bougie may conveniently be fixed. The bougie may be removed in four days and the suprapubic tube as soon as it is certain that the patient can pass water.

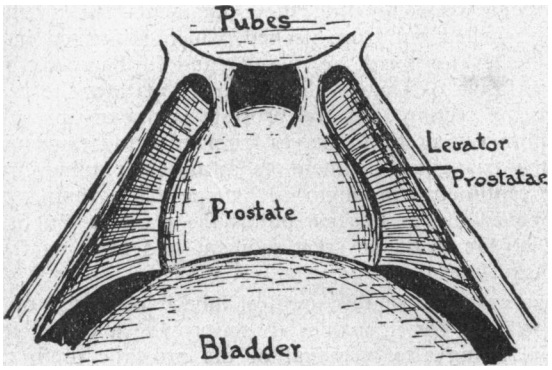


FIG. 6.—Normal anatomy.

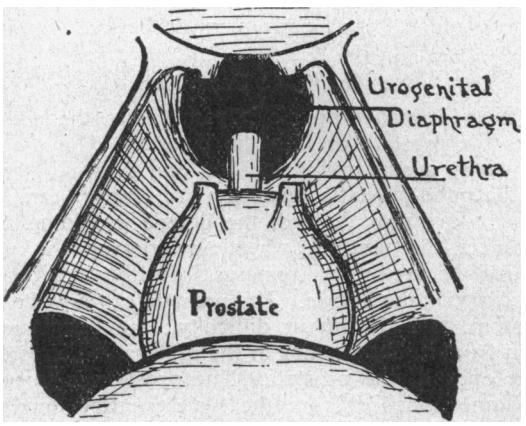


FIG. 7.—Ligaments divided; prostate retracted.

### Comment

The operation described is of course only a development of the brilliant operation devised by Millan, but it may be a development with considerable possibilities. If further experience confirms its practicability it would seem to present certain definite advantages. The prostate is removed as a whole and the technique of its removal is little affected by its precise pathology. Indeed, it might well be applicable to early carcinoma. The cavity left is completely obliterated and later haemorrhage is unlikely. A complete urethra is provided from the outset and the risk of a stricture is minimized. So far the operation has been carried out in only a few cases, and obviously a wide experience will be required before its value can be assessed. But it would seem to be based on sound anatomical principles, and sufficient success has already been achieved to convince me that it is worthy of an extended trial.

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The following recommendations on visual standards for candidates for the teaching profession have been made by the Faculty of Ophthalmologists at the request of the Ministry of Education: (1) Visual acuity, with correcting glasses, should not be less than 6/12 in the better eye. (2) At the age of 18 no refractive error should debar a candidate from training, but all cases in which the vision in either eye is less than 6/9 uncorrected must be referred for an ophthalmic surgeon's report and prognosis. (3) On reference to an ophthalmic surgeon information is required on the following points: (*a*) The nature and extent of the defect; (*b*) whether it can be corrected by glasses satisfactorily for the project in view; (*c*) whether it is progressive; (*d*) whether the existence of the defect is likely to interfere with the candidate's efficiency as a teacher.

# A NEW EUPHORIANT FOR DEPRESSIVE MENTAL STATES

BY

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### The Syndrome of Thalamic Dysfunction

The syndrome of thalamic dysfunction, or neurotic depression, is the commonest of psychiatric conditions encountered in general practice, and often one of the most intractable and difficult to treat effectively. The commonest forms of the condition are the chronic neurotic depressions, anxiety states, reactive and hysterical depressions, and obsessional disorders. The milder forms of depressions of later life, in which the dysphoria is unaccompanied by hallucinosis, delusions, and other gross psychotic symptoms, may also be included in this group of conditions.

The essential feature common to all of these disorders is a condition of the nervous system in which the perception-threshold for unpleasant affects and sensory impressions is markedly lowered, while that for pleasant affect and sensation is correspondingly raised—the anhedonic or dysphoric syndrome. The resulting dysphoria or mental pain may present itself in one or two forms, or a combination of both. In the manifest type it takes the form of conscious depression or unpleasant mental tension; in the sensorial or conversion type it presents itself as a persistent and disagreable bodily sensation, either localized or diffuse, common examples of which are pressure-headache, generalized pains, hyperalgesia, gastric pains without organic basis, vertigo, and feelings of abnormal tiredness and weakness.

Although it is generally taught at the present day that these conditions are entirely psychogenic in origin, there would appear to be strong evidence that the basis of the condition is primarily a disturbance of the thalamic-hypothalamic mechanisms, possibly a metabolic disorder. Suggestive facts are the absence in a large proportion of such cases of any evidence of mental conflict, and the concomitant symptoms of disturbed body-metabolism and autonomic imbalance, such as vasomotor disturbances, central nervous instability as shown by muscular tremors, hyperalgesia, and other sensory disorders, vegetative disturbances, and metabolic anomalies as demonstrated by biochemical tests.

The commonest symptoms of thalamic dysfunction in order of frequency are: depression, irritability, and emotional instability, with anxiety and sense of unpleasant mental tension, in the affective sphere; in the sensory sphere, pains and paraesthesias of various kinds, such as pressure-headache, various vague pains and aches of infinite variety, which may be referred to any part of the body, gastralgia, low backache, and dysuria or other symptoms referred to the urogenital tract; in the sphere of thought, inability to concentrate, obsessional thoughts, phobias, and transient periods of confusion ("black-outs"); in the motor system, tremors, sensations of weakness and loss of energy, with abnormal tiredness; and in the vegetative systems, insomnia, anorexia, gastro-intestinal disturbances, vertigo, sexual dysfunctions, and vasomotor symptoms such as flushing, palpitations, effort syndrome, and syncopal attacks without apparent organic basis.

The thalamic dysfunction state may be regarded as a response of the organism to stresses of various kinds. It is one of the commonest causes of chronic ill-health and

loss of efficiency, and one of the most unsatisfactory of conditions to treat. Its victims form a large proportion of the "chronics" who regularly attend hospital out-patient clinics, and there is probably no patient who is more dreaded by the overworked practitioner than the chronic neurotic-depressive.

Treatment of the thalamic dysfunction syndrome is often unsatisfactory because there is no specific drug therapy known at present for the condition. Psychotherapeutic methods are lengthy, tedious, and often unsatisfactory, since in a large proportion of such cases the causal factors (unsatisfactory home life, faulty conditioning in childhood, etc.) cannot be removed, while not uncommonly it is found that the neurotic behaviour-patterns persist even when the precipitating stresses have been removed. Psychotherapeutic methods usually require specialized training in the physician, and an effective symptomatic therapy aimed at keeping the patient fit and in full working efficiency during the period of analytic or other treatment is at present lacking, since the commonly employed remedies, such as cortical sedatives and stimulants, offer at best only partial relief on account of their lack of specific effect on the thalamic centres, while endocrine preparations, vitamins, and measures to improve the general health have, generally speaking, proved largely unsuccessful.

### Principles of Treatment by Euphorigenic Drugs

The most important therapeutic advances in psychiatry, as in general medicine, have been the discovery of specific pharmacological or physical agents for the various disease conditions. Similarly, the logical answer to the thalamic dysfunction states would be a drug possessing a specific reversing effect on the thalamic disturbance—in other words, a powerful euphorigenic drug which would be therapeutically effective and at the same time free from the objectionable properties usually associated with narcotic compounds.

The ideal euphoriant for clinical use should possess the following properties. It must induce a high degree of euphoria, must be stable and fully active by the oral route, be reasonably rapid-acting, and have a prolonged action. It must be of low toxicity, non-cumulative, and free from after-effects and undesirable effects on the higher cortical functions, such as impairment of concentration, judgment, and memory. Most important of all, it must not have the property of inducing the condition of addiction or physical dependence when administered for long periods.

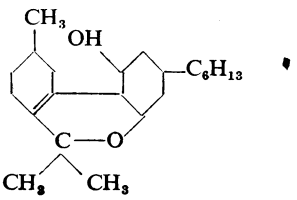
The last-mentioned point is of especial importance, since there is a common and widespread belief that all euphoriant drugs are necessarily habit-forming, whereas this is in fact not the case. The true addiction syndrome (physical craving, tolerance, abstention syndrome, and personality deterioration) is peculiar to the drugs of the ecgonine (or cocaine) and phenanthrene (or morphine) groups; whereas mescaline and cannabis indica, the two most powerful euphoriants known, do not induce a comparable addiction. The addiction-forming property would therefore appear to depend on chemical constitution rather than degree of euphorigenicity, since the two compounds just mentioned are chemically unrelated to the cocaine and morphine drugs. Theoretically, therefore, the addiction problem should not offer an insuperable obstacle to such a form of therapy, provided the compound employed is not one of the ecgonine or phenanthrene class.

Up to the present time no drug which fulfils these requirements has been known to medicine. During the last century attempts were made to utilize the euphorigenic properties of cannabis in the treatment of depressive states, but these were found to be unsatisfactory for various reasons: chief of these were the difficulty of obtaining reliable and stable preparations of this drug, its uncertain action, and its peculiar and undesirable side-effects, of which actual intensification of the dysphoria is one of the commonest. The discovery of the new synthetic cannabis-like derivatives of the dibenzopyran class within the last few years, however, has placed in our hands an entirely new type of euphoriant drug with properties which render it an extremely promising therapeutic agent in psychiatry.

### The Synthetic Tetrahydrocannabinols

These compounds have been produced as the result of the work carried out by Adams and his colleagues in America and of Todd and his colleagues and the Roche Research Department in this country.

Several compounds of this type are known, and one of the most active pharmacologically is the synthetic hexyl analogue called in America synhexyl, pyrahexyl, or parahexyl. Chemically it is 1-hydroxy-3-*n*-hexyl-6-6-9-trimethyl-7-8-9-10-tetrahydro-6-dibenzopyran, and has the following structural formula:




It is synthesized by condensation of ethyl-5-methylcyclohexanone-carboxylate-2 with 3 : 5-dihydroxy-*n*-hexylbenzene, followed by treatment of the condensation product with methyl magnesium iodide. It is a pale-yellow, translucent, very viscous, odourless resin, soluble in organic solvents but insoluble in water, alkalis, and acids. The synthetic lower homologue in which *n*-amyl replaces the *n*-hexyl radicle is pharmacologically less active. Its laevorotatory form is several times as active as the dextrorotatory form.

### Pharmacology of Synhexyl in Man

The pharmacological properties of synhexyl are in many respects similar to those of cannabis, but there are several important qualitative differences in the human subject. The following data were obtained as the result of a series of experiments which I carried out on myself, a group of normal subjects, and a group of 50 depressive patients. My findings confirm that the drug is a powerful euphoriant with a specific action on the higher centres, particularly the thalamic system and its cortical connexions. Synhexyl is rather more potent weight for weight than natural cannabis, the effective dosage being from 5–15 mg. in normal subjects to 60–90 mg. in depressive patients. In narcotic drug addicts doses of 60–240 mg. three times daily may be given without ill effects (Himmelsbach). On account of its resinous nature the drug is most active when administered by the oral route, and the preparation I used was in the form of a powder made by absorbing the drug on silicic acid and contained in gelatin capsules, or as compressed tablets after absorption on kieselguhr.

The general effects in normal man are as follows: There is first a latent period of 1½ to 3 hours before any effect is felt, this being about twice the latent period for the same dose of cannabis extract. The onset of the synhexyl effect is characteristically abrupt, with a sudden and peculiar sensation of lightness and mild intoxication accompanied by acceleration of the pulse and feelings of slight palpitation and oppression in the head and chest. Transient feelings of anxiety and vertigo may occur at the onset, but these usually pass off in the course of a few minutes to half an hour. The euphoric effect quickly

follows, and consists of a pleasant feeling of happiness and exhilaration with a marked sense of physical well-being and self-confidence; there is a sense of relief from tension and anxiety, and the threshold for unpleasant affect is markedly raised, while that for pleasant feeling-tone is correspondingly lowered. There is increased enjoyment of normally pleasant impressions, and zest for life and working capacity may be actually increased in the early stages of the intoxication. Later this effect gives way to a sense of dreamy apathy and contentment, which with the larger dosages may reach the stage of ecstasy. There is often increased speed of the stream of thought, with a marked increase in the power of fantasy and vividness of visual imagery. With the larger dosages there may in the early stages be a tendency to flight of ideas and pressure of activity. In the sensory sphere there is little or no true analgesic effect of the opiate type. With the higher doses there may be some degree of blunting of sensation, but the senses of taste and hearing may actually become more acute. A generalized sensation of pleasant warmth diffused throughout the body is characteristic.

Hallucinatory phenomena and distortion of the tempero-spatial perception sense of cannabis–mescal type are not found, although elementary visual sensations in the form of photopsias and simple coloured patterns may occur when the eyes are closed or the subject is in darkness. A peculiar visual illusion is sometimes seen in which the colours and outlines of objects appear abnormally vivid and a soft golden radiance seems to be diffused over the whole room. With larger doses visual illusions of cannabis type may be experienced in which simple patterns appear to acquire complex and fantastic forms, the whole effect being extremely pleasing to the subject. On the motor side there may be slight restlessness in the early stages, similar to what is found with moderate doses of benzedrine. Hyperreflexia is common, but ataxia and motor incoordination are seen only with the largest doses. Katatonia and rigidity as seen with mescaline are never found.

The vegetative effects are very slight, consisting of moderate tachycardia in the early stages, slight mydriasis, and dryness of the mouth. Appetite is usually increased, there is no respiratory or peristaltic depression, and sleep following the intoxication is normal and dreamless. Slight drowsiness may occur in the later stages, but "hangover" effects are seen only after very large doses.

Characteristic of the synhexyl effect is intermittency; the symptoms, as with cannabis and mescaline intoxication, occur in rhythmic waves with intervening periods of apparent normality. The average duration of the effects is from 8 to 10 hours from the time of onset of the symptoms.

With excessively large doses, the toxic effects are frightening rather than actually dangerous, resembling those of acute cannabis poisoning. The onset occurs with a sudden feeling of acute apprehension and collapse, with rapid bounding pulse, mydriasis and dryness of the mouth and throat, hyperreflexia, clonic twitchings, mental confusion, headache, and vertigo. Euphoria is absent, the emotional reaction being one of acute anxiety and apprehension. These symptoms usually pass off completely in 12 to 24 hours. The biochemical changes produced by the drug are slight, consisting of increased blood concentration and haemoglobin value, and mild hypoglycaemia. There may be slight diuresis and rise of temperature; other changes include a slight rise in blood pressure, cerebral hyperaemia, and increase in the venous pressures.

Absorption of the drug apparently takes place through the lacteal vessels of the small intestine, since it is a resinous substance and cannot therefore be absorbed direct through the stomach wall, as is the case with alkaloids and other water-soluble substances. This would account for the long latent period between ingestion and onset of symptoms of intoxication, which is normally of the order of two to three hours. The drug is partly destroyed by oxidation in the liver, but a certain proportion is excreted unchanged in the urine, in which respect it resembles natural cannabis and mescaline.

### Effects on the Intellectual Functions

Studies which I made on myself and a group of normal subjects show that with ordinary therapeutic doses there is little or no deleterious effect on the intellectual performance. Seven of my depressive patients were studied by means of psychometric tests selected from the revised Terman-Merrill scale. The results suggest that memory work calling for the use of reasoning powers and logical integration of facts suffers slightly after taking the drug, but that the more mechanical memory is unimpaired and may actually show a slight improvement. In normal subjects engaged in work of an intellectual nature there appears to be little or no falling-off of intellectual capacity, the only inconvenience experienced from the drug being the slight distractibility and pressure of ideas, and the tendency to day-dreaming and wandering of the stream of thought in the later stages.

### Therapeutic Trials in Depressive Patients

Therapeutic trials were made with the drug in a series of 50 patients showing the thalamic dysfunction syndrome, including cases of both the dysoxic (depressive-psychotic) and the neurotic-depressive types. The dosages employed varied from 15 to 90 mg., the drug being administered in all cases immediately on rising in the morning before a meal was taken. Suggestion and other psychological factors which might have vitiated the results were eliminated by substituting, without the patient's knowledge on certain days, inert control tablets of exactly similar appearance to those containing the synhexyl.

The general effects were found to be qualitatively similar to those in the normal subject, except that a considerably higher average dose was required to produce improvement of the depressive symptoms. It was found that the dysphoria itself was ameliorated to a much greater degree than the other symptoms (obsessional thoughts, pains, paraesthesias, etc.); these features, although themselves little affected, were rendered less distressing and obtrusive to the patient by the action of the drug.

Of the 50 cases tested 36 showed a definite improvement in affective reaction, while 14 were unaffected or made worse. Twenty-seven of the series were neurotic-depressives, 20 of whom showed improvement; of these 27, 12 were typical chronic mental hospital cases, of whom 9 benefited from the drug. Of these 12, 9 had previously been treated with electro-anoxia with no improvement, and 3 had been subjected to prefrontal leucotomy with no response. The remaining 23 patients were cases of dysoxic depression, of whom all but 4 were chronic institutionalized patients with mild symptoms of dysphoric type. Four of the 23 had previously received electro-anoxia with temporary improvement only; of these four, two responded favourably to the drug.

Of the whole series 16 patients showed associated organic diseases, as follows: gross bony deformity, 2; pulmonary tuberculosis, 2; cardiovascular disease, 5; senile changes, 4; malignant disease, 1; organic nervous disease, 1; thyrotoxicosis, 1. No untoward side-effects from the synhexyl were noted in any of these cases. Untoward effects were noted in 5 of the neurotic-depressive cases; these included tachycardia, slight dizziness, loss of concentration, drowsiness, and mild degrees of impairment of the intellectual performance.

The criteria for a positive response were taken as the following: amelioration of mood, as shown subjectively by the patients' own statements and objectively by clinical evidence of diminution of retardation, anxiety, and inward preoccupation; increased zest for and interest in work and occupation; and increased psychotherapeutic rapport. The effect of the drug on obsessional and depressive ideas and pains and paraesthesias of central origin was also noted. The nursing staff were carefully instructed to note during the tests any changes in the general behaviour and demeanour of the patients while receiving the drug. The results with synhexyl were then compared with the response to inert control tablets.

Of the dysoxic patients those in the chronic stationary phase of their disease made the best response. Three dysoxics in the acute depressive phase either showed no response or were actually made worse when synhexyl was given in doses of 60–90 mg.

Of the neurotic group, the quiet apathetic type with depression and general asthenia appeared to do best; this type required the smallest dosage to effect improvement —15 mg. The tense and over-anxious type also showed a good response but tended to require a rather higher dosage—30–60 mg. The anxiety cases with multiple pains and paraesthesias were found to improve considerably as regards the dysphoria, but the drug seemed to have little effect on the actual sensory features. Six of the neurotic cases were severe examples of the obsessive-ruminative type, only one of whom failed to improve with the drug.

Neurotic-depressive cases showing a negative response included psychopathic personality with dysphoric features (two cases) and acute hysterical grief reaction with pseudo-hallucinosis (one case).

### Illustrative Cases

*Case 1.*—A woman aged 60, with a history of recurrent attacks of depression over the last three years. On examination she was tense, agitated, acutely apprehensive, restless and excitable at times, and expressed self-depreciatory ideas of being wicked and worthless. Orientation and memory were unaffected and insight and judgment were moderately good, but she co-operated poorly in examination owing to her constant preoccupation with delusions of unworthiness. Physical findings were negative. She received electric convulsion treatment with no real improvement, remaining in the agitated state described above. After receiving 30 to 45 mg. of synhexyl daily she showed marked improvement; she said she felt brighter, and the agitation and tension were definitely diminished. Although the ideas of unworthiness persisted in mild degree, these were much less obtrusive and distressing. No untoward symptoms were noted, and response to control tablets was negative.

*Case 2.*—A man aged 65. The history was very incomplete, but it appeared that he was originally admitted in 1938, following the sudden onset of an acute depressive-confusional state with paranoid and possibly hallucinatory features. On examination he was depressed, apathetic, hypochondriacal and full of ideas of visceral dysfunction, totally lacking in initiative, but well behaved and clean in habits. There were no signs of hallucinosis or paranoid features, but he showed a mild degree of personality deterioration, being at times facile, rambling, and irrelevant in conversation. Physical investigations were negative. He responded fairly well to 30 mg. of synhexyl daily, becoming brighter, less querulous and preoccupied with his aches and pains, and stated that he felt more cheerful and energetic. The symptoms of cortical deterioration and institutionalization were, however, unchanged. No side-effects were apparent during the period of medication.

*Case 3.*—A woman aged 67 with a history of recurrent depressive attacks since 1936, and two previous admissions to hospital for acute depression. Examination showed her to be depressed, solitary, and lacking in interest and initiative. She complained of obstinate insomnia, and required constant nocturnal sedation. She displayed no evidence of delusions and hallucinations, but tended to be mildly retarded and sat about aimlessly all day in the ward. Physical examination revealed a slow-growing breast carcinoma, for which operation had been considered inadvisable. She had previously received E.C.T. with little or no improvement. She received synhexyl in a dosage of 15 mg. daily with considerable subjective and objective improvement. She felt brighter, more alert and cheerful, and showed increased initiative and spontaneous activity. Side-effects were absent, and administration of control tablets failed to reproduce the synhexyl effect.

*Case 4.*—A woman aged 45. She had a history of the onset, three months previously, of acute depression with agitation, ideas of bodily disease, and delusions of sin and unworthiness, apparently precipitated by an unhappy home environment. When she was first seen the acute phase of the illness had subsided and she talked rationally, showing considerable insight. She complained of mild depression, fatigability, and insomnia, with a variety of vague stomach pains and soreness and pains in her throat. She insisted that she had "swollen and painful glands" in her neck; but examination showed only a small palpable cervical gland on the right side, the throat and tonsils being normal. She also complained of feelings of "being all trembly inside." Delusions of unworthiness were not in evidence. She was a small, pale, anxious-looking woman, but no signs of organic disease were present. She was described by the nursing staff as depressed, solitary, and apathetic in habits. The administration of 45 mg. of synhexyl produced an immediate effect; she stated that she felt subjectively brighter and more cheerful, showed increased interest, and her hypochondriacal ideas receded into the background. Vasomotor side-effects were absent, control tests giving a negative result.

*Case 5.*—A woman aged 52, with thalamic dysfunction of conversion hysteria type. She had a history of depression for 18 months following evacuation during the flying-bomb raids and an accident to her son. She had also had a previous depressive attack 28 years ago. On examination she was depressed, tense, emotional, and anxious. Her main complaints were of insomnia, inability to face up to her household duties, and a persistent neuralgic pain located under the left breast. Physical findings were completely negative. A few weeks previously she received seven applications of E.C.T. with slight improvement but speedy relapse. The response to 30 mg. of synhexyl was immediate; she lost her anxiety and depression, said she felt much brighter, and the thoracic pain became much less insistent and distressing, although not completely abolished. Control tablets and bromide in full dosage failed to reproduce these effects. No side-effects from the synhexyl were complained of during the period of administration.

*Case 6.*—A woman aged 32 with thalamic dysfunction of anxiety type. She had a history of anxiety symptoms 18 months previously, and partial remission but recurrence four months before admission, at which time she had gone to live with and look after her invalid mother. On examination she was a superior and intelligent type of woman, outwardly cheerful in manner, but actually tense, anxious, and mildly depressed. She complained of insomnia, intermittent panic sensations with palpitation, and acute feelings of inner tension and "shivering sensations," and loss of concentration. Physical findings were negative, and no signs suggestive of thyroid hyperfunction were evident. The symptoms failed to respond to bromide therapy and psychotherapy. She responded well to synhexyl in doses of 30 mg. daily, the anxiety attacks and dysphoria being completely abolished. She stated that she felt much brighter, more confident, and was no longer apprehensive of the anxiety attacks. Her symptoms recurred on changing over to control tablets or discontinuing the synhexyl.

Of these six cases, selected at random from my series, the first four were dysoxic (psychotic-depressive) cases and the last two examples of simple thalamic dysfunction (neurotic depression). The four dysoxic cases were all patients who had passed through the acute phase of their illness and who presented as the principal symptom a residual dysphoria of chronic and intractable type. Of these four, one (Case 2) showed some degree of personality deterioration. The two neurotic cases were of recent onset and in the early stages of their illness. Of the six

cases, three (Cases 1, 3, 5) had previously failed to respond satisfactorily to E.C.T. It will be evident from this series that synhexyl is as effective in the milder forms of dysoxia as in the purely neurotic-depressive states.

As regards the mechanism of improvement, it should be pointed out that synhexyl does not effect a permanent "cure" in the same way as electro-anoxia does in typical dysoxic depressions. The effect lasts only during the period of administration of the drug; it is therefore a substitution therapy, like insulin treatment in diabetes or liver extract in pernicious anaemia. The action would seem to be a combination of stimulation and depression, resulting in a general raising of the anhedonic threshold. The principal site of action of the drug is almost certainly the thalamic centres and their cortical connexions, as is the case with morphine and other powerful central analgesic drugs.

The beneficial effects of synhexyl do not appear to be adversely affected by chronicity, concomitant organic disease, or the presence of an organic brain lesion, whether pathologically or surgically induced. There is evidence, however, that drugs of this class are ineffective in the acute dysoxic depressions, and cannot be regarded as substitutes for anoxic therapy in this form of metabolic brain disease.

### General Conclusions

The results of these preliminary trials would suggest that we have in this class of compounds a promising therapeutic agent for the treatment of the chronic and intractable depressive states. Synhexyl, the most active of this class, has the advantages of low toxicity, minimum of side-effects, ease of administration, and chemical stability. Its use is not contraindicated by the presence of coexisting organic disease, and it is suitable for out-patient practice. Its use does not interfere with other therapeutic measures, such as occupational therapy and psychotherapy. It is free from the risks and disadvantages of the more drastic forms of treatment, and might replace those methods for the milder depressions of later life where for any reason the more drastic procedures are contraindicated.

Its main drawbacks at present are its insoluble nature, slow and uncertain action, and comparatively weak analgesic effect, so that it is relatively ineffective in the severer forms of sensory thalamic dysfunction syndrome. Experiments are at present in progress with the object of producing a water-soluble form with a higher degree of analgesic activity.

### Summary

The syndrome of thalamic dysfunction and the principles of its treatment with euphorigenic drugs are described.

The properties and pharmacology of synhexyl, a new drug of the synthetic tetrahydrocannabinol class, are examined.

The results of therapeutic trials with the drug in a series of 50 depressive patients are given.

My acknowledgments are due to the following: The Research Department of Roche Products Ltd. and Dr. W. S. Maclay, of the Board of Control, for kindly providing supplies of synhexyl; Dr. W. A. Bain, of Leeds University, for kindly making up the material for administration; Prof. A. R. Todd, of Cambridge University, for kindly supplying purified cannabis extracts for clinical trial; and Mrs. E. Bathurst, psychologist, Warlingham Park Hospital, for kindly undertaking psychometric tests on the patients tested with the drug.

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# TYPE I TRIPLE CARDIAC RHYTHM IN NORMAL HEARTS

## A STUDY OF 1,360 NAVAL RECRUITS AND PERSONNEL

BY

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Triple cardiac rhythm is defined by Evans (1943) as "the cadence produced when three sounds recur in successive cardiac cycles." He then classifies such rhythm into types I, II, and III, which correspond respectively to the proto-diastolic, presystolic, and systolic forms of "gallop" rhythm of Potain (1856–1900). The term "gallop" is not used in Evans's classification because it is usually only when tachycardia is also present that a cadence somewhat inadequately described as resembling the gallop or canter of a horse is found to be present.

Type I triple rhythm results from the presence of a third heart sound occurring shortly after the normal second. Thayer (1908, 1909) called attention to the fact that the third heart sound, described by Gibson (1907), Hirschfelder (1907), and Einthoven (1907), and mentioned even earlier by Obrastzow (1905), could often be heard in healthy people; he found it in 65% of 231 consecutive individuals below the age of 40. Subsequently Gallavardin (1912) said that he heard it occasionally in young individuals. Bridgman (1915) reported it in 13 out of 16 normal boys aged 12 to 15 and found it in phonocardiograms of all. Obrastzow and Gubergritz (1919) heard the sound in 90 to 93% of normal men; Steinberg (1925) in 95% of boys between the ages of 4 and 14; and Melik-Gülnasarian (1932) in 57% of his cases, especially in young men between 20 and 25 years of age. Bramwell (1943) encountered it in 18.8% of 835 recruits referred to him by medical boards of the Ministry of Labour and National Service. Among the 228 individuals in this group below 20 years of age it was present in 43%. None of these recruits had a cardiac lesion.

The purpose of the present purely clinical investigation is to emphasize the frequency of type I triple rhythm in healthy males and to study its features. That its common incidence is not appreciated enough nor its features sufficiently well known is evident from the number of times it gives rise to a diagnosis of mitral stenosis—especially when accompanied, as it may well be, by a mitral systolic murmur and perhaps a split second sound in the pulmonary area. A history of rheumatic fever in such an individual is then accepted as the final link in the diagnosis. As Evans (1943) remarks, "A general acceptance of the fact that this form of triple rhythm is so common in young subjects is overdue." That it is far from rare in the not-so-young requires emphasis also.

### Method and Material

The subjects of this survey consisted at first of 1,000 consecutive healthy male adults between 17 and 30 years of age inclusive who underwent routine examination by me for a variety of purposes. Later 360 men above the age of 30 were examined. All these individuals were considered healthy on the grounds that they presented no symptoms or physical signs of any disease whatsoever; nor did they give any history of any cardiovascular disease. Some of the older men showed palpable thickening of the radial arteries commensurate with their age, but any who had blood pressures above 160 systolic or 90 diastolic were excluded.