bon deposition. Accordingly, the per cent necrosis data on the Table refer to gross necrosis that would be produced in a 1 cm tumor. The standard deviations are also tabulated.

As controls, a total of 24 tumors were injected with 0·03 ml of isotonic saline containing the usual proportion of carbon black. 12 tumors were excised after 1 day, 12 after 3 days. The average tumor necrosis produced by the saline injections was 3% with a standard deviation of 2%, for both the 1 day and 3 day time intervals.

Similar measurements of the necrotic effect of intratumorally injected methyl nitrogen mustard were carried out on Jensen sarcoma, in Sprague-Dawley rats. Three-hundreths of a milliliter of injectate, containing 0·67 mg per ml, were injected into each of 12 tumors. The average necrosis was 70% after 1 day, and 90% after 3 days (for the remaining 6 tumors).

Although the 3 aromatic nitrogen mustards listed in the Table were insoluble in saline, their effectiveness was comparable to the soluble agents. Also, β-naphthyl nitrogen mustard[8] and triethylene melamine, compounds which are normally administered orally to patients, were not less effective after intra-tumor injection than the two compounds which are generally administered intravenously, methyl nitrogen mustard and triethylene phosphoramide. Diethylstilbestrol and 6-mercaptopurine, which also have low solubility in saline were, nevertheless, relatively effective in producing tumor necrosis. The latter 2 compounds and β-naphthyl nitrogen mustard were individually tested for their ability to control the growth of Jensen Sarcoma in rats. Six tenths milliliter of a 50 mg/ml suspension of each compound were injected throughout the tumor on the 6th day after transplanting, and at three-day intervals thereafter. Each compound succeeded in keeping the tumor size down to 15–30% of the controls, and produced apparent disappearance of the tumor in some instances within 2 weeks—with survival periods longer than 6 months.

The intra-tumor administration of insoluble anti-tumor compound could reduce the systemic toxic effects frequently observed after the systemic administration of anti-tumor agents, since insolubility would ordinarily prevent rapid movement from the tumor. Of course, such administration of insoluble agents would be limited to the tumors for which radioisotopes have been used—bronchogenic, breast, prostate, cervical and other types of accessible tumors (and possibly for control of ascitic fluid formation). In principle, it would appear desirable to investigate the effectiveness of intra-tumor combinations of radioisotopes with one or more anti-tumor chemicals of the nitrogen mustard, hormone or anti-metabolite types.

S. W. Mayer and M. E. Morton

Radioisotope Research Unit, Veterans Administration Hospital, Long Beach, California, and the School of Medicine, University of California at Los Angeles, April 23, 1956.

Zusammenfassung

Mehrere klinisch wirksame, geschwulsthemmende Stoffe verursachten relativ rasch Nekrosen der Mäusesarkoma-180-Tumoren, wenn sie, entsprechend der klinischen Anwendung von radioaktiven Kolloiden, direkt in den Tumor injiziert wurden. Sowohl unlösliche, wie lösliche Verbindungen ergaben Nekrose. In den Tumor injiziertes 6-Merkaptopurin, Diäthylstilböstrol und β-Naphtyl-Stickstoff-Lost verminderten alle bei Ratten das Wachstum des Jensen-Sarkoms.

[8] A. A. Videbaek and S. Kaae, Acta med. Scand. *149*, 361 (1954).

Potentiation Action of Ibogaine (Bogadin TM) on Morphine Analgesia

Neostigmine[1], B-diethylaminoethyldiphenylpropylacetate hydrochloride[2], certain adrenocortical hormones such as DCA[3], and insulin[4] have been shown to potentiate morphine analgesia. Chlorpromazine prolongs the analgetic morphine effect[5] but does not necessarily enhance it[6]. Therefore, the reduction of morphine analgesia in mice pretreated with reserpine was a rather unexpected finding[5]. The combination effects of these phrenotropic agents with morphine prompted us to investigate the pharmacodynamic interactions of morphine with ibogaine, an indole alkaloid from *Tabernanthe iboga*[7] with characteristic central stimulant properties[8].

Potentiation of Analgetic Effect of Morphine Sulfate by Ibogaine HCl

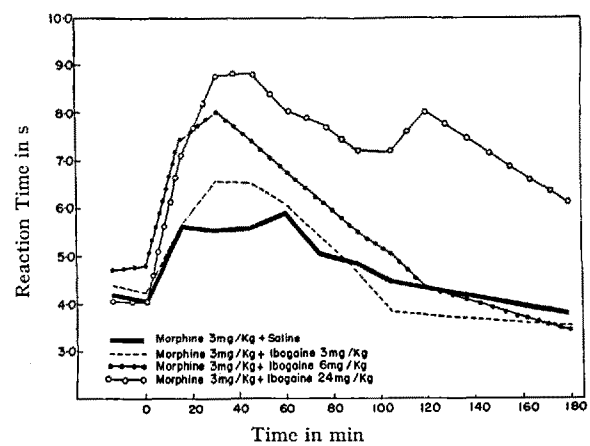

Fig. 1.—Comparison of average reaction time to a thermal pain stimulus applied to the mouse tail following subcutaneous injection of morphine alone and in combination with ibogaine. Each curve represents an average from a group of 10 mice. Prolongation of the reaction time following the combination of morphine and ibogaine becomes more pronounced as the dose of ibogaine increases.

Methods.— 370 female white mice (Webster strain) were tested for their reaction to pain by directing a beam of heat on the tip of their tails (Gross[9]). The reaction time was measured for each mouse as determined by the characteristic tail flick. Double readings ob-

[1] D. Slaughter and D. W. Nunsell, J. Pharmacol. exper. Therap. *68*, 104 (1940).

[2] L. Cook, G. Navis, and E. J. Fellows, J. Pharmacol. exper. Therap. *112*, 473 (1954).

[3] C. A. Winter and L. Flataker, J. Pharmacol. exper. Therap. *103*, 93 (1951).

[4] F. Gross and H. Kaufmann, Helv. physiol. Acta *12*, 284 (1954).

[5] J. A. Schneider, Proc. Soc. exper. Biol. Med. *87*, 614 (1954).

[6] J. Kopera and A. K. Armitage, Brit. J. Pharmacol. Chemother. *9*, 392 (1954).

[7] J. Delourme-Houde, Thesis, University of Paris (1944).

[8] J. A. Schneider and E. B. Sigg, Ann. N. Y. Acad. Sci. (in press).

[9] F. Gross, Helv. physiol. Acta *5*, C31 (1947).

tained for each group of mice were averaged and the standard deviations of the control values calculated. Analgetic effects following drug injection were either expressed in prolongation of the reaction time or by calculating the number of mice of each group showing significant analgesia. Significant analgesia was assumed when a reading of an individual animal was greater than the mean reaction time of the corresponding group by a factor of 2·32 times standard deviation[10].

Quantitative comparison of the analgetic effect of morphine alone and in combination with ibogaine. Each experiment represents a group of 10 mice.

Drug	% of Mice Showing Significant Analgesia		
	Control %	at Peak of Effect %	at 180 min %
Morphine 3 mg/kg	0	50	0
Morphine 3 mg/kg + Ibogaine 6 mg/kg	0	80	0
Morphine 3 mg/kg + Ibogaine 24 mg/kg	0	100	50

Results.— Ibogaine hydrochloride alone did not produce any significant analgetic effect in doses up to 40 mg/kg subcutaneously. However, when given in combination with morphine, a clearcut potentiation of the analgetic effect of morphine was demonstrated (Fig. 1). A standard dose of 3 mg/kg of morphine was combined with different doses of ibogaine, the ratio of the two drugs being 1:1, 1:2, and 1:8. As the amount of ibogaine was increased the analgetic effect became more pronounced. Statistical analysis of these data revealed that the percentage of animals showing significant analgesia at the peak of the drug effect increased from 50 to 100% as increasing amounts of ibogaine were added to a standard dose of 3 mg/kg of morphine (Table). Furthermore, the analgetic effect lasted longer following combinations of higher doses of ibogaine with morphine. Similar potentiations of analgesia could be obtained following combinations of ibogaine with ketobemidone, codeine and Demerol. However, ibogaine did not enhance the analgetic effect of aminopyrine. Parallel to the pronounced potentiating effect of ibogaine on morphine analgesia, an increase in toxicity could be observed when both drugs were administered simultaneously. Figure 2 represents percent of death in mice following single doses of morphine and ibogaine as well as after a combination of equal doses of each drug. As morphine and ibogaine had similar toxicities, a combination of both drugs increased their respective toxicities about five-fold.

Discussion.— Recent experiments performed by STEPHEN[11] confirmed the potentiating effect of ibogaine on morphine analgesia in human beings. Since ibogaine by itself does not produce analgesia, a simple additive effect can be excluded. One may therefore assume that it interferes with the metabolic process involved in the phenomenon of morphine analgesia. There is one point of attack that both morphine and ibogaine may have in common. According to BERNHEIM and BERNHEIM[12], EADIE[13], and WRIGHT and SABINE[14], morphine markedly inhibits cholinesterase activity. SLAUGHTER and NUNSELL[1] showed in addition that the analgetic action of morphine can be enhanced by neostigmine. Ibogaine was reported to inhibit cholinesterase activity by VINCENT and SERO[15], and was shown to produce a brainstem

The Effect of Various Doses of Morphine, Ibogaine and a Combination of Both on Lethality in Mice.

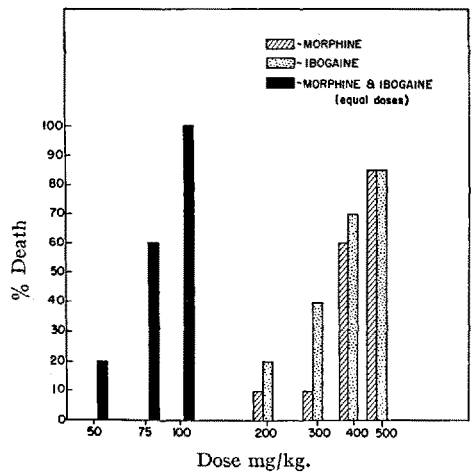

Fig. 2.—Demonstration of lethal effects of morphine, ibogaine and a combination thereof in mice. Doses graphed on logarithmic scale. Note the marked increase in toxicity of both drugs when administered in equal doses simultaneously.

arousal phenomenon, a cholinergic process which can be inhibited by atropine[8]. Provided that the cholinesterase inhibition by morphine is linked to its analgetic effect, the action of both drugs on the same enzyme may well offer an explanation for the potentiation action of ibogaine described in this paper.

J. A. SCHNEIDER and MARIE MCARTHUR

Research Department, Ciba Pharmaceutical Products Inc., Summit, New Jersey, May 28, 1956.

Zusammenfassung

Ibogain-hydrochlorid zeigte an der Maus einen ausgesprochen potenzierenden Effekt auf die analgetische Wirkung von Morphin und morphinähnlichen Analgetika und erhöhte, bei derselben Tierart, auch die Toxizität von Morphin. Die analgetische Wirkung von Aminopyrin hingegen wurde selbst durch hohe Dosen von Ibogain nicht beeinflusst.

[10] J. IPSEN, Acta pharm. tox. *5*, 321 (1949).
[11] R. STEPHEN, Personal Communication.
[12] F. BERNHEIM and M. L. C. BERNHEIM, J. Pharmacol. exper. Therap. *57*, 427 (1936).
[13] G. S. EADIE, J. biol. Chem. *138*, 597 (1941).
[14] C. I. WRIGHT and J. C. SABINE, J. Pharmacol. exper. Therap. *78*, 373 (1943).
[15] E. VINCENT and M. SERO, C. r. Soc. biol. *136*, 612 (1942).