anesthesia. With nitrous oxide anesthesia, the comparable dosage was 3 mg.

Relaxation produced by the initial dose of M-curare sufficed for surgical procedures, lasting 60 to 90 minutes. After this period, supplemental injections of .5 to 1 mg were infrequently required. The anesthesia level was maintained in lower plane I or upper plane II in all the patients. Reflexes were absent in 8 patients at the termination of surgery. Intubation was performed in 44 patients where the type of surgery made the technic mandatory.

No cardiovascular changes were noted in any of the patients. In no case could a fall in blood pressure be attributed to the drug.

Mild respiratory depression was observed in 9 patients in a series of 100 cases. In 7 of these, respiratory depression existed before surgery as the result of excessive premedication. One of the remaining cases received 7.5 mg of M-curare during a 15-minute period. Five minutes after the final injection, the rate of respiration decreased from a normal of 22 per minute to 14. Ten minutes later it had returned to the normal rate. Subsequently, the patient received injections of .5 mg and 1 mg without the development of respiratory embarrassment. Mild respiratory depression occurred in the other patient 3 minutes after the injection of 1.5 mg of M-curare. The rate of respiration decreased from a normal of 24 per minute to 16. This depression persisted for 5 minutes and the rate of respiration returned to a normal of 24. Subsequent injections of .5 mg and 1 mg of M-curare caused no untoward respiratory changes. Each of these patients maintained an adequate tidal exchange during the period of respiratory depression.

Discussion. The relaxation obtained with M-curare in this study was comparable to that obtained by other workers using *d*-tubocurarine chloride. The drug appears to have a selective action on skeletal muscle similar to that of *d*-tubocurarine chloride, but seldom affects the muscles of respiration.

No gross or microscopic changes were observed by Chen and Swanson[6] in any of the organs of the experimental animals which received lethal doses of M-curare. The median lethal dose (LD_{50}) of M-curare in rabbits by intravenous injection, plus and minus standard error, was found to be 0.031 ± 0.002 mg per kg of body weight. The average dose sufficient to produce head drop in rabbits was approximately 0.0167 mg per kg of body weight (usually referred to as a rabbit unit). A group of 8 rabbits tolerated one rabbit unit per day for 10 days. At the end of this period, 6 out of 8 rabbits succumbed to an LD_{50} injected intravenously. This gave evidence that neither tolerance nor cumulation had developed.

Summary. The administration of the dimethyl ether of *d*-tubocurarine iodide (M-curare) to 100 patients produced relaxation comparable to that of *d*-tubocurarine chloride. Respiratory depression was seldom observed and was of minor degree when present. Less M-curare than *d*-tubocurarine chloride is needed on a mg-for-mg basis.

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Effect of Two New Analgetic Agents on the Oxygen Consumption of Brain *In vitro*.

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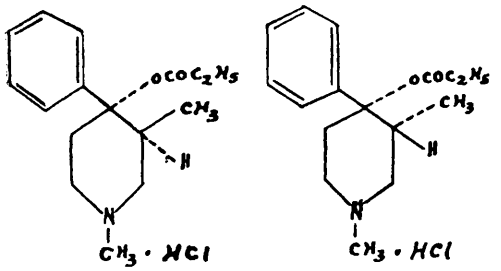
Quastel and others[1,2,3] have conducted investigations on the actions of hypnotics and anesthetic agents on brain metabolism in which they have indicated parallels to exist between *in vivo* and *in vitro* activity. Similar studies by Elliott, Warrens, and James[4] suggest that, except for their findings on succinate oxidation, there is no evidence that morphine,



Nu-1196 Nu-1779

FIG. 1.

demerol, and methadon exert their effects on oxidative processes in a manner similar to the anesthetics and hypnotics.

In the following investigation two new analgetic agents,[5] namely, (a) *dl*-α-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride (Nu-1196), and (b) *dl*-β-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride (Nu-1779)* were compared with methadon in regard to their *in vitro* effects on brain metabolism using the conventional manometric methods.[6,7] The formulae for these compounds are given in Fig. 1.

Randall and Lehman[8] have made studies on these compounds relative to analgesia in the rat. They report that Nu-1196 has about the same analgetic potency as morphine and Nu-1779 is about 5 times as active as morphine in rats. Studies[9] carried out in our laboratory indicate both of these new agents to be potent analgetics in normal subjects. Nu-1196, while being the least potent on a milligram basis, shows the greatest clinical promise since at comparable analgetic levels its side effects are minimal relative to Nu-1779 and morphine.

Procedure and Results. The oxygen consumption of brain cortex tissue slices (Rat) respiring in the presence of various substrates together with the three drugs Nu-1196, Nu-1779, and methadon were determined by the direct method of Warburg.

Cerebral cortex slices were cut with a razor and template[10] and the tissues were suspended in a modified Krebs-Ringer solution. The modified medium used was prepared according to the directions given by Elliott *et al.*[4] Phosphate buffer was used in all of the oxygen uptake measurements together with a gas phase of oxygen. After 2½ to 3 hours (*i.e.*, after at least 90% decrease in the initial O_2 uptake) the appropriate substrate was added. The shaking was continued for one hour after addition of the substrate. The drugs were made up in Ringer's solution and added to the tissues from the side arm after the control period of 60 minutes with substrate and continued for an additional 60-minute period. Each vessel, therefore, served as its own control and in addition controls were run for the entire 120-minute period.

Table I summarizes the experimental results expressed as per cent gross inhibition of oxygen consumption during the second hour over that obtained during the first hour. We have also summarized the oxygen uptake values in this table in terms of the mm^3 O_2 uptake per milligram of wet weight tissue per hour, due to the added substrate with and without drug. Table II summarizes the effect of the analgetic agents upon the oxygen uptake of brain after at least 90% decrease in the oxygen consumption where no substrate has been added. The per cent net inhibition of oxygen consumption due to drug alone was calculated by subtracting the per cent fall of the control during its second hour over its first hour from the respective per cent gross inhibitions due to the drugs.

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TABLE I.
Inhibition of the Oxygen Uptake of Brain Slices by Nu-1196 and Nu-1779.

Substrate and drug	No. of flasks N	Δ (net change) in O_2 uptake due to the presence of the given substrate in the absence and in the presence of the drug: First hr* without drug	Second hr† with drug	% Gross inhibition $m \pm \sigma_m$	% Net inhibition $M \pm \sigma_M$
Glucose 0.2%					
Methadon .01M	4	1.34	0.24	82.5 ± 1.2	74.7 ± 1.5
Nu-1779 .01M	8	1.43	0.88	48.0 ± 4.2	41.1 ± 4.4
Nu-1196 .01M	4	1.46	0.76	50.0 ± 5.5	42.2 ± 5.6
Control (no drug)	9	1.57	1.53	7.8 ± 1.1	
Glucose 0.2%					
Morphine HCl .01M	8	1.76	1.60	10.1 ± 5.2	2.1 ± 5.3
Control (no drug)	6	1.96	1.79	8.0 ± 1.2	
Lactate 0.2%					
Methadon .01M	11	0.40	0.31	68.7 ± 3.9	44.1 ± 5.9
Nu-1779 .01M	9	0.45	0.37	57.6 ± 6.3	33.0 ± 7.7
Nu-1196 .01M	12	0.44	0.24	51.0 ± 3.9	26.4 ± 5.9
Control (no drug)	9	0.44	0.41	24.6 ± 4.5	
Succinate 0.2%					
Methadon .01M	10	0.63	0.36	43.8 ± 3.2	19.5 ± 5.4
Nu-1779 .01M	10	0.62	0.49	36.9 ± 2.7	12.6 ± 5.1
Nu-1196 .01M	11	0.62	0.40	35.3 ± 2.5	11.0 ± 5.0
Control (no drug)	7	0.59	0.37	24.3 ± 4.3	
Pyruvate 0.2%					
Methadon .01M	7	0.47	0.11	74.9 ± 2.8	58.1 ± 5.3
Nu-1779 .01M	7	0.38	0.10	72.5 ± 2.9	55.7 ± 5.4
Nu-1196 .01M	7	0.36	0.11	69.3 ± 1.6	52.5 ± 4.8
Control (no drug)	6	0.36	0.30	16.8 ± 4.5	
Citrate 0.2%					
Methadon .01M	7	0.26	0.05	73.0 ± 1.3	39.0 ± 4.4
Nu-1779 .01M	6	0.20	0.03	86.2 ± 5.0	52.2 ± 6.5
Nu-1196 .01M	8	0.22	0.08	81.0 ± 2.1	47.0 ± 4.7
Control (no drug)	6	0.25	0.04	34.0 ± 4.2	
α + β-glycerophosphate .2% (52% α)					
Methadon .01M	4	0.40	0.32	49.0 ± 3.2	34.0 ± 7.3
Nu-1779 .01M	4	0.30	0.19	30.0 ± 8.8	15.0 ± 11.0
Nu-1196 .01M	4	0.34	0.17	18.2 ± 4.1	32.0 ± 7.7
Control (no drug)	4	0.34	0.26	15.0 ± 6.6	
Glutamate .2%					
Methadon .01M	4	0.28	0.07	58.0 ± 2.8	0.0 ± 4.2
Nu-1779 .01M	4	0.25	0.07	68.0 ± 1.9	10.0 ± 3.7
Nu-1196 .01M	4	0.25	0.10	74.0 ± 3.4	16.0 ± 4.7
Control (no drug)	4	0.28	0.11	58.0 ± 3.2	
Oxalacetate .2%					
Methadon .01M	4	0.35	0.14	62.5 ± 4.3	— 0.5 ± 5.7
Nu-1779 .01M	4	0.32	0.23	44.0 ± 1.9	—10.0 ± 4.1
Nu-1196 .01M	4	0.36	0.13	62.0 ± 1.8	— 1.0 ± 4.2
Control (no drug)	4	0.33	0.12	63.0 ± 3.7	

m = Mean % gross inhibition.
σ_m = Standard error of mean % gross inhibition.
M = Mean % net inhibition.
σ_M = Standard error of mean % net inhibition.
M = m experiment — m control.

$$\sigma_M = \sqrt{\sigma_m^2 \text{ experiment} + \sigma_m^2 \text{ control}}$$

* Net average mm³ O_2 uptake per hour per mg wet weight of tissue due to added substrate.
† Net average mm³ O_2 uptake per hour per mg wet weight due to added substrate after addition of drug.

TABLE II.
Effect of Analgetic Agents on Oxygen Uptake of Brain After at Least 90% Decrease* in Respiration on Endogenous Substrates.

	Average mm³ O_2 uptake per hr per mg wet weight of tissue			
	1st hr		2nd hr	
	No drug.	No added substrate	With drug.	No added substrate
Morphine 0.01M		.167		.019
Methadon 0.01M		.133		.029
Nu-1779 0.01M		.102		.042
Nu-1196 0.01M		.074		.011
Control		.161		.073

* Drug was added after 2½ - 3 hr of shaking in Warburg flasks. No substrate was added.

The effects produced by the drugs are compared at equi-molar concentrations with methadon (at 0.01M) on glucose as a reference substrate. This concentration of methadon was found experimentally to produce a significant inhibition of the oxygen consumption of brain respiring on glucose.[4]

Conclusion. Our experiments indicate that significant inhibitions of the oxygen consumption of brain slices may be obtained using the new analgetic agents Nu-1196 and Nu-1779 when this tissue respires on glucose, lactate, pyruvate, α- and β-glycerophosphate (52% α), citrate, and possibly succinate. It must be pointed out, however, that inhibitions due to drug with citrate as a substrate are to be considered quite dubious since the normal increase in O_2 consumption by this substrate alone is so small. Doubtful inhibitions were produced when brain slices respired on glutamate and oxalacetate. Nu-1196 and Nu-1779 showed insignificant effects at concentrations less than 0.01M.

As in the case of demerol, methadon, and morphine reported by Elliott *et al.*,[4] the concentrations of the new agents Nu-1196 and Nu-1779 required to produce significant inhibitions were vastly larger than that required in the production of *in vivo* effects.

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Reduction in the Number of Adult *Trichinella spiralis* in Rats After Treatment with Naphthoquinones.*

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The effect of naphthoquinones on the metabolism of *Schistosoma mansoni* has been studied recently.[1] 2-methyl-1,4-naphthoquinone inhibits the rate of glycolysis of *S. mansoni in vitro*. Administration of this compound with subcurative doses of "Fuadin" to mice infected with *S. mansoni* causes a marked decrease in the rate of glycolysis of the worms. Other naphthoquinones varied as to the degree of their anti-glycolytic activity *in vitro* as well as *in vivo*. The inhibitory effect on glycolysis manifested by these naphthoquinones is decreased markedly when the worms are incubated in dialysed blood serum instead of a protein-free salt solution. This suggests that interaction of the naphthoquinones with serum proteins would reduce any intrinsic activity of these compounds

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