been found in the rock shelter of Laugerie-Basse (Dordogne) and two of indifferent workmanship in the station of Le Perron (Haute-Loire).

It will be seen that the foregoing examples of complete rock crystal tools of Paleolithic age all come from three adjoining departments in south central France: Charente, Dordogne and Corrèze. A single center somewhere near the headwater of the Vézère river might well have been the source of rock crystal supply for the Paleolithic sites in question.

**VERSIBLE COAGULATION IN LIVING TISSUE. IX**

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A treatment for morphinism was proposed in the second paper of this series, using sodium rhodanate to peptize the colloids of the central nervous system that are agglomerated by the action of morphine. By demonstrating clearly that the theory works out in living tissue, a sound basis can be laid down for further work of the utmost importance. This study was made in order to pave the way to a greater appreciation of the use of sodium rhodanate in drug addiction. The theory is essentially the same no matter what the addicting drug; although the treatment of addiction to other drugs might vary somewhat.

As a result of their study of morphine addiction in dogs, Plant and Pierce say: "We believe that the observations reported in this paper show there is a marked similarity between morphine addiction and withdrawal in man and in dogs; that this similarity makes the dog a particularly suitable test object for the study of many phases of the morphine problem; that results obtained in experiments on dogs can be applied to the problems of morphine addiction with greater validity than those on any other laboratory animal." Contrary to this, Professor M. Miyajima has informed us that the monkey is the best laboratory animal on which to study drug addiction. Nevertheless, the comparative ease of procuring and caring for dogs led us to choose that animal for these experiments.

Six dogs were obtained and acclimatized to their new surroundings for a little over one month before starting the experiment. This collection of animals included one male collie, designation C1, about two years old; one female collie, designation C2, about two years old; one female mixed hound, designation H1, about one year old; and three female beagles (litter-mates), designations B1, B2, and B3, about two and one-half months old. At the start of the experiment all of the dogs were lively
and in good health. A pre-addiction study revealed that C1 was a wild, brainless dog, neither malicious nor interested in human beings. He would bark continuously at the sky when chained up outside. C2 was a thoroughbred, very quiet and ladylike, with a tendency to be shy. H1 continuously sought human affection. B1, B2, and B3 were typical puppies, full of life and interested in everything.

Morphine was administered daily by the subcutaneous injection of a distilled water solution of morphine sulphate containing one-half grain of the drug in each cc. of solution. In order not to disturb profoundly the general physiological processes of the dogs, addiction was brought about on a small amount of morphine, as shown in table 1. Likewise, the dosage of morphine was kept small enough at all times so that, while the dogs

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>DAILY MORPHINE DOSAGE AT START</strong></td>
</tr>
<tr>
<td><strong>DOG</strong></td>
</tr>
<tr>
<td>C1</td>
</tr>
<tr>
<td>C2</td>
</tr>
<tr>
<td>H1</td>
</tr>
<tr>
<td>B1</td>
</tr>
<tr>
<td>B2</td>
</tr>
<tr>
<td>B3</td>
</tr>
</tbody>
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*A 150-pound man addicted to 5 grains of morphine per day would be taking a daily dose of the drug which amounts to 4.76 mg/kg.

became drowsy at first, the drug did not exert its narcotic effect. Even so the dosage was increased too rapidly in the case of H1 for she lost weight rapidly and came down with a severe case of distemper which seemed to be largely intestinal. Although the data are given for H1, she played no rôle in this study because of her illness. No new symptoms were noticed when the drug was withdrawn from this dog.

The dogs were given the drug daily for several weeks; then C1 was given sodium rhodanate in capsules for two days, following which the morphine was abruptly withdrawn while the peptizing agent was continued. C2 and B3 received no sodium rhodanate. H1, B1, and B2 were given sodium rhodanate in a 10% aqueous solution by subcutaneous injection for five days prior to abrupt withdrawal, after which the sodium rhodanate was continued. The data are given in table 2.

During the period in which the dogs were addicted many of the common symptoms were noticed, i.e., vomiting, salivation, constipation, and comparative lassitude. The vomiting stopped after about three weeks; the salivation began after about two weeks, and continued until two weeks after withdrawal. Reach considers that salivation before and after the injection is an abstinence symptom. Pavlov, on the other
TABLE 2

<table>
<thead>
<tr>
<th>DOG</th>
<th>SEX</th>
<th>NUMBER OF DAYS ON MORPHINE</th>
<th>AMOUNT NaCNS BEFORE WITHDRAWAL</th>
<th>AMOUNT NaCNS AFTER WITHDRAWAL</th>
<th>DAYS NaCNS CONTINUED</th>
<th>TOTAL AMOUNT NaCNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>M</td>
<td>38</td>
<td>0.8 gm.</td>
<td>3.4 gm.</td>
<td>10</td>
<td>4.2 gm.</td>
</tr>
<tr>
<td>C2</td>
<td>F</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H1</td>
<td>F</td>
<td>35</td>
<td>1.0</td>
<td>0.5</td>
<td>5</td>
<td>1.5</td>
</tr>
<tr>
<td>B1</td>
<td>F</td>
<td>41</td>
<td>1.1</td>
<td>1.3</td>
<td>9</td>
<td>2.4</td>
</tr>
<tr>
<td>B2</td>
<td>F</td>
<td>41</td>
<td>1.0</td>
<td>1.3</td>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>B3</td>
<td>F</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

hand, calls it a conditioned reflex. We are inclined to agree with this latter view because increasing the dosage of morphine failed to stop the salivation; also, the amount of salivation decreased markedly when the drug was withdrawn in the case of the control animals. Further, the dogs all began to salivate upon the appearance of the experimenters no matter what the time of day, or whether before or after the morphine injections were made, although visitors did not induce this reaction. At times the reflex vomiting described by Pavlov was observed. For instance, one time while injecting a dog in the sight of another dog, the other dog began to vomit.

One dog, C1, began to gnaw at the wood supports in his cage after four weeks on morphine. This is considered to be a withdrawal symptom; still, on comparatively greater increases in morphine dosage the symptom was not alleviated.

The success of this experiment depended upon the appearance of withdrawal symptoms in the dogs that were not treated with sodium rhodanate, and the non-appearance of withdrawal symptoms in the dogs protected by sodium rhodanate. Reserving C1 for special comment, and ruling out H1 because of distemper, leaves C2, B1, B2, and B3; all four of these dogs were addicted in an identical manner except for dosage. That is, the dosage increase per unit of time, disregarding variation in weight, was the same. The dose was increased 0.0032 gram every other day from the 12th to the 41st day. B1 and B2 were given sodium rhodanate for five days previous to the abrupt withdrawal of the morphine; during this period the regular increase of the morphine was continued. While this was going on B1 and B2 became somewhat depressed, accompanied by a slight loss of appetite, which was reflected by a small decrease of weight.

There were no withdrawal symptoms shown by B1 and B2 upon withholding the drug. They became brighter in two days; their appetites were much better; there were many stools that were not soft; there were no evidences of diarrhea, tremors, or dilated pupils; they showed practically a straight line increase in weight. There was no nervousness. In
other words, no withdrawal symptoms were noticed under the sodium rhodanate treatment.

In contrast to this, C2 and B3 began to show withdrawal symptoms two days after the morphine was abruptly withdrawn. All four of these withdrawals were made on the same day. The second day after the drug was withdrawn C2 showed a desire for it which was manifested by excessive friendliness, in direct opposition to marked shyness during the addiction period. When she learned that she was not to have the drug she became retiring and paid no attention to the experimenters. When the hypodermic syringe was exhibited she nosed it (she is not an inquisitive dog) and became somewhat restless. C2 and B3 had slight diarrhea; the pupils of their eyes were widely dilated, a withdrawal symptom in human beings.8 C2 had a pronounced head tremor, and a fine body tremor; while B3 had a pronounced body tremor and a slight head tremor. At times B3 would walk around her cage in a nervous aimless way for short intervals. C2 seemed to blow air out with her mouth closed in such a manner as to make her upper lip move rapidly out and in. Both of these dogs lost weight slightly during the first six days of the withdrawal period, in contrast to a gain in weight by those on sodium rhodanate. The withdrawal symptoms subsided twelve days after the morphine was discontinued.

The behavior of these four dogs, C2, B1, B2 and B3, shows very definitely that sodium rhodanate can be used to control the abstinence symptoms resulting from the abrupt withdrawal of morphine from addicted tissues.

A close study of the actions, reactions and habits of this group of dogs, excepting C1, convinces us that the demand of the habituated tissue for the drug is reflected in the behavior of the animals. One example will illustrate the point aptly. After about three and one-half weeks on morphine, all of the dogs, except C1, began to wag their tails when they were injected. The episode did not begin when they were approached prior to the injection. Likewise, there was neither a response to the preliminary handling nor to the insertion of the needle under the skin. When the liquid began to enter the body from the syringe the dogs began to wag their tails rapidly. There was no such response to the injection of sodium rhodanate during the withdrawal period.

C1 provided a most interesting behavior study; before the start of the experiment he was observed to be highly excitable, scatter-brained, and hard to control. On being approached, he tended to be suspicious, and was without care for human company or affection. He was not a stray dog. He yelped senselessly at the sky for long spells. Eleven days on morphine quieted him down; he became slightly more approachable, less wild and nervous, and ceased barking at the sky. This was a period
when he was comparatively normal. Five more days carried him out of this stage into a different phase wherein he was somewhat restless, very unapproachable, but not mean. He tended to stand faced away from human beings, sometimes with his head in the corner. There was a very obvious hunted, maniacal look in the eyes of this dog during this period. He was so restless and uncontrollable that it was hard to inject him; but upon soothing him the task was sometimes easier. Three days on sodium rhodanate, after withdrawing the morphine, brought C1 back to a normal condition. Then, the sodium rhodanate was stopped for a day and a half, and the dog reverted to the condition which had been relieved by the peptizing agent. Resumption of the sodium rhodanate at first made C1 act more like a normal dog, and then his original scatter-brained condition reappeared.

The following diagram illustrates the reactions that C1 exhibited. The terms hypomanic and cycloid are used to denote agglomeration and more agglomerated, respectively, of certain of the brain colloids, as suggested now by Dr. Lang. Case 6 of their report illustrates a similar effect upon the behavior reactions of man when too much of an agglomerating or peptizing agent is administered.

The only withdrawal symptom shown by C1 was the gnawing which was also noticed during the time that the morphine dosage was being increased the greatest.

Abe\(^9\) explains tolerance, both natural and acquired, addiction, and withdrawal symptoms on the basis of changes in the ratio:

\[
\frac{\text{affinity of the tissues for morphine}}{\text{affinity of the blood serum for morphine}}
\]
His conclusions were based on a study of the relative concentration of the tissues and the blood serum for morphine under various conditions. It is a pity that Abe uses narcotics for the treatment of hypomanic patients rather than taking the shortest route and using peptizing agents. He has the details of the general theory well worked out.

The general conclusions of this paper are:

1. The theory demands that the rapid peptization of colloids agglomerated by morphine in living tissue should forestall or diminish greatly the abstinence symptoms when the drug is withdrawn.

2. Sodium rhodanate prevented the onset of withdrawal symptoms when morphine was withdrawn abruptly from dogs addicted to morphine.

3. Addicted dogs that were not given sodium rhodanate exhibited withdrawal symptoms when the morphine was abruptly discontinued.

4. Sodium rhodanate counteracts morphine in living tissue.

5. One dog was changed from a hypomanic state to a cycloid state via a quasi-normal state by morphine; sodium rhodanate forced him back to a quasi-normal condition, and finally to the original hypomanic state.

6. Many of the addicted dogs showed definite signs of a desire for the drug.

7. The way is clear for the use of sodium rhodanate in the treatment of drug addiction in human beings.

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** M.D.

† Eli Lilly Research Fellow.


3 Private Communication.


6 Pavlov, Conditioned Reflexes, 35 (1927).


8 Lambert, Am. J. Psychiatry, 10, 504 (1930).

9 Abe, Revue d'Hygiène, 52, 365 (1930).