CLINICAL EVALUATION OF METHYPRYLON (NOLUDAR®)+ AS A PREANAESTHETIC SEDATIVE HYPNOTIC

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MANY psychological factors affect the patient who requires an anaesthetic and an operation. To varying degrees these may influence the response to a curative or palliative operation, either to advantage or to disadvantage (1). These factors are of such an intangible nature that the wisest clinician has difficulty when he attempts to measure them either subjectively or objectively (2). The determination of the effect of drugs upon psychological changes induced by a stress situation in a hospital environment multiplies the complexity of the measurements (3).

It is exceedingly difficult for the clinical investigator to eliminate prejudice and bias, and it is even more difficult to formulate reliable and valid objective and subjective means for determining the value of procedures designed to influence favourably the psychological and physiological response of a patient to operation (4, 5). A few investigators have recently tackled this problem in a way which is unique in clinical medicine (6, 7, 8, 9, 10). They used combinations of sedative-hypnotic drugs and placebos in double blind studies. The results of such studies have provided us with highly revealing information. Herring (11) has studied this problem on an even wider base. In evaluating the effects of premedicant drugs he has referred to the psychological factors as "predictor" variables and to the factors representing the surgical response as "criterion" variables He divided the predictor variables into two categories: first, those measuring personality variables which may be elicited from patients prior to an operation, and second, the judgments made by psychologists using these measurements in an effort to predict responses during the operation. The criterion variables are also divided into two categories: first, the physiological response related to the operation (as determined by blood pressure, heart rate, tidal volume), the second, the judgments made on the basis of these factors by clinicians as to the patient's over-all stability. The predictor variables were categorized under nine different working variables, namely. anxiety or fear, lack of assertiveness, depression, instability or maladjustment, intellectual rigidity, high intelligence, introversion, primitive thinking and idiosyncratic stress reaction. It was stated that for patients showing any of the first eight factors unfavourable reactions on the physiological record (kept by the anaesthetist) would be presumed. Even with strict selective control as to the age, the sex, a normal cardiovascular system, the anaesthetic technique and the operative procedures in a group of 25 patients, Herring found the problem of predicting

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and the problem of evaluating critical tests of physiological and psychological parameters to be complicated, he concluded, "it may be found eventually that a more global analysis is required."

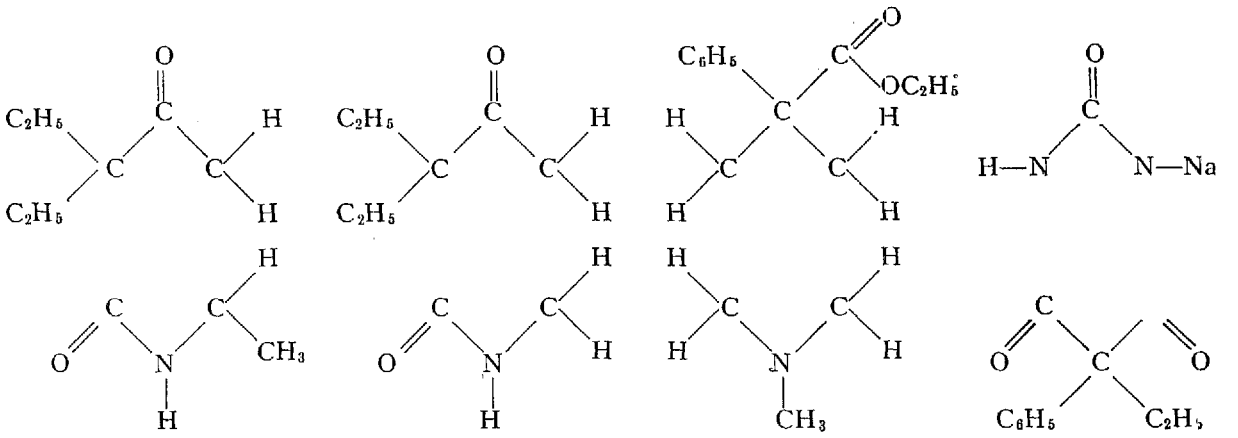
The many situations which can produce undesirable responses to anaesthesia and to operation have been reiterated by Wesley Bourne (12), who for many years has advocated that the patient should be brought to the anaesthetic induction in a dulled state, wherein all the circumstances and surroundings are clouded. Swerdlow and Lipworth (13) have discussed the broad approach to management of the psychological aspects of anaesthesia, an approach which may assist the patient throughout his stay in hospital. It involves mainly the development of close personal contact by the anaesthetist in order to induce rapport and provide reassurance to the patient. Catharsis of the patient's deep fears is urged and common sense measures to avoid morbid anticipation are recommended.

Because of the complexities of modern hospital procedures and hospital environment, the care of the patients by a variety of professional and non-professional personnel may, even with the best intentions, allow a wide range of undesirable psychic influences. These frequently enhance the undercurrent of anxiety or fear which first brought the patient to his physician and so to the hospital. Many years of experience have therefore led the clinician to rely more and more on drugs to produce the greatly desired tranquillity in patients. There are two aspects for the anaesthetist to consider. His most important problem is to determine whether the pharmacologically induced tranquillity is effective against the "predictor" variables. The other problem is the maintenance of stability of the "criterion" variables.

The most important desire of the patient is to have a sound, uninterrupted period of sleep the night before an operation, and on arrival in the operating room he should have a feeling of tranquillity and relaxation which renders him untroubled and unmindful of the entire situation until anaesthetic "sleep" is induced

A large number of drugs have been developed in the past few years which induce varying degrees of change in the outlook of the anxious, fearful patient, and the patient who is troubled by insomnia. Whether they work primarily for depression of functional complaints, or act as hypnotic sedatives, or change the patient's mood, or affect physical and mental overactivity is not of specific importance, provided that the over-all effect is desirable from the anaesthetic point of view in both psychological and physiological parameters (14, 15, 16)

During the past two years a mild sedative-hypnotic has received widespread clinical trials; it is said to have a pronounced soporific effect and provide prompt sedation in mild or moderate reactive agitation. This drug is now available in the open market without prescription of a physician This being so, it should be eminently free from ALL side effects and also have a wide margin of safety, while producing effective sedation and hypnosis. This drug is the pure piperidine derivative: 2,4-dioxy-3,3-diethyl-5 methyl piperidine. Its generic name is methyprylon. It is now known commercially as Noludar® (17). The structural similarity to Sedulon® (cough sedative), and the difference from Luminal® (sedative hypnotic) and Demerol® (sedative analgesic) are evident.



Chronic toxicity was studied by several clinicians in a large group of patients varying from those with mild insomnia to those with reactive agitation. No haematopoietic disturbances were observed with Noludar in several extensive studies (18, 19, 20, 21, 22). Bandman *et al.* (21) used large doses (1 Gm. daily) and found that with 500 hospital patients on this maintenance over two 7-day periods (with 2 weeks' rest between) there was a high incidence of nausea, vomiting, constipation, drowsiness, vertigo, and headache. With 1,000 hospital patients, given 250 mg of Noludar for night sedation only, drowsiness, vertigo, and nausea occurred with an incidence of only about 1 per cent each. This dose provided sleep within 29 minutes, and it lasted uninterrupted for 7 hours on the average Krause (23) found that 200 mg of Noludar appeared adequate for prolonged medication for night sedation. The response of patients with mild and severe insomnia was reliable, although this author found that those with nervous disorders responded best. Side effects noted were only occasional headache, nausea, restlessness, confusion or loss of appetite. In another study a double blind test of Noludar, Seconal® and placebo was carried out. Onset of sleep with the two drugs was similar (20–40 minutes) and duration of sleep was about 10 per cent longer with Seconal (5.9–6.5 hours). In another double blind study Cass *et al* (22) found that in patients with severe insomnia 500–750 mg Noludar reduced the delay in onset of sleep to one-fifth as compared to the placebo

If this drug is truly effective as a soporific and a sedative in the mildly agitated patient, these effects could be adequately tested in the patient being prepared for operation. The following study was therefore carried out to evaluate this drug as a preoperative sedative hypnotic.

Method

The day prior to a scheduled elective operation, a few patients were selected at random from the operative list to receive Noludar. The selection was made for convenience so that psychological and physiological parameters could be checked and recorded by the same person (F D.). The only limitation imposed was against children and patients scheduled for intracranial and cardiopulmonary operations (for whom established procedures were desired).

Each patient was seen once at the preoperative visit. At this time the record was checked and data were noted. An oral sleep dose of Noludar was ordered for bedtime, and an intramuscular dose of Noludar together with either atropine or scopolamine was ordered for injection one hour before the scheduled operation. At the preoperative visit, in addition to the routine procedures and questions, the patient was asked if sleeping pills were usually taken, past or present history of thyrotoxicity was checked, and the degree of nervousness was assessed. Blood pressure, pulse rate, respiration rate, and oral temperature were recorded. Tidal and minute volume of respiration was checked on an Emerson Breathometer.

When the patient arrived in the anaesthetic induction room the various predictor variables, as elicited from the patient by response to direct questions, were recorded. The judgments made by the anaesthetist in charge were recorded immediately thereafter This technique has been used in previous studies (2, 15) and is believed to be reliable and valid. Criterion variables consisting of preinduction vital signs and tidal volume measurements, the anaesthetic record of vital signs, the recovery room record, and the postoperative follow-up on the ward supplied the necessary physiological data. The judgments made of these factors by the anaesthetist indicated the patient's over-all stability in the specific stress situation.

Results

Table I summarizes distribution of patients by age (average 41 years), sex (mostly females) and size (average 1.64 square meters). In the preoperative psychological assessment of the patients in this study, 12 were considered very apprehensive and 159 were considered "normal." The majority of patients had received 300 mg. of Noludar at bedtime [157]. Twelve patients had received 250 mg. and 2 patients had received 200 mg. Of the 171 patients, 27 had taken night sedation previously (occasionally) and 17 patients had a history of thyroid dysfunction (not specified) The median time of onset of sleep after night medication was 30 minutes. The mean time of onset of sleep was 45 minutes. The nursing report indicated that sound undisturbed sleep was provided in the large proportion of patients (Fig. 1).

Premedication consisted of Noludar by intramuscular injection using 100 mg [157], 75 mg. [10], and 50 mg. [4] without other drugs [10], with 0.4 mg

TABLE I

Distribution by Age, Sex, and Surface Area

Age		10–19	20–29	30–39	40–49	50–59	60–	Totals
Sex	Male	2	3	5	3	5	8	26
	Female	4	33	39	28	25	16	145
Surface area, square metres	1.20–1.39	1	2	2	1	2	0	8
	1.40–1.59	2	20	17	8	6	4	57
	1.60–1.79	2	12	18	17	17	12	78
	1.80–1.99	1	2	5	4	4	8	24
	2.00—	0	0	2	1	1	0	4
Totals		6	36	44	31	30	24	171

atropine [104], with 0.6 mg. atropine [3], and with 0.4 mg. scopolamine [54]. The mean time interval from intramuscular injection of Noludar to induction of anaesthesia was 97 minutes. This time interval was fairly consistent within clinical limits.

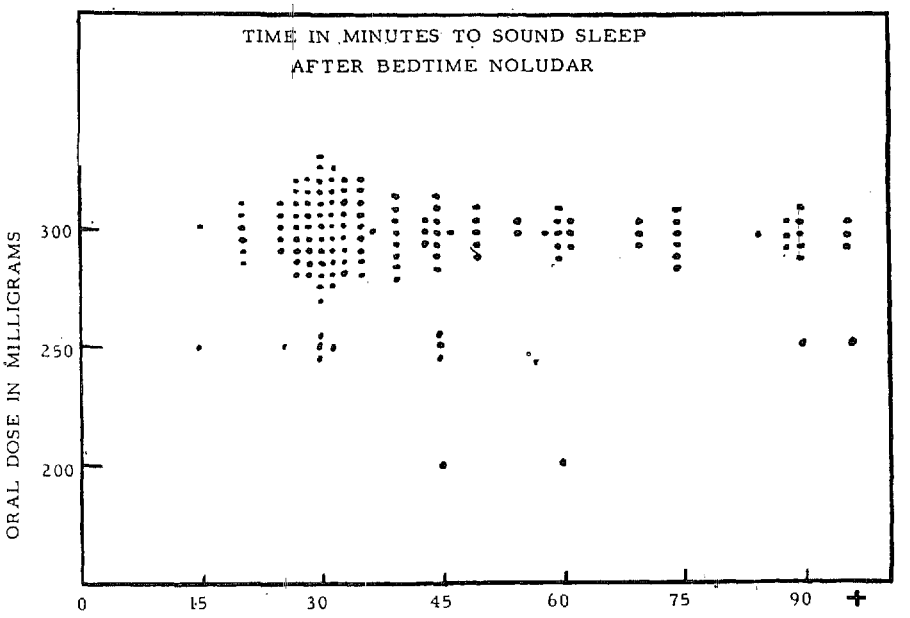


FIG. 1. Achievement of sound sleep after Noludar. Each dot represents time of onset of undisturbed sleep.

The effect of premedication on vital signs is summarized in Table II. Only slight depression of respiration was observed. No change in blood pressure or pulse rate was evident. Sites of operation are tabulated in Table III. In 162 patients in this study anaesthesia was induced with an average dose of 390 mg. of thiopental. In only 2 patients was a dose in excess of 500 mg. used. Anaesthesia was maintained by the semi-closed [121], semi-open with Fink valve [28] or closed system [13]. Maintenance was with nitrous oxide–trichlorethylene, nitrous oxide–ether or cyclopropane. Nine patients received a spinal anaesthetic with hyperbaric tetracaine.

Tables IV, V, and VI summarize the predictor variables studied and the judgments as to efficiency of premedication and facility of anaesthetic induction. It was evident that Noludar, with or without a belladonna derivative, did not provide adequate premedication. In Table VI slow or difficult induction indicates the occurrence of coughing, crowing, hiccoughs, mild laryngospasm, or

TABLE II

EFFECT OF PREMEDICATION ON VITAL SIGNS

	Temp. F.	B.P. mm./Hg.	Pulse /min	Resp. /min	Tidal vol. litres	Minute vol. litres
Admission	98.3	123–73	79	20	—	—
Presedation	98.2	120–72	76	18	.450	8.1
Pre-induction	97.8	121–75	81	16	.420	6.7

TABLE III

OPERATIVE SITE

Extremities.	Superficial	4
	Bone	9
Head and neck		5
Chest wall		12
Abdomen	Upper	11
	Lower	33
Pelvic	Gyn	85
	Other	12

TABLE IV

PREANAESTHETIC STATE

A Patients' answers to direct questions			
	Noludar alone (10) %	c̄ Atropine (107) %	c̄ Scopolamine (54) %
Discomfort	20	16	28
Worried	20	32	28
Tense	40	34	36
Euphoria	20	11	10
Drowsy	40	44	72
Nausea	0	11	22
Emesis	0	2	2
Diplopia	0	8	15
B Anaesthetist's own impression as to patients' state			
	Noludar alone (10) %	c̄ Atropine (107) %	c̄ Scopolamine (54) %
Discomfort	20	8	9
Apprehension	70	35	26
Excitement	30	8	13
Euphoria	0	10	4
Drowsy	40	34	70
Nausea and emesis	0	11	18
Talkative	20	21	33

TABLE V

CHARACTER OF INDUCTION WITH THIOPENTAL

(162 patients)*

Premedication	Smooth	Excess secretions	Slow-difficult	Stormy
Noludar alone (9)	1	6	2	0
Noludar + Atropine (102)	72	9	20	1
Noludar + Scopolamine (51)	38	4	7	2

*9 patients had spinal anaesthesia

TABLE VI

ANAESTHETIST'S IMPRESSION OF ADEQUACY OF PREMEDICATION

(Pre-induction 171 patients)

Premedication	Adequate (%)	Inadequate (%)	Excessive (%)
Noludar alone (10)	30	70	0
Noludar + Atropine (107)	40	60	0
Noludar + Scopolamine (54)	63	35	2

technical difficulty Three patients had a stormy induction because of crowing and fighting [1], severe laryngospasm [1], and severe bronchospasm [1].

Hypotension (60/30 mm. below preoperative level) on induction of anaesthesia occurred in 2 (of 10) patients receiving Noludar alone. Moderate hypotension (30/15 below preoperative level) occurred in 48 (of 107) receiving Noludar with atropine, and in 29 (of 54) receiving Noludar with scopolamine.

In the immediate postoperative period no patient had severe hypotension. Moderate hypotension (25/16 mm. below preoperative) occurred in 78 of the 171 patients. Most of these responded with a rise in pressure when the legs were wrapped or the foot of the bed was elevated. After completion of the operation, the patients receiving Noludar alone or Noludar with atropine were awake within 30 minutes (average 26 minutes). Those who received Noludar with scopolamine slept somewhat longer (average 37 minutes).

In the postoperative report, no amnesia was evident for injection of premedication, trip to the operating room and movement to the operating table, regardless of whether a belladonna derivative was given or not. Only 3 of the patients stated that induction of anaesthesia was unpleasant, while 33 stated that it was pleasant The remainder were indifferent During the immediate postoperative period (24 hours), 5 had urinary retention (3 per cent), 30 had shivering (18 per cent) and 73 had nausea and/or vomiting (43 per cent).

Discussion

The moment a patient is informed that an operation is necessary a deleterious psychic alteration may be initiated or enhanced. It is therefore of utmost importance that everyone who comes into contact with the patient should attempt to provide a relaxed and tranquil atmosphere which will imbue the patient with confidence and reassurance.

The physicians who care for the patient are at once faced with a dilemma. They must make an expert psychological assay of the psychic strength of this patient, and determine how much support is required both verbally and by pharmacological means Either one of these supports, if not wisely chosen, can aggravate the psychic trauma which may follow.

The anaesthetist, who briefly visits the patient for the first time on the evening before operation, must at this one contact assess this situation and attempt to evaluate the psychic and physiological stamina of the patient (24). He has no time to carry out an extensive psychological interview to develop a graphic picture of the patient's personality profile, nor should he be prepared to add such physiological parameters as a BMR determination and a Thorn test, unless there are clear and urgent indications for these. He must therefore depend on supportive therapy with premedicant drugs. The choice of drugs, or even placebos, is therefore of utmost importance (25, 26, 27, 28).

The role of the anaesthetist as far as the patient is concerned involves the provision of creature comforts. The period elapsing between information of an impending operation and recovery from the procedure provides the anaesthetist with a complex situation in which he must balance administration of pharmacological agents against the desire for maintaining physiological homeostasis.

In order to achieve this balance, the anaesthetist considers the drugs available, the patient's pathological and physiological condition, and the three fundamental desires described by Little and Stephen (29), namely. anaesthesia and operation should be safe and pleasant for the patient, the surgeon's work should be facilitated and the patient should reach the postoperative period of convalescence in a quiet and pleasant way, without disturbance of his physiological mechanisms for maintaining homeostasis. The importance of these fundamental requirements has been widely recognized. The place of premedicant drugs in this scheme is to initiate psychic sedation in order to allay apprehension and produce a tranquil, serene, calm patient who is untroubled by mental or emotional disturbances. These should also have an amnesic property, reduce salivary secretions, and depress autonomic reflex reactions. Other important considerations are that the effect of the drug should be highly predictable, that cardiorespiratory homeostasis remain intact, and that undesirable reactions such as excitement, delirium, nausea, vomiting, disturbed vision and headache rarely occur. When evaluating a new agent, "the six unities in medical research" should be respected (30)

The anaesthetist can usually accomplish the above desires with the following routine measures. The evening before operation the patient receives a capsule or tablet by mouth, which will induce sleep within a reasonable period of time (15 to 30 minutes). This sleep should last 6 to 8 hours and be dreamless, undisturbed, and without depression of cardiorespiratory function. When the patient awakens from this sleep, a refreshed feeling should be evident and no nausea, dizziness, or other discomfort should be felt. Before the patient is fully awake an intramuscular injection should be given to produce mild sedation, hypnosis, amnesia, and drying of salivary secretions. The effect of this injection should be optimal when the patient is moved to the anaesthetic induction room about 45 to 90 minutes later. The anaesthetist would like to find the patient somewhat drowsy, but easily responsive, and undisturbed by the preparations for induction of anaesthesia On checking the vital signs, there should be no wide alteration in the blood pressure, pulse rate, or rate and depth of respiration. Induction of anaesthesia should be smooth—without irregular breathing, hiccoughs, unexpected apnoea, or unexpected need for large doses of induction agents. The induction of anaesthesia should not be accompanied by sudden severe depression of cardiorespiratory homeostasis. Only when pharmacological agents fulfil these desires can the search for improved drugs cease

Although the method of study used here was slow and tedious and precluded a large series of patients it was felt that the information derived was clear cut and unequivocal in each determination Since collateral evidence was available we did not have to pass judgment solely upon this closed body of data (31).

From these results it was evident that Noludar was an excellent night sedative-hypnotic. Its effectiveness in the preoperative sedation, however, left much to be desired, and it should therefore be considered unsuitable for administration at that time, even though many were better sedated when scopolamine was added.

SUMMARY

A controlled clinical evaluation of the psychological and physiological effects of Noludar was carried out in 171 patients in the preoperative state, employing this drug as a night sedative-hypnotic, and as preoperative medication, with or without the belladonna derivatives. Noludar was found to be a valuable agent for night sedation, but unsuitable for sedation in the immediate preoperative medication.

RÉSUMÉ

On a fait une évaluation clinique contrôlée des effets psychologiques et physiologiques du Noludar sur 171 malades au cours de la période préopératoire, on a employé ce médicament aussi bien comme sédatif hypnotique la veille de l'opération que comme médication préopératoire, associé ou non aux dérivés de la belladone On reconnaît au Noludar une valeur comme sédatif nocturne, mais comme médicament préopératoire immédiat, sa valeur est faible.

REFERENCES

1 ALTSCHULE, M D Bodily Physiology in Mental and Emotional Disorders, pp 228 *et seq* New York Gruene and Stratton (1953)
2 COHEN, E N & BEECHER, H. K Narcotics in Preanaesthetic Medication, Controlled Study Report to Council on Pharmacy and Chemistry J A M A, *147*: 1664 (1951)
3 GOTTSCHALT, L A. *et al.* Explorations in Testing Drugs Affecting Physical and Mental Activity J A M.A, *161* 1054 (1956)
4 BEECHER, H K Experimental Pharmacology and Measurement of the Subjective Response Science, *116* 157 (1952)
5 —— Appraisal of Drugs Intended to Alter Subjective Responses, Symptoms Report to Council on Pharmacy and Chemistry J A M A, *158* 399 (1955)
6 LASAGNA, L A Comparison of Hypnotic Agents J Pharmacol & Exper Therap, *111*: 9 (1954)
7 LASAGNA, L, VON FELSINGER, J M & BEECHER, H K Drug-Induced Mood Changes in Man, I Observations on Healthy Subjects, Chronically Ill Patients and Post-Addicts J A M A, *157* 1006 (1955).
8 VON FELSINGER, J M, LASAGNA, L & BEECHER, H K Drug-Induced Mood Changes in Man, II Personality and Reactions to Drugs J A M A, *157*. 1113 (1955)
9 HARE, E H Comparative Efficacy of Hypnotics A Self-Controlled, Self-Recorded Clinical Trial in Neurotic Patients Brit J Social Med, 9 140 (1955)
10 LASAGNA, L A Study of Hypnotic Drugs in Patients with Chronic Diseases J Chronic Dis, 3 112 (1956)
11 HERRING, F H Response during Anesthesia and Surgery Psychosom Med, *18* 243 (1956)
12 BOURNE, W Mysterious Waters to Guard, pp 87 *et seq* Oxford Blackwell (1955).
13 SWERDLOW, M & LIPWORTH, M The Psychological Approach in Anaesthesia Anaesthesia, *6* 96 (1951)
14 LEAKE, C D New Mood-Changing Drugs Ohio State M J, 52 369 (1956)
15 DOBKIN, A B, GILBERT, R. G. B & MELVILLE, K I Chlorpromazine Review and Investigation as a Premedicant in Anesthesia Anesthesiology, *17* 135 (1956)
16 IMBODEN, J & LASAGNA, L An Evaluation of Hypnotic Drugs in Psychiatric Patients Bull Johns Hopkins Hosp, 99 91 (1956).
17 PARSONNET, A E, BERNSTEIN, A, KLOSK, E, HIRSCHBERG, E., RUBIN, S. H. & PIRK, L A Evaluation of a New Sedative Drug (3,3 diethyl-2,4 dioxo piperidine) J. Lab. & Clin Med, 33. 602 (1948).

18. PELLMONT, B , STUDER, A & JURGENS, R. Noludar, a New Sedative-Hypnotic. A Piperidine Derivative. Schweiz med Wchnschr., *85*. 350 (1955).
19 LOUGHLIN, E. H., MULLIN, W G., SCHWIMMER, J & SCHWIMMER, M Clinical Studies on Toxicity and on Hypnotic and Sedative Effects of RO 1–6463, Noludar (33 diethyl 24 dioxo 5 methylpiperidine) Intern Rec. of Med , *168* 52 (1955).
20 KEMPER, H Experiences in Psychiatry with a New Hypnotic from the Piperidine Series Deutsche med. Wchnschr , *80*. 1034 (1955).
21 BRANDMAN, O , CONIARIS, J & KELLER, H. E A New Mild Sedative-Hypnotic A Piperidine Derivative (Noludar) J M Soc. New Jersey, *52*. 246 (1955)
22 CASS, L J , FREDERIK, W S & ANDOSCA, J B Methyprylon A New Sedative and Hypnotic Drug New England J Med., 253 586 (1955)
23 KRAUSE, H Clinical Experience with a New Non-barbiturate Hypnotic ("Noludar") Schweiz med Wchnschr., *85* 355 (1955).
24 LOVSHIN, L L Signs that aid in Diagnosing Functional Disease Postgrad. Med , *19* 526 (1956)
25 FRIEND, D G & MCLEMORE, G A Some Abuses of Drugs in Therapy. New England J Med , *254* 1223 (1956)
26 EBAUGH, F G The Use and Abuse of Sedative and Hypnotic Drugs Postgrad Med , *19* 513 (1956)
27 REIDT, W U Fatal Poisoning with Methyprylon (Noludar), a Non-barbiturate Sedative New England J Med , 255: 231 (1956).
28 LESLIE, A Ethics and Practice of Placebo Therapy Am J Med , *16*: 854 (1956)
29 LITTLE, D M , Jr & STEPHEN, C R Modern Balanced Anesthesia Concept Anesthesiology, *15* 246 (1954)
30 ALBRITTON, E C The Six Unities in Medical Research J A M A , *161* 328 (1956)
31. WRIGHTON, R Statistical Experimentation in Therapeutics. Brit J Social Med , 9· 135 (1955).