lymphosarcoma. Finally, synthesis of macroglobulins by lymphosarcoma tissue *in vitro* has been described by Abrams *et al.* (1949).

Malignant lymphosarcoma tissue may acquire the functional capacity to synthesize "paraproteins" following the occurrence of a somatic mutation. Habich (1953) and Kanzow *et al.* (1955) have performed immunological experiments with human macroglobulins which supports this concept. They found, by precipitin testing, that the abnormal proteins from different cases of macroglobulinaemia differ antigenically (and therefore chemically) from each other. Moreover, a rabbit sensitized to a human macroglobulin developed anaphylactic shock when the same macroglobulin was reinjected, but not when challenged by a macroglobulin from a different patient (Di Guglielmo and Salvini, 1954). Immunological differences among macroglobulins must reflect genetic differences in the cells synthesizing these proteins; such genetic differences are best accounted for by postulating the occurrence of a somatic mutation in the malignant cell line (Mackay, 1956). This mutation may occur independently or result from the disturbing effects of x-rays or chemical agents on cell mitoses. Macroglobulins were detected after such therapy in two of our four cases, but may have been present before therapy was given. A similar suggestion of a mutation process has been invoked by Rosenthal *et al.* (1955) to account for the development of haemolytic antibiotics in lymphomas.

Thus macroglobulinaemia is considered to result from an independent or an induced mutation in a malignant lymphoma which is usually, if not always, a lymphocytic lymphosarcoma. This concept of macroglobulinaemia most adequately accounts for the observed features of the disease. Moreover, it provides evidence suggesting that the occurrence of somatic mutation does, in fact, play a general part in the evolution of cancer (Mackay, 1956).

Summary

Four cases have been described to illustrate the clinical features of the syndrome of primary macroglobulinaemia. The diagnosis was established by ultracentrifuge analysis in each case. The condition should be suspected in lympho-reticular hyperplasias simulating lymphosarcoma with evidence of an abnormal protein in the serum (rouleaux formation, elevated sedimentation rate, cryoglobulinaemia, and positive Sia test). Filter-paper electrophoresis of serum reveals a component indistinguishable from a myeloma protein; if the bone marrow shows a marked lymphocytic increase (40–80%), with scanty plasma cells, the diagnosis is almost certain.

The disease may be an individual entity, although there is a strong resemblance to lymphosarcoma. Histological and immunochemical evidence suggests that macroglobulin synthesis may be the result of a somatic mutation in malignant lymphocytic tissue, which may occur independently or be induced by x rays or cytotoxic drugs. This concept is in harmony with the general somatic mutation theory of cancer.

The concept of the origin of macroglobulinaemia in a somatic mutation was developed in discussions with Sir Macfarlane Burnet. We are indebted to Dr. Ian Wood for assistance in the preparation of this paper, and to Professor R. H. Lovell, Dr. Eric Clarke, Dr. Leslie Hurley, Dr. T. H. Hurley, and Dr. J. H. Bolton for kindly allowing us to study patients under their care. We are indebted to Miss Sara Weiden for glucosamine analyses.

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CLINICAL TRIAL OF GLUTETHIMIDE IN LABOUR

BY

T. M. ABBAS, M.D., F.R.C.Sed., M.R.C.O.G.

Lecturer in Obstetrics and Gynaecology, University
of Bristol

The new drug glutethimide (α -phenyl- α -ethylglutarimide; "doriden") has been described as a rapidly acting non-barbiturate hypnotic and an effective sedative producing minimal side-effects. These qualities, coupled with encouraging results obtained from a small pilot survey, suggested its possible value as a sedative in the management of the first stage of labour. Accordingly, a clinical programme was drawn up, and answers to the following four questions were sought for and ascertained from the collected data: (1) Is glutethimide an effective sedative early in the first stage of labour, and how does it compare with the more commonly employed drug, chloral hydrate? (2) Will the use of glutethimide reduce the amount of analgesic drugs required during labour? (3) Is there evidence that glutethimide is effective in lessening the apprehension which is commonly a feature of the first stage of labour, particularly in primiparae? (4) Are there any maternal or foetal hazards associated with the administration of glutethimide in labour?

Literature.—Since the introduction of α -phenyl- α -ethylglutarimide by Hoffmann and Kebrle (1952), several papers have appeared in the literature confirming its sedative and hypnotic value. It has been successfully employed in cases of insomnia by Rushbrooke *et al.* (1956), in neuropsychiatric anxiety states, and as a pre-anaesthetic medication by Matlin (1956). Electroencephalograms have also shown that a dose of 0.5 g. of the drug compares favourably with that of 1½ gr. (0.1 g.) of quinalbarbitone sodium (Ladwig, 1955). An extensive pharmacological study of glutethimide has been made by Gross *et al.* (1955), and few toxic side-effects were recorded. There are no reports in the literature on its possible value in labour.

Method and Procedure

This study is based upon a survey of 100 normal parturient patients aged between 16 and 43 years, admitted to the professorial unit at Southmead Hospital, Bristol. There were equal numbers of primiparae and multiparae. All patients were given two tablets of glutethimide (each containing 250 mg.) early in the first stage of labour, when it

was certain that labour was well established and uterine contractions were causing some distress. Before each administration cervical dilatation was assessed per vaginam or per rectum.

Of the 100 cases reviewed, 91 received two tablets of glutethimide, eight had two such doses within four hours, and one required three doses in eight hours. Dilatation of the cervix in the latter case had not exceeded four finger-breadths when the third dose was given.

The effect of this form of sedation was studied from the subjective and objective points of view, and all results were appraised according to the degree of relief of pain, relaxation, sleep, and general well-being of the patient. Regular observations of blood pressure, pulse rate, foetal heart rate, and uterine contractions were made, and notes taken of any untoward side-effects. The duration and complications of all three stages of labour, the need for additional sedation or the administration of analgesic drugs, and the condition of the infant at birth were carefully noted.

For control purposes a second series of 100 cases, also normal parturient patients within a similar age range and comparable in other respects, were treated with 30 gr. (2 g.) of chloral hydrate in the form of the syrup. The choice of this drug as a yardstick was made because of its traditional use as a sedative in early labour.

Evaluation of Results in the Treated Group

Subjective Reactions.—Each patient was interviewed within two hours of the administration of glutethimide and subjective reactions were recorded as poor, where no relief was experienced whatsoever; fair, where patient noted some relief; good, where the pain was considerably alleviated; and very good, where only slight pain was noticed at the height of each contraction. Of the treated patients, 9 were rated very good, 61 good, 12 fair, and 18 poor.

Objective Reactions.—These were also noted within two hours of the administration of glutethimide, and were as follows: poor, where the patient remained restless; fair, where restlessness was reduced but patients were unable to sleep between contractions; good, where mental and physical relaxation were sufficient to permit sleep between contractions; and very good, where, in addition to good mental and physical relaxation, the patient was very cheerful and optimistic. Eighteen were rated as poor, 10 as fair, 63 as good, and 9* as very good.

Effect on Labour

Of the 100 patients reviewed in the glutethimide group, 98 had their infants presenting by the vertex, and, of these, 88 confinements terminated spontaneously. There were 10 forceps deliveries (nine occurred in primiparae), and in six of these the indication was malrotation with occipito-posterior position of the foetal head. In the remaining two cases the babies presented by the breech; one had a caesarean section on account of relative disproportion, the infant weighing over 9 lb. (4 kg.) at birth, and the other was delivered successfully per vaginam.

In the control series, 79 had a spontaneous delivery and 16 required forceps. In nine of the forceps deliveries the occiput was posterior in position. Two cases had a caesarean section on account of disordered uterine action and foetal distress respectively. There were also three assisted breech births.

Table I shows the comparative length of the various stages of labour. In the glutethimide group the average length of labour was 12 hours for primiparae and 7½ hours for multiparae. In the control series the corresponding figures

were 13½ and 8 hours. The apparently shorter labours in the glutethimide cases may well have been due to the rapid cervical dilatation brought about by the calming and relaxing effect of the drug.

The total amount of blood loss in the third stage of all cases treated with glutethimide was 920 oz. (26.1 litres), as compared with 895 oz. (25.4 litres) in the control group. Examination of these figures, however, revealed that there was no significant difference in the incidence of post-partum haemorrhage in the two groups (see Table II).

TABLE I

Stage of Labour	Time	Glutethimide Group	Chloral Hydrate Group
First ..	Up to 10 hrs.	69	65
	11-15 hrs.	16	21
	16-24 "	12	10
	24+ hrs.	3	4
	Average duration	11.72 hrs.	12.16 hrs.
Second ..	Up to 1 hr.	85	79
	1-2 hrs.	14	18
	Over 2 hrs.	1	3
	Average duration	1.08 hrs.	1.12 hrs.
Third ..	Up to 10 mins.	76	70
	11-30 mins.	17	19
	31-60 "	5	9
	Over 1 hr.	2	2
	Average duration	14.45 mins.	16.05 mins.
Average length of labour:			
Primiparae		12 hrs.	13½ hrs.
Multiparae		7½ "	8 "

TABLE II

	Chloral Hydrate Group	Glutethimide Group
Manual removal of placenta	2	3
Post-partum haemorrhage	13	12

Effect on the Newborn

The effect on the newborn infant of glutethimide sedation as employed in this study is shown in Table III. Class A consisted of infants who breathed and cried immediately after birth, appeared in no way narcotized or cyanotic, and

TABLE III

	Chloral Hydrate Group	Glutethimide Group
Class A	75	68
" B	23	27
" C	2	3
" D	0	2
Total	100	100

required no resuscitation. Class B included infants who were cyanosed and at no time gave cause for anxiety, and responded well to oxygen administered by face-mask and aspiration of the upper respiratory passages by catheter. Infants failing to respond to whiffs of oxygen and appearing deeply narcotized, apnoeic, and showing a fair degree of anoxia, but responding satisfactorily within half an hour, were classed as C. Those failing to respond adequately within half an hour were regarded as severely affected, and were grouped as class D.

No infant in the glutethimide group was placed under class D, thus substantiating the impression obtained in the pilot survey that infants born of mothers receiving glutethimide were quite alert and active. The two babies classed under C were born after a general anaesthetic had been administered to the mother, in one case for a caesarean section and in the second for a forceps delivery after manual rotation of the head. Absence of any harmful effect of glutethimide on the newborn infants was particularly notice-

*One of these nine cases which showed very good subjective and objective reactions was that of a young unmarried mother who was particularly apprehensive and depressed on admission. Shortly after the administration of glutethimide there was a dramatic change in mood and she became euphoric. This persisted throughout labour.

able in the 16 infants born within three hours after administration of the drug. All the 16 infants were classed as A.

Discussion

In this series of cases treated with glutethimide there were no maternal or foetal deaths and no significant untoward effects attributable to the drug. Four patients complained of nausea and a further five vomited within three hours of administration of the drug. These figures are more striking when one considers that the corresponding incidence of vomiting in the chloral hydrate group was 77.

Sleep ensued about 30 minutes after administration of the drug in 65 cases, and in 17 of these the level of the systolic blood pressure fell by 10 mm. Hg and the diastolic by 5 mm. This drop in blood pressure was maintained for three hours.

Table IV shows that the total amount of pethidine needed for additional sedation and analgesia in the glutethimide group was substantially below that required in the control

TABLE IV

Amount of Pethidine Required	Glutethimide Group	Chloral Hydrate Group
None	9	2
100 mg.	78	63
200 "	11	28
Over 200 mg.	2	7

For the purpose of the χ^2 test, two classes only were formed: (1) none and 100 mg.; and (2) 200 mg. and over. χ^2 corrected for continuity results as 12.08, which, on pure chance, would arise less often than about 1 in 1,000. It is therefore regarded as highly significant of a real difference in the amount of pethidine required.

series. In the glutethimide group, 87 patients required 100 mg. or less of pethidine, while 13 required 200 mg. or more. In the control group, 65 patients required 100 mg. or less, whilst 35 required 200 mg. or more.

Glutethimide was well tolerated by all patients, and none showed any allergic reaction. The normal course of labour in the glutethimide series was unaffected, the average duration of each stage of labour (see Table I) being slightly less—though not significantly so—than in the control group, and the general management of the first stage was greatly facilitated by the mental and physical relaxation induced by the drug. All patients who initially were apprehensive lost their fear and became fully co-operative shortly after administration of the drug.

There was no significant difference in the incidence of post-partum haemorrhage between the two groups (see Table II).

Conclusion and Summary

Administered in early labour, glutethimide was found to be an effective sedative, and was more easily administered and showed less evidence of gastric irritation than chloral hydrate.

It greatly reduced the requirements of pethidine for analgesia and additional sedation, the difference being statistically significant.

It alleviated apprehension, thereby encouraging relaxation and co-operation, and produced no evidence of any maternal or foetal hazard.

I am indebted to Ciba Laboratories, Ltd., for the supply of doriden employed in this trial and to their medical adviser, Dr. A. K. Pittman. I thank the sisters in charge of the labour ward for their assistance during this clinical trial. I am also indebted to Dr. G. Hurden for his statistical analysis of this paper. I am grateful to Professor G. G. Lennon for helpful advice and criticism.

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Medical Memoranda

Chronic Bromism

Although there are four mixtures containing potassium bromide in the *National Formulary* 1955, the drug is not so frequently prescribed as previously. Barbour, Pilkington, and Sargent (1936) found that 14% of 200 consecutive prescriptions contained potassium bromide. For the year 1949, in England, the figure of 5.8% has been quoted by Dunlop, Inch, and Paul (1953). These authors, in a survey of prescribing in Scotland in 1951, found a further decline in the use of bromide; in that year 1% of prescriptions contained potassium bromide. This 1%, however, represents an appreciable number of prescriptions, since in the month of October, 1951, alone 4,000 prescriptions containing bromide and chloral hydrate were dispensed in Scotland. A personal scrutiny of 10,000 prescriptions issued by general practitioners in Aberdeen between January and December, 1954, revealed 1.1% with potassium bromide as a constituent.

It is well known that the long-continued use of bromide may produce symptoms of "intoxication," but because of the decline in its use chronic bromism may be forgotten and overlooked. Attention is again drawn to the insidious onset and clinical picture of that condition.

CASE REPORT

A housewife aged 52 was admitted to hospital in October, 1953, suffering from mitral stenosis and congestive heart failure, manifest by dyspnoea, venous congestion, hepatomegaly, and slight oedema. She was successfully treated, and was discharged a few weeks later on a regime which included digitalis, 2 ml. of a mercurial diuretic intramuscularly once a week, and a diet of ordinary food with no added salt.

On October 13, 1954, she was readmitted at the request of her general practitioner on account of dysarthria, ataxia, and fatigue. After leaving hospital in 1953 she had complained of increasing tiredness. In August, 1954, progressive slurring of speech was noted by the patient and by her friends. At no time was there weakness of any one limb, but she complained of generalized stiffness, and in September her gait became unsteady. By this time she was spending most of the day in bed, rising at 9 a.m. and returning to bed again at 11 a.m. because of overwhelming fatigue. When she was readmitted in October she was unable to stand without support and was complaining of inability to express her thoughts in words; she also had difficulty in using her arms because of tremor.

On examination she was drowsy, lethargic, and uncooperative. She wept frequently, and was completely disinterested in her surroundings, but at no time were hallucinations or delusions noted. Speech was slurred, but there was no nominal aphasia. There was a coarse tremor of the hands and some apraxia was present. The gait was grossly ataxic and she was quite unable to stand without support. There were no other abnormal neurological signs. The mouth was dry and salivation scanty. There was no skin rash. Mitral stenosis was present, associated with mild congestive heart failure, the neck veins being distended and the liver palpable; there was no oedema.

Further inquiry revealed that for a year she had been taking a dose of a mixture containing, in each fluid ounce (30 ml.), 30 gr. (2 g.) of potassium bromide, 30 gr. (2 g.) of chloral hydrate, and 30 minims (1.8 ml.) of tincture of opium every night. She regularly took $\frac{1}{2}$ oz. (15 ml.) of this mixture, but on many occasions repeated the dose. During this period she was having a diet low in sodium chloride and was being given a mercurial diuretic, 2 ml. weekly by intramuscu-