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

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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.

TABLE I

Case No.	Sex	Age	Incubation Period in Days	Period of Onset in Hours	Severity	Total Duration of Stay in Hospital in Days	Result	Day of Administration of Serum after Onset	Evidence of Sepsis
<i>Chlorpromazine Group</i>									
1	F	4 years	—	6	+	15	Cured	1	Nil
2	F	10 "	20	2	+++	20	"	3	Septic injury left foot
3	M	2 "	—	6	+++	2	Expired	2	Bronchopneumonia
4	F	20 "	5	24	+++	10	Cured	1	Puerperal sepsis
5	F	4 "	8	10	+++	19	"	8	Otitis media
6	M*	8 days	5	48	+++	1	Expired	4	Nil
7	F	16 years	9	8	+++	8/24	"	3	Puerperal sepsis
8	F	20 "	9	6	+++	30	Cured	6	"
9	F	22 "	2	5	+++	30	"	13	"
10	F†	22 "	4	10	+++	15	"	4	Nil
11	M	3 "	10/24	4	+++	14	"	3	Septic injury left toe
12	F	25 "	8/24	2	+++	16	"	8	Puerperal sepsis
13	M	12 "	4	48	++	12	"	4	Nil
14	M	40 "	—	8	++	7	"	15	"
15	M‡	20 "	4	6	+++	15	"	2	"
<i>Paraldehyde Group</i>									
1	M	9 years	4	48	+	30	Cured	4	Nil
2	M	15 "	7	48	+	15	"	7	Otitis media
3	M§	22 "	3	20	++	5	Expired	4	Septic injury
4	M	12 "	5	16	++	3	"	1	Leucocytosis
5	M	25 "	2	24	+++	3	"	5	Septic injury
6	F	26 "	1	12	+	30	Cured	4	"
7	M	30 "	30	24	++	30	Expired	2	Whitlow
8	F	40 "	—	10	+++	4	"	1	Nil
9	M	27 "	4	20	+++	30	Cured	1	Septic injury
10	M*	11 days	9	10	+++	6	Expired	4	Nil
11	F	24 years	—	25	++	15	Cured	5	"
12	M*	6 days	6	10	++	2	Expired	6	"
13	M	8 years	1	24	+	20	Cured	6	"
14	F	3 "	8	48	++	16	"	9	"
15	M	6 "	3	24	++	13	"	4	"

* Tetanus neonatorum.

† 300,000 units of A.T.S. given.

‡ Prophylactic dose of 3,000 units of A.T.S. given one day after injury.

§ Patient left against medical advice, treated as expired, as the condition had deteriorated during the stay in hospital.

|| Patient left against medical advice, treated as cured because the spasms and rigidity had disappeared during the stay in hospital.

Selection of Cases.—The trial was made on patients admitted to the Hamidia Hospital with a clinical diagnosis of tetanus. One or other treatment was given at random without any reference to the severity of

disease or the age group of patients. All other treatment given to both groups was standardized.

Standardized Treatment.—Immediately after admission each patient was put to bed in a dark room and was sedated with paraldehyde or chlorpromazine as decided upon at random. The drugs were given intramuscularly in all cases. A test dose of 800 I.U. of antitoxin was given subcutaneously (except in neonatal cases), and if no reaction occurred in half an hour, 100,000 units of antitoxin was administered intramuscularly and 100,000 units intravenously. If a wound was present it was dressed.

Chemotherapy.—Procaine penicillin, 400,000 units, was given intramuscularly daily to adults, and crystalline penicillin, 200,000 units twice daily intramuscularly to infants, for five days.

Feeding.—Nasal feeding was started only if patients could not swallow. Feeding was begun with egg-and-milk mixture.

Drug Dosage.—(1) *Paraldehyde group*:—In this group adults were given 6 ml. of paraldehyde intramuscularly six-hourly or four-hourly according to the severity and frequency of convulsions. The frequency of injections was gradually tapered off as the condition of the patient improved. For children and infants 2–3 ml. of paraldehyde was used. (2) *Chlorpromazine group*:—After an initial dose of 100 mg. adults were given 50–100 mg. of chlorpromazine intramuscularly, depending on severity of spasms. For infants a dose of 25 mg. twice daily was administered. If the spasms recurred in between, paraldehyde 3–6 ml. intramuscularly was sufficient to control them.

Criterion of Severity of Tetanus.—The cases were classified as follows: (1) mild—rigidity present without any spasm, shown in Table I as +; (2) moderate—one to four spasms daily, shown in Table I as ++;

TABLE II.—Comparison of Chlorpromazine and Paraldehyde Group

No.	Chlorpromazine Group			Paraldehyde Group		
	Average	Max.	Min.	Average	Max.	Min.
Duration of onset (hours) ..	13	48	2	24	48	10
Incubation period (days) ..	5 22 24 *(12/15)	20	8 24	6 10 24 *(13/15)	30	1
Days in hospital of survived cases ..	17.0	30	7	21	30	13
Days in hospital of fatal cases ..	1	2	8 24	8	30	2
Age ..	14.4 yrs.	40 yrs.	8 days	16.46 yrs.	40 yrs.	6 days
Age (non-neonatal cases) ..	15.57 yrs.	40 yrs.	2 yrs.	19 yrs.	40 yrs.	3 yrs.
	No. of Cases		Percentage	No. of Cases		Percentage
Male ..	6	—		11	—	
Female ..	9	—		4	—	
Severity group:						
Mild ..	1	—		5	—	
Moderate ..	2	—		6	—	
Severe ..	12	—		4	—	
Cure rate ..	15	80%		15	53%	
Cure rate in 3 severity groups:						
Mild ..	1	100%		5	80%	
Moderate ..	2	100%		6	50%	
Severe ..	12	75%		4	25%	
Mortality rate ..	15	20%		15	46.6%	
Mortality rate in neonatal cases ..	1	100%		2	100%	
Mortality rate in patients surviving more than 24 hours ..	13	7.7%		15	46.6%	
Mortality rate in non-neonatal cases surviving more than 24 hours ..	13	7.7%		13	38.4%	

* These figures represent the number of cases in which it was known—i.e., 12/15 = 12 out of 15 cases.

and (3) severe—more than four spasms daily, shown in Table I as + + +.

Duration.—The drugs were continuously administered till the rigidity had almost disappeared and the mouth could be opened fully.

The results are shown in Tables I and II.

Discussion

Although the number of cases was too small for statistical analysis a definite clinical impression was formed that a change over to chlorpromazine from paraldehyde treatment would be advisable, because it controls the spasms better and because it seems to us that it has helped to reduce the mortality. It is generally known that a comparison of mortality figures from different centres may be misleading, because of differences in nursing standards, which are of great importance. Nevertheless, a reduction in the mortality rate achieved at one institution should be a useful pointer to the efficacy of a new regime. With this background the following analysis seems worth recording.

Spasms.—The reflex spasms were dramatically controlled by chlorpromazine within half an hour of the intramuscular administration, and did not recur again before four hours in any case. Even if they reappeared they were transient and very mild, and were easily abolished by 4 ml. of paraldehyde given intramuscularly on occasions to some cases only. On these occasions only paraldehyde, and not additional chlorpromazine, was administered. In the paraldehyde group the spasms were not controlled so efficiently, and continued intermittently for a long time or until death.

Mortality.—Since the use of chlorpromazine it has been our feeling that the mortality rate has been much reduced. Though we appreciate that the number of cases is too small to be of any statistical value, yet one cannot fail to notice that in the chlorpromazine group of 15 cases there were only three deaths (20%). Of these three fatal cases, one (No. 6) was a neonatal case, another (No. 7) was in the hospital for about eight hours only and could hardly be said to have received any substantial treatment. If these two cases are excluded there is only one death out of 13 cases (7.7% mortality), 10 of which were serious. On the other hand, out of 15 patients in the paraldehyde group 7 died (46.6%); even if 2 neonatal cases (Nos. 10 and 12) are excluded there are 5 deaths out of 13 cases (38.4% mortality). The difference in mortality figures in the two groups speaks for itself, and in the non-chlorpromazine group the figures compare with those generally recorded in this hospital as well as those of Laurence *et al.* (52% non-neonatal and 71% neonatal) and Johnstone (56% and 52% in paraldehyde and amylobarbitone groups), and those quoted by various other workers. Johnstone, in his extensive series of 100 cases, has shown that the only consistent feature in 45% of fatal cases was that they all had reflex spasms which continued until death. All the factors which modify mortality occurred to the same extent in both our groups, and we feel that a quick control of spasms has helped to reduce the mortality rate in the chlorpromazine group.

Incubation Period.—The average incubation period was a little less in the chlorpromazine group, and this is consistent with the fact that there were more serious cases in the chlorpromazine group. Cases with an

incubation period under nine days are known to be of a serious nature, and this was confirmed in both our groups.

Period of Onset.—Cases with a period of onset less than 48 hours are known to have a graver prognosis. The average period of onset in the chlorpromazine group was shorter by 11 hours than that in the paraldehyde group, yet the mortality rate was reversed.

Toxicity and Complication of Drugs.—The highly irritant action of chlorpromazine described by Laurence *et al.*, causing induration of muscles, was not our experience, probably because of the low doses and infrequent injections administered by us. Similarly, the mental confusion and Parkinsonian tremor described by Packard *et al.* has not been seen in our cases so far.

Dosage Used.—We feel that 100 mg. of chlorpromazine, given immediately, followed by 100 or 50 mg. 12-hourly, may just be enough to control the spasms in adults. If, however, the spasms recur in between, 4 to 6 ml. of paraldehyde, given occasionally intramuscularly, will control them in most cases. We also feel that the high doses used by Laurence *et al.* in their series may be unnecessary and hazardous. Children and infants may be given proportionately smaller doses depending upon their weight and size.

Neonatal Cases.—As there were only three neonatal cases in this series they were not grouped separately. All three patients died in spite of the choice of therapy.

Summary

Chlorpromazine was administered to 15 cases of tetanus; most of them were serious.

The results were compared with those in 15 patients who were treated with paraldehyde. Results with chlorpromazine have been highly satisfactory, and a cure rate of 92.3% has been recorded in chlorpromazine-treated non-neonatal cases that survived more than 24 hours in hospital.

In the chlorpromazine group the drug was administered in comparatively small doses (50 to 100 mg. twice daily intramuscularly for adults), and paraldehyde was occasionally used as an adjunct.

We thank Professor S. M. Misra for permitting us to include three of his cases in this series.

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