

decide to concentrate their energies in carrying to further refinement and perfection a more limited department of science. Thus, happily for the progress of the world, specialism will not disappear from society. On the contrary, specialism is manifestly to be even more distinct than in the past, while specialists, as known to the broad and progressive profession of America, will be able to gain recognition only by conforming to severer tests than are now applied. It is safe to predict, therefore, that in the not distant future there will be fewer specialists, but, happily, better ones. The lines may, and possibly will shift. Existing specialties, or certain of them at least, through the influence of further segregation and final equilibration, may, and probably will, disappear into the general profession, while segmentation will be inaugurated at other points to result in the development of other specialties. Thus shall the great future witness the mutations of progress.

ORIGINAL ARTICLES.

A CONTRIBUTION TO THE PHARMACOLOGY OF CANNABIS INDICA.

Presented to the Section on Materia Medica, Pharmacy and Therapeutics at the Forty-ninth Annual Meeting of the American Medical Association, held at Denver, Colo., June 7-10, 1898.

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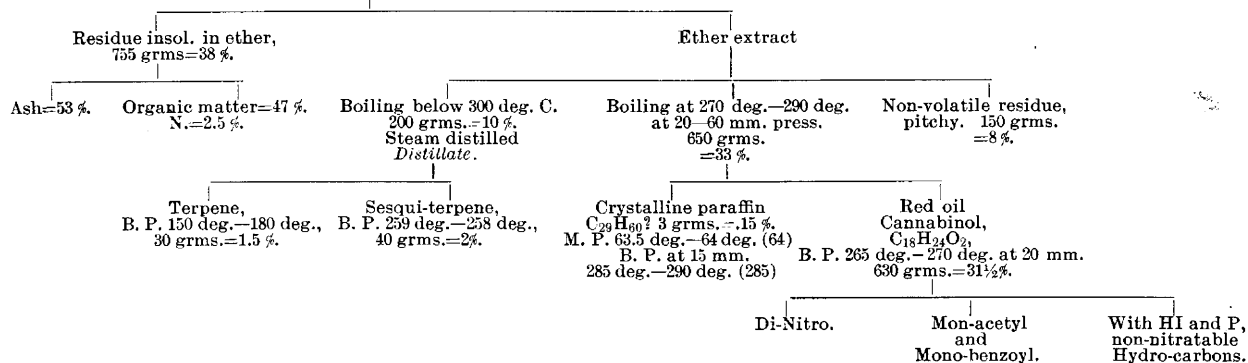
Notwithstanding the large amount of labor which has been expended on Indian hemp, we know comparatively little of its pharmacology. The active principle, it is true, has been isolated, in a more or less impure form, by O'Shaughnessy, Robertson, the brothers Smith, and more recent investigators, but the more important question of the changes this undergoes has not, as far as I am aware, until recently,

active principles of Indian hemp, I shall confine myself in this communication to the work of the most recent observers. Two and a half years ago three Cambridge chemists—Wood, Spivey and Easterfield—commenced a re-investigation of the chemistry of Indian hemp. They worked with charas, as being the most active preparation of the plant, and by extraction with organic solvents (alcohol, ether, petroleum ether, etc.) and subsequent fractional distillation, they isolated a mono- and sesqui-terpene, a crystalline paraffin and a resinous body (cannabinol); an indistillable pitch and an insoluble sandy residue were left behind.² The proportions of these substances are shown in the subjoined table, taken from a communication by Easterfield and Wood to the Cambridge Philosophical Society.³

Other samples more recently examined have not been found to be so good as this. A second lot contained only 15 per cent. cannabinol; and a third only 10 per cent. Furthermore, the cannabinol from these samples was not so pure as that obtained from the first sample and from the cannabinol obtained from the last the acetyl derivative of a higher homologue of the pure substance has been prepared. This homologue was present to the amount of 10-20 per cent.

The products (with the exception of the paraffin) and certain impure intermediate substances were passed on to me for pharmacologic examination. I naturally turned my attention first to the resin. The terpenes were present in too small an amount, and their chemic constitution and physical character were not such as to suggest a cannabis-like action. Personne,⁴ it is true, attributed the activity of the drug to an oily liquid, *cannabene* ($C_{13}H_{20}$), which Valenti,⁵ and more recently Vignola,⁶ have shown to be an impure sesqui-terpene; but Roux⁷ has proved physiologically that cannabene is not the active principle. On the other hand, numerous

Charas—2 kilos.



been attempted. To me this is the most interesting part of the inquiry. Apart from the great financial loss entailed by the growing inertness with age of the drug, the variability in the strength, its preparation has led to numerous misfortunes in medical practice, and a distrust in its use as a therapeutic agent. The isolation of the active principle of the drug would not matter if we could only insure our preparations being of constant strength. But, without knowing the cause of the increasing inertness, this it is impossible to do. With this cause, among other questions, I intend to deal in this paper.

As I have dealt elsewhere¹ with the history of the

investigators had shown that the active principle is of a resinous nature. The paraffin was only present in very small amounts, and from its constitution and properties it is easy to infer that it possesses no marked physiologic properties.

The resin was found to be active. It possessed, as far as I could see, all the peculiar effects of the hemp plant. The question to be settled was its purity. As it boils at 265 to 270 degrees C, under 20 m.m. Hg pressure, and possesses a constant composition, the

² Journ. Chem. Soc., Vol. lxi, i, p. 539, 1896.

³ Proc. Camb. Philosoph. Soc., Vol. ix, p. 148, 1897.

⁴ Journ. de Pharm. et de Chem., Vol. xxxi, p. 48 (1857).

⁵ Journ. Chem. Soc., Vol. xl, p. 284 (Abst).

⁶ Ibid., Vol. lxxvii, i, p. 623 (Abst).

⁷ Bull. Gén. de Therap., 1886, p. 492.

¹ The Lancet, Jan. 23, 1897, p. 235.

presence of an impurity seemed improbable. At least it could only be due to a stereo-chemical isomer or a substance with closely allied composition and properties. The possible presence of an alkaloid was avoided by treating the crude drug with dilute sulphuric acid before commencing the investigation. But no alkaloid has been found in charas.

In a more or less impure form cannabinol has been isolated from various commercial preparations, viz.: Merck's cannabinon, extractum cannabis Indicæ ethericum, resina cannabis Indicæ, and T. & H. Smith's cannabin.

PHYSIOLOGIC INVESTIGATIONS.

Experiments have been carried out on cats, dogs, rabbits and myself, and the investigations have been mainly confined to the administration of the various substances by the mouth—a condition necessitated by the comparative insolubility of the drugs. With the experiments in detail I do not intend to deal—admirable descriptions have been given by various observers, both in this and other countries—but in appendix I will be found types of experiments and in appendix II a synopsis of the experiments made. By combining these and referring to the text, little difficulty will be experienced in forming mental pictures of the condition in each individual experiment.

Most of my experiments were made upon two dogs. One was a mongrel puppy something like an Airedale terrier in breed; the other was a young adult fox-terrier. Later a third dog, an English terrier, was added. The first two dogs were of very different temperament; the one (Airedale terrier) was self-reliant and intelligent; the other was affectionate, but nervous to an extreme degree. The English terrier, although timid, possessed much more character than the last one. This question of temperament, I believe, is of considerable importance in dealing with the finer effects of cannabis indica. The cats were adults; the rabbits young, usually 3 to 4 months old.

The *terpenes* in the comparatively small doses in which I was able to give them, produced no noteworthy symptoms beyond slight diuresis. In rabbits there seemed to be slight transient excitement, but the compound given to these animals was impure. On myself 0.5 c.c. produced no effect; 2 c.c. (sesquiterpene) slight and transient listlessness and heaviness of the head.

The *resin*, cannabinol, in dogs constantly produced the same qualitative effect, although it varied slightly in the different animals and in the same animal from time to time. The first noticeable symptom (one-half to two hours) was slight lassitude and an appearance of heaviness about the eyes. Gradually the depression increased and sleepiness and usually sleep followed; yawning and sighing were not infrequent; the body when standing swayed from side to side and this gradually increased until the animal fell over or suddenly pulled himself up with an effort. Usually, after falling, he remained in this position and went to sleep. Sometimes the rocking motion occurred in an antero-posterior direction, especially in the fox-terrier. In this animal, too, the standing position was more characteristic, the hind legs being half bent. In this position and markedly unsteady he usually stood gazing into the fire. Distinct ataxia during walking was present or absent according to the dose. After large doses the attention was blunted, but after small doses no effect in this direction was noticed. After

three to six hours the animals began to improve. At this period the larger sometimes became extremely frolicsome and if played with would run about barking in a high-pitched voice. Usually both animals slept or lay before the fire until taken to the kennel for the night.

When under the influence of the drug, the pupils were sometimes slightly dilated, sometimes unaffected, occasionally contracted; the pulse and respiration were slowed, but whether more than could be accounted for by the condition of rest it was often difficult to decide. My general impression is that the pulse was slower than during ordinary sleep. The temperature, with one exception, invariably fell; at the most not more than 3 degrees C., usually not more than 1 to 2 degrees C. The fall naturally varied with the temperature of the room. It was most marked in the fox-terrier, and in this dog trembling was not an infrequent symptom. The reflexes were always present and the sense of pain was doubtfully blunted; the olfactory sense, however, seemed depressed. Vomiting was a frequent symptom; salivation, independent of any emesis, a rare one. In the fox-terrier, increased micturition was occasionally obtained. The influence of dose was not marked. Generally speaking, the symptoms were fairly constant; but owing to the insolubility of the material complete absorption was difficult to insure. Consequently, in dogs at least, a strictly quantitative comparison could not be made. Occasionally a small dose produced more marked symptoms than a larger one, but this was rare, and in the fox-terrier the onset of the symptoms as a rule was later and they lasted longer than in the other dogs. On the whole, however, the symptoms were fairly proportioned to the amount given. After small doses (0.02 g. per kg.) quietude, heaviness about the eyes, sleepiness and usually slight unsteadiness occurred; attention was not appreciably affected, and the symptoms almost passed away in five or six hours. In the English terrier this dose produced a very marked effect, the ataxia being as severe as after much larger doses to other dogs. After large doses (0.1 g. per kg.) there were marked depression, ataxia, vomiting and sleepiness, although sleep was not an invariable symptom. In the evening food was refused, but the following morning they seemed quite well.

In cats effects similar to those occurring in dogs were obtained, but the action was more severe and prolonged. After a dose of 0.058 g. per kg. improvement did not commence until after twenty-five hours. The depression and muscular weakness were more marked than in dogs, and salivation was a more constant symptom. Total anorexia and consequent loss of weight occurred after large doses. A detailed description of an experiment will be found in appendix I.

On rabbits preparations of cannabis indica exert comparatively little effect. This was observed by O'Shaughnessy, and it has been noted by more recent investigators. The same effect was obtained in my own experiments with cannabinol. But I am inclined to believe that the immunity is more apparent than real. After large doses, slight depression and quietude are the only observable symptoms, but on further examination a fall in the number of heart-beats and respiration and the temperature was found to occur; the animal refuses to eat and death usually ensues. The low cerebral development of these animals prevents them showing unmistakable signs of cannabis poisoning, and these are only found in observations

on the vegetative functions. The lethal dose, however, is much larger than for dogs or cats.

The effect on myself was very similar to that described by other observers as peculiar to Indian hemp. After large doses (0.1 g.) there was a sensation of dryness of the lips, and of increased viscosity of the buccal mucus, a pleasurable tingling throughout the body, muscular weakness, slight ataxia, risibility and loss of time sensation. My pulse was said to be increased in frequency, sensation was somewhat blunted, and the pupils were slightly dilated.

After small doses (about 0.02 g.) the first symptom was usually loss of power for mental work. A typical condition of mental exhaustion set in. Sentences could not be conceived, except by powerful efforts, and these were not often forthcoming.

After intermediate doses (0.05 g.) the ability to work was lost altogether. I usually sat before the fire doing nothing, almost thinking of nothing. There was a marked unwillingness to move. Pleasurable tingling in the limbs, very slight ataxia and other symptoms similar to those obtained after a larger dose were present. Time passed quickly. Sleepiness was sometimes, but not always, present. As an early symptom a peculiar indistinctness of the periphery of the visual field occurred, and later it was found that the point of regard was made to travel with greater difficulty, as along the line of a page. Depression usually continued throughout the following day.

The residual *pitch*, when dissolved in oil, was active, but much less so than cannabinal. The symptoms were the same. Given in the solid form it exerted little effect. In all probability the activity was due to unchanged cannabinal present. Certain intermediate impure products were tried, but none of these was as active as cannabinal. The insoluble residue was inactive.

THE ACTIVE PRINCIPLE.

Thus, by a process of elimination, cannabinal was found to be the most active ingredient of the charas products. But in order to determine its comparative activity, control experiments were made with the crude material and extracts obtained from it. The natural product exerted much the same action as cannabinal, but both spirituous and oily extracts were somewhat more active; a similar result was obtained with Merck's cannabinal. This raised the question as to whether cannabinal is the sole active ingredient of the plant. I think we must assume that it is, at least, the active principle. The symptoms produced by the natural product and the resin are practically the same, and this is an important point. It suggests that we must look for changes occurring in the resin either during its manufacture or subsequently; or to a diminished absorbability as compared with extracts of the crude product. That faulty manufacture, etc., will produce a more or less inert substance, will be seen from evidence given later; but I am inclined to attribute to the lessened absorption the more important rôle. The terpenes probably increase the rapidity of absorption of crude extracts, but this I have not yet been able to put to the test. That cannabinal does not possess all the activity of the hemp plant I am prepared to admit; but this is the case with most other crude drugs and their so-called active principles. In the case of charas the terpenes probably aid in its physiologic action, as the crude drug seemed to produce more excitement than pure cannabinal; and when the drug is smoked

it is possible that pyrodene and other bases, which are produced by the destructive distillation of the substance, may aid in its intoxicating effects. If any other substance aids in its action, we have at present no indication of it. Moreover, that cannabinal is the chief active ingredient is supported by the fact that the activity of different products is roughly proportionate to the amount of cannabinal they contain, and that the growing inertness of Indian hemp can be explained by changes occurring in this resin.

The question of the purity of cannabinal can only be settled by further research, and this, I may add, is being undertaken. The only demonstration of its purity in the present state of our knowledge, viz: the reconversion of the crystalline acetylated derivative into cannabinal, failed. The acetyl derivative was not crystalline, and the reconverted cannabinal was much less active, physiologically, than the parent substance. This might be explained in many ways, but at present it is idle to speculate.

The last and worst sample of charas yielded a substance which contained a higher homologue of pure cannabinal. This homologue regenerated from its acetyl compound was physiologically inactive. Whether it is active previous to acetylizing is at present impossible to say.

THE CAUSE OF THE INACTIVITY OF INDIAN HEMP.

The different samples of the same preparation of Indian hemp possess varying physiologic effects, and that good samples darken and deteriorate in keeping has long been known; but until recently no satisfactory explanation of this has been offered. In 1894 Leib Lapin,⁸ by means of fractional precipitation prepared a substance which he termed *cannabindon*. This presented the appearance of "a beautiful dark cherry-red mass of thick consistency, which took the form of the vessel in which it stood, and showed a smooth horizontal surface." Its formula he gives as $C_8H_{12}O$. It possessed distinct reducing properties, and rubbed up with chocolate and left a week, its physiologic action was in great part lost. The latter he explains as being due to an oxidation of the preparation resulting from its finely divided state and its contact with fat and air; and he strengthens his position by a reference to the similar behavior of ergot, which undergoes oxidation less readily than *cannabindon*. The oxidation product he states "is inactive or very slightly active."

Although I was aware of Leib Lapin's views, my own researches were carried out independently. What first drew my attention to the matter was the gradual darkening which cannabinal underwent when left exposed to the air in a test-tube; the darkening commenced on the surface and gradually extended downward; the superficial layers being affected rapidly, the deeper layers very slowly. In order to determine whether this was due to oxidation, and whether in consequence the activity was affected, oxygen was slowly passed through cannabinal kept fluid by immersion in a sulphuric acid bath at 150 to 160 degrees C. The material rapidly darkened and the consistency increased. After passing the oxygen through for six hours the activity was found to be decidedly less. It was then bubbled through for thirteen hours more, the temperature toward the end of the experiment being raised to 185 degrees C. in order to keep the substance fluid. On cooling, the substance set to a

⁸ Ein Beitrage zur Kenntniss der Cannabis Indica. Diss. Jurjero, 1894.

hard, brittle mass, exactly resembling pitch in appearance. No loss or gain of weight, within the limits of experimental error occurred. This pitchy material given in the solid form possessed scarcely any action, but this in part is due to the lessened solubility and higher melting-point, for if previously discolored in oil, a distinct, though comparatively slight, effect is obtained. Dr. Easterfield, who has made all the analyses in connection with the charas research kindly undertook one of the oxidized cannabinal. The percentages obtained, compared with those of cannabinal, were:

Calculated for $C_{18}H_{24}O_2$ (cannabinal)	Found.	Calculated for $C_{18}H_{22}O_3$
C=79.4	C=77.7	C=75.0
H=8.8	H=7.5	H=8.3

The product obtained was therefore not completely oxidized, and the activity it retained was in all probability due to unchanged cannabinal. As a control experiment carbon dioxide was passed through a similar sample of cannabinal similarly treated. Very slight darkening, probably owing to slight admixture with air occurred, but there was no increase in consistency. Only a slight diminution in activity was observed.

The influence of temperature was tried. Cannabinal distilled at 400 degrees C. under atmospheric pressure was found to be slightly less active than cannabinal distilled at 265 degrees C. under 20 mm. Hg. pressure, but when the substance was heated in sealed tubes at 220 to 260 degrees C. for twenty-four hours, no very great loss of activity occurred, although this was distinct. As slight oxidation may have resulted during the process, the influence of temperature *per se* may be disregarded. The action of aqueous vapor has not been determined.

It would therefore seem as if the loss of activity of Indian hemp was due to oxidation of the active ingredient. The terpenes, like other members of this class, readily hydrolize, and this, doubtless, exerts some effect in the deterioration of the crude drug. The obvious remedy is to keep cannabis preparations in air-tight vessels until they can be used. For practical purposes a well-corked bottle seems to be sufficiently protective, but hermetically sealed packages, especially for transport purposes, are to be prepared. In sealed tubes we have kept cannabinal for seventeen months without the slightest change.

The limitation of the oxidation to the superficial layers probably explains many of the accidents occurring in practice. If the preparation has been long in stock and imperfectly protected, these may have become comparatively inert, and scarcely any effect may be produced, while a renewal of the prescription from deeper parts—or the substitution of a more recent preparation—may produce very marked effects. I am certain that the accidental administration of superficial and deep layers of cannabinal will explain some discrepancies in my own results, which previously were inexplicable.

As regards a chemical test for the physiologic activity of cannabis compounds, none exists; and the only indication at present is in the direction of their reducing power. This will probably give us some information, and I hope to deal with the question later. As far as cannabinal is concerned, the transparency is the best ready indication of its purity. When placed in an ordinary test-tube print ought to be read through it with ease; any blackening is due

to admixture with oxidized material. If not carefully prepared impure products are readily obtained, and such give no more constant results than the ordinary preparations on the market. The transparency, however, is not an absolute indication of its purity, for the higher homologue of cannabinal, which, when derived from its acetyl compound is inactive, is almost as transparent as cannabinal itself. What the physiologic effect of this compound is in the natural state, it has not been possible to determine.

SUSCEPTIBILITY.

But the variation in activity of the preparations of Indian hemp will not account for all the differences in effect produced. A difference in individual susceptibility also exists. What this is due to we do not know. It is probable that certain types of men are more susceptible than others, and that certain habits, such as the alcoholic, have an inhibiting influence in this direction. The subject is a difficult one to treat from a purely experimental point of view. In the dogs the greatest effect seemed to be connected with greatest mental stability, but how much of this was due to variability of absorption and how much to individual differences it is difficult to say.

The following case which recently came under my notice is of interest in this connection, as it enabled me to compare the effect of the same dose on myself. A gentleman suffering from neuralgia took $\frac{1}{4}$ grain extractum cannabis indicæ (B.P.) in the form of a pill. The pills were made up by a well-known London druggist. The following account was written by the patient himself: "At about 4:30 on Sunday, feeling neuralgic pain in the right eye, I took one of the pills. I then had tea and read aloud for some time, feeling nothing unusual. But about 7:30, when dressing for dinner, I began to suffer from very curious feelings. I felt giddy and seemed to lose command of my actions; thoughts seemed to pass rapidly through my brain and I hardly felt responsible for myself. I went to my wife's room and described my feelings. She was alarmed at my appearance and said I was very white. I felt a sort of burning uncomfortable feeling inside and I tried to make myself vomit by drinking several tumblerfuls of hot mustard and water. This was partially successful, but I felt very ill and a doctor was called in. When he came I was unable to speak coherently; sentences were disjointed, and my memory partially failed me. I was ordered to bed and undressed with difficulty. I then shook violently all over, and my hands were cold and tended to contract. I was given some brandy and water and gradually I became more natural. Afterward I took some soup and fish. During my sleep I felt inclined to laugh, but I do not think I actually did so. The next morning I was comparatively well, but throughout this day and the next I did not feel quite well; there was a numbness and coldness in my legs and I feared I was in for an attack of influenza, but my temperature was normal." The neuralgia was cured, but afterward he told me he would rather bear the pain than the effects of the remedy. The remainder of the pills were given to me and on two occasions I tried them on myself. On both occasions the usual effects of Indian hemp were produced, viz., paresthesia in the extremities, inability to do mental work, and sleepiness, but not the giddiness and other symptoms produced in the case cited. The less effect may in part be due to my previous experience,

and the absence of fear in consequence, but this is insufficient to account for all the difference. The prescription was dispensed by a first-class pharmacist and there was no reason to believe that the extract was unequally shared.

THE ABSORPTION OF CANNABINOL.

For all practical purposes, cannabis preparations may be regarded as being quite insoluble in water. They are soluble in fats and organic solvents generally, but with the exception of fats these are not common constituents of the contents of the alimentary canal. It is even doubtful what part fats play in the absorption of the drug. If Moore and Rockwood's⁹ view of fat absorption be accepted, the only influence they could have would be a physical one—the substance would be brought into a state of finer division and thereby rendered more susceptible to other agencies. When given dissolved in oil, the onset of the symptoms is not distinctly earlier than in other cases, but as absorption probably only occurs from the intestine this observation is of little consequence. The more important question is the solubility of the active principle in dilute acids and alkalies respectively. According to Kionka¹⁰ the resin of Indian hemp is insoluble in alkalies. From the therapeutic point of view Germain Sée¹¹ states that cannabis is the peculiar sedative of the stomach. Both these statements suggest that the active principle is soluble in an acid medium, and this is supported by the fact that cannabinol is actually soluble in strong sulphuric acid and glacial acetic acid. But my results for dilute acids are opposed to this view, and contrary to the statement of Kionka, I find it soluble in dilute alkalies. The following experiment proves this: Two Erlenmeyer's flasks were taken; into one (A) was put 2.127 grammes cannabinol; into the other (B) put 2.335 grammes. Both were left over sulphuric acid until they attained a constant weight; 100 c.c., 1 per cent. caustic soda solution was then added to A and 100 c.c., 1 per cent hydrochloric acid (gas) to B. Both were shaken occasionally and left twenty-four hours. The alkaline solution soon became of a purplish color, which deepened; the acid solution remained perfectly clear. After standing twenty-four hours, both solutions were poured off and the remaining cannabinol was rapidly washed with distilled water until the washings were free from acid and alkali respectively. The flasks were again put over sulphuric acid and left until the weight became constant. The alkali-containing flask (A) had lost 0.03 gramme cannabinol; the acid-containing flask (B) 0.005 gramme, the latter being within experimental error.

It is therefore probable that the cannabis resin is absorbed under the influence of the alkaline juices of the upper part of the intestine. In the mouth, solution occurs to a slight extent, as is evidenced by the peculiar unpleasant taste, but this can not be of practical importance. The influence of other alimentary conditions has not been determined.

The condition of the stomach, however, plays an important part in the time of appearance of the symptoms, probably by hastening or retarding the course of the drug to the intestines. Thus in one case, when the drug was taken on an almost empty stomach, four hours passed before the onset of the symptoms, whereas if taken just before a meal, the first symp-

toms invariably occurred within one and a half hours. Taken after meals the appearance of the first symptoms is variable. In atony and dilatation of the stomach cannabis is said to be inactive (as a gastric sedative). The small solubility of the drug, even in alkalies, probably accounts for the insidious onset of the symptoms and its prolonged effect.

HABITUATION.

In order to determine roughly the influence of continued dosage on the activity of cannabinol, the two dogs were given very large doses every day for a week. A small dose, similar to one given just before the experiment, was then administered and its effects watched. The influence was certainly less than on the previous occasion, but the diminution was not marked. Whether habituation to this remedy occurs less readily than with other hypnotics can only be determined by practical experience, I know of no reliable observations on the subject, although it must be well known. In any case the tolerance is not likely to be so great as in the case of opium.

During my experiments with the two dogs, this question of tolerance often presented itself, and it was on this account that a third dog was obtained. Of the greater susceptibility of this there could be no doubt; but to a certain extent it was only apparent. The experience was new to him; he walked about and stumbled when the other dogs would have laid down. The same thing happened in the earlier experiments with these dogs; the ataxia was marked; later, they learned wisdom by experience, and laid down soon after the drug was given. It was often difficult to get them to stand sufficiently long for any indications to develop.

Although my experiments did not show any great amount of tolerance, they seemed to me to show some mental depression; the normal physical life of the animals seemed to run on a lower level, although this was difficult of proof. That cannabis indica exerts a powerful depressing influence, on some individuals at least, there can be no doubt, and from experiments on myself I have little hesitation in joining the ranks of those clinicians who regard Indian hemp as a causal factor of insanity. But this point, and others, I hope to develop in a later communication.

EFFECTS ON SPECIAL ORGANS.

Owing to the insolubility of cannabis preparations and the pressure of other work, exact experiments on the different organs have not been carried out. A solution of cannabinol was made by heating an excess of the substance in a 1 per cent. solution of sodium bicarbonate on a water bath, but the resulting product, which was of a brownish color and probably contained about 1 in 1000 cannabinol, had no distinct influence on blood-pressure. A solution of cannabinol phosphate (8 per cent.) in one experiment caused a slight fall and subsequent rise of blood-pressure, but from other points of view this substance was but slightly active.

Cannabinol is, however, somewhat depressant to the heart. A fall in the number of beats was constant, and in many cases this seemed greater than could be accounted for by the rest and sleep. Thus, in the largest dog, a pulse of 108 fell to one of 48, and a slight irregularity, also noticed in rabbits, occasionally occurred. That the blood-vessels were not dilated was inferred from a comparison with the action of chloral. After this drug, there was not the

⁹ Journal of Physiology, Vol. xxi, p. 58.

¹⁰ Liebereich's Encyclopedia der Therapie. Erst. Bd. s. 556.

¹¹ *ibid.* s. 557.

same marked fall in the number of the heart-beats, and the character of the beat was slightly different. After a large dose of cannabinal my own pulse increased in frequency; after a small dose no effect was noticed; after intermediate doses I invariably forgot to take it. No distinct effect on the respiration was observed. It was slower and deeper, as in ordinary sleep.

In the fox-terrier increased micturition was not infrequent; but this was not observed in the other dogs. Constipation was not an obvious symptom. After continued dosage some evidence of it existed, but this was not seen after single doses. In myself it was rarely present. Salivation was an occasional symptom, but as this occurs in dogs and cats after the exhibition of drugs possessing no specific properties in this direction, it is not probable that cannabinal exerts any specific action in this way. In my own case dryness of the mouth was a more constant feature.

The main action of cannabinal, however, is on the nervous system, and probably on the cerebral cells. From introspective analysis it is difficult to avoid the conclusion that some peripheral action exists, but as all the symptoms can be explained by a central influence, it is simpler, in absence of proof, to accept this.

One of the most prominent physical symptoms is the loss of time-sensation. This is mentioned by most writers. But it is not peculiar to Indian hemp, as it occurs after mescal button and other drugs of a similar nature. Its explanation, to my mind, is simple. The estimation of time is a complex act and dependent upon our calling to consciousness a series of events. When the physical state is depressed by Indian hemp a succession of ideas cannot be maintained; time ceases to exist, and it can not therefore be estimated. Even the apparently slowly travelling second hands of a watch, which is observed when under the influence of Indian hemp, may be explained in a similar way. The power of conception is more or less lost; current events are rapidly forgotten, while those fixed in the memory by older associations may still be recalled. Under the full influence of the drug, even those too are forgotten, and one's whole previous existence seems to be blotted out.

A most interesting condition, after large doses, is the occurrence, alternately, of loss of control and lucid intervals. During the latter, all the elements of complete sanity are present, but the physical state is below the normal level. In it the processes on which consciousness depends are readily exhausted, and the condition of irresponsibility develops. Slight mental strain during the lucid periods seems to hasten the occurrence of a state of irresponsibility. A more complete rest from thought brings back the rational intervals. The over-estimation of distance was never distinctly observed by me, except to a slight degree on one occasion. The effect is probably connected with the increased effort made to accommodate the ocular muscles to the required distance, and is dependent on deficient will-power. Hallucinations, too, of a very slight character, were only present in one instance—a result probably attributable to my lack of imagination. In dogs, after large doses, the attention was blunted, and they became less obedient. As far as I can see, there seems to be no selective influence on any psychical phenomenon. All such processes are depressed, but whether to an equal degree I am not prepared to state. With this question, however, I hope to deal at some future time.

ILL EFFECTS.

The most common ill effect, or rather after effect, I have experienced, has been depression, lasting the whole or greater part of the following day, after a large dose (0.1g.) This, and the accompanying mental exhaustion, were decidedly painful, and the effect was markedly prolonged by attempts to do an ordinary day's work.

In dogs, vomiting was not an uncommon symptom but this was much less marked than with morphin. A slight, occasional irregularity of the heart in these animals and rabbits, has been mentioned; and a similar condition, viz: an increase in the cardiac irregularity of heart disease has been observed by Prior¹² after cannabis preparations, in men.

DERIVATIVES OF CANNABINOL.

These have been investigated in connection with experiments on the constitution of this body. Oxy-cannabin ($C_{11}H_{11}NO_4$) is inactive, at least in moderate doses. Acetyl-cannabinal and the cannabinal regenerated from it were but slightly active. The acetyl compound of the higher homologue of cannabinal, as well as the substance (regenerated from the acetyl compound) itself, was inactive.

Tri-brom-cannabinal, a brownish powder, was found to possess hypnotic properties. In dogs the action was very slight, but on myself (after 0.1g.) sleep and depression were marked, and three days of mental exhaustion followed.

Attempts were made to obtain a more soluble preparation of cannabinal, and this was best accomplished by making a phosphoric ester. Cannabinal was heated to 100 degrees C. with phosphoric anhydride. The melt was boiled out with alkalis, which dissolved nearly the whole of it, and this was then neutralized by hydrochloric acid. An amorphous substance was obtained, which, on analysis, gave results agreeing with the supposition that it was cannabinal phosphate. Physiologically, however, the substance was not very active, and injected subcutaneously into a dog produced an abscess.

THERAPEUTIC INDICATIONS.

Therapeutically, cannabinal is likely to be a valuable hypnotic. It is purer and more reliable than the cannabis preparations on the market, but it does not appear to possess any other advantages over them. It is not a powerful cerebral depressant (except in relation to its dose), and belongs rather to the substances termed "sleep producers" than "sleep forciers." Owing to its comparative insolubility its action is prolonged, and this in my own case leads to depression. Its advantages are, that its lethal dose is considerable; it does not inhibit secretory activity; and it does not readily induce habituation. Its disadvantages are, the excitement produced by early doses and the depression which follows its use. It appears to be a slight analgesic, but how far its activity goes in this direction it is impossible, in the absence of experiments in which pain is present, to say. This can only be proved by clinical observation. Purely pharmacologic investigations do not support any other actions of this drug, but so far as they have been carried they do not deny their existence.

In conclusion, I express my thanks to Messrs. Wood, Spivey and Easterfield, for the material supplied me, and especially to Dr. Easterfield for the help he has given me during the progress of the work.

¹² Münch. Med. Woch. No. 33, 1888.

APPENDIX I.

TYPES OF EXPERIMENTS.

Descriptions of personal experiments will be found in the *Lancet*. P=heart beat; R=respiration; T=rectal temperature.

Dog (English terrier); wt. 7180 grams; P., 102; R., 16; T., 38.2 degrees C.; (room temperature 20 to 22 degrees C.); 12:10 o'clock, 0.14 gram cannabinal; 12:40, slight depression, distinct unsteadiness; 12:45, ataxia more marked, head unsteady, eyes heavy; 12:55, very unsteady, will not lie down, pricked up ears when cart passed window, no dilatation of pupils; 1:10, extremely unsteady, continually falling over; will not touch milk, P. 96, T. 37.7 C.; 1:40, ataxia rather worse, still walking about; 1:50, vomited small quantity, mainly yellowish fluid; 1:54, vomited again; 2:10, condition same, constantly falling over, P. 108, T. 38.6 C.; 2:20, vomited again; 2:30, circus movements, then sat down, got up and repeated several times; 2:40, vomited; 2:50, vomited; 3:10, slightly better, but still falling over, P. 108, T. 38.9 C.; 3:40, been laid down last twenty minutes, slept partly, just got up, ataxia very much better at first but soon developed again; 4:10, sleepy, P. 96, T. 38.5 C.; 4:40, still marked ataxia but much better; 5:15, further improvement, still unsteady and depressed, P. 96, T. 38.9 C.; following morning, apparently well. This was the only case in which a rise of temperature was noted.

Dog (Airedale puppy), wt. 6500 grams. 10:30 o'clock, 0.5 gram cannabinal given in bread, P. 192; 11:30, lively, no obvious effect; 11:45, sleepy, lay down; 12:30, still in same position, yawning, came when called but seems rather stupid; 1:00, walking about, when played with commenced to run about and bark in a higher pitched voice; 2:00, been asleep for last half hour, does not answer to name so readily, weak on legs, can not stand steadily; 3:00, condition same, asleep, P. 96; 4:00, still asleep, occasionally wakens up, yawns and stretches, will not answer to name; 5:30, condition much the same, still weak on legs and tired, sent to kennel, would not eat; following morning, apparently normal.

Cat, wt. 3600 grams. 1:30 o'clock, 0.15 gram cannabinal given in meat; 2:30, no apparent effect; 3:00, sleeping; 3:45, awakened, rather weak on legs, gait slightly unsteady; 5:00, much worse, distinct inco-ordinate gait but does not move about much, has been laid down mostly, with chin on ground, passed a loose motion, would not drink milk although seemed eager for it and only ate two small pieces of meat.

Second day, 9:30 o'clock, no apparent alteration, still stupid, would not come when called, distinct muscular weakness, gait still unsteady, pupils somewhat dilated, would not drink milk although a little had been drunk during the night; 2:30, slightly better, gait less unsteady; 5:30, still better, looks up when called, ataxia still present; following morning, seemed quite normal.

Rabbit, wt. 620 grams; P., 300; R., 76; T., 38.4 C.

First day, 2:25 o'clock; 2.4 grams cannabinal given in mucilage; 5:25, has been quiet since drug was given, eyelids partially closed, slightly depressed, doubtful muscular weakness; P. 216, R. 30, T. 34.1 C.

Second day, 10:00 o'clock, somewhat worse, head trembles slightly, sensation blunted but kicks on being handled, has not eaten any food, P. 204, R. 54, T. 31.4 C., placed before fire; 5:45, seems slightly better, P. 150, R. 30, T. 32.7 C.

Third day, 12:15 o'clock, condition much the same, trembling of head present, eyes half closed, P. 168, R. 60, T. 29.1 C.; 5:30, slightly increased muscular weakness, pupils more dilated, been laid before the fire all day. P. 204, R. 36, T. 31.8 C.

Fourth day, 11:00 o'clock, no noticeable change, P. 138, R. 39, T. 30.6 C.; 6:00, much worse, trembling very marked.

Fifth day, 9:00 o'clock, found dead, rigor mortis, cold; afternoon, few small patches in stomach, otherwise normal, stomach and cecum full of food.

APPENDIX II.

This appendix contains a summary of the experiments made on which the foregoing account is based. Only the briefest description is given, but some attempt has been made to indicate the comparative value of the experiments. The experiments are given in the order they were made. The time in parentheses indicates the period after administration of the drug at which the preceding symptom was noted; m., minute; h., hour.

EXPERIMENTS ON DOGS.

Three dogs were used; at first only two. All were fed at 9 o'clock A.M. Unless otherwise indicated the individual substances were given in gelatine capsules by the mouth.

1. May 5, 1897; Airedale terrier; weight 3100 gms.; 0.4 g. cannabinal phosphate; slight depression and sleepiness.

2. June 4, 1897; Airedale terrier, 4400 gms.; 0.4 g. cannabinal phosphate hypodermically; slight depression and sleepiness, fall in pulse rate; longer effect than in last case.

3. June 16, 1897; Airedale terrier, 5400 gms.; 1.1 g. acetyl-cannabinal; sleepiness and depression (30 m.), unsteadiness, occasional slight excitement, vomiting (3 h.), dilatation of pupils. Quite well next morning.

4. July 1, 1897; Airedale terrier; 0.5 g. cannabinal; slight sleepiness (75 m.), stupidity, muscular weakness and unsteadiness; slept most of day; normal next morning; effect more marked than 3.

5. July 15, 1897; Airedale terrier, 7520 gms.; 1 g. charas; tired, yawning (30 m.), sleepy, ataxia, etc., pupils somewhat dilated, very much excited (6 h.); seemed normal next day; effect somewhat greater than 4.

6. July 22, 1897; Airedale terrier; 0.3 c.c. $\frac{1}{4}$ alcoholic extract charas; depression (60 m.), temporary excitement (100 m.), weakness and unsteadiness (most marked 5 to 6 h.), shivering, involuntary micturition; slightly excited next morning; very marked effect.

7. July 28, 1897; Airedale terrier; 1 c.c. $\frac{1}{4}$ alcoholic extract charas; lay down (75 m.), but excited if played with; sleepiness, unsteadiness, etc., as in 6, but symptoms less severe; normal next morning.

8. July 30, 1897; Airedale terrier; 0.9 c.c. mono-terpene from charas; no effect.

9. Aug. 2, 1897; Airedale terrier; 1.1 c.c. sesqui-terpene from charas; no effect.

10. Aug. 3, 1897; Airedale terrier; 0.5 g. cannabinal distilled at 406 degrees C. (atmospheric pressure); lay down (30 m.), vomited (55 m.), depressed, head falling to one side (75 m.), afterward sleepiness, unsteadiness, etc., vomited twice (6 h.); effect almost as marked as 4.

11. Aug. 11, 1897; Airedale terrier; 1 c.c. greenish oil, intermediate between sesqui-terpene and cannabinal, unpleasant smell; vomited (45 m.); no effect beyond slight depression.

12. Oct. 19, 1897; Airedale terrier, 9650 gms.; 9.97 g. intermediate product between sesqui-terpene and cannabinal (distills below 300 degrees C.); slight depression, increased micturition; otherwise normal.

13. Fox-terrier, 7550 gms.; 0.75 g. intermediate product between sesqui-terpene and cannabinal (distills below 300 degrees C.); vomited four times (70 to 100 m.), increased micturition; no other effect.

14. Oct. 27, 1897; Airedale terrier, 10,700 gms.; 1.15 g. cannabinal, from Merck's cannabinal; depression (40 m.), sleepiness, muscular weakness and unsteadiness, dilated pupils, vomiting (140 m., 240 m., 255 m.); somewhat better, but still severely affected (5½ h.); would not touch food; apparently well next morning. Most marked effect yet.

15. Fox-terrier, 7950 gms.; 1.04 g. cannabinal, from T. and H. Smith's cannabinal. Unsteadiness (35 m.), which increased; became tired and sleepy but walked about much, vomited (4¼ h.); more unsteady but less depressed than other dog; would not touch food; well next morning.

16. Nov. 11, 1897; Airedale terrier, 11,250 gms.; 0.99 g. Merck's cannabinal. No effect (30 m.), usual symptoms marked (60 m.), continued to 180 m., afterward gradual improvement, very much better (6½ h.), salivation (2 h., continued 1 h.), vomiting (2 h.); depression and unsteadiness more marked than 14 but more transient.

17. Fox-terrier, 8100 gms.; 1.04 g. ext. cannab. indic. ether (Merck). Slight effect (60 m.), unsteadiness (75 m.), vomited (3¼ h.), ataxia main symptom; not much better (6½ h.); very little sleep, apparently well next morning; effect about the same as 15.

18. Nov. 18, 1897; Airedale terrier; 0.19 g. ext. cannab. indic. ether (Merck). Depression (45 m.), marked unsteadiness (60 m.), slight salivation (90 m.), sleepy, excited, vomited (3 h.), ataxia not much better when left (4 h.).

19. Nov. 22, 1897; Airedale terrier; 1.95 g. cannabinal. Slight effect (30 m.): unsteadiness, sleepiness, etc., developed, but symptoms not more severe than 18.

20. Fox-terrier; 1 g. ext. cannab. indic. (Merck). Commencing weakness (45 m.), more marked (60 m.), afterward became very severe; incontinence of urine, vomited (130 m., 135 m.), trembling from cold; slight improvement (3½ h.).

21. Nov. 26, 1897; Airedale terrier; 0.19 g. cannabinal (Merck) given in a piece of meat. Slight effect (2 h.); distinct unsteadiness (2½ h.), subsequently worse, depressed but not sleepy.

22. Fox-terrier; 0.55 g. extract cannab. indic. Sicc. (Merck). No distinct effect.

23. Dec. 1, 1897; Airedale terrier, 12,400 gms.; 0.15 g. alco-

hol ether extract charas [previously heated three times with dil. H_2SO_4]. Sleep main symptom, depression (60 m.), unsteadiness (90 m.), vomiting ($2\frac{1}{2}$ h., $3\frac{1}{2}$ h.); distinct improvement (5 h.).

24. Fox-terrier; 8800 gms.; 0.15 g. alcohol-ether extract charas [previously heated three times with dil. H_2SO_4]. Slight depression (35 m.), slight unsteadiness (75 m.), afterward very distinct; slept, salivation (3 h.), vomited (4 h.), not much improvement (6 h.); well next morning.

25. Dec. 3, 1897; Airedale terrier; 0.15 g. alcohol-ether extract charas [previously heated 14 hours at 260 degrees C.]. Effects similar to 23, but somewhat less marked and delayed—no obvious action except slight depression and sleepiness for three and one-half hours.

26. Fox-terrier; 0.21 g. alcohol-ether extract charas [previously heated 14 hours at 260 degrees C.]. Slight depression (60 m.), slight unsteadiness (3 h.), much more marked ($3\frac{1}{2}$ h.); improvement ($4\frac{1}{2}$ h.).

27. Dec. 6, 1897; Airedale terrier; 0.15 g. cannabinal rapidly distilled from alcohol-ether extract. No apparent effect (70 m.), later, usual symptoms developed, very distinct unsteadiness.

28. Fox-terrier; 0.54 g. pitch from extract, contains a little cannabinal. Slight depression; no other distinctive action.

29. Dec. 9, 1897; Airedale terrier; 0.15 g. distillation fraction previous to cannabinal than latter. Depression (30 m.), sleepiness, unsteadiness (85 m.), but not marked; attention good, excited ($5\frac{1}{2}$ h.).

30. Fox-terrier; 0.21 g. distillation fraction previous to cannabinal than latter. Mostly laid down at first; slight unsteadiness (2 h.), worse ($3\frac{1}{2}$ h.), slight sleepiness; symptoms not marked.

31. Airedale terrier; 0.21 g. charas extract, further heated for 60 hours at 220 to 260 degrees C. (cp. 25). Depression (60 m.), unsteadiness (105 m.), slept fairly well, much better ($5\frac{1}{2}$ h.); symptoms more marked than 25 but less than 23.

32. Fox-terrier; 0.39 g. charas extract, further heated for 60 hours at 220 to 260 degrees C. (cp. 25). Slight depression and unsteadiness (90 m.), much more marked (2 h.), still severe ($5\frac{1}{2}$ h.), sleepy; symptoms about equal to 24.

33. Dec. 28, 1897; Airedale terrier; 1.07 g. cannabinal (oldest). Laid down at first, could not be induced to stand long; very slight unsteadiness (3 h.) and depression, more severe (5 h.) but still fairly well; normal next morning.

34. Fox-terrier; 1.03 g. cannabinal (oldest). Slight depression (60 m.), unsteadiness (90 m.), still distinct (5 h.); depressed following morning.

35. Dec. 29, 1897; Airedale terrier; 0.92 g. cannabinal, distilled from another sample of charas. Asleep (55 m.), very unsteady (90 m.), continued as long as observed (6 h.); slept mostly.

36. Fox-terrier; 0.96 g. cannabinal, distilled from another sample of charas. Unsteadiness (55 m.), became very marked afterward, vomited (65 m. and 5 h.); slight improvement (6 h.).

37. Dec. 31, 1897; Airedale terrier; 1.1 g. cannabinal (oldest). Slight depression and unsteadiness (70 m.), increased later, slept mostly; more marked effect than 33.

38. Fox-terrier; 0.97 g. cannabinal (oldest). Unsteadiness (70 m.), which increased, still marked ($5\frac{1}{2}$ h.); effect greater than 34.

39. Jan. 3, 1898; Airedale terrier; 0.97 g. cannabinal, distilled from another sample of charas. No effect (60 m.), afterward slept, very slight unsteadiness, (2 h.), did not increase, lay down occasionally; slept remainder of day, playful when aroused.

40. Fox-terrier; 0.95 g. cannabinal, distilled from another sample of charas. No effect (60 m.), very slight unsteadiness (2 h.), soon became more marked, continued as long as observed, slept somewhat; slightly depressed next morning.

41. Jan. 4, 1898; Airedale terrier; 1.1 g. cannabinal, distilled from another sample of charas. Slight depression; no marked symptoms.

42. Fox-terrier; 0.99 g. cannabinal, distilled from another sample of charas. Depression and unsteadiness (2 h.) not very marked; slight depression next morning.

43. Jan. 5, 1898; Airedale terrier, 12,110 gms.; 1.03 g. cannabinal, distilled from another sample of charas. Slight depression (60 m.), slight unsteadiness, slept mostly; unsteadiness increased, vomited (125 m.), awakened to be taken to kennel, very unsteady.

44. Fox-terrier, 8210 gms.; 0.97 g. cannabinal, distilled from another sample charas. Slight depression and unsteadiness (60 m.), became more marked and continued as long as under observation ($6\frac{1}{2}$ h.), vomited a little ($5\frac{1}{4}$ h.), slept partly; apparently normal next morning.

45. Jan. 6, 1898; Airedale terrier; 1.01 g. cannabinal, distilled from another sample of charas. Slight depression (60

m.), slept mostly, unsteadiness less marked than 43; apparently well the following morning.

46. Fox-terrier; 0.97 g. cannabinal, distilled from another sample of charas. Slight depression (60 m.), unsteadiness (70 m.), effects similar but ataxia less marked than 44.

47. Jan. 7, 1898; Airedale terrier; 0.98 g. cannabinal, distilled from another sample of charas. Slept most of the time, unsteadiness slight.

48. Fox-terrier; 0.97 g. cannabinal, distilled from another sample of charas. Depression (30 m.), unsteadiness (60 m.), became very distinct, laid down mostly, slept partly; very slight depression next morning.

49. Jan. 8, 1898; Airedale terrier; 1.04 g. cannabinal, distilled from another sample of charas. Depression (60 m.), unsteadiness (90 m.), not further observed.

50. Fox-terrier; 0.99 g. cannabinal, distilled from another sample of charas. No apparent effect (90 m.); not further observed; apparently normal next morning.

51. Jan. 9, 1898; Airedale terrier; 1.02 g. cannabinal, distilled from another sample of charas. Not observed.

52. Fox-terrier; 1 g. cannabinal, distilled from another sample of charas. Not observed.

53. Jan. 10, 1898; Airedale terrier; 1.02 g. cannabinal, distilled from another sample of charas. Depression, distinct ataxia, but not marked; slept most of the time.

54. Fox-terrier; 1 g. cannabinal, distilled from another sample of charas. Sleepiness, depression and slight unsteadiness, symptoms less marked than usual; slight depression next morning.

55. Jan. 11, 1898; Airedale terrier; 0.22 g. cannabinal (as 31). No evident effect (60 m.), later transient depression, but no ataxia developed. Compare with 31.

56. Fox-terrier; 0.4 g. cannabinal (as 31). No effect (60 m.), later depression and unsteadiness but less than 32.

57. Jan. 25, 1898; Airedale terrier, 13,150 gms.; 0.21 g. cannabinal (as 31). Slight depression (60 m.), afterward sleepiness, unsteadiness, excited (5 h.).

58. Fox-terrier, 7980 gms.; 0.42 g. cannabinal (as 31). No effect (60 m.), later sleepiness, slight unsteadiness and depression.

59. Feb. 11, 1898; Airedale terrier; 0.16 g. third fraction cannabinal dissolved in .64 g. olive oil. Depression (30 m.) followed by sleep, no distinct unsteadiness, excited at times, vomited a little ($4\frac{1}{4}$ h.); still depressed ($5\frac{1}{4}$ h.).

60. Fox-terrier; 0.18 g. third fraction cannabinal dissolved in .64 g. olive oil. Depression (35 m.) and sleep, no ataxia observed but could not be induced to stand long; still depressed (5 h.).

61. Feb. 15, 1898; Airedale terrier; 0.16 g. second fraction cannabinal in .64 g. olive oil. Symptoms similar to 59.

62. Fox-terrier; 0.18 g. second fraction cannabinal in .64 g. olive oil. Slight depression and unsteadiness ($2\frac{1}{2}$ h.) but less marked than 60, vomited (5 h.).

63. Feb. 17, 1898; Airedale terrier; 0.16 g. first fraction cannabinal in .64 g. olive oil. Depression somewhat more marked than 61 but no unsteadiness, vomited slightly (3 h.).

64. Fox-terrier; 0.18 g. first fraction cannabinal in .64 g. olive oil. Some depression and slight unsteadiness, but doubtful if as marked as 62.

65. Feb. 22, 1898; Airedale terrier; 0.21 g. cannabinal distilled at atmospheric pressure, then heated 5 hours at boiling point. Slight depression and sleepiness, no ataxia observed; much better ($5\frac{1}{2}$ h.).

66. Fox-terrier; 0.23 g. cannabinal distilled at atmospheric pressure, then heated 5 hours at boiling point. Slight depression, no sleep; almost well ($5\frac{1}{2}$ h.).

67. Feb. 24, 1898; Airedale terrier; 2.1 g. cannabinal distilled at atmospheric pressure, then heated 5 hours at boiling point. Depression and unsteadiness, but symptoms not very marked, slept somewhat, vomited ($3\frac{1}{2}$ h., $4\frac{1}{2}$ h.), slight improvement (6 h.).

68. Fox-terrier; 2.2 g. cannabinal distilled at atmospheric pressure, then heated 5 hours at boiling point. Depression and distinct unsteadiness, did not sleep; somewhat better ($5\frac{1}{2}$ h.).

69. Feb. 28, 1898; Fox-terrier; 0.43 g. acetyl-derivation of higher homologue of cannabinal. No effect ($2\frac{1}{2}$ h.).

70. March 1, 1898; Airedale terrier; 0.2 g. cannabinal distilled in vacuo. Depression, sleep and unsteadiness, more marked than 67; decided improvement ($5\frac{1}{2}$ h.).

71. Fox-terrier; 0.22 g. cannabinal distilled in vacuo. Distinct unsteadiness (60 m.), slight depression; symptoms similar to 68; much better ($5\frac{1}{2}$ h.).

72. March 3, 1898; Airedale terrier; 0.45 g. pitch dissolved in 1.5 g. olive oil containing some cannabinal. Slight depression and unsteadiness; much better ($4\frac{1}{2}$ h.).

73. Fox-terrier; 1.03 g. cannabinal regenerated from old acetyl compound. Slight depression and sleepiness, no obvious ataxia.

74. March 8, 1898; Airedale terrier; 0.06 g. morphin acetate in capsule. Vomited frothy mucous-like vomit (12 m., 14 m., 17 m.), marked depression, much worse than any previous observation, retching (22 m.), rapid breathing, quick pulse, head-nodding (40 m.), salivation (44 m., continued to 120 m.), still much depressed, constant moaning, slight myosis (130 m.), fall of temperature 1.1 degrees C., sleepiness, slight unsteadiness; improvement (4 h.), but still depressed (5½ h.).

75. Fox-terrier; 0.1 g. morphin acetate in capsule. No effect (20 m.), head-nodding (30 m.), retching and vomiting of frothy colorless fluid (35 m., 38 m., 50 m., 55 m., 90 m., 105 m.), salivation, unsteadiness, depression (130 m.), not sleepy, salivation stopped (3¼ h.), fall of temperature 2.3 degrees C.; could not be induced to stand up, somewhat better (4½ h.).

76. March 16, 1898; 0.93 g. olive oil extract of charas, containing about .2 to .25 g. soluble charas products. Slight depression and unsteadiness (60 m.), sleepiness, vomiting (160 m.), ataxia more marked, excited (3½ h.), slight improvement (5¾ h.).

77. Fox-terrier; 1.86 g. olive oil extract of charas, containing .4 to .5 g. soluble charas products. Sleepiness and depression (30 m.), distinct unsteadiness (60 m.), which became more marked later, vomited (105 m.); no obvious improvement (5¾ h.).

78. March 18, 1898; Fox-terrier, 8840 gms.; 0.15 g. extract cannab. indic. (B. P.) in pills (from London chemist). No effect (90 m.), afterward depression and marked ataxia, vomited (2½ h.).

79. March 22, 1891; Airedale terrier, 13,580 gms.; 1.03 g. partly (¾) saponified acetyl derivative of higher homologue of cannabinal. No distinct effect.

80. Fox-terrier; 0.35 g. oxycannabinal. No obvious effect.

81. March 25, 1898; Airedale terrier; 1.02 g. cannabinal. Depression, very distinct unsteadiness (60 m.), sleepiness, vomited (2 h., 3¼ h.), no distinct improvement (4¼ h.).

82. Fox-terrier; 0.99 g. cannabinal. No obvious effect (60 m.), depression (75 m.), vomiting (105 m., 115 m., 130 m., 135 m., 255 m.), slight unsteadiness (120 m.), symptoms increased; no improvement (4½ h.).

83. March 30, 1898; Airedale terrier; 1 g. chloral hydrate in capsule. Sleepiness (15 m.), very slight ataxia, somewhat more marked (30 m.); fall of temperature 0.4 degrees C., apparently normal (4 h.).

84. Fox-terrier; 1 g. chloral hydrate in capsule. Sleepiness (15 m.), slight muscular weakness but no distinct ataxia; fall of temperature 0.4 degrees C., apparently normal (4 h.).

85. April 5, 1898; Airedale terrier; 0.5 g. chloralose in capsule. Slight depression and sleepiness, transient; fall of temperature 0.5 degrees C.

86. Fox-terrier; 0.0195 g. hyoscine hydrochlorid. Uneasiness (30 m.) followed by whining, dryness of the tongue, dilatation and less marked reaction of pupils to light, increased rapidity of heart beat (60 m.), improvement commenced (2 h.); no fall of temperature.

87. April 11, 1898; 0.21 g. cannabinal. Slight depression, sleepiness and unsteadiness, continued 6 hours.

88. Fox-terrier; 0.2 g. cannabinal. Slight depression (30 m.) but not much affected until (90 m.), became very unsteady, sleepiness, incontinence of urine, trembling, vomiting (2 h.); fall temp. 3 degrees C.; most marked effect obtained with this dose.

89. English terrier, 7180 gms.; 0.15 g. cannabinal. Less reserved (20 m.), slight depression (30 m.), sleepiness chief symptom, no obvious ataxia; slight improvement (5 h.).

90. April 15, 1898; Airedale terrier; 0.2 g. cannabinal kept in sealed tube since Dec. 12, 1896. Slight depression and sleepiness (45 m.), became much more marked; unsteadiness developed, attention became impaired, vomited (5 h.), then improved.

91. English terrier; 0.14 g. cannabinal, kept in sealed tube since Dec. 12, 1896. Slight depression and very distinct unsteadiness (30 m.), gradually increased until fell over every few steps, vomited (100 m., 104 m., 150 m., 200 m.), slept a little (3½ h.), much better but still markedly depressed (5 h.; temperature fell 0.5 degree C., then rose 1.2 degree C.).

92. Fox-terrier; 0.39 g. cannabinal, through which oxygen has been passed 3 to 4 hours at 150 degrees C. Slightly depressed (45 m.), very slight unsteadiness (60 m.), became somewhat more marked, slight sleepiness; symptoms not severe but temperature fell 1.4 degrees C.

93. April 19, 1898; Airedale terrier, 12,840 gms.; 0.22 g. cannabinal (as in 90), subjected to oxygen for 6 hours at 150 to 160 degrees C. Slight depression and sleepiness (30 m.), increased; distinct unsteadiness; not much improved (6 h.).

94. English terrier; 0.16 g. cannabinal (as in 93). Depressed,

restless (20 m.), sleepy (30 m.), slight unsteadiness (40 m.), gradually became worse, but not so bad as in 91; vomited (55 m., 115 m.), somewhat better (4½ h.), but no further improvement (5¾ h.).

95. Fox-terrier, 8270 gms.; 0.21 g. cannabinal (as in 90). Slight depression (30 m.), but not much affected during first hour, afterward much depressed, slight unsteadiness; no improvement (5¾ h.).

96. April 23, 1898. Fox-terrier; 0.19 g. cannabinal (as in 90). Asleep (30 m.), but no marked symptoms for three hours, then slight unsteadiness, which increased; distinct (6¼ h.).

97. Airedale terrier; 0.22 g. cannabinal through which CO₂ has been passed for 20 hours at 150 to 185 degrees C. Slight depression and sleepiness (30 m.) became more marked, unsteadiness (60 m.), vomited (105 m.); afterward improved but still under influence (6¼ h.).

98. English terrier; 0.2 g. cannabinal through which oxygen has been passed for 20 hours at 150 to 185 degrees C., pitchy appearance. Very slight depression and restlessness (30 m.) which quickly (1 h.) passed away; no ataxia.

99. April 27, 1898; English terrier, 7760 gms.; 0.2 g. tribromcannabinal. Depressed (60 m.), slight sleepiness but no distinct unsteadiness, apparently normal (4 h.).

EXPERIMENTS ON CATS.

100. Dec. 11, 1895; 2500 gms.; 3.5 g. charas given in mucilage (65 c.c.), chloroformed during injection. Vomited most of the substance (about 50 c.c.) after recovery from chloroform, depression, weakness, narcosis and death (4 h.); no characteristic macroscopic changes.

101. June 20, 1896; 2600 gms.; 0.15 g. cannabinal in meat, Sleepiness (90 m.), muscular weakness, marked ataxia, stupidity; commencing improvement (25 h.), complete recovery (44 h.).

102. May 26, 1896; 2700 gms., same cat; 0.27 cannabinal as pills with starch. Quiet (90 m.), restlessness and micturition, then salivation (3½ h.), muscular weakness and unsteadiness, anorexia; improvement (25 h.), almost well (28 h.).

103. June 2, 1896; 1.3 g. cannabinal in capsules. Tired, quiet (60 m.), salivation and unsteadiness (100 m.), marked ataxia, sleepiness, dilated pupils: improvement (30 h.), almost well (53 h.).

EXPERIMENTS ON RABBITS.

Substances were made into an emulsion with gum and injected through a catheter into the stomach.

104. Nov. 1, 1895; 1730 gms.; 0.895 g. impure (sesqui) terpine. Slight excitement.

105. Nov. 4, 1895; 1730 gms.; 0.895 g. charas with sodium bicarbonate. Slight excitement.

106. Nov. 5, 1895; 1730 gms. 0.876 g. petroleum ether extract. Slight excitement.

107. Dec. 17, 1895; 1440 gms.; 1.44 g. charas. No distinct effect.

108. Jan. 16, 1896; 1500 gms.; 3 g. petroleum-ether extract. Became quieter; number of heart beats and respiration, and temperature fell; death occurred on third day.

109. June 5, 1896; 1100 gms.; 2.2 g. cannabinal. Depression (60 m.), sleepiness, fall in pulse (252 to 100), respiration (142 to 18) and temperature (40.4 to 35.7 degree C.), diminished reflexes; improvement (20 h.), much better but not normal (29 h.).

110. June 10, 1896; 930 gms.; 2.2 g. charas. Quieter (90 m.), fall in pulse, respiration and temperature; died on fourth day, cold and marasmus.

11. April 5, 1898; 620 gms.; 2.3 g. cannabinal. Depressed, slight muscular weakness, sleepiness, fall in pulse, respiration and temperature; death, 3½ days.

PERSONAL EXPERIMENTS.

112. Feb. 19; 0.1 g. cannabinal, taken about 2:45 P.M.

113. Feb. 8, 1896; 0.1 g. cannabinal in 0.05 c.c. alcohol and 20 c.c. water. Slight mental depression.

114. March 9, 1895; 0.5 c.c. monoterpene in 20 c.c. water. No effect.

115. March 10, 1896; 0.05 g. cannabinal in 0.1 c.c. alcohol and 20 c.c. water. No distinct effect for 4 hours, then feeling of dryness in mouth, pleasant tingling, slight unsteadiness, happiness, unpleasant visions on closing eyes, time relation not completely lost, feeling of tiredness but no marked tendency to sleep.

116. March 28, 1897; 0.05 g. cannabinal regenerated from acetyl compound. Taken at 8 P.M., retired to bed at 10:30 feeling a little tired, slept soundly till 6 P.M., no distinct effect.

117. April 5, 1897; 0.05 g. cannabinal regenerated from acetyl compound. Taken at 10:30 A.M., slightly depressed in afternoon, no other effect.

118. April 5, 1897; 0.1 g. cannabinal regenerated from acetyl compound. Taken at 11 A.M., tired and sleepy in afternoon.

119. April 10, 1897; 0.2 g. cannabinal regenerated from acetyl compound. Taken at 1 P.M., slight dryness of mouth and paresthesia (160 m.) followed by sleepiness, depressed during evening, retired at 11:30.

120. April 13, 1897; 4 cannabinal tablets (a commercial preparation) — g. cannabinal. Taken at 5:08 P.M., feeling of lightness in head (5:55), dinner 6:00, afterward felt sleepy and slightly intoxicated; time relations altered but not annulled.

121. June 7, 1897; 0.2 g. cannabinal phosphate. Taken at 10:30 P.M., Retired at 12 M., no evident effect.

122. June 9, 1897; 0.4 g. cannabinal phosphate. No distinct action.

123. June 6, 1897; 0.8 g. cannabinal phosphate. Taken at 10:45 P.M., 11:40 very sleepy, retired, awoke at 7:20 A.M., feeling very sleepy, depressed all the morning.

124. March 17, 1898; 0.05 g. oily extract of charas, containing .013 g. soluble products. Dinner at 6:20, taken at 8:00, slight sleepiness and mental exhaustion followed.

125. March 18, 1898; 0.105 g. oily extract of charas, containing 0.13 g. soluble products. Taken at 6:25 P.M., dinner 6:50, 7:35 peculiar feeling of lightness in head, continued to work, 8:00 rather better, 11:00 retired feeling sleepy.

126. March 20, 1898; 0.016 g. ($\frac{1}{4}$ grain) ext. cannab. Ind. (B. P.) pill. Tea 5 P.M., slight indigestion, pill taken at 7:30, 10:30 no evident effect, 10:35 slight light-headedness, warmth of face and mental exhaustion, afterward fell asleep.

127. March 21, 1898; 0.14 g. partly ($\frac{3}{4}$) saponified acetyl derivative of higher homologue of cannabinal. Taken at 5:30 P.M., no effect.

128. March 22, 1898; 0.1 g. third fraction cannabinal. Taken at 5:45 P.M., dinner 6:30, 8:25 feeling of lightness in head and mental exhaustion, continued working, effect passed off in about 30 m.

129. March 23, 1898; 0.1 g. second fraction cannabinal. Taken at 5:45 P.M., dinner 6:45, 7:20 no effect, 9:25 slight dryness of lips and lightness in head, seemed to pass off but worse again at 7:43, happy, have difficulty in reading, sleepy, 10:00 just awakened from a short nap, read a little but soon exhausted, 11:20 retired, 6:45 A.M. awoke, felt well.

130. March 24, 1898; 0.1 g. first fraction cannabinal. Taken at 5:45 P.M., dinner 6:45, 7:45 no effect, 7:50 feeling of slight dryness of lips and lightness of head, 8:00 somewhat more depressed, not working well, 8:45 working better, 10:00 still somewhat depressed, 11:30 retired but did not succeed in sleeping for some time.

131. March 25, 1898; 0.1 g. cannabinal (oldest). Taken at 5:45 P.M., dinner at 6:30, 7:30 peculiar light-headedness and dryness of the lips, 7:45 slightly unsteady, parasthesia in head and legs, heaviness of eyelids, no correct estimation of time, 9:30 awakened from short sleep, 10:00 rather better but unable to work, 10:30 retired, somewhat depressed the following morning.

132. March 27, 1898; 0.35 g. acetyl derivative of higher homologue of cannabinal. Taken at 7:30 P.M., no effect.

133. March 29, 1898; 0.05 g. cannabinal pill made 18 months ago. Taken at 5:50, dinner at 6:30, 8:30 unsteady symptoms, cannot work, estimation of time not so good, 9:15 worse, energyless, 10:30 went out for few minutes, improved, 11:00 can read moderately well but eyelids heavy.

134. March 30, 1898; 0.09 g. Merck's cannabinal. Taken at 5:45, dinner 6:30, 7:20 lightness in head, loss of time relation, happy, amused, pleasant tingling, etc.; sleepy, 8:00 lay down, slept till 10:30 then retired, awakened (7:00 A.M.) feeling dull and depressed, lasted the whole morning.

135. April 14, 1898; 0.05 g. opium. Taken at 9:00 P.M., 10:00 no obvious action, 10:05 slight heaviness of eyelids, very slightly tired, 10:20 rather better, 11:10 feel somewhat tired, head rather heavy, slight sense of "well-being," 12:00 still heaviness of eyes and tiredness of head but have worked fairly well last half hour, not sleepy; retired, soon fell asleep, awakened at 7:00 A.M. feeling well, pleasant sense of gravity, which continued most of morning; no constipation.

136. April 15, 1898; 0.1 g. cannabinal through which oxygen passed 3 to 5 hours at 150 to 160 degrees C. Taken at 5:45, dinner at 6:30, 9:15 slight visual indefiniteness, slight and transient paresthesia, afterward felt slight incapacity for work but no marked effects, 11:45 not sleepy but retired.

137. April 17, 1898; 0.05 g. cannabinal sealed up since Dec. 28, 1896. Tea 4:30, drug taken 5:45, 6:50 slight mental exhaustion and feeling of lightness in head, 7:20 rather sleepy, 8:00 trying to read but have little energy for anything, 9:00 condition same, no estimation of time, feeling of warmth in face and head, 10:00 sleepy, retired.

138. April 21, 1898; 0.065 g. same cannabinal treated with

oxygen for 20 hours at 150 to 185 degrees C. Taken at 5:45, dinner 6:40, 8:05 slight feeling of lightness in head, 9:30 have been reading some time, at first had a little difficulty, now feel quite normal.

139. April 22, 1898; 0.05 g. same cannabinal treated with CO₂ for 20 hours at 150 to 185 degrees C. Taken at 5:50, dinner 6:30, 7:00 commencing light-headedness, 8:00 more distinct, a want of energy, 9:45 condition same, trying to read, 10:00 not able to do any work, 10:45 no improvement, retired.

140. April 24, 1898; 0.1 g. tribrom-cannabinal. Taken at 8:00 P.M., supper at 8:30, 9:30 slightly sleepy, 11:00 sleepy, no other peculiar effect of cannabinal, retired, slept till 6:45, depressed, suffered from mental exhaustion during three following days.

141. May 4, 1898; 0.065 g. oxycannabinal (as in 138) dissolved in oil. Taken at 5:45, dinner at 6:30. 7:15 went out for a walk, 8:15 arrived home, slightly tired, peculiar feeling in eyes and head grew slightly worse and continued the whole evening, but was insufficient to prevent me writing; 11:10 retired, slept soundly, 6:40 A.M. got up, felt sleepy.

142. May 6, 1898; 0.1 g. charas (best). Taken at 5:45, tea at 4:30, dinner at 7:00, 7:00 slight effect in head, worked in garden, felt want of energy, 8:30 influence more marked, agreeable heaviness of eyelids, very little energy, 10:00 retired, condition same, slept well, depressed following morning.

143. May 12, 1898; 0.016 g. ($\frac{1}{4}$ grain) ext. cannab. Indic (B. P.) in pill (cp. 126). Taken at 5:50, dinner at 6:30, 7:25 lightness in head, peculiar feeling about eyes, 7:50 pleasant tingling in face and feet, no other marked effect, reading fairly well, 8:40 tingling still present, unable to read with benefit, can not calculate time very well, symptoms continued throughout evening, became sleepy but managed to do some copying, 12:30 retired, 7:30 got up feeling tired but soon well.

144. May 19, 1898; 2 c.c. sesqui terpene taken in weak mucilage. Taken at 12:45, lunch 1:10, 1:15 slightly listless and slight heaviness of head, which soon passed away.

THE THERAPEUTICAL ECONOMICS OF OPEN COMPOSITION.

Presented to the Section on Materia Medica, Pharmacy and Therapeutics, at the Forty-ninth Annual Meeting of the American Medical Association, held at Denver, Colo., June 7-10, 1898.

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There is only one restriction upon the character of medicines supplied to the public, to be expected at the hands of the law-makers in the period now before us, namely: restriction, with the intent to put a stop to concealment of composition and identity. That legal restriction to this effect may be instituted in some of the States at any time, and is likely to become prevalent, appears manifest from the temper of the law-making mind, shown in various ways, especially in the scope of the enactments against adulterations. Any alteration of composition is prohibited if it be not made known to the purchaser (or consumer), but is allowed if it be so made known. Various irregular admixtures are specifically authorized upon the one condition that they shall be explicitly announced on the label. On the other hand, various colorings and facings of food, which are harmless in themselves, are prohibited because they tend to deceive the consumer as to identity or quality of the article. The same intent appears in legal rulings for uniform standards of concentration of foods and of medicines, and it appears in the early requirements of poison-labels, lately extended, in some instances, to proprietary mixtures sold without a physician's order and without any account of contents.

Granting that some of these prohibitory measures have been worked for as a means of protection to certain industries, and that in other cases the legislation has been proposed by unscrupulous persons, who seek opportunity to levy bribes, etc., it still remains true