

NEONATAL TETANUS IN SIERRA LEONE

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This report is the result of an analysis of 114 consecutive cases of neonatal tetanus treated at the Nixon Memorial Hospital over the period of five years seven months preceding September, 1960. Approximately half-way during this time chlorpromazine therapy was introduced, and one purpose of this paper is its evaluation in this condition.

The town of Segbwema is in the South-Eastern Province, 260 miles (420 km.) from Freetown, and has a population of about 4,000. Its 130-bed Mission Hospital serves a wide area. In 1959 there were 86,000 outpatient attendances and 3,000 patients were admitted.

Ecological Background

The people comprise a predominantly agricultural community, apart from chrome mines 30 miles (48 km.) away and diamond mines 60 miles (96 km.) away. Most of the patients come from villages of fewer than 500 people. There are no horses and few cows in this area, but it is common to see goats, hens, sheep, and sometimes pigs wandering around the houses. At night the hens are taken indoors, and other animals often shelter on the veranda. The usual method of disposal of human faeces is by a pit latrine; this is frequently too shallow and often attracts flies.

There are relatively few trained village midwives, and, so far as is known, all the cases here discussed were delivered by traditional village midwives—usually Bundu Society elders. Birth usually takes place on a grass mat spread on the earth floor of a mud-walled thatched house. According to the custom of the local Mende tribe, as soon as the baby is born a woman will run to the village and borrow a particular knife kept by an old man; the knife may be hanging in a raffia bag on the wall, on the top of a cupboard, or in a box together with other possessions. The umbilical cord is tied with native spun thread, then "medicine" is applied by the midwife, and subsequently each morning by the grandmother. The application usually consists of the juice from a young banana shoot, squeezed out by rolling it between the hands. Sometimes leaf fragments are added. It is interesting to note that the banana trees are commonly grown behind the native houses; it is customary to throw house sweepings and refuse around the bottom of the trees, and animals root among this in search of food scraps. A young banana shoot originates from its parent stem below ground and thus comes into close contact with the debris around the tree base.

Description of the Present Series

The only selection in this series has been to exclude six cases which were so mild that a diagnosis of tetanus was disputable; all but one of these recovered. During the same period of time 11 cases of tetanus were diagnosed in older children or adults, and these too are not discussed.

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Most of the 114 cases were severe: of the patients who died the average duration of life after admission was 2.4 days. There were 60 boys and 54 girls. Of the cases studied in the five completed years, 51 occurred in the wet season (May–October) and 32 in the dry season (November–April)—a finding different from that of Trowell and Jelliffe (1958) and Tompkins (1958), who reported a predominance of cases in the dry season.

The average age on admission of those who lived was 10.5 days, whereas for those who died it was 6.3 days; these figures should be regarded as approximate only, for the local people do not "number their days" with our sense of accuracy. Almost all the mothers stated that the trouble had started on the previous day, and it has not proved possible to analyse the number of hours between onset of symptoms and commencement of treatment. Trismus, causing inability to suck, was usually stated to have been the first sign, and this was quickly followed by widespread muscular rigidity, severe spasms being provoked by attempted passive movement of flexed limbs. In advanced cases very minor stimulation provoked spasms.

Nursing Care

The importance of expert and gentle nursing cannot be overemphasized, for it is vital to recovery.

General Care.—The child is nursed on its side, lying horizontal, but is turned every two or three hours. So far as possible all nursing treatment is synchronized so that the baby is minimally disturbed. Handling is gentle and ideally the room should be quiet.

Feeding.—Expressed breast milk is given through a fine-bore nasogastric tube. Oral spoon-feeding is impossible in a severe case, and inadvisable in moderate cases because of the necessity for very frequent feeds, with the inevitable accompanying stimulation and the danger of inhalation pneumonia.

Care of Umbilicus.—The umbilicus is thoroughly cleansed with hydrogen peroxide on admission, then a dry dressing is applied. Sometimes marked stump infection makes daily cleansing necessary. Local surgery or antitoxin injection have not been employed.

Oral Hygiene.—Trismus renders routine measures impossible, but mucus accumulating in the pharynx is removed with an extractor.

Drug Therapy

Chlorpromazine.—This was given by four-hourly 10-mg. intramuscular injections until spasms were controlled—usually for 24 hours, but sometimes longer—then a 10-mg. injection was given six-hourly until there was obvious improvement in the tonic rigidity and general condition, when an eight-hourly dosage was substituted. If reduction in frequency of dosage was followed by reappearance of spasms a shorter interval was readopted. The last 70 children were treated in this way. The average duration of such therapy for those who recovered was 9.6 days, and on one occasion was prolonged for 17 days.

Antitetanus Serum.—This has been given to all patients, usually in a single dose of 10,000 units on admission; but prior to the use of chlorpromazine dosage varied between 20,000 and 50,000 units, depending on severity.

Penicillin.—All cases were given oily penicillin, usually 300,000 units at once and 150,000 units daily for five days. If there was marked umbilical sepsis or if chest complications supervened, a larger dosage was used, and crystalline penicillin given in addition.

Sedatives.—(a) Prior to the introduction of chlorpromazine either chloral, potassium bromide, or a combination of these was used routinely, 2 gr. (0.13 g.) of each up to four-hourly if necessary. Injections of phenobarbitone sodium, $\frac{1}{4}$ – $\frac{1}{2}$ gr. (16–32 mg.), were given to 7 out of 44 patients, and paraldehyde injection, 15 min. (0.9 ml.), was given to one child only. (b) After the introduction of chlorpromazine no other sedatives were given from June, 1958, until the beginning of 1960, apart from phenobarbitone on one occasion. But in 1960 all children were given chloral, 2 gr. (0.13 g.) p.r.n., an occasional dose being allowed between injections of chlorpromazine if spasms recurred. In this year also two children were given injections of phenobarbitone sodium, $\frac{1}{4}$ – $\frac{1}{2}$ gr. (16–32 mg.), and one child was given an injection of paraldehyde.

Mephenesin ("myanesin").—Before the use of chlorpromazine 24 children were given elixir of mephenesin orally or through nasogastric tube. The usual dose was 1 dr. (3.5 ml.) six-hourly. After chlorpromazine was brought to use, mephenesin therapy was discontinued.

Results

Before Use of Chlorpromazine.—Of the 44 patients treated without chlorpromazine, 12 (27.3%) lived and 24 (54.5%) died in hospital. Eight were taken away against advice, and almost certainly died, making the probable mortality 72.7% (Table I). Of 24 children

TABLE I.—Annual Analysis of Cases

	1955	1956	1957	1958		1959	1960
				Chlorpromazine			
				Without	With		
Lived	3	4	3	2	13	10	13
Died	7	4	4	9	2	7	13
Taken away:							
Worsening ..		2			1	1	3
Improving ..						3	1
Condition not recorded ..	3			3	1	1	1
Total	13	10	7	14	17	22	31

to whom mephenesin was given, 5 (20.8%) lived, and 19 (79.2%) died. The average stay in hospital of those who lived was 13.2 days, of those who died 1.9 days, and of those taken away against advice 3 days.

After Introduction of Chlorpromazine.—Of the 70 patients treated with chlorpromazine, 36 (51.4%) lived and 22 (31.4%) died in hospital. Twelve were taken away against advice, and most likely died, although 4 were showing signs of improvement. The probable mortality was therefore 48.6%. The average stay in hospital of those who lived was 14.7 days, of those who died 3 days, and of those taken away against advice 3.6 days. One child developed jaundice after two days of treatment and was taken away against advice on the third day.

The proportion of babies taken away against advice was similar for both periods—18.2% in the first period and 17.1% in the second. The increase in the percentage of babies living was statistically significant, the difference being 24.1 ± 9.5 .

Subsequent History

Detailed follow-up of all the patients who recovered has not been possible; but the subsequent records of 34 successful chlorpromazine-treated cases have been examined.

Ten children living locally were advised to attend the weekly baby welfare clinic held at the hospital; all were alive and well at the time of writing. Four have been seen for more than 12 months after discharge, three for between 6 and 12 months, and three between 1 and 3 months.

Most of the other children came from homes situated many miles away, often in inaccessible little villages, and they would normally not be seen again at hospital unless they contracted a further illness. Of the 24 cases in this category we have records of seeing only nine subsequently—five after more than 12 months and two after between 3 and 12 months—none of these has had trouble referable to tetanus or its treatment. Of two other patients the records note residual stiffness in one after four days, and failure to gain weight in the other at 10 days after discharge, and in each case there was no subsequent attendance.

Therefore of the 34 cases we have satisfactory subsequent records of three months or longer in 16. The majority of the others may well be alive, but their inaccessibility makes it impracticable to verify this. It may be noted here that in this area the overall child mortality from all causes under the age of 5 years is 62%.

Discussion

Exact statistical analysis is often difficult in the local circumstances of tropical hospitals. It is much more regrettable from a humanitarian viewpoint that of the 114 children 20 were taken away from hospital against medical advice after a very short therapeutic "trial period." If death is likely to take place, the Mende people prefer this to be in the home rather than in the hospital. It is encouraging to note an annual decline in this custom, reflecting as it does more than just a growing confidence in technique. Again, it may be noted with astonishment by some that the average stay in hospital was only about a fortnight. This also must be viewed in context: the economic domestic need of the mother to return home as soon as possible; also there is a constant need to admit so many seriously ill children.

Methods of nursing treatment have been comparable throughout this series of cases. There seems to be no reasonable doubt that chlorpromazine therapy has been responsible for a reduction of mortality from 72.7% to 48.6%. In this statement the death of those taken away against advice is assumed. Had they remained in hospital some undoubtedly would have lived. Thus in more ideal conditions this mortality figure should be much lower. Yet a review of the literature shows that it is usually much higher in this disease. Even with the use of chlorpromazine it is often between 70 and 95% (Table II). A comparison of the mortality figures can be misleading, since there may be more than one variable element between two series of cases. Apart from possible alterations in the virulence of infection in different localities, it is felt that three factors merit discussion.

1. *Incubation Period.*—If we equate the incubation period and admission age, then 10.5 days is longer than many reported. We would agree with the statement of Spivey *et al.* (1953) that the prognosis is relatively much better with an onset of tetanus after rather than before the seventh day of life. But an assumption that the

TABLE II.—*Reported Mortality of Treated Neonatal Tetanus*

	Author	No. of Cases	Mortality
Without chlorpromazine	Vinnard (1945)	11	55%
	Jelliffe (1950)	25	96%
	Spivey <i>et al.</i> (1953) ..	26	77%
	Lorenz (1957)	19	58%
	Pinheiro (1957)	256	77.3-92.5%
	Tompkins (1958)	141	89.6%
	Adams <i>et al.</i> (1959) ..	20	90%
With chlorpromazine	Laurence <i>et al.</i> (1958) ..	31	93%
	Adams <i>et al.</i> (1959) ..	20	95%
	Wright (1960)	34	94%
With chlorpromazine and barbiturate	Sarrouy <i>et al.</i> (1956) ..	20	80%
	Earle and Mellon (1958) ..	32	25%
	Adams <i>et al.</i> (1959) ..	44	71%
	Wright (1960)	77	76%

infection was necessarily introduced at the time of cord severance is not necessarily correct, because a potentially highly infected application was used on the cord daily thereafter.

2. *Dosage of Chlorpromazine.*—Adams *et al.* (1959) note that there is a "maximal dose above which anti-tetanus activity is not increased, and indeed the tetanus may be increased at very high doses." They used 25 mg. intramuscularly up to four-hourly, and the mortality was 95%: commenting on this, they observed that "over-dosage cannot be excluded as a cause of death," and subsequently in a selected group of 44 cases used 100 mg. in divided doses daily, supplemented by sodium phenobarbitone, with a mortality of 77%. Wright (1960) used 100-200 mg. daily, with a 94% mortality; but with a reduced amount of 12.5-100 mg. daily and the addition of sodium phenobarbitone the mortality fell to 76%. These reports were from South Africa. Earle and Mellon (1958) reported a 25% mortality in 32 cases in Haiti. All fluid requirement for the first six to eight days was given intravenously, and to this was added chlorpromazine, 1 mg./kg. four-hourly, supplemented by sodium phenobarbitone. Sarrouy *et al.* (1956), in Algeria, used a chlorpromazine dosage of 2-3 mg./kg. together with phenobarbitone, with a mortality of 80%. After a great deal of experimental and clinical experience in the therapy of this disease, Laurence (1958) deduced that beyond 3-5 mg./kg. the condition was likely to be worsened. The particular dosage described in the present series was largely empirical initially, and we have sometimes had to resist the temptation to increase the amount. It is approximately 4.5 mg./kg. (10 mg./lb.) daily to start with, declining to 2.3 mg./kg. (5 mg./lb.) daily later, in divided doses, intramuscularly. This was sufficient to control spasms fairly well in most cases, but in 1960 the occasional addition of chloral by nasogastric tube helped some children to rest better between injections, and the slight rise in mortality as compared with 1959 is not significant. In this connexion it may be noted that in the latter part of 1958, when the new chlorpromazine therapy had been introduced at the hospital, the mortality in 17 cases was under 25%.

3. *Barbiturates.*—Over the past 20 years in this hospital the accumulated clinical impression of a number of workers has on the whole been unfavourable towards the routine use of barbiturates in neonatal tetanus. At one time paraldehyde was in common use

in preference to phenobarbitone. In the 70 chlorpromazine-treated cases of this series one or two small doses were given to each of three patients only. It is not the purpose of this paper to evaluate barbiturate usage in neonatal tetanus, but the evidence presented does not support the statement by Wright and Adams (1960) that chlorpromazine is "useful in the treatment of this most severe form of the disease only when combined with a barbiturate."

There are two more therapeutic points of interest in this series: (1) Pinheiro (1957) described a lowering of mortality from 92.5% to 77.3% with the use of mephenesin intravenously. In the present series mephenesin elixir was given orally or by nasogastric tube without improvement in prognosis. (2) The high dosages of antitetanus serum in earlier years have now fairly generally been abandoned. In the present series a single dose of 10,000 units was found adequate.

In the face of the extremely high mortality figures reported for this disease, curarization and the use of an intermittent positive-pressure respirator is on trial in a number of centres (Glossop and Low, 1957; Lawrence and Sando, 1959; Smythe and Bull, 1959; Poulsen and Nørby, 1959; Alhady *et al.*, 1960). But the majority of cases of tetanus neonatorum occur in areas of the world where hospitals do not have these facilities. The present series suggests that with a particular dosage of chlorpromazine the position might not be quite as bad as formerly thought. Even so, a mortality figure between 31% and 48% is very serious. Our reaction to the present situation is to train more local village midwives, even of a poor educational background if necessary, and to carry out a programme of simple instruction in hygiene for the village people.

Summary

A series of 114 consecutive cases of neonatal tetanus treated at the Nixon Memorial Hospital, Segbwema, Sierra Leone, is reported. Seventy infants were treated with chlorpromazine and 44 without: in the latter group 24 were given mephenesin. The ecological background is described.

The introduction of chlorpromazine therapy enabled the mortality to be reduced from 72.7% to 48.6%. These figures would probably have been lower, but 20 children were taken away against advice, and are assumed to have died. Nevertheless the mortality is less than some other series recently reported: in trying to assess the reason for this in the chlorpromazine group, it is thought that the optimum dosage is a factor of considerable significance in neonates.

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DEFECTIVE BIOSYNTHESIS OF OVARIAN STEROIDS IN THE STEIN-LEVENTHAL SYNDROME

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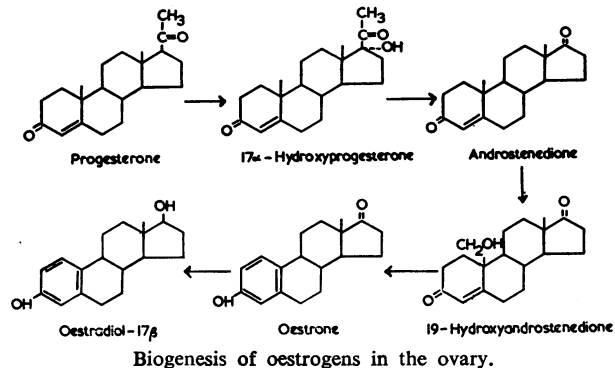
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Although the Stein-Leventhal syndrome was first described in 1935 (Stein and Leventhal, 1935), its aetiology is still obscure and its treatment empirical. There can be little doubt that the associated hirsutism is due to an increased production of androgens, and there has been much discussion on whether they are of adrenal or ovarian origin. The studies of Gallagher *et al.* (1958), Prunty *et al.* (1958), Perloff and Channick (1959), and Shearman *et al.* (1961) have all suggested that the adrenals may be involved. On the other hand, there is much circumstantial evidence to implicate the ovaries; for example, the condition responds successfully to such varied surgical procedures as ovarian wedge resection (Stein, 1955), ovarian eversion (Ingersoll and McDermott, 1950), or ovarian medullary resection (Allen and Woolf, 1959).

With the recent elucidation of the pathways of oestrogen biosynthesis in the ovary (Meyer, 1955; Solomon *et al.*, 1956), it became apparent that at least



one androgen, androstenedione, is normally produced by the ovary as an intermediate in the synthesis of oestradiol-17 β from progesterone (see Formulae).

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A method has recently been described for the simultaneous determination of progesterone, 17 α -hydroxyprogesterone, androstenedione, oestrone, and oestradiol-17 β in small samples of follicular fluid (Short, 1961). Since each of these five steroids has been identified in human ovarian tissue (Zander, 1958; Zander *et al.*, 1959; Smith, 1960), it seemed important to establish the levels of these compounds in the cyst fluid of patients with the Stein-Leventhal syndrome, and to compare them with the levels found in a control group of subjects.

Material and Methods

Cyst fluid was obtained at operation from the ovaries of five patients exhibiting the characteristic features of the Stein-Leventhal syndrome; seven additional samples were obtained from women in whom ovarian cysts or follicles were an incidental finding at laparotomy. After collection the fluid was stored in the deep-freeze until it could be assayed.

Four of the five Stein-Leventhal patients were shown by pelvic radiography after pneumoperitoneum to have enlarged ovaries before submitted to laparotomy. In addition, a number of routine urinary hormone assays were carried out on these patients as further aids to the diagnosis of the syndrome. 17-Ketosteroids were determined by the method of Gibson and Norymberski (1954), and 17-ketogenic steroids by minor modifications of the method of Norymberski *et al.* (1953). Pregnanetriol (5 β -pregnane-3 α :17 α :20 α -triol) was determined by the method of Bongiovanni (1954). "Total gonadotrophins" were measured by the method of Loraine and Brown (1956a, 1956b). The atlas of Greulich and Pyle (1950) was used for the determination of bone age. Progesterone, 17 α -hydroxyprogesterone, androstenedione, oestrone, and oestradiol-17 β were measured by the method of Short (1961).

Case Reports

Case 1.—Aged 24, menarche at 13; her periods were infrequent, and eventually she became completely amenorrhoeic, with a history of three years' infertility. On examination she was minimally hirsute, with a male distribution of pubic hair. The biochemical findings in the urine were: 17-ketosteroids, 8.8 mg./24 hr.; 17-ketogenic steroids, 13.2 mg./24 hr.; gonadotrophins, 21.5 and 16 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries with thickened capsules, the right ovary measuring 6 by 3.5 by 2.5 cm., and the left 6.5 by 3 by 2.5 cm. A bilateral wedge resection was carried out. Histologically the ovaries revealed a thickened theca interna layer; there was no corpus luteum present. Post-operatively she had regular monthly periods and the temperature chart showed evidence of ovulation; she has recently become pregnant.

Case 2.—Aged 20, menarche at 14; her periods lasted five days every two months initially, but eventually they occurred only once a year. There was a history of four years' infertility. On examination she showed minimal facial hirsuties, with a male distribution of pubic hair; the clitoris was normal. The biochemical findings in the urine were: 17-ketosteroids, 14.7 mg./24 hr.; 17-ketogenic steroids, 5.6 mg./24 hr.; gonadotrophins, 9.5 and 8.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries, the right ovary measuring 6 by 6 by 3 cm., and the left 5 by 5 by 3 cm. A bilateral wedge resection was carried out; histologically the ovaries showed a thickened capsule and follicular cysts with a prominent theca interna. Post-operatively she had regular monthly periods.

Case 3.—Aged 16, menarche at 10; her periods lasted five days every six months, and she had been hirsute for four years. On examination she was obese, grossly hirsute, and