tonin (*13*). To investigate the possibility that capsaicin might elicit thermal analgesia by depleting substance P within descending raphe-spinal neurons, we destroyed the spinal terminals of raphe-spinal neurons by the intrathecal injection of 20 μg of 5,6-dihydroxytryptamine (5,6-DHT). Seven days later we measured the animals' responses to the hot plate and tail-flick tests, then killed them and measured substance P in their spinal cords (*14*). Intrathecal injections of 5,6-DHT produced a 50 percent depletion in the substance P content of the lumbar spinal cord; however, this depletion was not associated with analgesia. These animals, in fact, exhibited a significant decrease in nociceptive threshold ($P < .05$) (Fig. 2B).

Intrathecal injection of capsaicin produced no significant change in the substance P of the brainstem or the forebrain. In addition, intraventricular injection of capsaicin (40 μg in 20 μl) did not produce analgesia. It is known that capsaicin exerts profound peripheral actions, producing intense pain when applied peripherally and causing the activation of C fibers in peripheral nerve (*7*). Capsaicin (30 μg) given via the tail vein evoked no agitation and no changes in the nociceptive threshold up to 7 days after injection (Fig. 2A). Spinal substance P concentrations in animals given capsaicin intravenously did not differ from those in control animals without implanted catheters (Fig. 2A). These experiments suggest that thermal and chemical analgesia evoked by intrathecal capsaicin is not mediated by the diffusion of the drug to either supraspinal sites or the peripheral nervous system.

How does capsaicin produce prolonged thermal and chemical analgesia? We do not believe the effect to be related to the general alteration in spinal function. Animals treated with intrathecal capsaicin maintained good signs of motor function as well as normal responses to non-noxious peripheral stimuli and to noxious mechanical stimuli applied to the extremities; such responses were qualitatively similar to those of control animals. Treated animals also showed no signs of self-mutilation which characteristically accompanies rhizotomies in the rat (*15*), suggesting that capsaicin does not produce a chemical axotomy. The levels of serotonin and norepinephrine in the spinal cord are unchanged by intrathecal capsaicin (*16*), whereas glutamic acid decarboxylase activity and opiate receptor binding are unaffected by systemically administered capsaicin at doses sufficient to deplete substance P (*6*). Capsaicin-produced analgesia was not abolished by administration of the opiate antagonist naloxone (2 mg/kg), and although intrathecal injection of morphine elicits analgesia, the effect is of short duration (4 to 6 hours). Furthermore, intrathecal opiates produce analgesia not only to thermal and chemically induced pain, but also to noxious mechanical stimuli (*8, 17*). Thus, capsaicin-elicited analgesia seems independent of endogenous opiate systems.

We propose that the analgesia resulting from intrathecal capsaicin may be the consequence of a series of events in which capsaicin rapidly liberates most releasable stores of substance P from primary afferent terminals and then induces a prolonged and possibly permanent depletion of substance P from primary sensory neurons associated with the transmission of thermal noxious stimuli. From these studies it is not clear whether the effect of capsaicin is restricted to small-diameter chemo- and thermoreceptive primary afferents. Capsaicin may also deplete other components that play a role in the transmission of nociceptive information. Although the present experiments cannot be construed as supporting a clinical use for capsaicin, the ability to deplete, in a specific manner, a nociceptive transmitter at the level of the first-order afferent synapse may represent the future direction of research for improved analgetic therapy.

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9. Capsaicin was dissolved in 50 percent dimethylsulfoxide and saline. All control injections consisted of this vehicle except where noted.
10. Under double-blind conditions, the degree of agitation in rats was assessed on a scale of 1 to 4 every 5 minutes for a period of 2 hours. The mean rating score for vehicle-treated animals in the first and second hour was 3.4 ± 0.4 and 2.5 ± 0.6, respectively ($N = 5$); in capsaicin-treated animals, the same measures were 1.7 ± 0.2 and 0.8 ± 0.3 ($N = 8$). When we used the sign test, the capsaicin group showed a significantly lower ($P < .01$) agitation rating than untreated controls during each hour.
11. Phenylquinone, 0.25 ml of 0.02 percent alcohol solution, was injected intraperitoneally and the animals housed in individual plastic cages. The number of times each animal rubbed its belly on the floor (writhes), was accumulated. The mean number of phenylquinone-induced writhes in vehicle-treated animals was 32 ± 6 ($N = 6$) compared to 6 ± 2 ($N = 6$) in the capsaicin-treated animals ($P < .01$; sign test).
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14. This treatment causes a 70 to 90 percent depletion of cord serotonin at 7 days with no changes in brainstem concentrations of 5-hydroxytryptamine (5-HT) or any changes in either brainstem or spinal concentrations of norepinephrine. The depletion of spinal 5-HT is associated with a reduction in the nociceptive threshold which is thought to reflect the loss of a descending modulatory influence (T. L. Yaksh and G. M. Tyce, and H. Proudfit and T. L. Yaksh, unpublished observations).
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18. T.M.J. is a Harkness Fellow. Supported by grant NS 14629 from the National Institute of Neurological and Communicative Disorders and Stroke and grant DA-02110 from the National Institute for Drug Abuse to T.L.Y.

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Stereospecific Sorption of L Amino Acids by Colloidal Clay

The statement by Bondy and Harrington (*1*) that "the stereospecificity of [clay-organic reactions] has not been investigated" is incorrect. In 1971 I reported data demonstrating preferential adsorption and polymerization of L isomers of amino acids relative to D isomers and DL mixtures by kaolinite crystals (*2, 3*); a preliminary note on my findings was published by Degens *et al.* (*4*). The results were tentatively ascribed to the inherently enantiomorphic crystal structure of the clay.

Several other investigators have attempted comparable experiments, the results being positive in some cases (*1, 5,*

0036-8075/79/1026-0483$00.50/0

6) but negative in others (7, 8). Probably the priming or poisoning of the catalytic surfaces by trace impurities is of crucial importance in determining the success or failure, respectively, of such endeavors (9, 10).

Finally, there is no justification for asserting (1), on the basis of the paper by Bernstein *et al.* (11), that preferential decomposition of optical isomers by radiation has been "disproved." Several workers have published evidence for preferential reaction of optical isomers with inherently asymmetric β-radiation (12, 13) and circularly polarized ultraviolet light (14). The role of asymmetric radiation in the prebiotic synthesis of proteins merits further study.

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3 May 1979

The conclusion of Bondy and Harrington (1) that L amino acids and D-glucose bind to clay (bentonite) more tightly than their enantiomers is surprising because it is contrary to theoretical expectations. Clay consists of fine particles of hydrated aluminum silicates and other minerals formed by geological processes (2). The reason why such particles should bind more tightly to L amino acids than to D amino acids and more tightly to D-glucose than to L-glucose is not apparent and is not discussed in the report. The authors correctly state that "while L and D amino acids are chemically identical, they may have different properties when covalently bound to or complexed with other molecules that are themselves chiral." Therefore, if there is any difference in binding affinity for clay between L-leucine and D-leucine, a necessary conclusion would be that the clay itself is chiral. In other words, the clay would have to possess a preponderance of right-handed over left-handed binding sites, or vice versa. It would be misleading to state that the differential binding reported reflects an intrinsic "difference in the ability of such enantiomers to be absorbed onto solid surfaces" without specifying that the surfaces must be asymmetric. Thus, the data reported do not point to any previously unknown differences between D and L amino acids, but rather lead to the conclusion that bentonite is an asymmetric form of clay. Although evidence for stereospecific interaction between optical isomers of amino acids and clay minerals has been published previously (3), there has been no direct experimental verification of the chirality of clay.

The authors also discuss the problem of why living organisms contain predominantly L amino acids and D sugars, and they suggest that the selective adsorption of the enantiomers which they report may provide an explanation. Although the results presented may bring us a little closer to the answer, the problem is still unsolved. It is only pushed one step back. The origin of asymmetry in the clay must now be accounted for.

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30 March 1979

Although there is some evidence for the chirality of clay (1, 2), further verification is certainly necessary. Asymmetric mineral crystals such as quartz have been recognized for some time.

The essential difference between the data in our report (3) and the earlier work of Jackson (2) is that we found very high-affinity and saturable sites participating in the specific binding of some L-amino acids to clay, whereas in the work of Jackson a thousandfold higher concentration of amino acids was used. In this latter work, no evidence of specificity or saturability was presented and, as Jackson points out, an attempt to replicate his data was unsuccessful. Since the relevance of studies of amino acid binding to clay pertains to the possible prebiotic assembly of polypeptides, it seems important to establish that these mechanisms could have concentrated amino acids from very dilute solutions such as may have constituted the primordial ocean.

With regard to the question of the preferential decomposition of stereoisomers, there seems to be little definitive evidence for such an effect, although this area has been actively investigated for some years.

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4 September 1979