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ANALGESIC AND OTHER ACTIONS OF SOME DITHIENYLBUTENYLAMINE COMPOUNDS IN MAN

BY

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Adamson (1950) synthesized some dithienylalkenylamines which had atropine-like, antihistaminic and local anaesthetic properties. In addition, it was found that these compounds were powerful analgesics in animals (Adamson and Green, 1950; Green, 1953). Since they have a different chemical structure from other drugs which produce a morphine-like action it was obviously important to study their actions in man.

In this paper we describe such an investigation which has been divided into two parts, the first dealing with observations on the effects of these drugs in normal subjects, and the second describing the results of a pilot trial in patients.

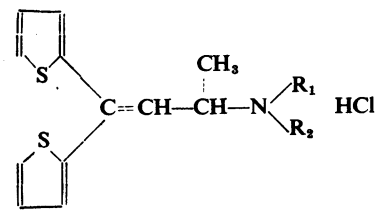
The observations on normal persons have been designed mainly to study side-effects of the drugs, which can be more accurately recorded in this way than in a clinical trial (Denton and Beecher, 1949). The effects on respiration have been fully investigated.

Previous studies had shown that the dithienyl compounds were less potent than morphine, but rather more potent than pethidine in relieving experimental ischaemic muscular pain (Keele, 1952). However, we agree with Beecher (1951) that a clinical trial is the only satisfactory way of estimating the analgesic potency of a drug, so as soon as possible we began to make observations on patients.

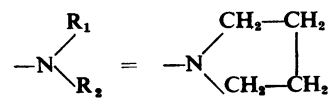
Owing to the occurrence of certain side-effects in normal subjects we had to make these studies more of a "pilot trial" than a controlled investigation. Nevertheless, we have recorded results which, in our opinion, justify definite conclusions concerning the therapeutic value of these dithienyl compounds.

METHODS

Drugs Used.—(*a*) The general formula of the dithienylbutenylamine series is:

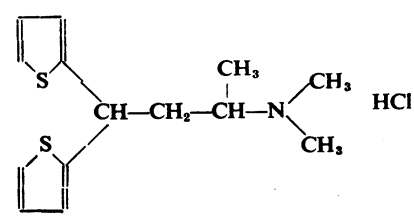


The compounds used were: 1C50, where R_1 is CH_3 and R_2 is C_2H_5; 191C49, where R_1 and R_2 are both C_2H_5; and 268C49, where



(Adamson & Green, 1950)

The following dithienylbutylamine compound, 489C49, was also used:



(Adamson, Duffin, and Green, 1951)

Compound 489C49 is readily soluble in water; the solution can be sterilized by autoclaving, and is stable for several months. It was made up as a solution containing 100 mg. in 1-ml. ampoules. Compound 268C49 has similar physical properties and was made up in a solution containing 75 mg./ml.

Compounds 191C49 and 1C50 are unstable in aqueous solution, and were available as granular white powders (50 mg. in a glass phial); the powder was easily dissolved in 1 ml. of sterile water before injection. (*b*) Other analgesic drugs used were: morphine sulphate, pethidine hydrochloride, and (±)- and (−)-methadone hydrochloride.

All the drugs were injected intramuscularly (into the deltoid) in both normal volunteers and in patients. The dithienyl compounds are inactive by mouth.

Studies in Normal Volunteers

The drugs were administered to 9 male and to 3 female student volunteers, aged 22 to 29 years, in order to record the degree of respiratory depression and the occurrence of side effects. The effect on breathing was measured by recording the amplitude and rate of respiration.

On the day of an experiment the subjects had a normal breakfast at 8 a.m., after which they took no more food till the experiment was over. They came to the B.M.R. Department of the Courtauld Institute of Biochemistry at about 1 p.m. and lay on couches for ½ hr. before the first respiratory record was made. Breathing was graphically recorded by the Benedict-Roth closed circuit apparatus; the subject breathed oxygen, and the CO_2 was absorbed by soda lime. Each subject used the same individual machine throughout these studies. Each respiratory record was taken for 7 min., the last 5-min. period being used for measurements of the rate and amplitude of breathing, from which the pulmonary ventilation was calculated.

Preliminary respiratory records were made after ½ hr. and after 1 hr. of rest on the couch. The drug or control solution was then injected and further respiratory records were made ½, 1, 2, 3, and 4 hr. after the injection. In all these experiments the nature of the injected solution was unknown to the recipient, and on many occasions it was also unknown to the administrator. The occurrence of side effects was noted, and arterial blood pressure and heart rate were recorded during most of the experiments.

Estimation of Respiratory Depression

In calculating the effect of a drug on respiration the second of the two preliminary records (after 1 hr. rest) was taken as the normal standard of reference, and subsequent changes in respiratory rate and amplitude, and in pulmonary ventilation, were expressed as percentage deviations from these standard values.

The total respiratory depression (or stimulation) after injection of the drug was calculated from the percentage deviations plotted against time. The total effect was proportional to the area under the curve expressed in arbitrary units (see Fig. 4).

Methods in Clinical Trial

The clinical trial was performed almost exclusively on patients with post-operative pain, the patients being selected according to the following criteria:

1. The pain had to be of sufficient intensity for the patient to require a powerful analgesic drug.

2. The post-operative condition of the patient had to be good enough to justify the administration of a new drug whose side effects were not well known.

3. The patients had to be sufficiently intelligent, and sufficiently recovered from the effects of the anaesthetic drugs, to understand and answer simple questions concerning their feelings.

4. Patients who had had abdominal operations were generally excluded from the trial, since the pain associated with spasm or distension of the gut is variable in its time-course, and can be relieved by measures which lead to the passage of flatus.

The patients were, of course, unaware of the nature of the drug which they were given, and did not know that they were participating in a clinical trial. We should also have preferred the administrator to be ignorant of the nature of the drug which he injected, as in the investigation described by Keats, Beecher, and Mosteller (1950). However, in our trial we were dealing, not with well-tried drugs of known toxicity, but with new compounds which had to be suspected of undesirable properties. We considered that it was not justifiable to give such compounds as "unknowns" to patients just recovering from operations. Other factors concerned in the administration and assessment of the drugs were dealt with as follows:

All drugs were given intramuscularly into the deltoid by one of us (P. F.) who also made all the observations on the effects. In recording the time-course of the pain it was not possible to use pain charts made by the patient as described by Hewer, Keele, Keele, and Nathan (1949) in their studies on the effects of analgesic drugs in patients with chronic pain. Instead, the patients were carefully questioned at frequent intervals concerning the site and intensity of pain, and notes were made on their general appearance, and on the presence of restlessness or anxiety. In recording the intensity of pain the observer questioned each patient so as to grade the pain on the following scale: none=0, slight=1, moderate=2, severe=3, very severe=4. In many cases it was obvious from general appearances, even before questioning the patient, that there had, or had not, been any relief of pain. The intensity of pain was recorded before injection of a drug, ½ hr. after the injection and then at hourly intervals until another injection was required, or until it appeared that the pain was not likely to recur. In addition to the usual data recorded on case sheets, particular attention was paid to the occurrence of side effects, and arterial blood pressure, heart rate and respiratory rate were recorded when the patient was questioned about his pain. It quite often happened that a patient was asleep when the time for questioning arrived; pain was then assumed to be absent and the patient was allowed to sleep on.

The new drugs of the dithienylbutenylamine series were given as first injections as often as possible, in

order to obtain a sufficiently large number of observations on their action. Even where only one injection was given it was useful to know that the drug had apparently been effective, the more so since the number of patients who require analgesic drugs for post-operative pain is relatively small. Of course, much more valuable information was obtained when several injections of analgesic drugs were needed, so that the effects of a new drug could be compared with those of morphine and pethidine.

We did not think it was justifiable to use injections of saline as controls, since, as described by Beecher (1951), they give satisfactory pain relief in no more than 20% of patients. What we did to test our patients' powers of discrimination was to see if they could distinguish the effects on their pain of two different doses of the analgesic drugs. In some instances the small doses were quite ineffective, which was more valuable information than would have been provided even by injections of saline, as it gave us the lower limit of effective dosage. This procedure was particularly valuable in our studies of compound 1C50.

In addition to pethidine hydrochloride and morphine sulphate, the following dithienyl drugs were used in the clinical trial: 268C49; 489C49; 1C50; a few injections of 191C49 were also given.

RESULTS

Studies in Normal Subjects

Actions of Drugs on Respiration

Effect of the Spirometer on the Rate of Breathing.—Early in the course of the breathing experiments it was noted that the respiratory rate at rest was reduced when the subjects were made to breathe into the spirometer. In 50 experiments the rate was counted just before the machine was connected, and again from the subsequent graphic record. Table I shows the effect of the spirometer on the rate of breathing in two subjects who received 50 mg. pethidine and 25 mg. 1C50 respectively. The rate of breathing is seen to be slower when the subject is "on the machine," and analysis of the 50 records showed that connexion to the spirometer reduced the respiratory rate by an average of 21%. This change is probably due to the resistance presented by the valves in the machine, and the amplitude of breathing is presumably increased to compensate for the reduction in rate.

TABLE I

EFFECTS OF PETHIDINE AND COMPOUND 1C50 ON THE RATE OF BREATHING (BREATHS PER 5 MIN.) IMMEDIATELY BEFORE AND AFTER CONNECTING THE SUBJECT TO THE BENEDICT-ROTH SPIROMETER

Drug, Dose, and Subject		Time after Injection (Hr.)					
		0	½	1	2	3	4
Pethidine HCl 50 mg. (subject, L.P.)	Before	70	80	70	70	80	70
	After	60	61	60	56	54	57
Compound 1C50, 25 mg. (subject, E.G.)	Before	75	60	50	50	70	65
	After	57	30	37	41	45	58

Effect of Drugs on Breathing.—The effects of the drugs on breathing were studied in 250 experiments on 12 normal volunteers.

Typical effects of two of the drugs are seen in Figs. 1 and 2, which show the two different ways in which respiratory depression may be revealed. Fig. 1 shows the response of subject L.P. to 25 mg. 1C50. It will be noted that the amplitude of respiration was much reduced (mean tidal volume lowered from 580 ml. to 330 ml.), the rate of breathing being unchanged. On the other hand, as shown in Fig. 2, the response in subject E.G. to 5 mg. (−)-methadone was characterized by slowing

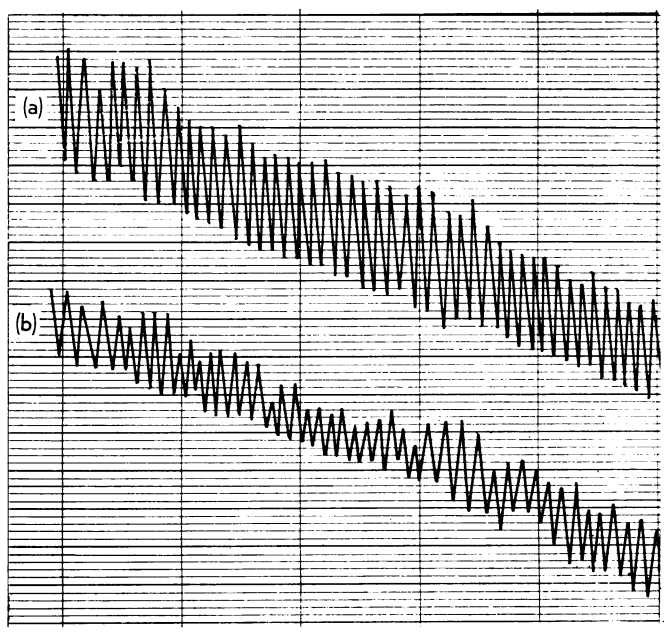


FIG. 1.—Effect of compound 1C50 on spirometer record of breathing. Subject L.P., ♂ (*a*) record taken before drug; (*b*) record taken ½ hr. after intramuscular injection of 25 mg. 1C50. In (*a*) respiratory rate, 46/5 min.; mean tidal volume 580 ml.; pulmonary ventilation in 5 min., 26.68 l. In (*b*) respiratory rate, 45/5 min.; mean tidal volume, 330 ml.; pulmonary ventilation in 5 min., 14.85 l.

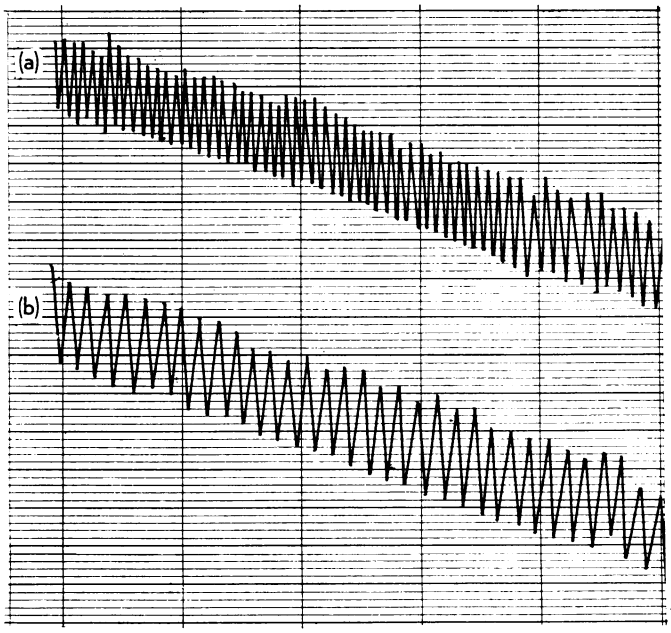


FIG. 2.—Effect of (–)-methadone on spirometer record of breathing. Subject E.G., ♀ (*a*) record taken before drug; (*b*) record taken 1 hr. after injection of 5 mg. (–)-methadone hydrochloride. In (*a*) respiratory rate, 59/5 min.; mean tidal volume, 450 ml.; pulmonary ventilation in 5 min., 26.55 l. In (*b*) respiratory rate, 32/5 min.; mean tidal volume, 510 ml.; pulmonary ventilation in 5 min., 16.32 l.

from 59 to 32 breaths/5 min., and the mean tidal volume was actually increased from 450 ml. to 510 ml.

Fig. 3 shows a typical response to a saline injection in subject H.C. There was no significant change in the character of the respiratory record after the injection.

In assessing the effects of these drugs we have calculated the pulmonary ventilation during the last 5 min. of each period of recording. In the experiment illustrated in Fig. 1 the pulmonary ventilation was reduced from 26.68 to 14.85 l./5 min. In the experiment shown in Fig. 2 the pulmonary ventilation was reduced from 26.55 to 16.32 l./5 min. After saline (Fig. 3) the pulmonary ventilation fell from 26.22 to 25.49 l./5 min.

The total respiratory changes during the experimental period are illustrated in Fig. 4, which shows the areas obtained in subject E.G. after injections of saline (4*a*) and 25 mg. of compound 1C50 (4*b*). After saline the area was −6.7, and after 1C50 it was −49.5 arbitrary units (see Method for explanation). In this way the effects of various injections were summarized numerically, and comparisons of the activity of different compounds could be made by standard statistical treatment of the area values.

The results obtained in 12 subjects after injection of saline, 25 mg. of 268C49, 25 mg. of 489C49, 50 mg. of pethidine, 10 mg. of morphine and 25 mg. of 1C50 respectively, are presented in Fig. 5, in which the means of the areas of percentage deviations, with 95% fiducial limits, are shown graphically. The results are set out to show the order of increasing depression of breathing from saline, which caused no depression, to compound 1C50, whose effect was greater than that of morphine.

A statistical analysis of the effects of these injections was made. The results are presented in Table II, which shows the values for "t" and the levels of significance for comparison of the means of the injections with the mean of saline. Table III shows the

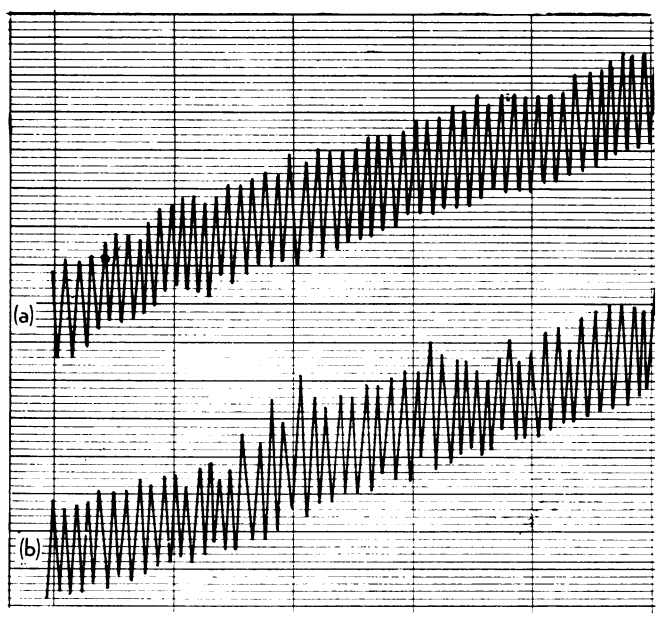


FIG. 3.—Effect of saline on spirometer record of breathing. Subject H.C., ♂ (*a*) before injection; (*b*) 1 hr. after injection of 1 ml. 0.9% NaCl solution. In (*a*) respiratory rate, 49/5 min.; mean tidal volume, 535 ml.; pulmonary ventilation in 5 min., 26.22 l. In (*b*) respiratory rate, 48/5 min.; mean tidal volume, 531 ml.; pulmonary ventilation in 5 min., 25.49 l.

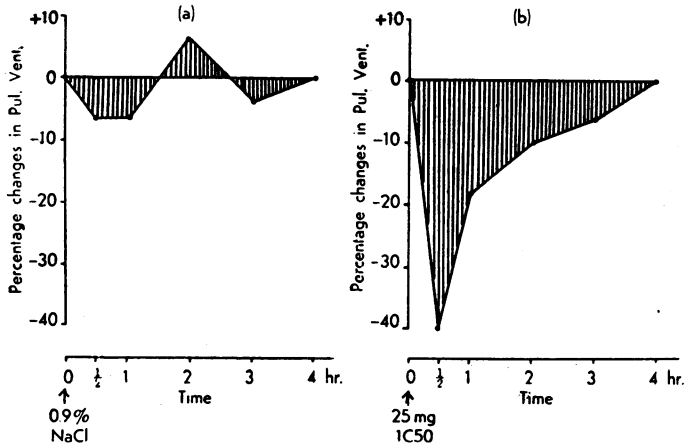


FIG. 4.—Effect of saline and compound 1C50 on respiration. Subject E.G., ♀. Ordinates: percentage changes in pulmonary ventilation, the zero value being the 2nd pre-injection reading. Abscissae: time in hours. (*a*) Injection of saline. The area under the curve is −6.7 arbitrary units (see Methods). (*b*) Injection of 25 mg. 1C50 i.m. The area under the curve is −49.5 arbitrary units.

significant differences found between the means of some of the injections. These data confirm the order of respiratory depressant potency seen graphically in Fig. 5.

TABLE II

STATISTICAL ANALYSIS OF THE EFFECTS OF THE VARIOUS INJECTIONS ON RESPIRATION. THE RESULTS ARE ARRANGED DOWNWARDS IN ORDER OF INCREASING EFFECT

Injection	No. of Readings	Mean of Area of % Deviation	Comparison of Means of Injections with Mean of Saline		
			t-value	Degrees of Freedom	Level of Significance
Saline	28	+1·2	—	—	—
268C49, 25 mg.	16	−18·1	1·96	42	—
489C49, 25 mg.	18	−27·1	2·94	44	1%
Pethidine, 50 mg.	17	−33·0	3·54	43	0·1%
Morphine, 10 mg.	17	−40·5	3·96	43	0·1%
1C50, 25 mg. ..	20	−50·3	5·77	46	0·1%

TABLE III

COMPARISON OF RESPIRATORY DEPRESSANT ACTIONS

To show significant differences found between means of drug injections (see Fig. 5 and Table II). (The remaining comparisons of groups showed no significant differences)

Between Groups	t-value	Degrees of Freedom	Level of Significance
268C49 (25 mg.) and morphine (10 mg.) ..	2·36	31	5%
268C49 (25 mg.) and 1C50 (25 mg.) ..	4·50	34	0·1%
489C49 (25 mg.) and 1C50 (25 mg.) ..	3·18	36	1%
Pethidine (50 mg.) and 1C50 (25 mg.) ..	2·42	35	2%

Effect of N-Allylnormorphine on Respiratory Depression by 1C50.—The effect of N-allylnormorphine (nalorphine) on the respiratory depression produced by compound 1C50 was studied in three subjects. A typical result is seen in Fig. 6, which shows the effect of intravenous injection of 10 mg. nalorphine on the spirometer record of subject H.C. when his breathing had been previously depressed by injection of 25 mg. of 1C50. Both rate and depth of breathing were stimulated within 1 min. of the injection.

Effects of the Various Drugs on Blood Pressure and Heart Rate.—Although there were frequent reductions in blood pressure (e.g. 10–15 mm. Hg systolic and 5–10 mm. Hg diastolic) and in heart rate (e.g. 10–15 beats/min.), after injections of the drugs, these changes were not consistently greater than those seen after saline, and will not be further analysed.

Other Effects

The symptoms and signs produced by the various injections in all 12 subjects are listed in Table IV. *Drowsiness* was the only symptom which followed

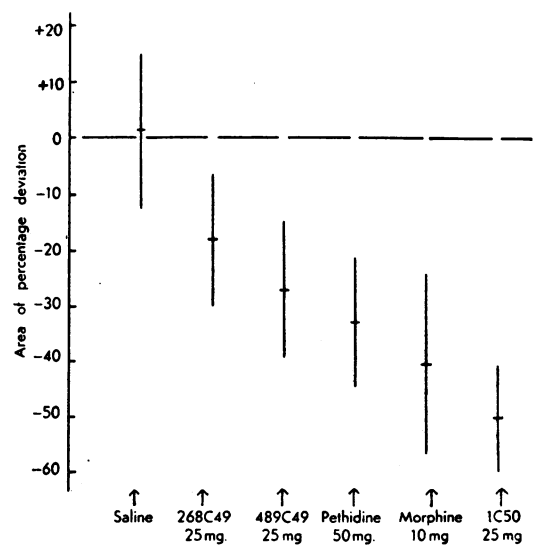


FIG. 5.—Summarized effects of drugs on respiration. The graph shows the means, with 95% fiducial limits, of the areas of percentage deviations in all subjects who received the substances indicated. The substances have been arranged in order of increasing potency of respiratory depression from saline through compound 1C50. See Table II for further details and analysis of these results.

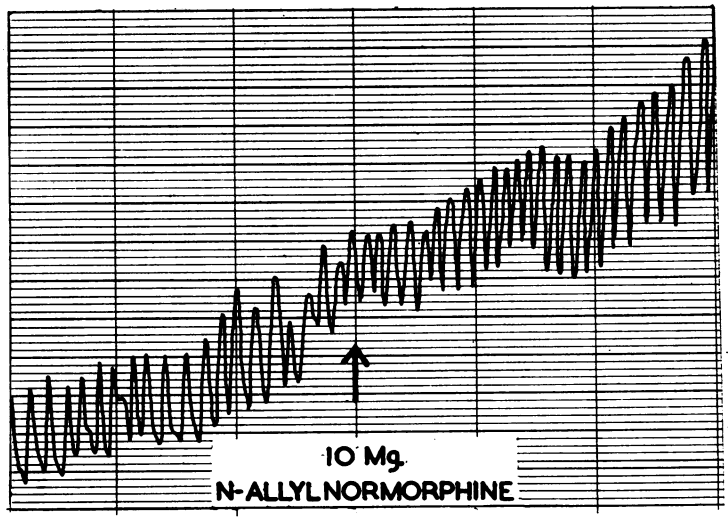


FIG. 6.—Effect of intravenous N-allylnormorphine on respiratory depression from compound 1C50. Spirometer record from subject H.C., ♂. Tracing to left of arrow shows breathing depressed by prior injection of 25 mg. 1C50. At arrow, 10 mg. N-allylnormorphine was injected i.v. Note rapid onset of respiratory stimulation.

injection of saline (5 out of 37 occasions) and it was only recorded when the subject was under the impression that he had received an active drug. With the drugs, drowsiness occurred almost invariably, and *sleep* quite frequently, especially after 489C49 and 1C50.

TABLE IV

SIDE-EFFECTS OF DITHIENYL COMPOUNDS IN 12 NORMAL SUBJECTS

The numerals in brackets at the head of each column indicate the total number of injections)

Side-effect	Drugs and Doses						
	Saline	Morphine SO_4 10 mg.	Pethidine HCl 50 mg.	489C49 25 mg.	268C49 25 mg.	1C50 25 mg.	(-)-methadone 5 mg.
	(37)	(29)	(28)	(19)	(18)	(23)	(13)
Drowsiness ..	5	21	23	19	14	21	9
Sleep	—	7	9	15	6	12	—
Uneasy stomach	—	6	—	2	—	—	1
Nausea ..	—	16	3	2	1	1	2
Vomiting ..	—	2	—	—	—	—	1
Pallor and sweating	—	7	—	1	—	—	1
Faintness ..	—	4	—	—	—	—	—
Ataxia	—	5	—	2	—	—	1
Light-headedness	—	—	2	4	1	2	2
"Drunkenness"	—	1	—	5	—	—	1
Euphoria ..	—	7	10	5	3	11	6
Headache ..	—	3	1	—	—	—	—
Photophobia ..	—	—	—	8	—	1	—
Dizziness ..	—	2	1	4	1	9	1
Difficulty in focusing ..	—	3	2	3	—	3	1
Mistiness of vision ..	—	—	—	8	1	4	—
Warm glow ..	—	5	7	8	2	8	1
Itching	—	—	1	—	—	5	—
Dry mouth ..	—	5	7	8	2	8	1
Muscular weakness	—	—	—	9	1	4	—

Table IV also shows that *nausea* was much more frequent with morphine than with any of the other drugs, the dithienylbutenylamine compounds being particularly free from this complication. After morphine the syndrome of nausea, pallor, sweating, faintness, and occasionally *vomiting* was most liable to occur when the subjects stood up and walked about at the end of the experiment.

The occurrence of *euphoria* with the new compounds was frequent enough to show that these drugs must be regarded as possible drugs of addiction.

Among the other symptoms, *dizziness* occurred most frequently with the dithienyl compounds, particularly 1C50. *Mistiness of vision*, also most marked with the new substances, was usually described as an appearance of "smoke moving up the wall." Photophobia was most frequent with 489C49.

A most important side action was the development of *muscular weakness*, most often with 489C49, but also recorded after 1C50 and 268C49. It did not occur after morphine, pethidine or (−)-methadone. The weakness was widespread but was greatest in the hands and arms, and in one subject (H.C.) the facial muscles were so greatly affected as to give a "myasthenic facies." This muscular weakness appeared to be idiosyncratic, since it did not occur in most subjects even when larger doses than those used here were given. The symptom was very unpleasant to those who experienced it (2 out of 12 subjects), and its occurrence led us to be very cautious in making our initial therapeutic invesigations on the analgesic actions of these drugs in patients. The development of muscular weakness in patients after 489C49 will be described in the next part of this paper.

Dr. G. A. Mogey, when at the Wellcome Research Laboratories, studied the actions of 489C49 on the cat's sciatic nerve–gastrocnemius preparation and on the rat's phrenic nerve–diaphragm preparation. In the cat the drug produced no signs of neuromuscular block, but in the rat diaphragm there was some evidence of direct depression of the muscle fibre with concentrations exceeding 1.0 mg./100 ml. Smaller concentrations (0.2 mg./100 ml.) reduced the size of repetitive

responses to long stimuli (5.70 msec.) and potentiated the paralysis produced by (+)-tubocurarine.

Clinical Trial

Illustrative Records

Table V shows the effects of 1C50, pethidine, morphine and 396C50 (a new methadone derivative) in a patient with post-operative gangrene of the foot. It will be noted that 50 mg. of compound 1C50 had no effect on two occasions; on one other occasion this dose was effective when given 1 hr. after a previous dose of 50 mg.; 100 mg. of 1C50 was effective on five occasions. Compound 396C50 in a dose of 5 mg. had no effect.

TABLE V

ACTIONS OF VARIOUS DRUGS, IN ORDER OF THEIR ADMINISTRATION, ON PAIN ASSOCIATED WITH GANGRENE OF FOOT FOLLOWING ARTHRODESIS IN PATIENT R.A. (♂, 50)

Drug and Dose	Pain*		Time (Hr)	
	Before	After	Peak	Duration
1C50, 50 mg.	3	3	—	0
1C50, 50 „ (1 hr. later)	3	1	½	6+
1C50, 50 „	4	4	—	0
Pethidine HCl, 100 mg.	4	0 (s)	—	5+
1C50, 100 mg.	3	0	½	4½
1C50, 100 „	3	0 (s)	½ (s)	6½
1C50, 100 „	3	0 (s)	½ (s)	8½+
Morphine SO_4, 10 mg.	3	1	½	4½
1C50, 100 mg.	3	1	½	5½
†396C50 5 mg.	3	3	—	0
1C50, 100 mg. (1½ hr. later)	3	0 (s)	½ (s)	6½+

* Scale of pain: 0=no pain, 1=slight pain, 2=moderate pain, 3=severe pain, 4=very severe pain, 0 (s)=sleep.

† Compound 396C50 is the methylethylamino-analogue of methadone.

The + sign after duration figures means that end-point was not observed.

In Table VI are shown the results of a number of injections in a patient with secondary deposits in the spine associated with carcinoma of the breast (the patient was having radiotherapy). In this Table the results have been grouped according to the drugs used and not in the order of injection. Morphine "X" was a microcrystalline preparation which was supposed to be long acting. Injections of 32 and 50 mg. of this preparation were quite ineffective, suggesting that it was not absorbed in adequate amounts. Morphine mucate (32 mg.) has a longer action than morphine sulphate (16 mg.) but it is impossible to say whether this difference is due to the difference in dosage of morphine or to slower absorption of the mucate. Pethidine (100 mg.) appeared to be the weakest and shortest lasting of the effective drugs. Compound 1C50 had a particularly marked hypnotic action in this patient. We should like to emphasize that the small or negative responses to 50 mg. of 1C50 and to 5 mg. of 396C50 in Table V, and to 32 and 50 mg. of morphine "X" in Table VI, serve as controls for the positive effects of the other injections.

TABLE VI

ACTIONS OF DRUGS ON PAIN DUE TO SECONDARY DEPOSITS IN SPINE IN A PATIENT (G.N., ♀, 56) WITH CARCINOMA OF THE BREAST

Pain scale as in Table V

Drug and Dose	Pain		Time (Hr.)	
	Before	After	Peak	Duration
*Morphine "X," 32 mg.	3	4	—	0
50 „	3	3	—	0
Morphine mucate, 32 mg.	3	1	1½	8½
	3	0 (s)	½ (s)	7½
	3	1	3	8
Morphine SO_4, 16 mg.	3	1	½	4½
	4	0 (s)	1½ (s)	4½
Pethidine HCl, 100 mg.	3	2	1½	4½
	3	2	½	2
	4	1	½	3
1C50, 100 mg.	3	0 (s)	1 (s)	7½
	4	0 (s)	½ (s)	9
	4	0 (s)	½ (s)	2½+
	3	0 (s)	½ (s)	5

* Microcrystalline preparation of morphine.

Relief of Pain After 268C49

This drug was given in doses of 75 and 100 mg. and was clearly a less effective analgesic than 489C49 and 1C50. On 13 out of 26 occasions injection of 268C49 did not produce satisfactory relief of pain.

Relief of Pain After 489C49

This drug produced complete relief of pain in all of 10 injections (50 mg.). However, the side-effects, especially the muscular weakness which will be discussed later, led us to abandon further trials of this otherwise promising drug.

Relief of Pain After 1C50

In view of the relative ineffectiveness of 268C49 and the toxicity of 489C49, we decided to restrict our further investigations to 1C50. The results are set out in Table VII. We have assessed the effectiveness of 50 and 100 mg. of 1C50 by comparison with 100 mg. of pethidine hydrochloride and 10 mg. of morphine sulphate on the relief of severe or very severe pain and have classified the results under the headings "complete relief" and "satisfactory relief."

The first point which Table VII reveals is the capacity of the patients to discriminate between the effects of 50 and 100 mg. of 1C50. This is most strikingly shown by comparing the percentage of occasions on which complete relief of very severe or severe pain occurred, following the two doses of this drug. With 50 mg. complete relief occurred after 26 (38%) out of 69 injections. With

TABLE VII

RELIEF OF SEVERE OR VERY SEVERE PAIN BY COMPOUND 1C50, PETHIDINE, AND MORPHINE

(Satisfactory relief = pain reduced to slight or zero intensity)

Drug and Dose	Pain Before Drug Administration	Total No. of Drug Administrations (Figures in brackets show No. of Patients)	Administrations giving Complete Relief	Administrations giving Satisfactory Relief
1C50, 50 mg.	Very severe	22 (11)	5	12
	Severe	47 (26)	21	33
		69	26 (38%)	45 (65%)
1C50, 100 mg.	Very severe	14 (8)	7	13
	Severe	70 (37)	56	69
		84	63 (75%)	82 (98%)
Pethidine HCl, 100 mg.	Very severe	8 (6)	3	3
	Severe	48 (31)	24	39
		56	27 (48%)	42 (75%)
Morphine SO_4 10 mg.	Very severe	11 (6)	6	9
	Severe	25 (21)	18	25
		36	24 (67%)	34 (94%)

100 mg. complete relief occurred after 63 (75%) out of 84 injections. The value of P for the standard error of the difference between these two percentages is <0.00001.

A similar comparison of the effects of 100 mg. of pethidine hydrochloride with 50 and 100 mg. of 1C50 gave values of $P=0.26$ and <0.001 respectively. Comparison of 100 mg. of 1C50 with 10 mg. of morphine sulphate gave $P=0.38$.

Thus, the following equianalgesic doses may be suggested from these findings:

50 mg. 1C50 ≡ 100 mg. pethidine hydrochloride
100 mg. 1C50 ≡ 10 mg. morphine sulphate

The figures in the column headed "satisfactory relief" show similar comparative potencies for the different drugs.

Duration of Action

Table VIII shows the mean duration of action of the drugs when given in effective doses. Although 10 mg. of morphine sulphate and 100 mg. of 1C50 have the most prolonged actions, the differences between the various drugs are not statistically significant.

TABLE VIII

AVERAGE DURATION OF ACTION OF SOME ANALGESICS

Drug	Dose mg.	No. of Injections	Average Duration of Action
Morphine ..	10	22	5 hr. 24 min.
489C49	50	6	5 „ „
Pethidine ..	100	37	4 „ 42 „
268C49	75	12	4 „ 36 „
1C50	50	50	4 „ 24 „
	100	58	5 „ 42 „

TABLE IX

OCCURRENCE OF SIDE-EFFECTS IN PATIENTS

(The numerals in brackets at the head of each column indicate No. of injections)

Side-effect	Drugs and Doses: 1C50 50 mg.	1C50 100 mg.	268C49 75 mg.	489C49 50 mg.	Morphine SO_4 10 mg.	Pethidine HCl 100 mg.
	(71)	(86)	(23)	(10)	(35)	(56)
Nausea	—	1	—	—	5	—
Vomiting ..	3	2	—	2	—	2
Vertigo	3	4	1	1	5	5
Drowsiness ..	9	3	2	1	5	5
Euphoria ..	1	—	—	4	—	1
Muscular weakness	—	—	—	2	—	—
Coloured urine..	1	7	—	—	—	—

Effects on Respiratory Rate, Blood Pressure and Heart Rate

The effects of 1C50, morphine and pethidine on the rate of breathing, on blood pressure and on heart rate were slight and difficult to evaluate owing to the many variables which had to be taken into account.

Side Effects

The side effects noted during the clinical trial of the dithienylbutenylamine compounds are listed in Table XII. The following deserve comment:

Drowsiness and Sleep.—The occurrence of drowsiness and sleep is a valuable accompaniment of analgesia during the immediate post-operative period, and is, perhaps, hardly a side-effect. Table X shows the number of occasions when 1C50, pethidine and morphine produced satisfactory relief of pain with and without the simultaneous occurrence of sleep. Like the other two drugs, 1C50 has a true analgesic action but with the 100

TABLE X

NUMBER OF OCCASIONS ON WHICH ANALGESICS PRODUCED SATISFACTORY RELIEF OF PAIN WITH AND WITHOUT SLEEP

Drug and Dose	Relief With or Without Sleep	Relief Without Sleep
Compound 1C50:		
50 mg.	45	25
100 „	82	29
Pethidine HCl:		
100 mg.	42	22
Morphine SO_4:		
10 mg.	34	19

mg. dose the hypnotic effect predominates, and is greater than with 100 mg. of pethidine hydrochloride or 10 mg. of morphine sulphate.

It is, of course, a quite arbitrary choice to regard the production of sleep as complete relief of pain. However, since for our purposes the occurrence of painless oblivion is a useful therapeutic achievement we have felt justified in our choice. In any case, as may be seen in Table XI the number of occasions when sleep followed the administration

TABLE XI

TOTAL ADMINISTRATIONS OF VARIOUS ANALGESICS, BY NIGHT AND BY DAY, AFTER WHICH SLEEP OCCURRED
(Night, 9 p.m.–5 a.m.)

Drug and Dose	No. of Injections and when Administered	No. in which Sleep Occurred
1C50, 50 mg.	32 (day)	6
	39 (night)	26
100 „	38 (day)	14
	48 (night)	46
268C49, 75 mg.	17 (day)	3
	6 (night)	6
489C49, 50 mg.	8 (day)	2
	2 (night)	2
Pethidine HCl, 100 mg...	36 (day)	6
	20 (night)	16
Morphine SO_4, 10 mg. ..	19 (day)	5
	16 (night)	11

of the different drugs was much greater by night than by day. After 100 mg. of 1C50 sleep occurred on 46 out of 48 occasions at night, and only on 14 out of 38 occasions during the day.

Nausea and Vomiting.—These occurred very rarely and their relation to drug administration was difficult to evaluate.

Euphoria.—This was seldom seen in patients. It appeared to occur most frequently with 489C49.

Muscular Weakness.—We had previously noted in two normal subjects that 489C49 caused marked muscular weakness in doses of 12.5–25 mg. We were therefore prepared for this complication in our clinical trial and in fact we observed it in two out of eight patients who received this drug. The weakness was most marked in the arms and hands, there was great difficulty in speaking, and one of the patients had numbness of the cheeks and lips. Associated with this weakness there was marked sweating and flushing of the face and the physiological reactions were accompanied by considerable distress and restlessness. This most undesirable complication compelled us to abandon further use of 489C49. We did not observe this reaction with effective analgesic doses of 268C49 and 1C50.

Coloured Urine.—In one patient after 50 mg. and in seven patients after 100 mg. of 1C50 the urine passed several hours after injection was pink to purple in colour, becoming greenish-brown on standing. In one patient who received frequent injections of 100–150 mg. of this drug the pigments indigotin (blue) and indirubin (red) were identified and other yellow and yellow-green pigments were also presumed to be indigo derivatives. In all the patients who passed coloured urine, Obermayer's test for indican was positive. In this, ferric chloride and conc. HCl are added to the urine. $CHCl_3$ is then added, the urine is shaken and a blue colour develops in the $CHCl_3$ layer. However, the colour of the urine is not necessarily due to indigo derivatives, as the metabolic products of the drug are themselves coloured.

DISCUSSION

We propose to comment firstly on some of the methods which we have used in this study, and secondly on our assessment of the actions of the dithienylbutenylamine compounds.

Methods for Studying Analgesic Potency of the Drugs

The dithienyl compounds were given to us for studies in man after Adamson and Green (1950) had shown that these substances raised the pain threshold to heat and pressure stimuli in rats, rabbits and dogs (Green, 1953).

In previous work we had not been able to get consistent results when testing analgesic drugs with the radiant heat method of Hardy, Wolff, and Goodell (1940), so we made some preliminary observations with two methods in which the capacity of the drugs to relieve ischaemic muscle pain was studied.

(*a*) The method of Hewer and Keele (1948) was first used. The drugs under investigation are injected intravenously into one arm after ischaemic muscle pain of moderate intensity has been induced in the opposite forearm. The smallest dose of an analgesic drug which relieves this pain can be readily measured in this way, and it was found that the dithienyl compounds were intermediate in analgesic potency to morphine and pethidine (nearer the latter) (Keele, 1952). This agreed very well with the results in the dog (Green, 1953) and also with the clinical results reported in this paper.

(*b*) One of us has previously reported on the effectiveness of intramuscular injection of a dithienylbutenylamine compound (191C49, not discussed in the present paper) in increasing the number of ischaemic muscle contractions required to produce pain. This method, which was first

used by Harrison and Bigelow (1943), gives information concerning duration of action as well as analgesic potency.

However, we should like to emphasize that we do not attach too much importance to tests on analgesic drug action in experimental pain induced in normal persons. We agree with Denton and Beecher (1949) that the only satisfactory way to assess the analgesic capacity of a drug is to study its actions in patients with pathological pain, so that account can be taken of the complexity of the experience for which relief is desired. Hewer, Keele, Keele, and Nathan (1949) and Nathan (1952) have described a clinical method for studying analgesics in patients with chronic pain in whom subjective estimates of pain intensity are graded so as to provide quantitative data for the assessment of drug action. This method can be well controlled so that neither the patient—who usually keeps his own records—nor the person administering the drug, knows the nature or dose of the substance being given. Unfortunately, this procedure could not be used in the present study since the combined hypnotic properties of the dithienyl compounds made them more suitable for the relief of acute post-operative than of chronic pain. For this reason we had to modify the method of Hewer *et al.* (1949) and we came nearer to the procedure described by Keats, Beecher, and Mosteller (1950) for studying the effects of drugs on clinical pain.

There were, however, three respects in which our procedure differed from that of Keats *et al.* (1950):

(i) The dithienyl compounds, whose actions we were investigating for the first time in patients, had to be regarded as possibly toxic drugs. Indeed, we had already observed one very unpleasant side action—marked muscular weakness—with 489C49 in two normal subjects, and we had to be on the lookout for this and other toxic effects in patients. For this reason, we did not feel justified in using the dithienyl compounds as "unknowns" to the person who administered the drugs and observed the responses, though the nature of the injections was always unknown to the patient. We should, therefore, prefer to call our investigation a "pilot trial," though we think that the information we have obtained justifies certain definite conclusions concerning the therapeutic value of the drugs studied. It is, of course, easy to evaluate drugs which are either ineffective or toxic in therapeutic doses, and our method soon revealed the inadequate analgesic potency of 268C49 and the undesirable muscular weakness produced by 489C49. In comparing 1C50 with morphine and pethidine we have paid attention only to very clear-cut effects. For example, as shown in Table VII, we have taken as our significant end-point the complete relief of severe or very severe pain, and only the figures so obtained have been used to compare the effectiveness of the different drugs. Furthermore, in the statistical analysis of our results we have demanded more highly significant differences than are usually considered necessary; in no case have we regarded a difference as significant unless the value of P was <0.001.

(ii) We did not consider that it was justifiable to use injection of saline as a control, since Keats and Beecher (1950) have shown that this gives relief in only about 20% of patients. We feel that this proportion is too small for the carrying out of an extensive investigation in which the co-operation of both nursing staff and patients is required. We therefore decided to test the discriminatory power of our patients by administering two different doses (50 and 100 mg.) of 1C50, and Table VII shows the highly significant difference which was recorded between them ($P<0.00001$). Sometimes the 50 mg. dose gave no relief whereas 100 mg. was very effective; the absence of response to the smaller dose thus not only gave information which could have been obtained by injection of saline, but also indicated the lower limit of effective dosage of 1C50.

(iii) We have regarded sleep as equivalent to complete relief of pain, and we consider a combined hypnotic-analgesic drug very useful for post-operative pain. At night, when sleep is most necessary, the hypnotic action of all the drugs studied was much greater than by day (Table XI). We have not woken our patients to find out whether pain was still present, but we can get some idea of the analgesic, as distinct from the hypnotic, potency of the drugs from the number of occasions, chiefly by day, when pain was relieved without the patients going to sleep.

Effects of Dithienyl Compounds on Respiration

Owing to the many variables which influence respiratory rate during the post-operative period, we were unable to obtain reliable observations on patients, so the effects of the dithienyl compounds on breathing were studied in 12 normal subjects. Our results showed conclusively that pulmonary ventilation was reduced by these new compounds as much as by morphine and pethidine. Since the doses of the dithienyl compounds and of pethidine used in the normal subjects were no more than half those required therapeutically for relief of pain it can be said they were all at least as depressant to

respiration as morphine. Indeed 25 mg. of 1C50 appeared to be more depressant than 10 mg. of morphine, even though this represented only one quarter of the equianalgesic dose (i.e., 100 mg. of 1C50 is equianalgesic with 10 mg. of morphine). Our finding that pethidine is a powerful respiratory depressant is contrary to widely held opinions, but agrees fully with the results reported by Prescott, Ransom, Thorp, and Wilson (1949) and by Loeschke, Sweel, Kough, and Lambertsen (1953) who measured the respiratory depression in terms of a reduced response to the inhalation of CO_2-rich mixtures.

Assessment of the Dithienylbutenylamine Compounds

As a result of our studies on normal subjects and our pilot clinical trial in patients, we are now in a position to assess the status of the dithienyl compounds in comparison with morphine and pethidine.

Analgesic Potency.—The dithienyl compounds are somewhat more potent than pethidine and definitely less so than morphine. The most powerful member of the group, compound 1C50, is about twice as potent as pethidine and 1/10 as potent as morphine. These findings agree well with the results in the dog (Green, 1953) and with the observations reported by Keele (1952) for measurement of their analgesic potency against ischaemic muscular pain.

Hypnotic Action.—The dithienyl compounds have a greater hypnotic action than equianalgesic doses of morphine and pethidine. With 1C50 this additional effect was therapeutically helpful to patients with post-operative pain.

Euphoria.—The occurrence of euphoria in some of our subjects suggests strongly that the dithienyl compounds are capable of causing addiction. This agrees with the finding of Isbell, Fraser, and Wikler (1953) that 1C50 was a complete substitute for morphine in morphine addicts. Compound 1C50 and, to a less extent, the other members of the group must be regarded as drugs of addiction.

Respiratory Depression.—Like morphine and other powerful analgesics the dithienyl compounds are strong respiratory depressants. It is strange that it has so far proved impossible to find an analgesic drug with a morphine-like action which does not depress respiration. We found that the respiratory depression produced by the dithienyl compounds was fully antagonized by N-allylnormorphine (nalorphine), and Isbell *et al.* (1953) have also noted that nalorphine produces an abstinence syndrome in subjects receiving 1C50. These antagonisms by nalorphine bring 1C50 into line with morphine and all other substances with a morphine-like action, and differentiate it from other central nervous depressants, such as the barbiturates, which are not antagonized by nalorphine.

Nausea and Vomiting.—The dithienyl compounds are much less liable to produce nausea and vomiting than morphine. This difference is most clearly seen in ambulant normal subjects, the occurrence of these symptoms being very infrequent with all the drugs in post-operative patients. None of the drugs appeared to affect the alimentary tract (or bladder) in our patients.

Muscular Weakness.—The profound muscular weakness produced by 489C49 in a few normal subjects and patients was sufficient to contraindicate further trials with this drug. The other dithienyl compounds have much less action of this kind in normal persons and no muscular weakness has been detected in patients given 1C50.

Coloured Urine.—After 100 mg. doses of the dithienyl compounds (particularly 1C50) a purple coloration of the urine is liable to occur. In a few instances indican has been detected in the urine, but the coloration might also be due to breakdown products of the drug. There is no evidence that this coloration is harmful.

Other Effects.—Dizziness occurs more frequently with the dithienyl compounds than with morphine and pethidine. The same is also true for visual symptoms such as *photophobia* and *mistiness of vision.* The *pupil* is slightly *constricted. Blood pressure* and *heart rate* are not significantly affected.

Conclusions

Compound 191C49, previously studied (Keele, 1952), is a moderately effective analgesic drug which is occasionally liable to produce muscular weakness.

Compound 268C49 is too weak an analgesic to justify an extended therapeutic trial.

Compound 489C49 is a very good analgesic drug but its liability to cause alarming muscular weakness contraindicates its further use.

Compound 1C50 is an effective analgesic-hypnotic drug. It is an addictive drug which is not clinically superior to morphine except that it is less liable to cause nausea and vomiting. It has not caused muscular weakness, but it is a strong

respiratory depressant and causes a purple coloration of the urine. It has the disadvantage that it is unstable in aqueous solution and must be freshly dissolved before injection.

Summary

1. The analgesic and other actions of the following compounds have been studied in normal subjects and in patients with post-operative pain:

3-diethylamino-1 : 1-di-α-thienyl-1-butene (191C49).
3-ethylmethylamino-1 : 1-di-α-thienyl-1-butene (1C50).
3-pyrrolidino-1 : 1-di-α-thienyl-1-butene (268C49).
3-dimethylamino-1 : 1-di-α-thienyl-n-butane (489C49).

2. In a pilot clinical trial on 200 patients all the compounds had analgesic actions when injected intramuscularly in doses of 50–100 mg. The most potent member of the group was 1C50, the weakest was 268C49. Compound 1C50 was about twice as potent as pethidine and 1/10 as potent as morphine in the relief of post-operative pain. The dithienyl compounds were not active by mouth.

3. Both in normal subjects and patients these compounds had greater hypnotic actions than equianalgesic doses of pethidine and morphine.

4. The dithienyl compounds produced euphoria in normal subjects, and must be regarded as potential drugs of addiction.

5. In normal subjects these drugs depressed respiration as much as morphine and pethidine, 1C50 being the most potent in this respect. Nalorphine antagonized this respiratory depression.

6. The dithienyl compounds were much less liable to cause nausea and vomiting than morphine.

7. Other side-effects included:

(i) Muscular weakness, which was greatest with 489C49; this symptom was not encountered during the clinical trial with 1C50.

(ii) Purple coloration of the urine, which was sometimes associated with the presence of indican. Breakdown products of the drugs are also coloured.

No significant side-effects on the circulation, the alimentary tract or the bladder were seen in the patients.

8. Compound 1C50 had the highest therapeutic ratio of the dithienyl compounds. In equianalgesic doses in post-operative patients it was preferable to pethidine, but not quite so satisfactory as morphine.

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One of us (P. F.) was research assistant in the Departments of Anaesthesia and Pharmacology at the Middlesex Hospital when this work was done.

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