

(both by volume) has thus far proved the most efficient menstruum—tinctures made with this representing 80 to 90 per cent. of the drug used. Such a menstruum is, however, very strongly acid.

LABORATORY OF PARKE DAVIS & Co., DETROIT, MICH.

#### DISCUSSION.

F. R. Eldred stated that in his experience the best way to dry the residue of cantharidin was in a vacuum desiccator, at room temperatures, as there was practically no loss when it was dried in this manner, and it was very easy to get rid of the solvent.

Charles Caspari, Jr., said he hoped that Mr. Scoville would continue his work with cantharides and the different solvents, and give the Association a table of his experiences. If, with the present methods, only one-third of the cantharidin was extracted by percolation, it showed the absolute necessity of some general, improved formula.

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### THE PHYSIOLOGICAL ACTIVITY OF CANNABIS SATIVA.

#### *Comparison of Extracts from Indian and American-grown Drug Upon Human Subjects.*

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It has been claimed by various investigators that the common hemp (*Cannabis Sativa*) grown in the United States contains the same active constituent as is found in *Cannabis Indica*, the name of the official drug which is grown in India. Botanists do not distinguish between the two, the plant being identical wherever grown.

The fact that the Indian grown drug was used in all the early accounts of its intoxicating action may have led to the belief that the peculiar climate of India is accountable for the presence of an active constituent not normally present in the plant.

No recorded data have been advanced, however, to substantiate the claim that drug grown elsewhere does not contain such constituents. On the other hand Wood (Proc. Am. Phil. Soc., Vol. XI, p. 226), Houghton and Hamilton (Am. Journal of Pharmacy, Jan., 1908), True and Klug (Proc. A. Ph. A., (1909), True (Am. Journ. of Pharmacy, Jan., 1912), and Hamilton (Am. Jour. Pharmacy, March, 1912), have submitted the drug to careful pharmacological tests, and report that extracts from American grown drug are no less active than those obtained from India.

Dr. H. H. Rusby raised the question whether the test for activity on dogs can be accepted to prove its activity as a therapeutic agent.

Much of our knowledge of the action of drugs is obtained by observing their effects when administered to animals. The physiological action of almost every powerful drug is so characteristic as to be almost unmistakable to an experienced observer. Any one who has observed the characteristic effect of *Cannabis Indica* on susceptible dogs, symptoms which almost invariably appear in an hour after administering one to two grains of an active extract, and then has observed the same effect from an equal dose of an extract from the American drug, is inclined to accept it as proved that the two are identical.

The question raised by Rusby is, however, very pertinent and logically calls for proof of a different character. A series of experiments was therefore outlined which, it was hoped, would throw light on this much mooted question. To make a complete experiment it was decided that three persons would co-operate, each in turn, one taking the same quantity of each lot of drug, while two would remain normal to observe its effect.

There is not much of interest in observing the effect of the drug on others, since its action is more mental than physical. One's own description, if it could be recorded at the time, would mean much more than that of others. The subject, however, is not in a condition at the time to record these observations and if of a nervous disposition needs the presence of companions. Otherwise drowsiness is often the most characteristic effect of the drug.

The evening was taken for these experiments partly to give opportunity for sleep immediately afterwards and partly to have everything quiet with no disturbing affairs going on to distract attention.

One of the three (Hamilton) had on a previous occasion taken two grains of an active extract *Cannabis Indica* and was, to that extent, familiar with its action. On that occasion there were developed some disagreeable symptoms but nothing serious.

Nausea and vomiting occurred which were magnified by the imagination to an extent that was far from pleasant. Therefore, to duplicate conditions as nearly as possible the capsule containing 2 grains extract *Cannabis Americana* was taken at 5:30, followed by dinner at 6 o'clock.

#### EXPERIMENT I.

He relates his experience as follows:

About one hour after taking the drug a pleasurable sensation was experienced which can be described only as one of well-being and complete satisfaction. This was marred to an extent by the dread that the trip to the laboratory might not be entirely comfortable and that in the street car or on the street my behavior might be ridiculous without the cause being known. The walk to the car, the two-mile ride and several blocks' walk to the laboratory, seemed interminable, although no unpleasant feelings were experienced during the trip. One other fact was observed, namely, the difficulty in holding my mind on one subject long enough to express my thoughts.

About two hours after taking the drug, an uncomfortable feeling was experienced, followed shortly by nausea and vomiting. Several ideas impressed me strongly; I had a morbid fear that some one other than my associates would observe me, also that the effect of the drug on me would deter the others from taking it. I was opposed to doing anything and wished most earnestly for a comfortable seat or bed. A feeling of constriction and dryness in my mouth and throat was observed. Later a feeling of depression and drowsiness followed and I appeared to sleep. Whether I did or not is uncertain as I thought I remained conscious all the time. I knew that something in my condition was decidedly abnormal because of comments made by the observers, but I didn't know nor care what it was.

About four hours after taking the drug I felt much better and aroused entirely from my drowsy state. On the trip home I dozed off on several occasions but for only a few minutes each time. A comfortable night's sleep followed and no unpleasant after effects could be noticed.

The result of this experience convinced me that no difference could be detected in the action of extracts from Indian and American hemp, for, although in the former experiment there were several phases which did not appear in this one, the general effect was identical in each case. On the former occasion all the peculiar sensations were more vivid, time dragged more slowly, the nausea was greater, even suggesting the fear of death, the constriction in the throat was so great as to suggest choking to death, there was a greater willingness to give free rein to my imagination and to relate experiences and therefore greater difficulty in keeping the mind on one subject at a time. These differences were, however, in degree and not in kind and may be explained in part by my having become familiar with the drug and descriptions of its effect on others.

*L's Observations on Subject H. Ex. I.* About 6:30 H began to manifest a certain amount of uneasiness and difficulty in concentrating his thoughts. Coming from down town to the laboratory it was observed that he seemed to be more or less worried and to lose to a certain extent, sense of time, expressing the feeling that we had consumed an hour coming from down town, whereas the time for the trip was not more than ten or twelve minutes.

The laboratory was reached at 7:00 and H. expressed a strong desire to lie down or become ensconced in a comfortable chair. From 7:00 to 7:30 he appeared generally depressed and became irritated about seemingly trifling matters. At 7:40 pulse was taken and found to be 120, weak, irregular and easily compressible. Skin was cold and clammy and he expressed a belief that he was going to be nauseated. 7:50, pulse had dropped to 96, but was still weak and irregular.

|       |           |                  |
|-------|-----------|------------------|
| 8:00  | Pulse 92, | Severe vomiting. |
| 8:15  | " 96,     | Vomited.         |
| 8:30  | " 88      |                  |
| 9:00  | " 84      |                  |
| 9:30  | " 86      |                  |
| 10:00 | " 96      |                  |

The last record was taken after H. had been up walking around the room, which undoubtedly accounts for its increase over the one previously taken. It was observed throughout that when H. exercised, even to a slight extent, the heart action was markedly accelerated. In one instance the pulse rate was taken immediately after H. had been walking and was found to be 96. When taken less than a minute afterwards it was about 80, and was again increased to 96 by comparatively slight muscular movement. The pulse rate varied from 96 to 80 or 82 within a minute's time. Throughout it was soft and obliterated by slight pressure. During the whole evening his ideas seemed to be more or less confused, and it was apparently impossible for him to concentrate his thoughts on any particular subject. After beginning to make a remark, he would lose entirely his trend of thought, and be quite unable to complete it. At 10 p. m. the more marked effects of the drug had worn off.

*P.'s Observations on Subject H. Exp. I.* H. showed no symptoms whatever until about 6:30, when it became evident that he was worried and somewhat nervous. He said that the effect of the drug was coming on and expressed a desire to go to the laboratory as soon as possible. On the way he worried and fretted, at times fearing that he would be unable to walk and would make a spectacle of himself before reaching the laboratory. However, nothing of particular interest happened during the trip except an evident lapse of memory and evidence of nervousness. On arriving at the laboratory he expressed a desire for a comfortable chair or a bed and complained of feeling sick at his stomach. He was pale and his skin was cold and moist. Before long he vomited freely. This was repeated after a few minutes, but did not seem to relieve him greatly. He complained of a dryness in his throat and was continually wetting his lips. His pulse rate was almost alarming, varying greatly in rate from 84 to 120 within a minute, but for the most part being very fast and weak. His skin was cold and clammy and respiration somewhat shallow.

For over two hours he lay back in his chair in a sort of stupor, seeming to be asleep, but easily aroused. He had no disposition to attempt anything, not even to talk. During the early part of the evening he was evidently much worried, fearing that his condition would deter his colleagues from taking the drug. He also seemed to have a dread that some one other than those associated with him in the experiment would see him. He was asked to write, but firmly refused even to attempt it. When asked if he were having beautiful dreams and visions, his only reply was, "I wish I could tell you." He remained in this semi-conscious condition until about 10 o'clock when suddenly he aroused himself, said he felt all right and was ready to go home.

He dozed off momentarily twice on the car, and felt all right the next day except for a very faint headache.

#### EXPERIMENT II.

*Personal Experience.* A 2-grain dose of solid extract Cannabis Americana was taken upon an empty stomach. For fully two hours no symptoms of any kind were experienced. Then there was a peculiar unnatural sensation. This initial manifestation is difficult, in fact, impossible of description. No distress was evidenced nor was the feeling exceptionally pleasant. It was simply a recognition of the fact that I was not quite myself. Following this period there shortly developed a feeling of great elation, and a sense of well being. With no particular reason for being so, I felt inexpressibly happy. There was a twitching and drawing of the corners of my mouth and an uncontrollable desire to laugh, although I could not laugh aloud. Everything pleased me and I felt that my happiness was absolutely complete. The only tinge of regret that I experienced was that my colleagues were not having the same delightful experience. The more marked effects of the drug appeared to come in waves, although the general sense of elation was never lost. An occasional undulation would sweep over me and I would feel as though my body was swaying and there was an inclination to strike the table with my hands in an exuberance of delight. At times I had great trouble in coördinating my thoughts, although between the paroxysms which have been de-

scribed, my mind seemed reasonably clear. I felt that I was acting in an exceedingly foolish manner but had no power to control myself and in fact did not care to. As it grew late in the evening the stimulating effects of the drug decreased and I became somewhat irritable and touchy about trifling matters. At 10 o'clock the greater part of the effects had worn off, although I did not feel entirely normal. After a light lunch I retired and slept very soundly. No after effects of any kind were experienced on the following day.

*H.'s Observations on Exp. II.* L.'s experience was almost entirely one of enjoyment. There was no nausea and no evident discomfort, although he once remarked that the earlier effects were much the more pleasant. There was unquestionably the same well-being, expressed by his repeatedly saying, "I just feel so good." Hearty laughter for which there was no evident reason was explained in this way. At no time was there any desire to carry on conversation more than to answer any questions addressed to him. This would account for there being no noticeable difficulty in keeping his thoughts collected.

Later a sensation of drowsiness was evident and with it expressions of irritation when anything of a disturbing nature was said or done. The effect of the drug was long delayed in appearing, nothing being noticed either by himself or the others until nearly two hours after its administration. This probably explains why its effect was so persistent, intoxication being very evident fully six hours after the drug was taken.

*P.'s Observations on Exp. II.* No effect was noticed for about two hours when a slight twitching of the corners of the mouth was observed and a tendency to smile. When asked why he smiled he said he didn't know, just felt good but could not define the sensation, it was simply one of enjoyment. He said that he felt sorry for us, as he was the only one enjoying himself. Presently he broke into a restrained, but hearty laugh. When questioned, he said it was simply because he couldn't help laughing. He admitted that he was making a fool of himself, but said he couldn't help it and didn't care anyway. At one time he pointed at an article of furniture in the room and had another laughing spell. When asked the reason he merely said that it was funny. He answered all questions put to him, but showed no tendency to be talkative, most of his answers being short.

These spells would last for probably a minute or two and then there would intervene a normal period of ten to twenty minutes. He said he was simply "happy" drunk, and he looked and acted that way. Later in the evening he showed a decided disposition to be annoyed by talking or answering questions and remarked that the earlier effects of the drug were much the more pleasant. At 10 o'clock the action of the drug had worn off sufficiently so that he felt inclined to go home. He was somewhat irritable on the walk from the laboratory and said afterwards that he was very drunk on the way home. He ate lunch before retiring and enjoyed a comfortable night's sleep and felt fine the next day, with no bad effects whatever. Observations were taken of the blood pressure (systolic) and of the pulse rate at intervals during the evening, but nothing abnormal was noticed. The pulse was full and steady and the rate averaged about 80, not varying more than six beats at any time. The blood pressure was 130 mm. of mercury throughout the evening.

## EXPERIMENT III.

P. relates his own experience as follows: At 4:30 I took a capsule containing two grains S. E. Cannabis Americana on an empty stomach. About one hour later, while talking to my colleagues about the best time for them to go out for a lunch, they asked me if I didn't feel anything; I answered, "No," and truthfully I did not, but no sooner had I spoken than I experienced a peculiar sensation. The corners of my mouth commenced to draw and I could not refrain from laughing; I laughed so heartily that I was tired afterwards, although nothing seemed particularly amusing. This spell lasted for probably half a minute, although it seemed much longer to me.

Then my associates left me, and I was alone in the laboratory. At this time I felt most exhilarated. Everything seemed so enjoyable and I was extremely comfortable. I walked up and down the corridor, swinging lightly along, seeming to walk on air or feathers. My feet weighed nothing. It was no effort to walk; it was more like floating along. My sense of proportion was lost, my feet seemed miles away from me, my arms were long and big. The corridor was miles long; I walked or rather floated up and down apparently for hours, waving my hands and arms, marking time to imaginary music. All this while I was smiling and enjoying myself immensely. All my faculties were not impaired, however, because to test myself I read part of a typewritten notice on the bulletin board. I was standing there when a person who knew nothing of the experiment passed by. We greeted each other and evidently he noticed nothing peculiar in my appearance nor actions. I was surprised at this, for it seemed to me that he must see how silly I looked and how I swayed when I walked, but especially he should have noticed my voice, which sounded to me like the deepest bass. It seemed to me to be musical and full toned and I liked to hear myself talk. My colleagues, however, did not appear to notice it nor did they appreciate that I felt so good toward them and myself.

After what seemed hours of walking I sat down to await their return from lunch. Several waves swept over me during this time and also later on, which are very difficult to describe adequately. The feeling was one of well being and perfect satisfaction beginning with a sort of numbness or fullness in the extremities, a feeling of unreality in the surroundings. I knew that my hands were normal in appearance, but when not observing them, they seemed to be detached and not a part of me. We played a game of cards and in playing a card I seemed to be throwing some enormous but very light article over a great distance. These spells usually started by smiling and ended in laughing rather hysterically, pounding the table with my fist. But I could not laugh aloud because of the peculiar drawing and constriction about my face and neck previously noted. As the effect began to wear off these paroxysms became less frequent but no less irresistible. I felt no unpleasant symptoms at any time. About 10 o'clock I was hungry and ate some sandwiches with great relish before going home. I reached home without any difficulty, not feeling drowsy and without any change in my feeling of enjoyment. Upon arriving home I retired immediately because I felt that I was not entirely normal. Before going to sleep, however, I experienced another wave.

I awoke early the next morning very much refreshed and none the worse for my experience.

*H.'s Observations on Exp. III.* The experience of P. was practically a duplicate of L.'s. The effect appeared one hour after taking the drug and except for an occasional lapse, his normal condition was regained five hours afterwards. There was more uncontrollable laughter in his case, no irritability and no apparent discomfort at any time. He seemed to give himself up more completely to the enjoyment of his sensations than the others. At times he seemed to be addressing an imaginary audience, pacing back and forth, gesturing and appearing to talk to himself.

We were inclined to question whether some of his actions were not assumed and voluntary; but he assured us that he was acting just as he felt.

*L.'s Observations on Exp. III.* P. began to feel the effect about an hour after the administration of the drug. He seemed to be possessed of a desire to move about, paced up and down the corridors, declaring he felt as though he weighed not more than fifteen pounds. He was apparently very much pleased with himself, and bubbling over with happiness. At times he would be seized by fits of uncontrollable laughter, which in some cases was spontaneous and without apparent cause, but usually it was incited by the others laughing at or with him. Between these paroxysms of laughter P.'s condition was practically normal, he could talk rationally, and his mind, as far as indications could be depended upon, was clear. At no time did there seem to be a loss of coördination. It was observed that the action of the drug was apparently produced in waves, while between these seizures one's condition would be practically normal.

During the three experiments recorded above the one under observation felt a certain restraint, knowing that the others were watching for every abnormal action. For this reason it was decided to vary the conditions in the further experiment and have all three under the influence of the drug at the same time. It was hoped in this way to eliminate the restraint evident in each of the individual experiments and perhaps observe some new features in the action of the drug.

#### EXPERIMENT IV.

In this experiment H. took Extract of Cannabis Americana again, while L. and P. took extract Cannabis Indica. This gave an opportunity for L. and P. to compare the effect of the two varieties, both on themselves and on the others, while H. took this opportunity to repeat the experiment with all the conditions the same, except that he ate no dinner until the effect was practically gone. All three took the drug at 4:30 on empty stomachs, the dose in each case being two grains.

This last experiment, while not developing any new features, was in other respects successful. H. had no unpleasant experience and the evening was one of unalloyed pleasure, proving that all the discomfort was directly traceable to the nausea from having food in the stomach. L. considered the effect to be much less intense and of shorter duration in this experiment than that from the American drug, while P. took the opposite view in his case.

H.'s account of the experiment is as follows: L. was the first to note the characteristic effect of the drug while P. and I remained unaffected for fully two hours after it was taken.

The same feeling of well-being and complete satisfaction was experienced by all, this being as evident to the observers as to the subject himself. Uncontrollable laughter was more frequent and longer continued than in the individual cases, probably because during a cannabis intoxication so little is necessary to excite it on, and when one started the others joined in the hilarity. No one felt inclined toward any activity, but only to give himself complete relaxation. Each of the three was emphatic in stating that he knew when he was making himself more or less ridiculous, but could not control the impulse nor did he wish to restrain himself.

About six hours after taking the drug, at the end of a quiet card game, without any comment, each of the three assumed as comfortable a position as possible and fell into a doze. It was apparently not sleep in any case, as each was fully conscious of noises in the building and annoyed by them.

This lasted not more than ten minutes, at the end of which we all felt fully aroused and ready for something to eat. This ended the experiment as outlined in advance. The only variation from the original plan was, as noted, for all three to experience the effects at the same time. No point was lost because of this, since the subject is at all times acutely conscious of everything occurring.

*L.'s Account of Experiment IV.* My personal experience with Indian Cannabis was very much the same as those already narrated as occurring with the Cannabis Americana, although the effects were developed somewhat more promptly, and were not quite so pronounced or lasting. P's feeling seemed also to duplicate very closely those which he had had from the Cannabis Americana, but contrary to my own were somewhat more pronounced. He did not have any of the nausea or any of the other uncomfortable features which occurred during the first experiment, indicating very clearly that these symptoms were due to the hearty dinner which he had eaten, and were not to be construed as characteristic of Cannabis. The drug in this last experiment was taken at half past four, and the greater part of the effects were felt from about half past six to eight o'clock. After that time the more exhilarating action had worn off, and I experienced only a drowsiness. For a half or three quarters of an hour after I had ceased to feel any more marked effects of the drug H. and P. continued to be very much exhilarated. About 9 o'clock all three of us became drowsy, and as if by mutual consent laid our heads on the table in a sort of doze, although none of us really went to sleep. This condition continued about ten to fifteen minutes after which we felt much refreshed.

*P.'s Account of Experiment IV.* L. was the first one to show any symptoms from the effect of the drug. He had practically the same experience as on the previous occasion. H. and I did not feel any effect for fully an hour later than L., but finally went under the full influence of the drug very suddenly, there being no premonitory symptoms whatever. At times one of the three would have a paroxysm of laughter alone, but usually one would start laughing and the others join him at once. It was observed, however, that L. was getting over his intoxication early and he sat there seemingly rather bored and provoked at the others for being so happy. The

effect on myself was apparently more intense than that of the previous test, and more so than was experienced by the others, laughing spells being more frequent and inclined to be hysterical. No unpleasant symptoms were experienced by any one of the three during the evening. After several hours playing cards and talking a peculiar thing happened. Suddenly and without a word from any one we stopped the game, lay back in our chairs and dozed. It seems to me that I slept for a long time although it was in reality only about ten minutes. It probably was not really sleep as I remember hearing the watchman on his rounds and I wondered whether he would come into the room where we were. As suddenly and spontaneously as we had dozed, we aroused and, having practically recovered from the effects of the drug, prepared to go home.

In conclusion it may be stated with certainty that the physical and mental condition of the human subject at the time of administering this drug influences its effects both in degree and kind. For that reason no two persons can be expected to exhibit the same symptoms as a result of ingesting equal quantities of the same drug, and no person can be depended upon to react in exactly the same manner from the same drug on different occasions. With these facts in mind the differences in the three personal experiences above related are readily explainable and there is no reasonable ground for doubting that *Cannabis Sativa* grown in India and America contains the same active constituent.

The method for assaying extracts of *Cannabis Sativa* described in detail by Houghton and Hamilton (*Am. Journ. of Pharm.*, Jan., 1908) makes use of dogs for exhibiting the characteristic effect of the drug. Attention is called in this article to the fact that the animals must have been specially selected for the purpose. They must not only be susceptible to the drug but their behavior under its influence must have been determined by preliminary observation. We may thus avoid errors due to their individual idiosyncrasies. There are, apparently, no such marked differences in the character of the reaction in dogs as are observed in human subjects nor are they so variable at different times if they have been carefully selected as described above.

When proper precautions are observed the activity of an extract *Cannabis Sativa* relative to a standard extract may be determined with reasonable accuracy. My personal experience of twelve years in observing tests of *Cannabis Sativa* obtained from different countries, Africa, India, Germany, Greece and various localities in North America has convinced me that they all contain the same active constituent.

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## SOME COMMERCIAL SAMPLES OF DRUGS.

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The purpose of this paper is to report the results of a series of determinations which were made with the object of ascertaining, as far as possible, the purity and quality of certain drugs, especially some of the gum-resins, as furnished to the trade by the wholesalers of the middle west. The samples were obtained