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The indolethylamine with which this paper deals is 3-β-amino-ethylindole. It is the amine corresponding to the amino-acid tryptophane. A number of amines formed from the native amino-acids by the elimination of CO_2 have been shown to be physiologically active substances.[1, 2, 3, 4]

It appeared probable that indolethylamine would be physiologically active, and a brief investigation of its action on the normal animal be of some interest. The synthesis of this amine was accordingly undertaken by Mr. A. J. Ewins,[5] to whom I am indebted for a supply of material for physiological experiments. At the same time I prepared a small quantity of the base by putrefaction from tryptophane (see Note on p. 150).

The Intact Animal. Subcutaneous administration of the hydrochloride of indolethylamine to cats and rabbits gives rise to practically no symptoms, a rapid heart is the only certain symptom observable after 100 mgm. doses. (In the cat, symptoms of nausea, uneasiness, salivation, etc., may occur.) It will be seen later that indolethylamine produces vaso-constriction; its absorption after this method of administration will therefore probably be somewhat slow; the effects it produces are of short duration, and hence symptoms will not be well marked unless very large doses are given by this means. Ten milligram doses were given to rabbits by the marginal ear vein. In each case, immediately after the injection, a spastic condition of the limbs developed, on which was superimposed a fine, rapid tremor of fore and hind limbs; this condition persisted for about one minute and then rapidly disappeared. The respiration became slow, temporarily, and then recovered. The heart one minute after the injection was accelerated. A

1. Dale and Dixon, *Journ. of Phys.*, XXXIX, p. 25, 1909.
2. Barger and Dale, *Journ. of Phys.*, XLI, p. 19, 1910.
3. Ackermann and Kutscher, *Zeit. für Biol.*, LIV, p. 387, 1910.
4. Dale and Laidlaw, *Journ. of Phys.*, XLI, p. 318, 1910.
5. Ewins, *Trans. Chem. Soc.*, XCIX, p. 270, 1911.

small cat was given 20 mgm. of indolethylamine hydrochloride intravenously (long saphena vein), and a remarkable series of symptoms ensued. Within thirty seconds of the administration violent convulsive movements of limbs and body occurred, quite suddenly these clonic spasms became tonic: the fore limbs were spread out straight in front, paws off the ground and claws protruded; hind limbs stiff, flexed on the trunk, and claws extended. A fine tremor was present in all limbs. The pupils were dilated, salivation was marked, and although the animal had purred contentedly during the injection it now exhibited a high degree of excitement. These symptoms were maximal in one minute, and passed off in about three minutes. The cat sat up, all signs of muscular spasm had disappeared, it was once more docile and purred when stroked. Salivation continued for three or four minutes more. The pupils became small slits about three minutes after the injection and remained so even in dull illumination. Fifteen minutes after the first symptoms the cat appeared to be perfectly normal. The heart beat was good throughout the experiment, but respiration was severely interfered with during the convulsive stage, being jerky and irregular. It is very probable that a slightly larger dose would have caused death from respiratory failure.

The convulsive movements seen in the intact animal on intravenous administration of indolethylamine appear to be due to a transient stimulation of the central nervous system. A very similar series of muscular movements is seen when a spinal cat, under artificial respiration, is given a small dose intravenously. On complete destruction of the cord these symptoms disappear. It is noteworthy that the effect is peculiar to warm-blooded animals. Frogs receiving doses of 10 mgm. showed no sign of convulsions. The symptoms shown by the latter animal are a gradually increasing depression culminating in coma.

The Vascular System. Indolethylamine produces a large rise of blood pressure in the spinal cat when administered intravenously (see fig. 2). The pressor effect has a superficial resemblance to that produced by a small dose of adrenine. The rise of pressure is very rapid, and is accompanied by an increased rate of heart beat and the return to normal follows quickly upon the attainment of the maximum. Tonic contraction and tremors of trunk and limb muscles also occur, which may help in producing the rise of pressure through raising the intra-abdominal pressure. This, however, is quite a subsidiary factor since large rises of pressure are obtainable with the abdomen laid open. Direct comparison of rises of pressure produced by equal doses before and after opening

abdomen is untrustworthy, since a second dose of the base rarely produces quite as large an effect as the first. In the animal anaesthetised with volatile anaesthetic the rise of blood pressure is never as great as in a spinal animal. The normal blood pressure is higher, the cardio-inhibitor mechanism prevents any large rise, the anaesthetic depresses the heart's response to most drugs, and, therefore, a large rise of blood pressure is impossible. Moreover, large doses cannot be given in this condition since the respiratory centre, already somewhat depressed by the anaesthetic, may be paralysed by comparatively small doses of the base. Five milligrams may cause respiratory arrest in an anaesthetised animal, while an intact cat, as shown above, survived 20 mgm. The difference can only be due to the anaesthetic depression of the respiratory centre.

The rise of blood pressure is due to vaso-constriction and increased cardiac activity. Fig. 1 shows a tracing of the isolated heart of a rabbit, together with a drop record of the coronary outflow; between the arrows 3 mgm. of indolethylamine were injected into the perfusion cannula. It will be observed that there is a considerable rise in the tone of the heart muscle, accompanied by a greatly increased rate of heart beat; a count of the heart beat shows that the rate is increased by one-half (from 18 to 27 in equal time intervals). The coronary outflow is quicker. It is probable that the last-mentioned feature of the tracing is due to the increased rate of heart beat, and not to an actual dilatation of the coronary vessels. The heart beat exerts such a profound influence on the coronary circulation that the increase seen in this tracing could easily be explained in this way. Moreover, as will be seen later, all forms of plain muscle, elsewhere in the body, which respond to the new base, show motor effects irrespective of innervation, and it is improbable that the coronary vessels behave in an exceptional manner. The vaso-constriction may be observed on inspection of the viscera after intravenous administration, and also after local application of a 1 in 1000 solution to a highly vascular surface. The effect is not nearly so striking as that produced by adrenine. A diminution of viscus volume is not readily demonstrated in oncometer experiments. As a rule, the first effect is constriction, but this is often followed by a secondary dilatation. This diphasic response is probably due to the vessels in the plethysmograph giving an abnormal response. The exposure, cooling, and manipulation necessary in the introduction of a viscus into a plethysmograph frequently destroys the sensitiveness of the preparation. The initial constriction is the true result, and the

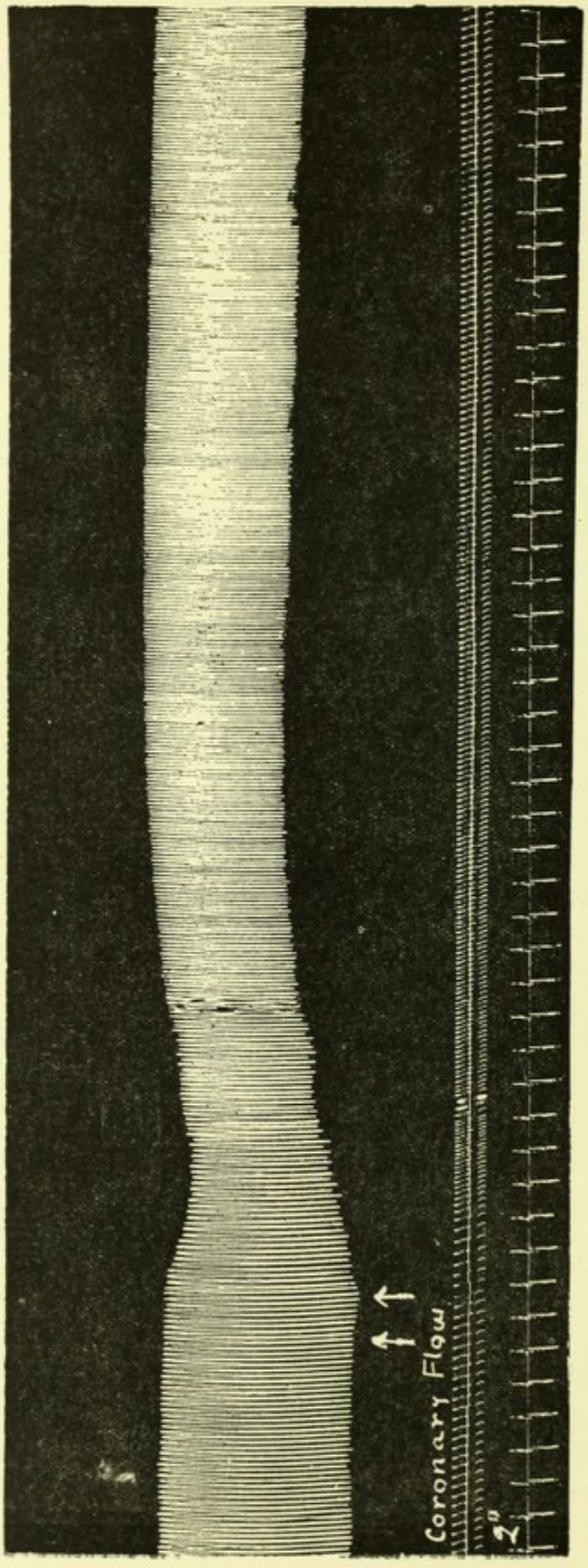

FIG. I.—Isolated heart, rabbit, Locke Langendorff. Between arrows 3 mgm. indolethylamine injected into perfusion cannula.

dilatation following is due to the large rise of blood-pressure dilating arterioles which, though stimulated to constrict, owing to abnormal conditions are unable to do so against a large rise of blood pressure. Occasionally a pure diminution in volume is observed. There can be no doubt that considerable vaso-constriction does occur, but the exact method by which this vaso-constriction is brought about is not so certain. The vaso-constriction is undoubtedly due in part to a peripheral effect of the amine upon the plain muscle of the arterioles, because after large paralytic doses of nicotine or curare have been given to a spinal cat, a rise of blood-pressure is still obtainable with 3 or 4 mgm. indolethylamine. This rise is, however, diminished by about half by the administration of nicotine. In this experiment the ganglion cells and the paths from cord to periphery are paralysed completely. It is possible that the diminution in response to the new base brought about by paralytic dose of nicotine is an expression of the cutting-out of vaso-constrictor impulses of central origin. A similar effect is observed after paralytic doses of ergotoxine. In cats which had received ergotoxine in sufficient quantity to reverse the adrenine response (Dale[1]) a pressor effect is still elicited by indolethylamine, but this pressor effect is not nearly so striking as that observed previous to the administration of ergotoxine. If one could regard nicotine and ergotoxine as having a selective paralytic action on the nervous structures, a central factor in the pressor effect induced by indolethylamine would be proved. Unfortunately nicotine and ergotoxine have a decided effect on plain muscle itself. As far as these experiments are trustworthy they suggest a central factor of some importance. This suggestion is borne out by the following further evidence. In a spinal cat preparation, the rise of blood pressure brought about by the intravenous administration of 2 mgm. indolethylamine was recorded. The cord was then completely destroyed, and after a short interval the effect of the same dose of indolethylamine was recorded once more. The effect of the second dose was about half the first. The evidence of a general stimulant effect on the cord, as illustrated by the generalised muscular spasms, has already been described. The balance of evidence is decidedly in favour of a mixed origin of the vaso-constriction: (1) central from vasomotor centres in the cord, and (2) peripheral upon the plain muscle of the arterioles.

One or two features of interest are met with in the responses of the

1. Dale, *Journ. of Phys.*, XXXIV, p. 163, 1906, and *Bio-Chem. Journ.*, II, p. 240, 1907.

several organs of the body containing plain muscle; of these the uterus and the eye are the most interesting.

The Uterus. Fig. 2 shows the typical action of indolethylamine upon the virgin cat's uterus *in situ*, and upon the blood pressure. Just after the rise in blood pressure has started to develop, the uterus

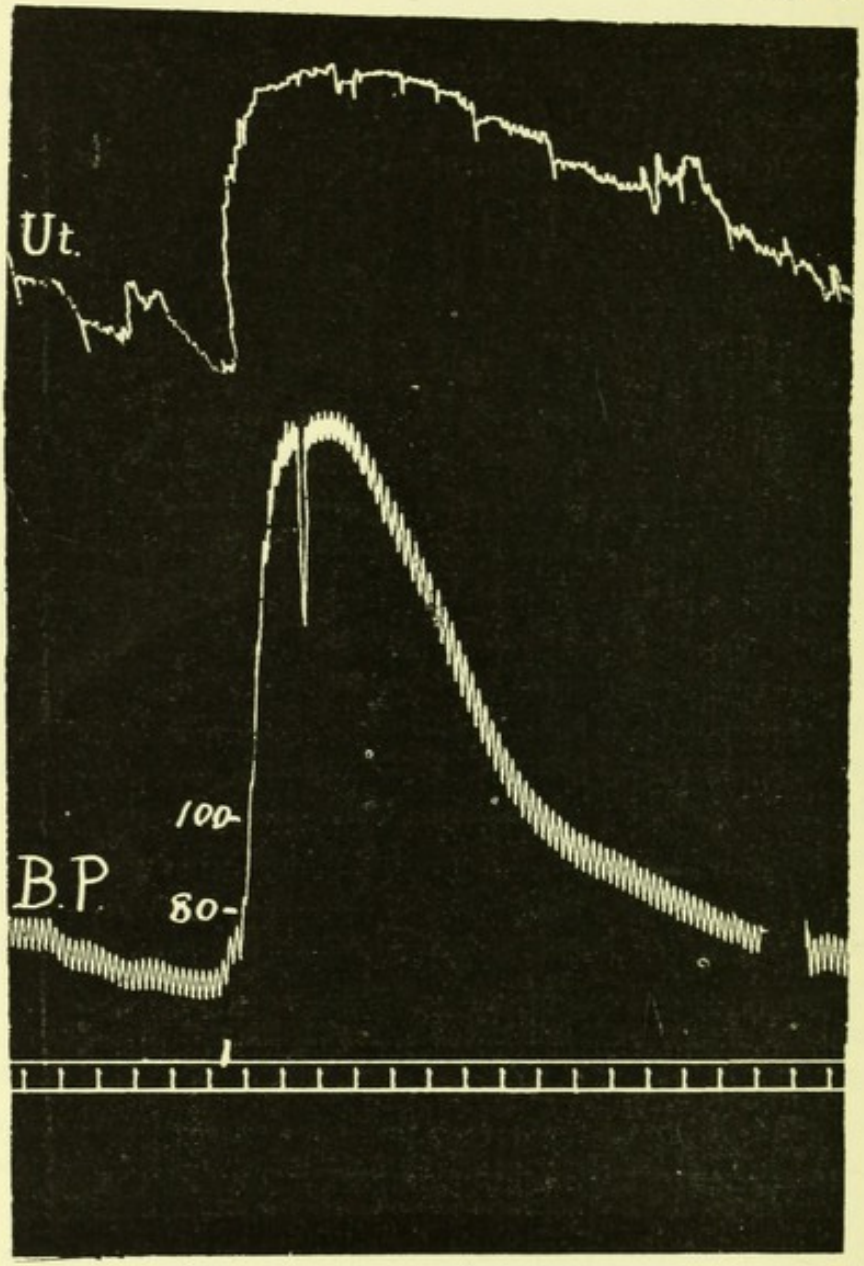

Fig. II.—Spinal cat. Virgin. Effect of 2 mgm. indolethylamine. Uterine Contractions. Blood Pressure.

commences to relax. This effect is not abolished by section of the hypogastrics. This combination of effects is suggestive of an adrenine type of action. But this is not borne out by further experiment, for if the virgin cat's uterus be isolated, suspended in Ringer solution, and its movements recorded graphically, the opposite result is obtained. The

new amine always produces motor responses from a virgin cat's uterus in this condition. Fig. 3: In the pregnant cat a well-marked motor response is obtained on administration of indolethylamine. Fig. 4: The rabbit's uterus and the guinea-pig's do not respond well to the new base. In two rabbits, where adrenine and other drugs produced well-marked contractions of the uterus, indolethylamine was without action. This difference in action on the virgin cat's uterus *in situ* and when isolated, is one that is not readily explained. If it were demonstrable that the new amine had an action resembling that of nicotine, the explanation is obvious. The result in any given experiment would be the sum of two variables: (1) stimulant action on plain muscle, hence motor response in the isolated organ; (2) stimulation of sympathetic ganglion cells or peripheral neurone supplying the uterus. The dominant supply in the case of the virgin cat is inhibitor, hence relaxation *in situ*. The dominant supply in the pregnant cat is motor, and thus the nervous influence aids the muscular one. Experiments with a view to demonstrating a nicotine-like action of indolethylamine on the superior cervical ganglion or on the splanchnic system all failed. It is quite possible that this substance has an action on the peripheral neurone supplying the uterus as well as on the muscle of the organ, but not on the peripheral sympathetic neurones elsewhere. Very similar effects have been described by myself with a number of other substances (hydrastinine, cotarnine, and 6:7-dimethoxy-2-methyl-3:4-dihydro isoquinolinium chloride), and the same explanation was tendered. There is some peripheral structure which does not survive excision, and determines the action of many substances upon the cat's uterus *in situ*. From the manner in which the response varies with the dominant nerve supply to the uterus, and the close parallelism which exists between the action of these substances and that of nicotine on this organ, it is suggested that the unknown peripheral structure is nervous, probably the peripheral neurone. It is, unfortunately, impossible to submit the problem to the crucial experiment of excision of these ganglion cells, owing to their scattered peripheral distribution.

The Iris. Upon the plain muscle of the iris indolethylamine has a well-marked effect in doses of 10 to 20 mgm. If a dose of this size be given intravenously to a cat with pithed brain, the pupil becomes constricted to a fine slit (fig. 5). This contracted pupil persists for several minutes. Smaller doses produce smaller effects which are less lasting. A further dose of 20 mgm. produces a dilatation of the pupil, and the elongated oval opening tends to become circular. This dilatation

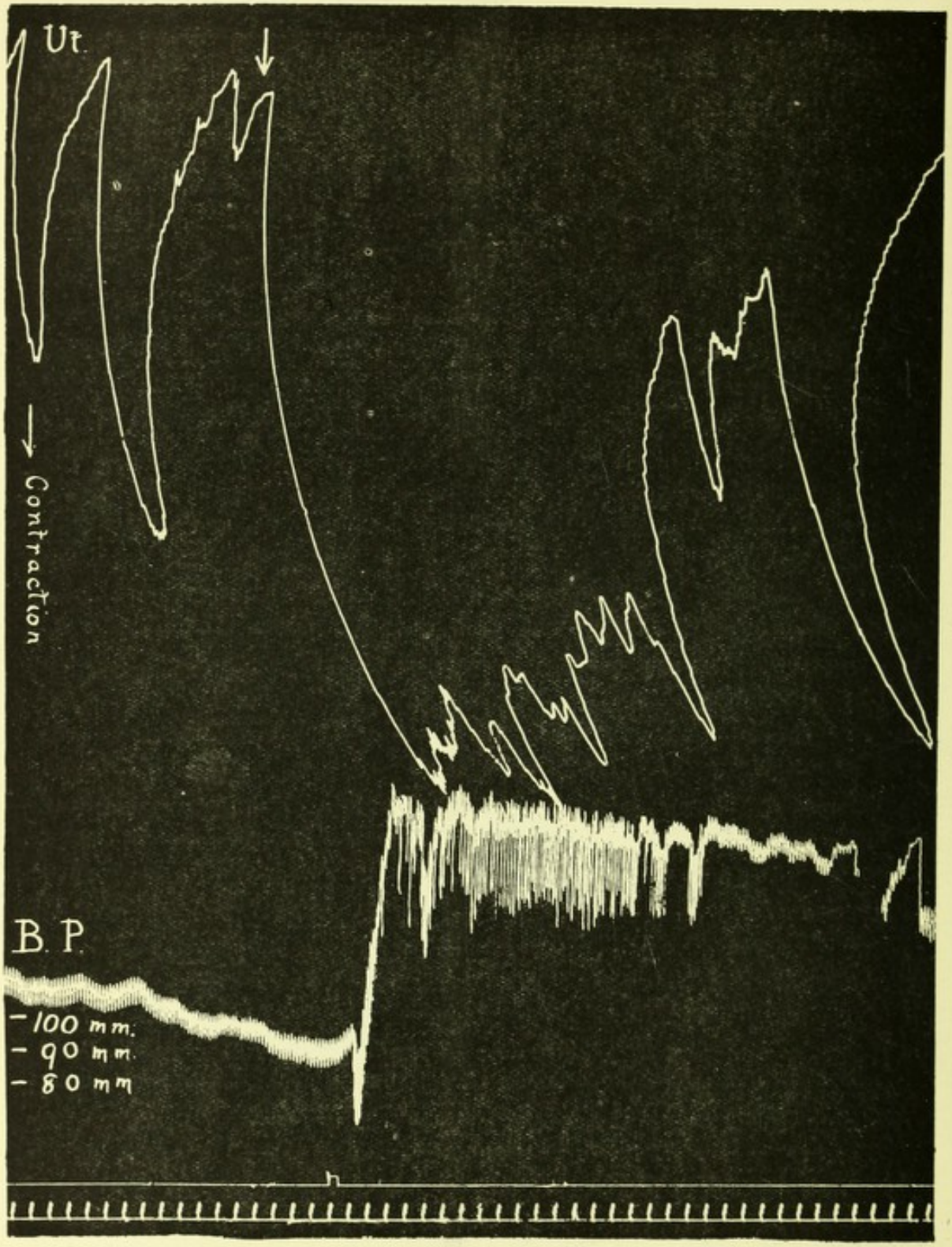

FIG. III.—Isolated uterus. Virgin cat. Effect of 10 γ gm. indolethylamine in 250 c.c. Ringer's solution.

gradually gives way again to profound constriction, and once more a thin black slit is all that is visible. Stimulation of the cervical sympathetic can still produce some dilatation at this stage. Full doses of atropine do not abolish the slit-like pupil or prevent its appearance. It must, therefore, be regarded as of direct muscular origin. The tendency to form a circular pupil after the second injection indicates a simultaneous motor effect upon both sphincter and dilator muscles, the sphincter muscle being the more powerful, ultimately overcomes the dilator muscle and produces the slit-like pupil. The effect is not observable in cats anaesthetised with chloroform or ether, nor in an intact cat which received 100 mgm.

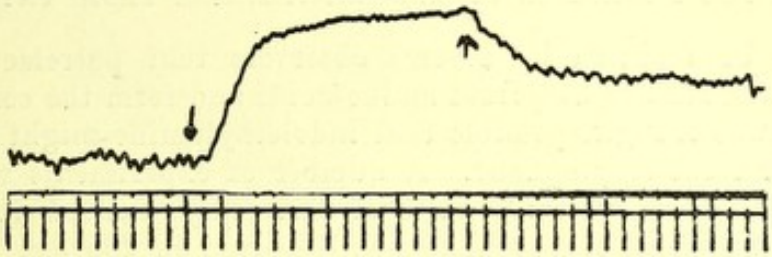

FIG. IV.—Cat. Ether. Pregnant. Effect of 10 mgm. indolethylamine. Uterine Contractions. Blood Pressure.

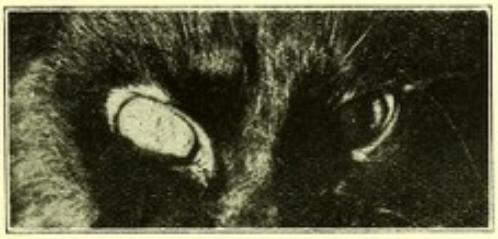

FIG. V.—Cat. Pithed brain. Circulation to left eye impaired by cannula in left common carotid. Effect of 20 mgm. indolethylamine on pupil of right and left.

hypodermically. It can only be produced by intravenous administration to an intact animal or one which is anatomically anaesthetised. Instillation, like hypodermic administration, is without effect.

Other plain muscle. The plain muscle of the intestine is mildly stimulated by indolethylamine. The effect is better shown in the isolated organ, but even in this condition the effect of 20 mgm. of the base in 250 c.c. Ringer solution is very small. The retractor penis of the dog also gives weak motor responses to the amine when isolated from the body. The plain muscle of the bladder is thrown into contraction on administration of 2 or 4 mgm. of indolethylamine; and a bladder, which before administration of the base was quiescent, may develop a slight rhythm. The amount of contraction of the bladder volume under the influence of indolethylamine is increased on destruction of the cord.

The salivation observed in cats receiving hypodermic or intravenous

doses of the new base must be central in origin, for no evidence of salivary secretion could be obtained in the anaesthetised animal. The pancreatic secretion in the dog is unaffected by indolethylamine. Ten milligrams of indolethylamine were given intravenously to an anaesthetised cat in which the urinary secretion was being recorded. A marked slowing of the urine flow was observed during the rise of blood pressure, which, however, soon passed off. The effect is in all probability the expression of a transient constriction of the arterioles of the kidney. Experiments in conjunction with Mr. A. J. Ewins, are in progress with regard to the metabolism of the new base.

Note on the Formation of Indolethylamine from Tryptophane

It has been shown by several observers that putrefactive micro-organisms will remove CO_2 from amino-acids and form the corresponding amine. It was thought possible that indolethylamine might be made in this manner from tryptophane. A number of experiments were carried out with different mixtures of bacteria: only one of them proved successful. 0·5 gram tryptophane was dissolved in 250 c.c. of a simple culture medium.[1] This was then infected from a putrid pancreas subculture which had been shown to be capable of forming β-iminazolyl-ethylamine from histidine and *p*.hydroxyphenylethylamine from tyrosine. After one fortnight's incubation the mixture was found to produce a good rise of blood pressure, and indolethylamine could be isolated from it. The mixture was boiled with charcoal and filtered. It was then evaporated to about 100 c.c. and excess of picric acid added. On cooling, the highly insoluble indolethylamine picrate separated out as a deep orange-red crystalline precipitate. The crude product was then recrystallised from alcohol and again from aqueous acetone, when crystalline form, colour reactions, melting point, and physiological action were found to be identical with those of the synthetic product. The yield from the one experiment which went in the desired direction was poor, about 140 mgm. of pure picrate being obtained from 0·5 gram tryptophane.

Summary

(I) Indolethylamine produces a transient stimulant effect upon the central nervous system, causing clonic and tonic convulsions, tremors of limbs, and vaso-constriction.

(II) It has a direct stimulant action on plain muscle, which is most marked in the arterioles, the iris, and the uterus.

(III) The formation of indolethylamine from tryptophane by bacterial action is described.

1. Peptone 2 grm., dextrose 8 grm., trace sodium phosphate, trace magnesium sulphate, precipitated calcium carbonate 5 grm., and tap water to the litre.