used in this report. I am also indebted to those of my house-physicians who were responsible for carrying out the desensitizing injections.

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NEONATAL TETANUS IN NIGERIA*

BY

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Between April, 1953, and August, 1956, 141 cases of tetanus in newborn babies were treated in the children's department of University College Hospital, Ibadan, then in the Adeoyo Hospital. This disease is rare under modern conditions, and few series have been published which are large enough to permit statistical analysis, the largest being that of Loh Siew Gek (1951), who reported 174 patients from Singapore.

The mode of infection was described by Jelliffe (1950). The cord is cut at birth, often with a sharp stick or palm leaf, and is then dressed with a variety of unsterile materials, including clay, salt, shea-butter, a mixture of gin and palm oil, and "native medicine" which may contain cowdung. Finally a hot fomentation is applied.

The newborn baby has no immunity to tetanus (Cooke *et al.*, 1948), for even if the mother has previously had tetanus the amount of toxin absorbed in non-fatal tetanus is too small to provide an effective stimulus to antitoxin production (Cooke and Jones, 1943). A case occurred in this hospital in which a woman went into labour while suffering from tetanus. The baby was unaffected (D. D. Johnstone, 1956, personal communication).

Seasonal incidence of neonatal tetanus during the two-year period from June 1, 1954, to May 31, 1956.

Seasonal Incidence and Mortality

The incidence of neonatal tetanus during the two-year period June 1, 1954, to May 31, 1956, is shown in the Chart. The incidence is lower during the wet season (June to October) than during the dry period, averaging 3 cases a month for the wet season and 4.6 a month for the dry.

The mortality is shown in Table I. The results reported by other writers are set out in Table II. The sex incidence and mortality are shown in Table III.

TABLE I.—Mortality

Total No. of patients	141
Removed against advice	6
Recovered	14
Mortality in completed cases	89.6%

TABLE II.—Mortality in Other Series

Author	Place	No. of Patients	Mortality
Vinnard (1945)	New Orleans	11	55%
Jelliffe (1950)	Ibadan	25	96%
Friedlander (1951)	Durban	8	75%
Loh Siew Gek (1951)	Singapore	174	91%
Kao Yung-En (1951)	China	6	0%
Spivey <i>et al.</i> (1953)	U.S.A.	26	77%
Klenerman and Scragg (1955)	S. Africa	4	25%

TABLE III.—Sex Incidence and Mortality

	Male	Female
No. of patients	78	56
Recovered	10	4
Mortality	87.2%	92.5%

The mortality in the two sexes is not significantly different. $\chi^2=1.1$, $P=0.30$. The 6 patients removed against advice and 1 patient whose sex was not recorded are excluded.

Incubation Period

It may reasonably be assumed that, in neonatal tetanus, infection takes place soon after birth, and that the age of the patient at the time of onset represents the incubation period, although infection of the umbilicus can no doubt occur at any time before it is healed.

According to this assumption the incubation period was known for 135 patients, in whom it averaged 7.7 days. For the 14 who recovered the mean was 10.7 days, with a range of 6.5 to 20 days; for the 121 who died the mean was 7.3 days and the range 3 to 15 days.

Fifty-five patients had incubation periods of more than seven days, and 42 (76.4%) of them died. Among 80 patients with incubation periods of 7 days or less there were 79 deaths (98.7%). If the numbers of deaths in these two groups are compared, $\chi^2=18.0$, $P<0.01$, a very significant difference.

Similarly, among 16 patients with incubation periods of more than 10 days there were seven deaths (43.7%), whereas 119 patients with incubation periods of 10 days or less showed 114 deaths (95.8%). If these groups are compared, $\chi^2=41.0$, $P<0.01$.

Hines (1930) collected the records of 21 patients who recovered and found that the mean age at onset was 7.9 days, with a range of 5 to 14 days, whereas the 25 who died had a mean age at onset of 6.9 days and a range of 3 to 10 days. In Spivey, Grulee, and Hickman's (1953) series the mean age at onset of the six patients who recovered was 8 days (range 6 to 9 days), but for the 20 who died it was 6 days (range 4 to 9 days). Only one baby died among those whose incubation period was more than 7 days, and only one recovered among those in whom it was 7 days or less. Klenerman and Scragg's (1955) three patients who recovered had incubation periods of 4, 6, and 6 days.

Onset Interval

The onset interval is the period which elapses between the appearance of the first symptom, usually failure to suck, and the onset of tetanic spasms. Cole (1938, 1940) first drew attention to its prognostic importance when he found that the case mortality in tetanus varied inversely with the duration of the onset interval.

It was not easy to estimate the onset interval in these patients because of the uneducated African's vague sense of time, but a tentative estimate could be made in 42 cases, and the results are shown in Table IV.

The 36 patients who died had a mean onset interval of 0.9 days, the 6 who recovered a mean of 3.6 days. If the number of patients having an onset interval of 24 hours

*This paper formed part of a thesis accepted by the University of London for the M.D. degree, 1957.

TABLE IV

Onset Interval	No. of Patients	Deaths	Mortality
0-12 hours ..	22	21	95.4%
12-24 " ..	8	8	100%
24-48 " ..	5	4	80%
Over 48 " ..	7	3	42.8%

or less is compared with those having an onset interval of more than 24 hours, $\chi^2 = 10.3$, $P < 0.01$, which is very significant.

I could not find any reference to the prognostic value of the onset interval in neonatal tetanus, although its importance in older children and adults is well recognized. Cole (1940) stated that in patients who died the survival time never exceeded four times the period of onset, but these neonatal patients were often found to survive longer than would have been expected according to this rule.

Signs and Symptoms

Severity on Admission.—The patients were divided into two groups: (1) mild or moderate, and (2) severe, according to the degree of rigidity and the frequency and severity of the spasms on admission. The relation of severity to mortality is shown in Table V. If the number of deaths in these two groups is compared, $\chi^2 = 20.0$, $P < 0.01$, which is very significant.

TABLE V

	No. of Patients	Deaths	Mortality
Mild or moderate ..	44	32	72.7%
Severe ..	91	89	97.8%

Though from this it is evident that severity on admission is an important prognostic sign, the mortality is high even among cases assessed as mild. The administration of antitoxin before the onset of convulsions does not prevent them developing later (Diaz-Rivera *et al.*, 1948).

Pyrexia.—Spaeth (1940) considered that pyrexia was an adverse prognostic sign. In his series no death occurred among the 21 patients who were consistently apyrexial, but these were all older children.

An attempt was made to relate the mortality to the maximum and minimum temperatures of the patients in the present series. No correlation could be found between maximum temperature and mortality, but the mortality was found to be significantly higher in the group of patients whose minimum temperature did not fall below 98° F. (36.7° C.), as shown in Table VI. This finding probably indicates that sustained elevation of temperature is more serious than fluctuation.

TABLE VI

Minimum Temperature	No. of Patients	Deaths	Mortality
98° F. (36.7° C.) or less ..	102	88	86.3%
Over 98° F. ..	33	33	100%

$$\chi^2 = 5.0, P = 0.03.$$

Clinical Features.—The first symptom is always failure to suck from the breast. Sometimes the mother will complain that the baby is unable to open its mouth. Stiffness of the body and tetanic spasms develop after an interval which varies from a few hours to several days. As a rule development is rapid and the baby will show severe rigidity and frequent spasms in less than 24 hours. The umbilicus was never completely healed and often appeared to be infected, but gross sepsis was uncommon, although Spivey *et al.* (1953) stated that 18 of their 26 patients had gross umbilical sepsis and only one of these recovered. When the diagnosis was in doubt trismus was found to be the most reliable physical sign. Risus sardonicus and spasm of the orbicularis oculi muscles were not common in the absence of generalized spasms, and abdominal rigidity is difficult to assess in a baby.

Treatment

No special accommodation could be found for these patients, and they had to be nursed in a corner of the overcrowded children's ward close to patients with pneumonia and gastro-enteritis.

Jelliffe (1950), working in the same hospital, described the difficulty of nursing neonatal tetanus, and particularly the trouble caused by the mothers lifting their babies from their cots and carrying them on their backs. Nursing has improved a great deal since his article was written, and the mothers are now content to leave their babies undisturbed and to allow the nurses to feed and handle them.

Local Treatment.—Simple dressings were applied to the umbilicus when necessary, but no other local treatment was used. Vinnard (1945) and Dietrich (1951) both recommended umbilicectomy. Spivey *et al.* (1953) advised local infiltration of the abdominal wall around the umbilicus with antitoxin, and this was also used by Klenerman and Scragg (1955), who gave the antitoxin mixed with "hyalase," but they abandoned this form of treatment towards the end of their series.

Penicillin.—All the patients received from 150,000 to 300,000 units of procaine penicillin daily.

Use of Antitoxin

The dose of antitoxin ranged from 0 to 100,000 units, the whole dose being given as a single intramuscular injection without hyalase soon after admission. No patient was given antitoxin intravenously or intrathecally. The results obtained with the different levels of dosage are set out in Table VII.

TABLE VII

Units:	0-10,000	—20,000	—70,000	Over 70,000
No. of patients ..	20	15	81	17
Deaths ..	19	12	71	17
Mortality ..	95%	80%	87.6%	100%

If the number of deaths among those patients who received 10,000 units or less of antitoxin are compared with the number among those who received more than 10,000 units, χ^2 (with Yates's correction) = 0.23, $P = 0.6$. If 20,000 units is taken as the dividing line for a similar comparison, χ^2 (corrected) = 0.01, $P = 0.9$; and if the comparison is made around the 70,000 unit level, χ^2 (corrected) = 1.2, $P = 0.3$. These calculations do not reveal any significant difference in mortality associated with the different doses.

As a further test an examination was made into the survival time of patients receiving the different doses, recoveries being excluded. The results are shown in Table VIII. These figures show a significant increase in

TABLE VIII

Dose of Antitoxin	Survived		χ^2	P
	5 Days or Less	Over 5 Days		
0-20,000 units ..	27	4	5.4	0.02
Over 20,000 " ..	52	36		
0-70,000 " ..	71	31	2.3	0.12
Over 70,000 " ..	8	9		
20,000 to 70,000 units ..	44	27	0.72	0.40
Over 70,000 " ..	8	9		

the number of five-day survivors among the group receiving more than 20,000 units, but no further increase when the dose is raised to more than 70,000.

It is difficult to see why an increased dose of antitoxin should lead to a significant difference in survival time without any difference in mortality, but the practical conclusion is that a dose of 50,000 units of antitoxin is adequate in neonatal tetanus.

Sedation

At the beginning of the series the sedative used was sodium amylobarbitone, given intramuscularly in doses of 1 gr. (65 mg.) whenever necessary for the relief of spasms. This was thought to produce too much respiratory depression and was reduced first to $\frac{1}{2}$ gr. (32 mg.) and then to $\frac{1}{4}$ gr. (16 mg.) as necessary. It was then replaced by chloral hydrate, given by mouth in doses of 1-4 gr. (65-260 mg.), sodium amylobarbitone still being given to patients who could not swallow. Later still intramuscular paraldehyde was used almost exclusively in doses of 0.5 to 1 ml. as required.

The patients treated during the last nine months of the period under review received sodium phenobarbitone, 1 gr. (65 mg.), on admission and repeated after three or four days. This acted as a basal sedative and was supplemented with intramuscular paraldehyde when necessary. It was thought that this combination gave smoother sedation than paraldehyde alone.

The results obtained with the different sedatives (113 patients) are shown in Table IX. χ^2 is calculated by comparing the number of deaths occurring in the group of

TABLE IX

	Amylo- barbitone	Chloral	Paraldehyde	Phenobarbi- tone and Paraldehyde
No. of patients ..	15	18	46	34
Deaths ..	12	14	43	31
Mortality ..	80%	77.8%	93.5%	91.2%
χ^2 (corrected) ..	0.45	1.3	1.2	0.07
P ..	0.5	0.35	0.35	0.8

patients treated with each of the four sedatives with the number of deaths in the composite group treated with the three others. It shows that none of the sedatives used was significantly better than the others.

Feeding

All the babies were breast-fed up to the time of admission. At first, feeding with expressed milk was continued after admission, by spoon if the baby could swallow, by tube if it could not. Tube feeding was never very satisfactory, and was often difficult owing to trismus and the lack of tubes fine enough to be passed by the nasal route. Indwelling "polythene" tubes were tried, but were thought to cause more discomfort than the intermittent passage of fine rubber catheters.

The impression was gained that many of the babies died from asphyxia caused by the inhalation of regurgitated milk, since many of them collapsed and died soon after a feed. Unfortunately no post-mortem evidence could be obtained to confirm or refute this view, as at the time this work was done it was almost impossible to obtain consent for post-mortem examinations.

To avoid this danger, in the more severely ill patients it became the practice to dispense with oral feeding and to maintain hydration by giving daily subcutaneous infusions of 4.3% dextrose in 0.18% saline with hyalase. It proved difficult to give enough fluid in this way, and biochemical investigations carried out on the later patients in the series showed evidence of water depletion and nitrogen retention. Whenever there was clinical or biochemical evidence of dehydration, fluid was given intravenously to correct the defect. No attempt was made to satisfy calorie or protein requirements by the parenteral route.

As soon as the patients were able to swallow, oral feeding was resumed. It was found that if they were able to take feeds by mouth by the fourteenth day after admission they usually recovered, but if parenteral fluid had to be given for more than 14 days death ensued.

Tracheotomy was not employed, but it is possible that the lives of several patients might have been saved by it (Spivey *et al.*, 1953; Forbes and Auld, 1955).

Illustrative Case

A female infant was admitted on August 17, 1955, when 9 days old. The cord had separated on the third day and she had remained well until August 16, when she refused to suck from the breast, could not open her mouth, and began to have spasms. On admission her temperature was 98° F. (36.7° C.) rising to 102° F. (38.9° C.). She showed generalized muscular rigidity with frequent severe tetanic spasms. There were no other abnormal physical signs.

She was given 10,000 units of tetanus antitoxin on admission and sedated with paraldehyde, 0.5 ml. intramuscularly, as required. Oral feeds were not given, but she received daily subcutaneous infusions of glucose-saline with hyalase. The spasms gradually lessened and from September 3 she was able to take milk by spoon. When discharged on September 12 she was still very rigid, but was not having spasms. She attended the out-patient clinic after discharge and soon appeared to be perfectly normal.

Summary and Conclusions

This paper represents one of the largest personally treated series of neonatal tetanus cases yet published. The number is large enough to permit statistical analysis of the evidence presented upon the value of prognostic criteria and the results of treatment. It is not claimed that the results are good.

The mortality rate was 89.6%, including patients who died within 24 hours of admission. No significant difference was found in the mortality rates for males and females.

The incidence of the disease was higher during the dry season than during the wet, probably because of the greater amount of dust.

The length of the incubation period was found to be closely related to the mortality, the mean incubation period of those patients who recovered being 10.7 days and for those who died 7.3 days, the age at onset being assumed to be identical with the incubation period.

The onset interval was also found to bear a close relationship to the mortality, which was significantly higher in patients in whom the onset interval was less than 24 hours than in those in whom it was longer.

Pyrexia was not found to have an unfavourable effect upon the prognosis, but the mortality was significantly higher among patients whose minimum temperature never fell below 98° F. (36.7° C.).

The severity of the disease on admission was found to be a valuable but not infallible guide to the prognosis, as there was a significant difference in the mortality rates of those patients who were graded as severe and those graded as moderate.

The clinical picture of the disease presented no unusual features. Failure to suck from the breast was usually the first symptom.

No correlation was found between mortality and the dose of antitoxin, but there was a significantly longer survival time among those patients who received a dose of more than 20,000 units and who subsequently survived than among those who received less, though increasing the dose above 70,000 units did not lead to any further increase in survival time. From this it is concluded that a dose of 50,000 units is adequate.

Sedation is an essential part of the treatment, but no convincing evidence was obtained that any of the sedatives used possesses any particular advantage over the others. Sedation should be kept as light as possible to control spasms without producing respiratory depression.

The difficulty of feeding the patients and the frequency of respiratory complications when tube feeding was employed led to the practice of withholding food by mouth and maintaining hydration and electrolyte balance by parenteral fluid administration without regard to calorie or protein requirements.

Respiratory complications accounted for a number of deaths. Recent writers stress the importance of maintaining a good airway, if necessary by tracheotomy. It is likely that some of the deaths could have been avoided if this operation had been carried out.

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CALCIUM AND PHOSPHATE METABOLIC STUDIES IN PATIENTS WITH URINARY CALCULI*

BY

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As approximately 60% of urinary calculi contain calcium and 30% phosphate, it is tempting to think that abnormalities of calcium and phosphate metabolism play an important part in their development. The influence of the parathyroid glands on the metabolism of these ions, established by MacCallum and Voegtlin in 1908 and Greenwald in 1911, has been extensively investigated (Albright *et al.*, 1929, 1934) by balance studies and calcium infusion tests (Howard *et al.*, 1953; Nordin and Fraser, 1956), and the incidence of urinary calculi in cases of hyperparathyroidism has been stated to be 5% (Albright and Reifstein, 1948) and 8% (Beard and Goodyear, 1950): the high urinary output of calcium and phosphate which occurs in such circumstances predisposes to this.

The present investigation was undertaken to determine the incidence of calcium and phosphate metabolic disorders in a series of patients with urinary calculi. It was thought that such studies might reveal previously overlooked cases of parathyroid dysplasia and perhaps also demonstrate the incidence of "idiopathic" hypercalciuria (Flocks, 1940) and/or hyperphosphaturia. Eighty-five patients were studied after their urological treatment had been completed.

* Details of this paper were read at the Annual Meeting of the Surgical Research Society, held on July 19, 1957, at the Hammersmith Hospital and Postgraduate Medical School of London.

Methods

The patients were first screened by a simple out-patient test which was applied without preliminary dietetic or fluid restriction. A urethral catheter was passed and the bladder was emptied and washed with distilled water: the specimen was kept for analysis. The catheter was then clamped and left in position for one hour, at the end of which time the bladder was emptied again and the urine kept separately. A venous blood specimen was taken at the mid-point between the two urine collections.

Blood and urine specimens were quantitatively analysed for calcium, phosphate, and creatinine, and the urine calcium concentration/urine creatinine concentration (mg./100 ml.) and the urine phosphate concentration/urine creatinine concentration (mg./100 ml.) ratios were calculated.† Calcium in the blood and urine was determined by the method of Clark and Collip (1925), phosphate by the method of King and Wootton (1956), and creatinine by the method of Brod and Sirota (1948).

When abnormal values were found in the blood calcium and blood phosphate, or when abnormal urine calcium/creatinine or phosphate/creatinine ratios were detected, the particular patients were asked to come into hospital so that 24-hour urine calcium and phosphate excretions could be determined and in some cases calcium infusion tests carried out: 29 patients were found with one or more of these abnormalities, but only 15 agreed to come in. A low calcium diet (100 mg. daily) containing 500–700 mg. of phosphate preceded for four successive days the 24-hour urine collections, which were separately analysed for calcium, phosphate, and creatinine content; daily blood samples were obtained for creatinine estimations so that 24-hour creatinine clearances could be determined.

Intravenous calcium infusion tests were carried out on the fourth day of the low-calcium diet: 15 mg. of calcium per kg. body weight was given and 10% calcium gluconate in 500 ml. of 0.9% sodium chloride was used. The infusion was administered for four hours, from 10 a.m. to 2 p.m. Voided specimens of urine were obtained every four hours throughout the 24 hours which succeeded the commencement of the infusion and were kept separately. Blood specimens were taken at 9 a.m., 2 p.m., and 10 p.m. on the day of the infusion and at 10 a.m. on the following day. The blood and urine specimens were quantitatively analysed for calcium, phosphate, and creatinine.

The amount of calcium excreted in the urine in the 12 hours after the infusion is expressed as a percentage of the intravenous dose after due allowance is made for the 24-hour basal calcium output.

Iliac crest bone biopsy was performed on three patients, but no bone changes were found.

The Sulkowitch test was not done. It is a qualitative test and is positive when the urine contains 7–10 mg./100 ml. of calcium. It has little diagnostic value except when the total urinary output for 24 hours is known.

Results

Blood calcium values were estimated in all 85 patients: in 49 patients these were less than 10.5 mg./100 ml.; in 19 they ranged between 10.5 and 11 mg.; and in 17 they were greater than 11 mg. In 14 of the 17 patients who had

† Calcium clearance = $\frac{\text{urine calcium}}{\text{plasma calcium}}$ (mg.) and creatinine clearance = $\frac{\text{urine creatinine}}{\text{plasma creatinine}}$ (mg.) then $\frac{\text{calcium clearance}}{\text{creatinine clearance}} = \frac{\text{urine calcium} \times \text{plasma creatinine}}{\text{plasma calcium} \times \text{urine creatinine}}$. This ratio is found to be 0.03 in normal subjects when the average daily excretion of creatinine is 1.5 g. in males and 1 g. in females. And since the serum calcium value is approximately 10 mg./100 ml. and the plasma creatinine value 1 mg./100 ml., it is more convenient to use the urine calcium/creatinine ratio, which is found to be 0.3 in normal subjects. The phosphate/creatinine clearance ratio, deduced in a similar way, is found to be 0.12 in normal subjects (B. E. C. Nordin, personal communication).