

SYNTHETIC CANNABIS PREPARATIONS IN PSYCHIATRY:
(1) SYNHEXYL.

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FIFTY years ago in a discussion on the pharmacology of cannabis indica, Dixon (1899) said, "Hemp therefore exerts its effect differently according to the preparation used . . . In fits of depression, mental fatigue, nervous headache, and exhaustion a few inhalations produce an almost immediate effect, the sense of depression, headache, feeling of fatigue disappear and the subject is able to continue his work feeling refreshed and soothed. I am further convinced that its results are marvellous in giving staying power and altering the feelings of muscular fatigue which follow hard physical labour . . . It is to be feared, however, that cannabis indica can never become popular until its active principle has been isolated, that is, the isolation of a compound of fixed strength."

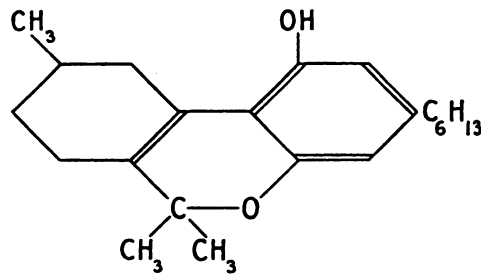
The opportunity to use compounds having fixed strength was accorded to Stockings in 1947 and he reported on clinical trials with Synhexyl. He also laid down criteria for the ideal euphoriant and concluded: "Results of these particular trials would suggest that we have in this class of compounds promising therapeutic agents for the treatment of chronic intractable depressive states."

Later Parker and Wrigley (1947) described the effect of Synhexyl on normal subjects and pointed out its euphorigenic effect. In Stockings' series the trials were made with Synhexyl in a series of 50 patients. These were said to show thalamic dysfunction syndrome and included cases of the depressive-psychotic and the neurotic-depressive types. Numerous case results were quoted to illustrate the points and hope was raised that in Synhexyl, a very promising substance had been found for the treatment of psychiatric conditions.

Recently a quantity of Synhexyl was placed at our disposal for clinical trials and the results and the method of the trial are described below.

Synhexyl is 1-hydroxy-3-n-hexyl-6, 6, 9-trimethyl-7, 8, 9, 10-tetrahydro-6-dibenzopyran, and its structural form is as shown on next page.

There were available the different types of patients usually found in mental hospitals and attending psychiatric clinics and it was decided that it would be profitable to administer the drug to a fairly wide range of patients to see if any particular group could be selected as having been influenced more than another. To this end we treated—



- (1) Psychotics of various types.
 (2) Depressives of various types.

The number originally treated was quite large but we were left, after discharges, etc., with a final figure of 62 patients who had completed the course, of which 16 were out-patients. The dosage employed was at first round about 30 mg. daily but it soon became apparent that doses of this order tended to produce sedation and that more beneficial effects regarding the euphoria would be obtained from smaller doses. This was confirmed also by our personal experience. Consequently in the main a dosage of 10 to 20 mg. daily was employed in this group of patients, though as the trial progressed it appeared that some intractable patients improved generally as the dose was stepped up. This was probably due to its sedative quality. Some of the patients who had previously refused food began to demand it and some of the out-patients said that they felt very much better. Analysis of the results of this study showed that out of the 62 patients treated two groups consistently reported general improvement as judged by their subjective symptoms, by nursing staff observation and by us.

The two groups showing improvement were melancholia and neurotic depressions and it was decided, therefore, to take cases from these two groups, sub-divide them and treat some with active material and some with dummy tablets. The tablets were prepared and designated "Synhexyl A" and "Synhexyl B," and *no one administering the tablets* or assessing the clinical results was aware which contained the active material. The active tablets each contained 5 mg. of Synhexyl and the others contained inert material. The patients were arbitrarily selected from both hospital and out-patient cases and none had previously been treated with Synhexyl. The summarised results of this trial are given below. The degree of improvement being recorded in a standardised way to avoid non-comparable terms:—

SYNHEXYL A.

		Male	Female	Total
Definite improvement	..	3	3	6
Improvement	5	2	7
Slight improvement	..	1	1	2
No improvement	3	8	11
		<hr/>	<hr/>	<hr/>
		12	14	26
		<hr/>	<hr/>	<hr/>

SYNHEXYL B.

	Male	Female	Total
Definite improvement ..	3	2	5
Improvement	3	6	9
Slight improvement ..	—	2	2
No improvement	7	8	15
	13	18	31

From a study of these results it will be apparent that there is nothing to choose between the therapeutic results in the two series A and B. Some observers have suggested that there is a little extra improvement in the group designated "Synhexyl A," but the batch of tablets designated "Synhexyl B" was the one which contained the active substance, so it can be said that there is nothing arising from this trial that would justify the claim that Synhexyl is a potent substance for the relief of cases of melancholia and endogenous depression. Our findings therefore do not confirm those originally reported by Stockings (*loc. cit.*).

DISCUSSION.

Despite the conclusions reached as outlined above, we know from our own experiences and those of other members of the medical and nursing staff that Synhexyl has definite pharmacological effects and does produce euphoria. This is confirmed also by Adams (1942). Perusal of the literature, Bromberg (1939), Todd (1940), Lancet annotation (1940), Macdonald (1941), Lancet annotation confirms that active fractions of cannabis are euphorigenic. Williams *et al* also (1943), (1946) showed that euphoria was produced in six subjects given *ad lib* doses of Pyrahexyl (U.S.A. terminology) for 26 to 31 days. Personality changes in the direction of lessened inhibitions were observed. E. E. G. studies were also undertaken and it was seen that during prolonged medication the dominant frequencies were markedly slowed. It does appear, however, that despite its obvious pharmacological action Synhexyl is not beneficial to cases usually seen in psychiatric practice. Further evidence on this point is presented by Pond (1948), Watts (1948), and Edwards (1948). It is probable that the failure to influence pathological depression is due to the "wave-like" action of the drug. This may prevent a sustained effect. In normal individuals in whom euphoria was induced this might not be noticed, it not being necessary to "iron-out the trough."

The difference between our results and those of Stockings and the impressions gained from perusal of the literature makes the problem very interesting, and we feel that further work on Synhexyl and allied substances is justified, especially since we feel that a drug of this type might be very useful for tiding over depressions and would help in keeping cases out of mental hospitals. Substances of this type might also be useful in assessing prognosis in psychiatric practice. In large doses it appears to accentuate schizoid symptoms, especially retardation and inaccessibility.

Stockings records the dosage employed as varying from 15 to 90 mgm., the drug being administered in all cases immediately before breakfast. He also reports that the main drawbacks, at present of Synhexyl in the form in which he used it are its insoluble nature and slow and uncertain action and that experiments are at present in progress for producing a water-soluble form with a higher degree of activity. In our series the smaller dose appeared to be well absorbed, this being ensured by the special method of manufacture of the tablets. Therefore, although the dose employed was smaller, we feel that it was an effective one and was based on the observed effect of larger doses, excitation being produced with small amounts and sedation with larger doses.

In no case during this study was there any change in the blood picture, in the urine or blood pressure of any of the patients treated.

SUMMARY.

A trial is described of Synhexyl in cases of melancholia and neurotic depression.

The results do not confirm those reported by Stockings (1947). Synhexyl has marked pharmacological activity and further work on this and similar substances is recommended.

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