cerebral dysrhythmia, a focal lesion perhaps of vascular type produced at the time of her toxæmia of pregnancy and a persisting epileptic disorder.

Anaemia in Pregnancy

The blood volume increases during pregnancy and there is a relative increase of blood plasma, which produces a fall in haemoglobin and in cell concentration. An iron-deficiency anaemia is not uncommon, but another complication which may occur is the development of a megaloblastic anaemia. This may be due to pernicious anaemia of pregnancy—a self-limiting condition responding to folic acid—in which the blood returns to normal after delivery. However, the effect of anticonvulsants on blood formation must not be forgotten. Hawkins and Meynell (1958) have described the occurrence of macrocytosis and anaemia in treated epileptics. The abnormality of the red cells was attributed to a competitive inhibition by the drugs of some enzyme process normally involving folic acid as a co-factor, for this vitamin has a general structural similarity to anticonvulsants. It was observed that when anaemia was due to macrocytosis from drugs the administration of folic acid, 10 mg. daily, was followed by a marked improvement in the fits and in the macrocytosis. It is important to have full blood counts carried out during pregnancy to detect the appearance of macrocytosis in epileptic patients on anticonvulsants.

Cerebral Tumour in Pregnancy

The possibility that pregnancy may cause the appearance of focal signs due to a tumour is well known, as Bickerstaff *et al.* (1958) have shown in the case of the meningioma. Increased vascularity of the neoplasm has been suggested as a cause, but Weyand *et al.* (1951) reported actual changes in the cytology of meningiomas. The cytoplasm of the cells was characterized by a foamy appearance, attributed to an increase in intracellular fluid, and there was no evidence of mitosis suggesting an increase in number. These findings would explain the appearance of convulsions and focal signs in pregnancy.

General Management

A direct request for a personal or family history of disturbances of consciousness should be made to the patient and, if possible, also to relatives. If a patient has been free from epileptic attacks for some years sedatives may have been discontinued and she may forget to mention that she has had an epileptic tendency. The indications for anticonvulsants are the same as in the non-pregnant epileptic, phenobarbitone, $\frac{1}{2}$ –1 gr. (32–64 mg.), or phenytoin, 0.1 g., two or three times a day, being useful in major or focal epilepsy. Primidone,

0.25 g., may be used in combination with phenytoin for major attacks instead of phenobarbitone if the response has not been satisfactory. A drug of the dione group, 0.3 g. three times a day, may be required for true petit mal. Phenobarbitone in a slowly absorbed form ("spansule"), given at night, may carry the patient over the morning hours when retention of tablets is difficult owing to vomiting. It may be necessary to give sodium phenobarbitone, 3 gr. (0.2 g.), by injection to maintain the anticonvulsant level during vomiting or at the time of delivery.

Avoidance of an excessive gain in weight during pregnancy is a matter for close co-operation with the obstetrician. Rest in bed, restriction of salt, and a high-protein, low-carbohydrate, low-fat diet are employed, or, alternatively, as is used in America, a combination of a low-calorie diet, restriction of salt, with acetazolamide ("diamox"), 250 mg. b.d. This diuretic is a powerful inhibitor of the enzyme carbonic anhydrase, an action which results in a loss of bicarbonate. The systemic acidosis produced has been thought by some workers, including Suter and Klingman (1957), to make acetazolamide particularly appropriate in the treatment of retention of fluid in pregnancy with increase in epileptic attacks. Alternatively, a sodium-binding ion-exchange resin may be used to prevent retention of sodium. Suter and Klingman report good results with "resodec," 15 g. two or three times a day for periods of a fortnight, to reduce any excess weight gained. The use of the oral diuretic chlorothiazide has been investigated by Watson *et al.* (1958) in pre-toxaemia; they found that an oral dose of 2 g. produced a substantial diuresis in six hours, but was without effect on the blood pressure. This may prove a valuable drug, but further clinical experience is necessary.

Hypertension and fits complicating pregnancy indicate the use of a hypotensive drug from the point of view of control of the epilepsy as well as the hypertension. It is of interest that McClure Browne and his colleagues (Kincaid-Smith *et al.*, 1958) have managed a pregnancy successfully in a severely hypertensive patient with the use of pentolinium, 40 mg. t.d.s. by injection, followed by mecamlamine, 10 mg. b.d., with reserpine ("serpasil"), 0.1 mg. t.d.s. orally. Maintenance of the erect posture then is important instead of rest.

Both iron-deficiency and macrocytic forms of anaemia should be treated. The usual treatment for the latter, provided the case is not one of true pernicious anaemia, is folic acid, 10 mg. b.d. It may be necessary to employ packed-cell transfusions where there is a severe iron-deficiency anaemia or a low nutritional level with anaemia associated with fits.

Status epilepticus may be guarded against by admission of any patient whose attacks cannot be satisfactorily controlled and whose serial E.E.G.s show deterioration. Paraldehyde, 5 ml. intramuscularly, may be given two-hourly, or sodium phenobarbitone, 3 gr. (0.2 g.) subcutaneously. Hospital procedures include intravenous thiopentone, sodium phenytoin, and, in severe cases, D-tubocurarine combined with controlled respiration. Termination of pregnancy by surgical induction may be indicated (Burnett, 1946).

Where fits may be symptomatic it is important to examine the nervous system carefully for focal signs. Investigations for a neoplasm include x-ray films of the skull and chest, and an E.E.G.; admission for contrast radiography may be necessary.

Summary

As a result of better therapeutic and social management the epileptic woman has increased opportunities of marriage and epilepsy is likely to become a more frequent complication of pregnancy.

The effect of pregnancy on the epileptic is unpredictable. The attacks may increase in number or remain unchanged. Reduction in incidence of fits is often related to better therapy. Epilepsy associated with menstruation usually persists in pregnancy. When attacks first appear in pregnancy (gestational epilepsy) these are likely to be partial or focal in character.

The metabolic changes in pregnancy—hydration, hyperventilation, and dilution of calcium, sodium, and magnesium in the serum—favour an increase of fits. The variations in excretion of aldosterone are probably compensatory to fluctuation in sodium intake. Excessive gain in weight and sodium retention may precede the onset of increased fits.

A genetic or constitutional factor is important in the appearance of seizures in toxæmia of pregnancy. A persistent epileptic tendency may result. Status epilepticus is a rare but grave complication, especially when occurring in later pregnancy, and has a higher mortality than eclampsia. The onset of status in pregnancy may be the first manifestation of a cerebral dysrhythmia.

The epileptic woman should not be discouraged from pregnancy unless the attacks are difficult to control in the non-pregnant state, but there is no excuse for regarding this complication of pregnancy lightly. Antenatal care should be as thorough as in suspected toxæmia of pregnancy.

Management of pregnancy consists of suitable anticonvulsants, with dosage corrected for gain in weight. Phenobarbitone in capsule form ("spansule") may be useful in vomiting of pregnancy. Anaemia should be treated, and macrocytic forms, whether due to pregnancy or anticonvulsants, will require folic acid. Excessive gain in weight should be controlled by diet, restricted salt intake, and rest. If the response is unsatisfactory the use of acetazolamide or ion-exchange resins should be considered. Status epilepticus may require the use of continuous intravenous anticonvulsants, with controlled respiration.

Investigation of gestational epilepsy to exclude a neoplasm may be indicated.

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A PRELIMINARY REPORT ON
CHLORPROMAZINE IN TETANUS

BY

AJAI SHANKER, M.D.

Lecturer in Medicine, Gandhi Medical College, Bhopal, India

AND

L. S. MEHROTRA, M.B., B.S.

Assistant Surgeon, Hamidia Hospital, Bhopal; formerly
House-Physician, Department of Medicine, Gandhi
Medical College, Bhopal, India

Prior to the work of Hougs and Andersen (1954) and Kelly and Laurence (1956) it had been shown by Courvoisier *et al.* (1953) that chlorpromazine antagonizes some central convulsant drugs and prolongs the effect of relaxant drugs like D-tubocurarine and mephenesin. Dasgupta and Werner (1955) showed that it inhibits motor activity induced by cortical stimulation in cats and also suppresses the postural responses which occur on stimulation of cerebellar cortex and reticular formation; and its paralytic effect on skeletal muscles was demonstrated by Burn (1954). It was these qualities of chlorpromazine, together with its better-known qualities as a sedative, a tranquillizer, and as a potentiator of other hypnotics and sedatives, which probably suggested its rational use in tetanus. It was used in mild cases or as a useful adjunct by Adriani and Kerr (1955), Bodman *et al.* (1955), and Cole and Robertson (1955), and it is interesting to note that Andersen *et al.* (1955) regarded it as a failure. It is apparent that a dosage on the small side was used by them. Laurence *et al.* (1958) described their results in 37 cases. Success in individual cases, both serious and unusual, was also reported by Barr (1958), Packard *et al.* (1958), Azmi (1958), and Hutchinson and Hurrell (1958). Johnstone (1958) describes rather unfavourable results with small doses of chlorpromazine and amylobarbitone in 17 patients, 11 of whom died.

Adams (1958) reported the results of a carefully controlled clinical trial of chlorpromazine, chloral hydrate, and barbiturates in the treatment of nearly 200 patients of tetanus. His impression was that a mixture of barbiturates and chlorpromazine was better than any other drug alone, and he stressed that smaller doses of each could be given. He slightly preferred barbiturates for the treatment of neonatal cases, but thought that chlorpromazine could dramatically control the laryngeal spasm and could be given intravenously.

Laurence (1958) has reported that phenothiazine derivatives like chlorpromazine were by far the best in abolishing spasm and were superior to centrally acting relaxants like mephenesin.

We have been using chlorpromazine in the management of tetanus cases for some time at Hamidia Hospital, Bhopal. We have so far given a smaller dose than Laurence *et al.* and have occasionally used paraldehyde as an adjunct. This method gave us a very favourable clinical impression and prompted us to publish this preliminary report on 30 cases. The trial is still going on, and we propose to publish a report on a bigger series later on.

Method and Material

Patients were divided into two groups at random—one group receiving chiefly chlorpromazine while the other received only paraldehyde.