Summary

A study is described of the part played by the umbilical cord of the newborn infant as a source of infection in a maternity hospital.

The cords of one group of babies were treated with triple dye. Nasal and skin swabs were compared with those of an untreated group in another unit and counts made of *Staph. aureus* colonies on settling-plates put down in the two nurseries. After a fortnight, treatment was introduced into the unit which had previously acted as a control, and similar investigations were carried out.

There was a significant difference between the treated and untreated groups in respect of both the nasal and skin swabs and the numbers of *Staph. aureus* colonies isolated from settling plates.

In a second investigation, treated and untreated babies were kept together in the same nursery. Skin swabs again showed a significant difference, but the nasal infection rates were the same in both groups.

The practical value of these findings is discussed in relation to the prevention of cross-infection among newborn infants.

This work was done while I was working at the Public Health Laboratory, Cardiff, and I would like to thank Professor A. S. Duncan, Professor A. G. Watkins, and the matron and staff of Cardiff Maternity Hospital for their co-operation. I am also grateful to Professor Scott Thomson and Dr. G. S. Wilson for their help with the presentation of this paper.

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In 1955 the British Council for Rehabilitation set up a working party to investigate "the gastric problem" in industry. The working party has now reported. Its chairman was Dr. F. AVERY JONES, and among its members were two professors of industrial health, six industrial medical officers, a physician, a psychiatrist, and a medical statistician. The report is very short (6 pages) and intended for lay readers. The principal conclusions are that gastric and duodenal ulcer are common among men to-day; that those prone to ulcer must avoid undue fatigue, anxiety, and irregular meals; and that both management and worker can help to reduce the problem. The report, entitled "Gastric and Duodenal Ulcer: A Modern Industrial Problem," can be obtained for 1s. 6d. from the British Council for Rehabilitation, Tavistock House (South), Tavistock Square, London, W.C.1.

BARBITURATE ANTAGONISTS TO SHORTEN DROWSINESS AFTER SEDATED B.M.R. DETERMINATIONS

BY

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The reliability of determinations of the basal metabolic rate depends largely on the certainty of the patients being basal during the test. It has been shown that preliminary sedation to the point of sleep can ensure this in nervous patients (Bartels, 1949; Fraser and Nordin, 1955). This technique, however, may leave the patient drowsy and confused for a variable and sometimes prolonged period after the test. We have therefore conducted the clinical trial reported below to assess whether the drowsy period can be shortened with barbiturate antagonists.

Two substances, bemegride (β -ethyl- β -methylglutaramide; "megimide") and amiphenazole (2:4-diamino-5-phenylthiazole hydrochloride; "daptazole") have been advocated for the treatment of coma due to barbiturate overdosage (Shulman *et al.*, 1955). Bemegride is a specific barbiturate antagonist, while amiphenazole has a similar weaker action but also acts as a nervous and respiratory stimulant (Shaw *et al.*, 1954). It seemed likely that these drugs might also shorten the period of drowsiness and confusion following smaller doses of barbiturates.

Method

The trial was arranged on a series of 10 patients whose sedated B.M.R. was being determined in hospital on each of two successive days. After the B.M.R. determination on one day they received the antagonist bemegride, the other day being used as a control. On both days the rate of awakening was carefully assessed so that any consistent difference between rates of waking on the two days could be determined and perhaps attributed to the antagonist drug.

Drug Dosage.—On each day the patient was sedated with three oral doses of 200 mg. (3 gr.) of sodium amylbarbitone ("sodium amytal") at 7, 8, and 9 a.m. Subsequently, at 10.30 and 11 a.m. on one day, he or she received two oral doses of the antagonist bemegride (each of 150 mg. in a 0.5% solution), while on the other, or control day, he or she received two apparently similar doses containing only saline. In the case of four patients the observer also was unaware which was the control day.

Assessment of Wakening.—From 10.30 a.m. the patient's drowsiness was assessed at half-hourly intervals until fully awake, using the following criteria:

Appearance		Speech		Gait	
Asleep	3	..	Incoherent	3	..
Drowsy	2	..	Slurred	2	..
Normal	1	..	Normal	1	..
				Gross impairment	4
				Moderate	3
				Slight	2
				Normal	1

Occasionally, observations on a control day were not followed through until the patient was completely awake.

These patients have been graded as fully awake half an hour after the last observation, an assumption which would tend to weigh against any waking effect of bemegride.

We are at present testing by similar means whether the addition of amiphenazole to the present regime will influence the rapidity or degree of waking. The results of this investigation are not yet complete.

Results

Time of Wakening.—In the accompanying Chart the average state of drowsiness at half-hourly intervals on all control days is compared with that on all bemegride days (10 control days, 13 bemegride days, 10 patients). This shows that on the control day normal speech was usually regained at 4½ hours, normal appearance at 5 hours, and normal gait at 6 hours, while after bemegride the corresponding times were much shorter: 3½, 3, and 3 hours respectively. The trial was planned so that the initial status of each patient should be as near the same as possible on each day. The

Average time in hours to reach normality on control days and bemegride days (13 patients).

mean initial values are seen to be very nearly equivalent, so that the more rapid waking after bemegride appears to be due to this drug.

Speed of Awakening After Bemegride Compared With Control Day

Cases*	Initial Status on Bemegride Day	Difference between Control Day and Bemegride Day (in Minutes) until Fully Awake as Judged by:		
		Appearance	Speech	Gait
1 (a)	Deeper	-120	120	120
1 (b)	"	-130	210	210
2 (a)	"	90	60	90
1 (c)	Equivalent	30	60	30
2 (b)†	"	90	30	60
3 (a)†	"	300	0	390
4†	"	30	-150	90
5†	"	300	300	300
6	Lighter	150	150	120
7 (a)	"	210	120	90
7 (b)	"	210	120	120
3 (b)	"	90	180	180
2 (c)	"	0	-90	120
	Mean Standard deviation	135 35.1	111 31.7	192 27.8

* Numbers indicate patients tested. Letters in parentheses show where the same patient was tested on more than one occasion.

† Blind assessments (observer unaware of which day was the control). Negative values record instances in which the patient took longer to reach normality on bemegride day than on control day.

The consistency with which this effect was observed is shown in the Table. Each patient's results are recorded separately, and the shortening of the time to reach normality after bemegride compared with the control day is shown for each of the three criteria. Any instances of lengthening of the time after bemegride have been recorded as negative values. The patients have also been grouped according to their initial status—whether it was judged slightly deeper, equivalent, or slightly lighter than on the control day. This grouping does not seem to have influenced the shortening of waking-time observed, confirming that this effect was not merely a reflection of differing initial drowsiness. On nine of the bemegride days waking was more rapid by all criteria. On the other four days waking was judged slower by only one criterion and never by that of gait, the most precise assessment of all three. These apparent exceptions therefore probably reflect merely the crudeness of the assessments.

It should also be noted that the four patients tested "blind" show as much evidence of bemegride effect as the others.

The average shortening in waking-time attributable to bemegride is 135 minutes for appearance, 111 minutes for speech, and 192 minutes for gait. This acceleration in waking-time is clearly significant when the mean values for all these differences in waking-time are considered; for each criterion alone, $P < 0.01$ by *t* test.

Toxic Reactions

Of the 10 patients who were closely observed, two became nauseated. This was the only toxic effect, and occurred after the second dose of bemegride in both instances. Under normal circumstances the second dose would probably have been withheld from one of these patients, since he was already sufficiently awake after the first dose. That this would have lessened the incidence of toxicity is shown by a consideration of the toxic effects observed in a further 45 patients who were not so closely observed, and from whom the second dose was sometimes withheld if the patient was reasonably awake after the first. In this group, two patients became agitated, four were nauseated, and two developed a skin rash.

Mental.—During the early period of the trial one nervous thyrotoxic patient became confused and agitated after the standard dose of bemegride. The significance of this effect was misinterpreted and a further dose given, with worsening of her excitement. A second patient, with myxoedema, became agitated after the two doses of 150 mg. In both instances the excitement was controlled by sodium amylobarbitone, 200 mg. by mouth, and subsequent sedated B.M.R.s followed by smaller doses of bemegride were performed without incident.

Gastro-intestinal.—Three patients complained of nausea and one actually vomited after the two standard doses of bemegride. One further patient complained of slight nausea after the first dose but did not vomit. Single doses repeated on subsequent days on the first three patients were unaccompanied by gastro-intestinal upset.

Skin.—Two patients developed a diffuse irritating erythematous rash on the trunk and limbs within 48 hours of bemegride administration. In both instances the rash was controlled by antihistamines and disappeared within 48 hours. The cause of the eruptions remains uncertain, as both bemegride and sodium amylobarbitone had been given in each case.

We conclude that the overall incidence of possible side-effects is 15% and that this figure may be much lower if the second dose of bemegride is withheld in all instances where the patient appears sufficiently awake after the first 150 mg.

Discussion

Previous workers have used bemegride in the treatment of barbiturate overdosage (Shulman *et al.*, 1955; Montuschi and Wickenden, 1955; Holten, 1955; Perinpanayagam *et al.*, 1955). From their findings it seemed likely that the drug would shorten the waking-time after barbiturate anaesthesia. Bentel *et al.* (1956) have recorded their results in a series of 108 patients in whom bemegride was used to terminate thiopentone anaesthesia. The drug was given by intravenous injection in doses usually of 25 and 50 mg. All patients were awake five to nine minutes after the injection, and side-effects were noted only after doses subsequently believed to have been excessive. Harris (1955) reported a similar series of 73 patients with no side-effects. Unfortunately there were no controls in either of these trials.

It could not be inferred from the results in barbiturate coma or anaesthesia that bemegride would also shorten the drowsiness following smaller doses of barbiturate. Our results give clear evidence of the effectiveness of oral bemegride in shortening the drowsiness and confusion following moderate barbiturate sedation. It can be seen that sedation adequate for B.M.R. tests may be followed by four to six hours of drowsiness and mild confusion which can be

shortened by an average of two to three hours by the use of bemegride. We have gained support for these observations in another series of 20 patients without control observation and in a further 25 patients who were not so closely observed.

The dosage used in the present series was standardized for purposes of comparison, and in the great majority this proved to be satisfactory. In practice, it should suffice to give one dose and follow it with a second only if the patient is still drowsy (and not nauseated) half an hour later. Only very occasional patients have shown slight agitation or nausea after the first dose of 150 mg. and only 5 out of 55 have shown these toxic effects after the two doses used. As nausea or vomiting is likely to be one of the earliest toxic effects, there is advantage in giving the drug orally. There was no evidence that thyrotoxicosis or myxoedema predisposed to toxic reactions.

On the basis of the above findings, we can now recommend oral bemegride as a practical and safe means of shortening the period of drowsiness which follows barbiturate sedation. One oral dose of 150 mg. in 0.5% solution should be given, and be followed by a second in 30 minutes only if the patient is then still drowsy and not nauseated. In this series barbiturates had been given in order to carry out sleeping B.M.R. estimations. There are many other diagnostic and therapeutic techniques, however, which require sedation and have therefore usually necessitated admission to hospital. If such barbiturate sedation is terminated by bemegride these procedures can be simplified, and may then even be performed in the out-patients department.

Summary

A series of 13 patients sedated with barbiturates for the purpose of B.M.R. determinations were studied to evaluate the action of a barbiturate antagonist, bemegride. A two- to three-hour shortening of the drowsy period was noted after bemegride compared with a placebo.

Bemegride was given in two oral doses of 150 mg. in 0.5% solution at an interval of half an hour. Toxic reactions were few and related mainly to the second dose.

Bemegride appears to have considerable value in facilitating the performance of therapeutic and diagnostic procedures which need barbiturate sedation.

We thank the nursing staff of Hammersmith Hospital who co-operated in this trial; also Dr. Edmund Alcock, medical officer, A. & G. Nicholas Ltd., for generous supplies of megimide.

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The British Council for the Welfare of Spastics has published a pamphlet containing four addresses on cerebral palsy. They were given at a conference for doctors in Birmingham last October, under Professor J. M. SMELLIE'S chairmanship. Professor R. S. ILLINGWORTH discusses the "Early Diagnosis of Cerebral Palsy"; Dr. FRANCES BRAID "The Aetiology of Cerebral Palsy"; Dr. H. M. COHEN "Cerebral Palsy and the School Health Service"; and Mr. A. INNES, F.R.C.S., "The Management of Cerebral Palsy." The pamphlet (pp. 40) may be obtained from the council at 13, Suffolk Street, Haymarket, London, S.W.1, price 3s. 6d. (post free).

FATAL DUODENAL PERFORATION DURING PREDNISONE THERAPY

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Prednisone, or Δ^4 -dehydrocortisone, is regarded as superior to cortisone both because of its greater potency and because, within the normal range of therapeutic doses, it has less sodium-retaining effect with little tendency to produce oedema. Bollet *et al.* (1955), however, reported the development of symptomless duodenal ulcers, identified radiologically, in 3 of 18 patients receiving prednisone or prednisolone (Δ^4 -dehydro-hydrocortisone) for rheumatoid arthritis.

The following report concerns the development during prednisone therapy of a symptomless duodenal ulcer which remained unsuspected until perforation and peritonitis were revealed at necropsy.

Case Report

A man aged 61 was first admitted to hospital on April 20, 1956, complaining of bilateral rib pain and a purpuric rash. On May 5 a diagnosis of multiple myeloma was made by sternal marrow examination, and was confirmed biochemically and radiologically. There was no history of digestive upset. Treatment was with urethane for 25 days and cortisone for 8 days. On June 14 prednisone, 5 mg. three times a day, was substituted for cortisone, while urethane therapy was continued. He was discharged from hospital somewhat improved five weeks later, and continued to receive these drugs at home. On August 14 he was readmitted complaining of vague abdominal pain, constipation, and dyspnoea, of one week's duration. By this time he had received a total of 920 mg. of prednisone. He was pale, with a recurrence of the purpuric rash which had been observed intermittently for the past year, and there was evidence of considerable weight loss since his last admission. The abdomen was soft and was not distended. Tenderness was not elicited in any area, nor was there any guarding or rigidity. Bowel sounds were heard. The rectum was full of soft faeces, but there was no tenderness. Pulse rate 80 per minute; blood pressure 95/50 mm. Hg. He became comatose shortly after admission, and died four hours later.

Post-mortem examination showed that death had been due to generalized peritonitis following perforation of a duodenal ulcer. The peritonitis was maximal in the upper abdomen and right iliac fossa, and there was a frankly purulent exudate between liver and diaphragm. The ulcer, which measured 3 by 0.6 cm., was situated vertically on the posterior wall of the duodenum, immediately beyond the pyloric sphincter. Histologically, it was a peptic ulcer of acute type which, except at the site of perforation, was almost confined to the mucosa and submucosa, with a minimal degree of fibrosis and virtually no involvement of the muscle coat. The probable duration of the ulcer was two to four weeks. The remaining positive findings were those of multiple myeloma.

Discussion

While there have been reports of dyspepsia developing during prednisone or prednisolone therapy (Bunim *et al.*, 1955; Margolis *et al.*, 1955; Fisher, 1956), a more striking finding was that of Bollet *et al.* (1955), who observed radiological evidence of duodenal ulceration, without corresponding symptoms, in three previously ulcer-free patients on