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The Use of Psychopharmacological Agents in China: Historical and Current Perspectives

It has been known for centuries that certain preparations can affect human mental functioning. The fable that Shen Nung tested plants has been continually read with admiration by the people of our country for thousands of years. It describes, in simple and vivid language, how our ancestors made important discoveries in their active exploration of the possibility that certain edible vegetables and herbs might enhance the health of their descendants and the prosperity of the Chinese nation. It is said that this mythical Chinese emperor, Shen Nung, had a good knowledge of medicinal herbs and was the first to record that marijuana could be used as a drug. He described its hallucinogenic effect in *Shen Nung's materia medica* as follows: "Marijuana . . . if taken in excessive amounts, can cause hallucinations and madness. . . ." This is the first written record of a hallucinogen in history.

Thousand of years ago, sages in primitive communes often used the magical effect of hallucinogens to induce hallucinations and particular psychological changes for the purposes of prayer, fortune-telling, and treating diseases. The *Introduction to medicine* written by Li Ting in the Ming dynasty stated: "Men become mad after too much drink and food," and "Men become mad and hot-tempered after ingesting fragrant grass and stone medicine." The datura flower can induce a trance, for instance, and this had already been recorded in our medical literature. Moreover, the literature described and recorded the tranquilizing and analgesic effects of some drugs, how the ability to learn and memorize could be enhanced by medication, and so on.

Reserpine and chlor- promazine were compounded and put to clinical use in the 1950s. They furthered the creation and development of modern psychopharmacological preparations and aroused great interest among psychiatrists, neuroscientists, and psychologists in our country. Many people recommended and reported, in relevant journals at home and abroad in the mid-1950s and early 1960s, on the introduction of, development of research on, and clinical use of psychopharmacological agents.

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The Pharmacology Division of the Chinese Physiology Society held a seminar, in Shanghai in 1962, to discuss, in particular, the issue of how to study psychopharmacological agents. Subsequently, a book entitled *Advances in psychopharmacology* was published to introduce the research achievements and principal theoretical systems of foreign countries on this subject and to emphasize the importance of work in this area. Although research on psychopharmacological agents drew the attention of research psychologists in our country at the beginning of 1960s, it was not until 1964 that actual work on the subject began. In 1966 we completed a study entitled "The effects of chlorpromazine and chlorpromazine-amphetamine antagonism on the learning and behavior of the rhesus monkey" [1], which was the first treatise on psychopharmacological agents by research psychologists in our country.

In October 1980, the First National Congress on Neuropharmacological Research was convened by the Chinese Pharmacological Society. It was a tremendous gathering of people from pharmaco- logical and neurophysiological circles in our country. Researchers on psychopharmacology were invited to attend the meeting, and presented a report, "The effects of anisodine on discriminative learning, memory, and electrical activity in animals" [2], that aroused considerable interest among the audience. Since the Chinese Psychological Society resumed academic activities in 1979, research psychologists have been invited to, and presented many papers at, relevant national seminars [3].

Through study of psychotropic drugs, we are trying to determine the proper hallucinogens to use to create models of experimental psychosis so that we can increase our understanding of how psychopharmacological agents influence human mental functioning and of the material basis for the changes these preparations produce. We are sure that this will help us further our knowledge of the mechanisms of mental disorder, of the reasons for alterations in consciousness, and will reveal ways of finding and choosing new drugs for treating psychoses.

At present, a group of psychopharmacological researchers who are in the prime of life has been formed, and is reaching maturity. Moreover, some specialized research institutes have been established. The following summary will give some idea of the progress that has been achieved in our psychopharmacological work.

The effects of hallucinogenic plants on human and animal behavior

Yunnan Province is known as a botanical kingdom. In cooperation with the Kunming Institute of Botany and the Psychiatric Hospital of Yunnan Province, we investigated the resources in hallucinogenic plants in Yunnan Province several years ago [4] and found abundant natural sources of such plants. Families, genera, and species that exist in foreign countries can nearly all be found in Yunnan. Moreover, some especially valuable hallucinogenic plants that have not been reported or recorded by foreign researchers have also been discovered. We here describe two of them.

Boletus speciosus

Boletus speciosus falls under the category of a fungus and is a species of Boletaceae. It is widely distributed in Yunnan and has a very large yield. Every year it is sold on the market from June to August. Because of its delicious taste, many people eat it. In general, it is quite safe if consumed in small amounts along with rice or bread; large amounts, however, will produce psychotic symptoms, and those particularly sensitive to it can suffer a mental disorder from ingesting even a small amount. Visual hallucinations usually appear 6 to 24 hours after ingestion. Poisoned patients often complain of lilliputian hallucinations. Those who have been slightly poisoned gradually return to normal within a few days. The seriously affected often have symptoms of toxic psychosis, such as auditory and/or visual hallucinations, disturbed thinking, and aberrant behavior, and may even become stuporous. Their clinical symptoms are very much like those of schizophrenia.

In our investigation we found two typical cases. One took place on 17 June 1959. As soon as 18 of 21 students and a teacher at Chuxiong Medical School suffered toxic psychosis after eating *Boletus speciosus*, they began to quarrel among themselves. The other incident took place during the rainy season of 1975. In this instance there were more than fifty cases of toxic psychosis from *Boletus speciosus* in a factory with more than a thousand employees.

In addition, we analyzed 300 cases of patients suffering from *Boletus speciosus* in the Yunnan Province mental hospital. Among these patients 174 were male, and 126 were female; the oldest was 66 years old, and the youngest, 8 years; most of them were young people. All the poisoned patients complained of lilliputian hallucinations and claimed that they saw little people and animals moving about everywhere: they saw them on their clothes when they were dressing and saw them on their dishes when eating; the hallucinations were even more vivid when their eyes were closed.

The more seriously ill patients suffered pareidolia and personality disintegration. For example, some patients felt that the mountains or buildings surrounding them were pressing down upon them. The less seriously ill, in contrast, treated their visual hallucinations with a critical attitude; they knew the hallucinations were caused by eating *Boletus speciosus* and were able to control their behavior. Sometimes, however, they were able to more or less give expression to feelings, especially inner emotions, that they would not ordinarily display. The seriously ill, on the other hand, were unable to deal with their hallucinations calmly: they became confused, uneasy, and panicky. They would undress, beg for mercy on their knees, sneer at and quarrel with each other, or perhaps be unable to fall asleep and feel depressed.

In 163 of the 300 patients, the disorder ran its course in less than ten days. The patients gradually returned to normal when the hallucinations subsided. In 94 cases, the disorder ran its course in 10–30 days; in 43 cases, it lasted more than a month; and in 5 cases, half a year. All the patients, however, have fully recovered. There were no deaths or relapses.

Twenty-eight of the most seriously ill patients became stuporous. Initially they displayed particularly clear symptoms of excitement and restlessness, accompanied by thinking disorders of various degrees of severity. After a few days (2–13), they suddenly fell into a stuporous state: they became silent and obstinate, refused to eat, and stared blankly into space. The most seriously ill would lie motionless in bed; they became constipated, did not urinate, and suffered an increase in muscle tonus. This stuporous state could last for half a month to a month, or even longer. The clinical picture was difficult to distinguish from schizophrenia. It is interesting to note that the patients could recall their weird hallucinations and fantasies during this stuporous state. About half of the patients gradually returned to normal as the stupor subsided. But the symptoms of hallucinations and fantasies in the other half became even more marked after the disappearance of the stupor and before final recovery.

During the stuporous stage, the patients' EEGs were similar to those of people under the influence of LSD, displaying diffuse lower voltages, desynchronous and fast waves, and a few θ-waves. With recovery, their EEGs gradually presented an α-rhythm until they had fully recovered. Improvement in their clinical symptoms was in keeping with the return to normal of their EEGs. Chloropromazine was effective in controlling the symptoms.

Because *Boletus speciosus* can causes psychosis and its symptoms are very similar to those of schizophrenia, we inferred that it must contain certain psychomimetic ingredients. We therefore made a liquid extract of *B. speciosus* for an experiment (p.o.) so we could observe its effect on the behavior of dogs and rhesus monkeys. The dogs displayed obviously abnormal behavior six to eight hours after the extract had been administered. They stared with a look of inquiry and fright, and they barked and were unable to fall asleep. In general, their abnormal behavior in some cases lasted up to 12 hours. Some animals had numb legs and walked haltingly. They did not return to normal until two days later.

The rhesus monkey displayed similar abnormal bahavior 5 to 12 hours after being given an enema with the extract. In the accompanying photos, on the left the rhesus is sitting motionless and gazing fixedly and angrily; on the right it is in a stuporous state.

Wild litchi

Litchi is a dicotyledon plant of the Sapindaceae family. Its scientific name in botany is *Dimocarpus fumatus*. It is of the same family as *Litchi chinensis*, but of a different genus. Its fruit looks very much like litchi and grows on a wild tree, which is why people call it "wild litchi." It grows in the areas of He Kou and Bin Bian of our Yunnan Province and in the northern part of Viet Nam. It is considered a valuable tree, one not found anywhere else in the world. Wild litchi trees bear fruit from May to June every year. The fruit has thin pulp and tastes sweet. Its kernel is bitter; once boiled, however, it becomes sweet and palatable, just like the Chinese chestnut. But it can also cause the symptoms of psychosis.

Rhesus monkey 5–12 hours after being given an extract of *B. speciosus*. In the photo to the left, it is motionless and has a fixed and angry expression; in that to the right, it has lapsed into a stuporous state.

Therefore, the natives call it "madfruit" and forbid people to eat it or even to throw it at each other in fun.

Following the upsurge in developing and building border areas, however, many people from other parts of the country have come to this region. As the newcomers know nothing about the toxicity of wild litchi, they have often been poisoned by its kernel. Here we should like to report a case of group poisoning.

On the morning of 12 May 1961, 50 people on a certain farm in the Red River area ate wild litchi. Some ate as many as 60 kernels or more, and others, at least a few. That afternoon, 32 of them developed psychosis, one after another. They became agitated and restless and had abundant visual hallucinations. Following emergency treatment on the spot, 23 people recovered in 1–3 days. Nine of the more seriously ill were sent to a hospital at once, and seven of them returned to normal after one or two weeks. One young man, however, became stuporous after the agitation and mania had subsided; he was accidentally run over by a train because of carelessness. There was one particularly serious case, and the following is a brief case report of this patient's condition:

> The patient was a 33-year-old male. At 9 in the morning of 12 May 1961, he ate about 60 boiled wild litchi kernels. One hour later, he felt dizzy and nauseated, and vomited a little. He then "saw" a large group of young men and women dressed in colorful garments, beating drums and gongs to welcome him. He felt heroic and elated, and began making gestures and talking incessantly. It seemed to him that even the buildings were moving around according

to his will. He could not sleep, and disturbed others. When his wishes were not obeyed, he began to fight with others and to destroy things. He refused to see a doctor. As he was being escorted by force to the hospital, he led eight of the other more seriously ill patients in shouting, "We will meet our death like heroes."

While in the hospital, the patient suspected his wife of collaborating with the doctors in a plot to murder him. He refused food and medicines and objected to being seen by the doctors. He climbed over a wall in an attempt to escape. He was treated with chlorpromazine and gradually recovered. He was released from the hospital on 6 July. In a follow-up visit to him in 1976, we found that the patient had been normal since leaving the hospital.

The other 18 patients who had eaten only a few litchi kernels did not experience the above-described symptoms; they said they were just a little dizzy.

The effects of certain psychopharmacological agents on animal behavior and electrical activity

We studied the effects of certain psychopharmacological agents on animals' emotional behaviors, learning, memory, EEGs, and ECoGs. Using chronic microelectronic technology, we also studied the influence of LSD on the electrical activity of single nerve cells of the hippocampus and on the behavior of domestic rabbits. The following are our principal findings.

Chlorpromazine and amphetamine

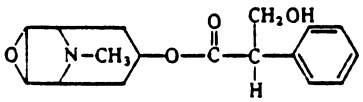
An experiment was conducted with an adult rhesus monkey. We first set up a positive learning experiment with sound stimulation as the signal and feedback cue and food delivery and reinforcement as the basis of the positive learning. We next set up a negative learning situation with light stimulation as the signal and feedback cue and 50 Hz electric shock reinforcement as the basis of negative learning. After operant conditioning had been firmly established, we observed the effects of drugs on the "learning" and emotional behavior of the monkey. On the basis of repeated studies, we found that 0.2–0.3 mg/kg of chlorpromazine and 0.25 mg/kg of amphetamine inhibited both positive and negative "learning" by the rhesus monkey to some extent, and there was an obvious antagonism between the two.

We also investigated the influence of chlorpromazine on the EEGs of 16 rhesus monkeys. The results indicated that chlorpromazine can cause changes in the rhesus's EEG to some extent, principally high voltages and slow waves in the whole cortex. It also improves the driving response elicited by the photic stimulation [5].

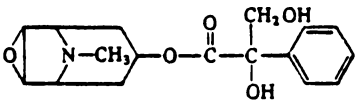
Anisodine

Anisodine is a new alkaloid isolated from *Scopolia tangutica* (*Anisodus tangutious*) by our phytochemists, subsequent to the isolation of anisodamine. The chemical structure of this new alkaloid is different from that of scopolamine only

in a hydroxy group on the tropic acid moiety of the anisodine molecule. The pharmacological action of anisodine has been shown to be relatively weaker than that of scopolamine and atropine, and it is much less toxic. An overdose of anisodine, however, will cause auditory and visual hallucination and disorientation. Its structure is as follows:



Scopolamine



Anisodine

With rats as subjects, maze brightness discrimination was employed in a learning and memory experiment. The results of the experiment indicated that anisodine influenced the learning and memory of maze brightness of rats to some extent. The principal findings were that the frequency of the rat's mistaken responses increased, response time was prolonged, and the proportion of conditioned passive avoidance reactions decreased. A large dose of anisodine can cause high voltages and slow waves of the whole cortex, resulting in obvious inhibition of conditioned responses (to a 50 Hz, 80 dB, pure tone) on the ECoG. In individual cases, the conditioned response of certain animals may disappear completely. Except for certain animals, anisodine has almost no influence on the unconditional response (electric shock) on the ECoG. A small dose of anisodine inhibits the spontaneous potential of the ECoG of rabbits, and the inhibition manifests itself in an increase in Δ-activity and a decrease in θ-rhythm. It lowers the convulsive response of the whole cortex and hippocampus to new stimulations and leads to high-amplitude and slow-wave activity of the whole cortex. In addition, a small amount of anisodine has a clear and harmful influence on the unstable electrode avoidance conditioned reflex of the rat, but not a noticeably harmful one on a good, stable reflex. After anisodine is injected for one hour, the level of acetylcholine (Ach)in the hippocampus and cortex of the rat drastically declines. Compared with a control group, the difference is significant ($P < 0.001$). Forty-eight hours later, we can still observe a sharp decline in Ach, but it returns to normal after 72 hours [6].

LSD effects on the behavior and activity of neurons in animals

Eighteen domestic rabbits were chosen as subjects. A small dose of LSD was injected into the midbrain raphe or the vein and, using chronic microelectronic technology, we observed the influence of LSD on the activity of neurons in the dorsal hippocampus in rabbits. The results showed that the influence was displayed principally in the following two ways: an increase in the firing frequency and a change in the form of the firing [7]. The influence of LSD on the behavior of 30 rabbits was shown mainly in their frequent licking and rotating acrivity [7].

Conclusion

In sum, illumination of the effects and mechanisms of psychopharmacological agents is not only helpful in clinical applications of such agents and in exploring new ways of producing more up-to-date and more effective drugs but also very meaningful in explaining the mechanisms of psychosis and regular patterns of human thinking. Thus, more and more Chinese scholars have come to realize the importance of further study of psychopharmacological agents. To enhance people's mental health, prevent mental disorders, and treat patients with psychosis more effectively, we believe there will soon be a new upsurge in the study of psychopharmacological agents. As is known, our people have had rich experience in fighting disease for thousands of years. Moreover, we have abundant natural resources in medicaments. Hence, simultaneously with efforts to learn from countries that are advanced in science and technology and to absorb the achievements of related disciplines, we must energetically tap our own nation's medical legacy and do our best, in studying psychopharmacology, to contribute to enhancing our people's physical and mental health.

References

1. Guan Linchu & Liu Shiyi (1979) [The effects of chlorpromazine and chlorpromazine-amphetamine antagonism on learning and behavior in the *Macacus rhesus*]. *Acta Psychologica Sinica*, *3*, 342.

2. Guan Linchu, Wu Qine, & Shao Daosheng (1981) [The effects of anisodine on discriminated learning, memory and electrical activity in animals]. *Acta Psychologica Sinica*, *2*, 239.

3. Guan Linchu, Kuang Peizi, & Wu Qine (1981) [The effects of some psychological drugs on behavior and electrical activity in animals]. [*The Third National Congress of the Chinese Psychology Society and Conference on Its Sixtieth Anniversary. Abstracts of selected works*]. Vol. 2, pp. 162–63.

4. Kunming Institute of Botany, Academia Sinica, Psychiatry of Yunnan Province, Institute of Psychology, Academia Sinica (1977) [Toxic psychosis from *Boletus speciosus*]. [*New Medicine, Diseases of the Nervous System*], *4*, Suppl., pp. 217–20.

5. Wu Qine, Guan Linchu, & Liu Shanxun (1981) [The effects of chlorpromazine on the EEGs of rhesus monkeys]. *Acta Psychologica Sinica*, *1*, 93.

6. Kuang Peigan, Kuang Peizi, Dai Fulin, Chen Shuangshuang, & Chang Fengying (1982) Effects of anisodine on memory. *Journal of Traditional Chinese Medicine*, 2(4), 277.

7. Sun Gongduo, Guan Linchu, He Guoling, Chen Shuangshuang, Wang Jianjun, & Kuang Peizi (1984) [The effects of LSD on behavior and activity of neurons in the dorsal hippocampus nucleus in rabbits]. *Acta Psychologica Sinica*, *3*, 319.