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(*From the Wellcome Physiological Research Laboratories.*)

CONTENTS.

Introductory. The elucidation of the structure of the active principle of the supra-renal medulla by the work of Abel[1], v. Fürth[2], Takamine[3], Aldrich[4], Pauly[5], and Jowett[6], and its synthesis by Stolz[7] and by Dakin[8], almost simultaneously, led to the physiological investigation of substances nearly related to it in chemical structure. Loewi and Meyer[9], working with Stolz's preparations, investigated a number of ketones of the general formula $(OH)_2C_6H_3 . CO . CH_2NR_1R_2$ and the corresponding secondary alcohols $(OH)_2C_6H_3 . CHOH . CH_2NR_1R_2$, obtained by reduction of the ketones, among these reduction products

[1] *Johns Hopkins Hosp. Bull.* VIII. p. 151. 1897. *Zeitschr. f. physiol. Chem.* XXVIII. p. 318. 1899.

[2] *Zeitschr. f. Physiol. Chem.* XXIX. p. 105. 1900. *Hofmeister's Beitr.* I. p. 243. 1901.

[3] *Amer. Journ. of Pharmacy*, LXXIII. p. 523. 1901.

[4] *Journ. Amer. Chem. Soc.* XXVII. p. 1074. 1905.

[5] *Ber. d. deutsch. chem. Ges.* XXXVI. p. 2944. 1903 and XXXVII. p. 1388. 1904.

[6] *Journ. Chem. Soc.* LXXXV. p. 192. 1904.

[7] *Ber. d. deutsch. chem. Ges.* XXXVII. p. 4149. 1904.

[8] *Proc. Roy. Soc.* LXXVI. B. p. 491. 1905.

[9] *Arch. f. exp. Path. u. Pharm.* LIII. p. 213. 1905.

being synthetic dl. adrenine. Dakin examined similar series[1] and found, as Loewi and Meyer had done, that in most cases the reduction of the ketones to the secondary alcohol greatly intensified the adrenine-like action which most of the bases possessed in some degree: but in the case of several of the ketones examined by Dakin, in which the amino-group was substituted by more complicated radicles, no such increase of activity on reduction occurred.

All the active bases examined by these and other observers have been catechol derivatives. Dakin, indeed, concluded that the catechol nucleus was the essentially active group in the adrenine molecule, basing this view on the observation that catechol itself causes a rise of blood-pressure when injected intravenously, while the base methyl-amino-ethanol, $CH_2(OH)CH_2.NHCH_3$, which may be regarded as the detached side-chain of the adrenine molecule, has no such action. The same conception has been adopted by Schultz. Recently, however, we found that certain amines produced by putrefaction, none of them possessing a catechol nucleus, have an action very similar to that of adrenine. On the other hand we shall give evidence that the rise of blood-pressure produced by catechol is due to an action of an entirely different type. It became clear, therefore, that the conception put forward by Dakin, and adopted by others, was inadequate, and it became of interest to trace the variations in the intensity of the specific action through a series of compounds intermediate between the putrefactive animes—in particular *p.* hydroxyphenylethylamine—and adrenine itself. This was the main object of our investigation, but incidentally the changes of physiological activity accompanying other changes of structure have been studied.

G. Barger has throughout been responsible for the chemical side of the investigation, and the new compounds dealt with, except where other sources are acknowledged, have been prepared by him or Mr A. J. Ewins. Only brief indications of the processes of preparation are given here, details being reserved for publication elsewhere. For the physiological experiments H. H. Dale is alone responsible.

Experimental Methods. The action with which we are concerned is the immediate peripheral effect on involuntary muscle and gland cells produced by intravenous injection. This, in the case of adrenine itself, has been shown (Langley[2], Brodie and Dixon[3], Elliott[4]) to

[1] *Proc. Roy. Soc.* LXXVI. B. p. 498. 1905.
[2] This *Journal*, XXVII. p. 237. 1901.
[3] *Ibid.* XXX. p. 476. 1904.
[4] *Ibid.* XXXII. p. 401. 1905.

simulate with considerable precision the effects of stimulating nerves of the true sympathetic system, being limited to muscle-fibres and gland-cells innervated by this system and producing in them responses which are, for the most part, in the same direction, whether of augmentation or inhibition, as those which the sympathetic nerve-impulses produce. We are dealing with a range of compounds which thus simulate the effects of sympathetic nerves not only with varying intensity but with varying precision. In some cases the points of chief interest in the action of a compound are those in which it differs from the action of adrenine. A term at once wider and more descriptive than "adrenine-like" seems needed to indicate the type of action common to these bases. We propose to call it "sympathomimetic," a term which indicates the relation of the action to innervation by the sympathetic system, without involving any theoretical preconception as to the meaning of that relation or the precise mechanism of the action.

It is clear that the production of a rise of arterial blood-pressure, though a convenient quantitative index of an action referred to this type on other grounds, does not in itself afford adequate ground for such reference. Some or all of the other effects of sympathetic nerves must be observed, and any considerable reproduction of the effects of autonomic nerves other than sympathetic must be excluded, before the action can properly be classified as sympathomimetic. Dilatation of the pupil and contraction of the plain muscle in the orbit, a flow of saliva and tears not readily abolished by atropine, inhibition of the tone and rhythm of the muscular walls of the mammalian intestine and of the cat's urinary bladder, are familiar and easily observed sympathetic effects. Particularly valuable as an index of this type of action is the response of the cat's uterus. This organ is innervated by sympathetic nerves only, and its response to them and to adrenine changes with its functional condition, being in the main motor during pregnancy and inhibitor in its absence. Exceptions to this rule are found occasionally, but it is easy to obtain a cat's uterus of which the activity is simply inhibited by adrenine—the virgin organ is invariably so in our experience—and it can conveniently be treated as an isolated organ, suspended in warm, oxygenated Ringer's solution. Under these conditions the peripherally placed ganglion-cells rapidly lose their responsiveness, so that nicotine and substances which act like it cause contraction of the uterus as an isolated organ, even though they inhibit it, by stimulating sympathetic ganglia, when they are injected into the circulation of the

living animal. We believe that the association of a pressor action, due to arterial constriction and cardio-acceleration, when the substance is injected into the whole animal, with inhibition of the tone and rhythm of the isolated non-pregnant uterus of the cat, is almost sufficient evidence to warrant the attribution to a substance of an action of the sympathomimetic type. We have, however, in all cases confirmed the diagnosis by observing several of the other sympathetic effects above mentioned. In the case of homologous series and closely related compounds we have usually performed this analytical identification of the action completely in the case of one typical member only, being content in the case of others to observe that the action was of the same general type. It must be understood, however, unless the contrary is specifically stated, that the action of any substance spoken of as sympathomimetic has been proved to be so.

As a general quantitative index of the activity of a substance, of which the type of action has been identified as sympathomimetic, we have adopted the effect on arterial blood-pressure. This has obvious advantages in the ease with which it can be observed and measured, and its adoption makes our results to some extent comparable with those of other observers who have used it for this purpose. We shall show, however, that this method affords only a broad and rough indication of the order of activity of the different bases. In the case of closely related bases the relative values obtained by different observers differ somewhat widely. The animals used, the mode of anæsthesia employed, and probably less obvious differences of technique, as well as individual variations of response in animals of the same species, all affect the results. We shall show, further, that the indications of relative activities obtained by the blood-pressure method by no means hold good for the action on other organs innervated by sympathetic nerves. The effect on the blood-pressure is, indeed, so complex that the determination of the relative efficiency of some closely related bases in its production has not much more than a conventional value, until the results are analysed in the light of observations on other sympathomimetic effects. For the comparison of pressor activities we have used decerebrate cats almost exclusively. When other animals were used, or the brain not destroyed, the fact is stated and the anæsthetic mentioned. In most of our experiments the spinal cord was cut at the level of the axis vertebra, the neural arch of the vertebra being removed. Up to this point complete anæsthesia was maintained by ether and chloroform. The brain was then

completely destroyed, bleeding being stopped by modelling clay and by plugging the foramen magnum with a cork. Artificial respiration was then applied. Recently in several experiments the animals have been decapitated under anæsthesia according to the method described by Sherrington[1]. By either method a preparation is obtained which for hours gives a low steady blood-pressure, free from the irregularities due to variations in activity of the respiratory or vaso-motor centre, and which is therefore particularly well suited to the comparison of the effects of pressor substance. In the case of bases most nearly related to adrenine a quantitative comparison of activities can be made with considerable accuracy, since such bases will give practically identical effects with a succession of equal injections. As described by Elliott[2], for estimating the relative strengths of solutions of adrenine, and by Cushny[3], and by Schultz[4] for comparing the activities of different bases, the activities can be expressed as the reciprocals of the doses required to produce equal submaximal rises of pressure, care being taken to make the injections equal in volume and uniform in rate. We made injections always by the femoral vein and recorded the pressure in the carotid artery by the ordinary mercurial manometer. The recording drum was moved back by hand between injections so as to cause overlapping of the curves and facilitate comparison.

As the structure of the amines examined becomes increasingly remote from that of adrenine the accuracy of the comparison becomes continually less. For example, successive equal doses of an amine of the primary fatty series usually produce rapidly diminishing effects. In such a case we have been content to arrange the members of the series in order of activity, testing each in comparison with the next lower and higher in the series. To guard against error due to diminishing response to successive injections we have always given a series of alternating doses, *B* being judged more active than *A* only if, in a series of equal injections, *ABA* or *BAB*, *B* always produces a rise of pressure higher than that produced by the equal dose of *A*. By equal injections, in such a case, must be understood equal volumes of equimolecular solutions, the volumes being so chosen as to give submaximal rises of pressure.

For experiments in isolated organs, suspended in warm oxygenated Ringer's solution, we used an apparatus, which we shall describe in detail in another connexion, which enables the Ringer's solution to be

[1] This *Journal*, xxxviii. p. 375. 1909.
[2] *loc. cit.*
[3] This *Journal*, xxxvii. p. 130. 1908.
[4] *Hygienic Laboratory Bulletin*, No. 55. Washington. 1909.

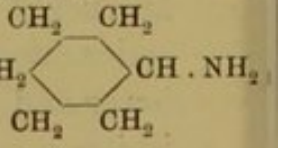
changed without disturbing the continuity of the record. The action of a series of amines could thus be tested on a single isolated organ, such as the horn of a cat's uterus, or the retractor penis of a dog or goat.

A. Aliphatic amines.

Some of our results with this series were outlined in a preliminary note[1]. One of them, isoamylamine, was identified by Barger and Walpole[2] as a pressor constituent of putrid meat: it is probably the "urohypertensine" of Abelous and Bardier[3]: and Barger and Dale[4] found traces of it in ergot. Its action has been described in detail by Dale and Dixon[5]. It is only necessary here to recall that it was shown to have an action definitely of the sympathomimetic type, which, however, differed from that of adrenine, not only in being relatively weak, but in reproducing the motor more powerfully than the inhibitor effects of true sympathetic nerves and in being less strictly limited to structures innervated by that system.

The following members of this series have been tested :—

Primary amines.

(1) Methylamine $CH_3 . NH_2$.
(2) Ethylamine $C_2H_5 . NH_2$.
(3) *iso.* Propylamine $(CH_3)_2 . CH . NH_2$.
(4) *n.* Propylamine $C_2H_5 . CH_2 . NH_2$.
(5) *iso.* Butylamine $(CH_3)_2 . CH . CH_2 . NH_2$.
(6) *n.* Butylamine $C_2H_5 . CH_2 . CH_2 . NH_2$.
(7) *iso.* Amylamine $(CH_3)_2 . CH . CH_2 . CH_2 . NH_2$.
(8) *n.* Amylamine $C_2H_5 . CH_2 . CH_2 . CH_2 . NH_2$.
(9) *n.* Hexylamine $C_6H_{13} . NH_2$.
(10) *n.* Heptylamine $C_7H_{15}NH_2$.
(11) *n.* Octylamime $C_8H_{17}NH_2$.
(12) *n.* Nonylamine $C_9H_{19}NH_2$.
(13) *n.* Endekylamine $C_{11}H_{23}NH_2$.
(14) *n.* Tridekylamine $C_{13}H_{27}NH_2$.
(15) Cyclo-hexylamine 

Secondary, tertiary amines etc.

(16) Diethylamine $(C_2H_5)_2 NH$.
(17) Methylisoamylamine $C_5H_{11} . NH . CH_3$.
(18) Di-isoamylamine $(C_5H_{11})_2 . NH$.
(19) Trimethylamine $(CH_3)_3 N$.
(20) Tetraethylammonium iodide $(C_2H_5)_4 NI$.

Diamine.

(21) Pentamethylene-diamine (cadaverine) $NH_2 . C_5H_{10} . NH_2$.

[1] This *Journal*, xxxviii. p. xxii. (*Proc. Phys. Soc.*) 1909.
[2] This *Journal*, xxxviii. p. 343. 1909.
[3] *Journ. de Physiol.* p. 34. 1909.
[4] This *Journal*, xxxviii. p. lxxvii. (*Proc. Phys. Soc.*) 1909.
[5] This *Journal*, xxxix. p. 25. 1909.

Most of the above substances were obtained from well-known commercial sources: where necessary they were purified by recrystallising their salts. No. (11) was prepared from *n.* octyliodide and ammonia; Nos. (12)—(14) by Jefferies' method from the amide of the next higher acid; No. (15) by electrolytic reduction of cyclo-hexanone-oxime.

All were tested in $\frac{N}{10}$ solutions as hydrochlorides. The most active members of the group are found among the primary amines. In the doses which were used—1 to 2 c.c. of the $\frac{N}{10}$ solution—the activity did not extend in any significant degree to members lower in the series than *n.* butylamine, which in activity comes immediately below *iso.* amylamine, the type-member, for us, of the series. *Iso.* butylamine had practically no pressor effect in the dosage indicated, though doubtless, if injected in larger volume or stronger solution, it, and even lower members of the series, could be shown to possess a perceptible pressor effect. Under such conditions mere volume-effects complicate the record, and we only mention the probability of such activity in order to avoid the suggestion that a new characteristic suddenly appears in the series.

The relative weakness of the *iso.* as compared with the normal bases is shown by the amylamines as well as the butylamines. *Iso.* amylamine

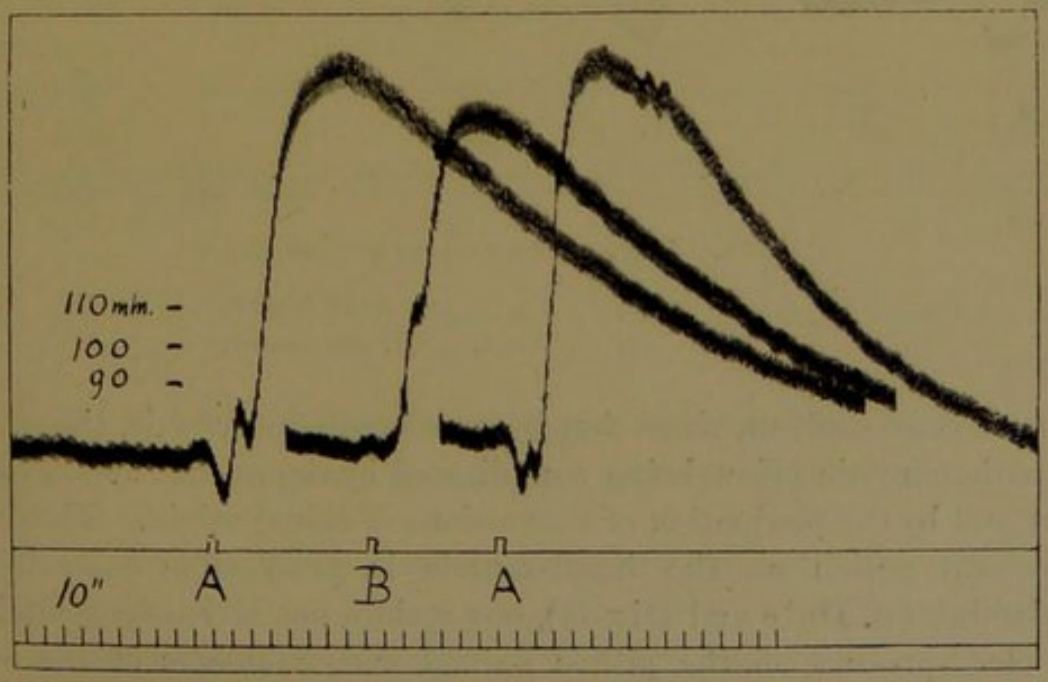


Fig. 1. [Figs. 1 to 4, 6, 8 to 10, 14 and 15 show carotid blood-pressure. Injections intravenous. Bases as hydrochlorides.]

At *A*, *A*, 1 c.c. $\frac{N}{10}$ *n.* amylamine.

B, ,, ,, *iso.* amylamine.

is several times as active as *n.* butylamine: *n.* amylamine is again distinctly, though not very greatly, more active than *iso.* amylamine (Fig. 1). The *iso.* amylamine in question is the base $(CH_3)_2CH_2CH_2CH_2NH_2$ which occurs as a putrefaction product of leucine. The other isomeric amylamines were not available for examination: they would probably have been less active, since, in this series, the activity seems to increase with the length of the straight carbon-chain up to six carbon atoms.

Of the bases above amylamine only the normal (straight-chain) representatives were available. Normal hexylamine is the most active of the normal series. Normal heptylamine is slightly, but distinctly less active (Fig. 2). With the higher members of the series comparison

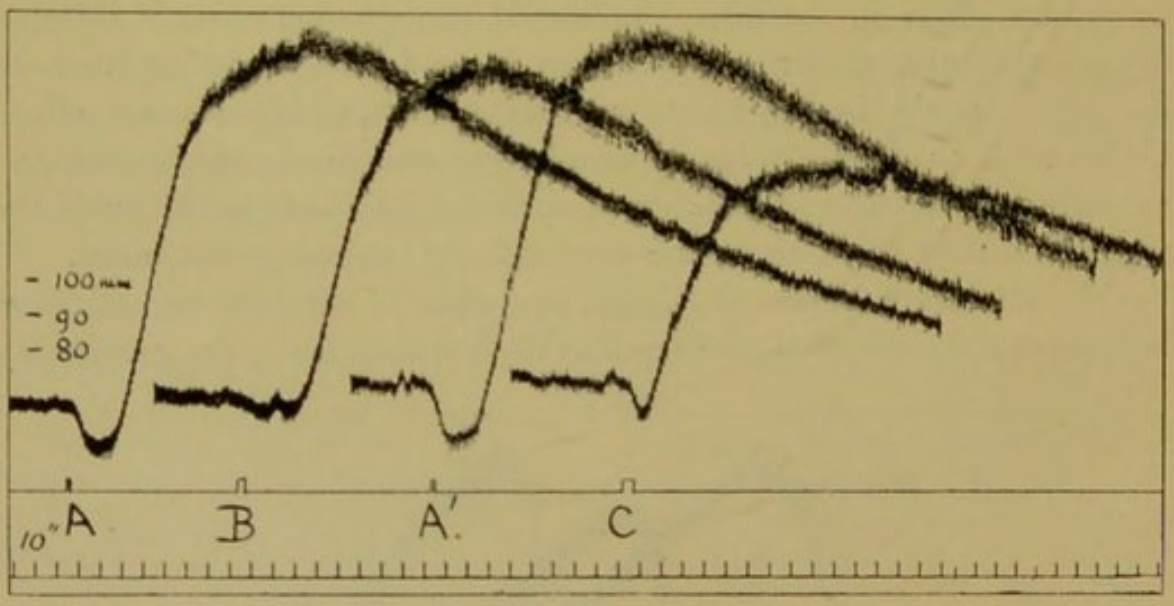


Fig. 2. At *A*, *A'*, 1 c.c. $\frac{N}{10}$ *n.* hexylamine.
B, ,, ,, *n.* heptylamine.
C, 2 c.c. ,, *iso.* amylamine.

becomes more difficult, since they become increasingly toxic, the specific sympathomimetic effect being complicated by depressant action on the heart and by the production of convulsions of spinal origin. The direct, depressant action on the heart-muscle is perceptible even in *iso.* amylamine (cf. Dale and Dixon), but it does not seriously complicate the blood-pressure of the pithed animal with members of the series lower than octylamine. One dose of these higher amines greatly depresses the effect of succeeding doses, so that injections in the order *ABA* are no longer useful for comparison. Octylamine is definitely less active than heptylamine, but beyond that comparison

is impossible, since whichever of the higher bases is injected first produces the bigger effect. It may simply be stated that the pressor action is still distinct in tridekylamine, though the sympathomimetic nature of the pressor effect of these higher bases is merely a probable inference from analogy. Pentadekylamine was prepared, but its hydrochloride is almost insoluble in water and could not be tested. Cyclo-hexylamine (hexahydro-aniline) has a pressor action quantitatively very similar to that of normal hexylamine, though somewhat slower and more prolonged. Sufficient of the base was not available, however, for a detailed examination of its action, and the possibility is open that this is not of the sympathomimetic type.

Of the secondary amines diethylamine was found to be inactive, as might be expected from the negligible activity of *iso.* butylamine. The only other secondary amines examined were those with the *iso.* amyl radicle. Methyl-*iso.* amylamine possesses the action, but is considerably weaker than *iso.* amylamine, being roughly one-half as active. Di-*iso.* amylamine has very little of the action.

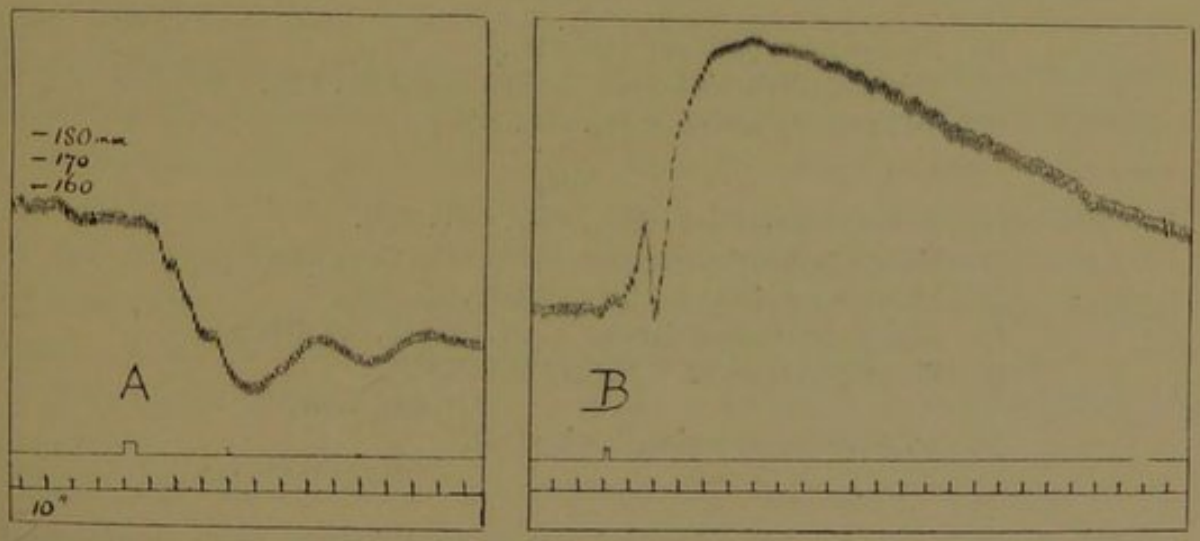


Fig. 3. At *A*, 1 c.c. $\frac{N}{10}$ cadaverine ($NH_2 . CH_2 . CH_2 . CH_2 . CH_2 . CH_2 . NH_2$).
B, ,, ,, *n.* amylamine ($CH_3 . CH_2 . CH_2 . CH_2 . CH_2 . NH_2$).

Trimethylamine was examined chiefly because a pressor action has been attributed to it by Abelous and Bardier[1]. They were working with a rather higher scale of dosage (1 centigram per kilogram in the dog, as compared with 6—12 milligrams for a cat of 2—4 kilograms, as employed by us) and with an animal with intact vaso-motor centre and normal respiration. Abelous and Bardier find that trimethylamine

[1] *C. R. Soc. de Biol.* LXVI. p. 347. 1909.

is only $\frac{1}{200}$ as active as urohypertensine, which they regard as identical with the base obtained by them from putrid meat, and identified by Barger and Walpole as *iso.* amylamine. We should ignore an action $\frac{1}{200}$ as powerful as that of *iso.* amylamine, and from our point of view trimethylamine is inactive. Of quarternary aliphatic ammonium bases we examined only tetra-ethylammonium iodide. The toxicity of this base is well known, but we found it inactive in the direction under investigation.

Of diamines only pentamethylene-diamine (cadaverine) was tested, which may be regarded as normal amylamine, with one hydrogen atom of the terminal methyl group substituted by a second amino-radicle. Fig. 3 shows that the action is thereby entirely changed, the pressor action of amylamine being replaced, in cadaverine, by a depressor action, the nature of which has not been further analysed.

B. Aromatic amines without a phenolic hydroxyl.

The following amines were examined :—

(1) Phenylamine (aniline) $C_6H_5NH_2$.

(2) Phenylmethylamine (benzylamine) $C_6H_5CH_2.NH_2$.

(3) α-Phenylethylamine $C_6H_5.\underset{\displaystyle CH_3}{\underset{|}{CH}}.NH_2$.

(4) β-Phenylethylamine $C_6H_5.CH_2.CH_2.NH_2$.

(5) Methyl β-phenylethylamine $C_6H_5.CH_2.CH_2.NHCH_3$.

(6) Phenylethanolamine $C_6H_5.CHOH.CH_2NH_2$.

(7) Methylphenylethanolamine $C_6H_5.CHOH.CH_2NHCH_3$.

(8) Phenylpropylamine $C_6H_5CH_2CH_2CH_2NH_2$

(9) *ac.* β-tetrahydronaphthylamine $C_6H_4\begin{cases}CH_2—CH_2\\ \quad\quad\quad|\\ CH_2—CHNH_2\end{cases}$.

Of these Nos. (1), (2), (4) and (9) were obtained from commercial sources. Nos. (3) and (8) were prepared by reduction of the oximes of acetophenone and cinnamic aldehyde respectively, No. (5) was obtained by reducing the product of condensing phenacetaldehyde with methylamine: Nos. (6) and (7) resulted from the action of ammonia and methylamine respectively on styrene chlorohydrin.

Our starting-point in this series was No. (4), β. phenylethylamine, which was identified in putrid meat as a factor in the pressor action. Its activity is distinctly greater than that of the most active (hexylamine) of the aliphatic amines. The action was not so completely investigated as that of *iso.* amylamine and that of *p.* hydroxyphenylethylamine, but

sufficient evidence was obtained to warrant the conclusion that it is of the sympathomimetic type. In addition to the rise of blood-pressure it produces the characteristic dilatation of the pupil, relaxation of the urinary bladder (in the cat), and inhibition of the tone and rhythm of the virgin cat's uterus. Its activity in all these directions is intermediate between that of the fatty amines and that of the phenolic base *p.* hydroxyphenylethylamine. It may be noted that it stands between them also in respect of approach to adrenine in structure. The carbon-skeleton of β-phenylethylamine is, indeed, identical with that of adrenine.

Taking β-phenylethylamine as our starting-point, we investigated first the effect of varying the length of the side-chain. It was shown that lengthening the carbon chain of the purely aliphatic bases up to a certain point was attended with increase of activity. In the case of the fatty-aromatic base, however, we found that the side-chain of two carbon atoms gave the optimum of activity. Aniline, which has no side-chain, and is therefore a purely aromatic base, had none of the specific action: benzylamine had a mere trace: and α-phenylethylamine, in which, again, only one carbon atom intervenes between the amino-group and the aromatic ring, was also very feebly active. Increasing the side-chain beyond two carbon atoms also resulted in a decline of activity, phenylpropylamine being much less active than phenylethylamine (Fig. 4). The optimum constitution of a fatty-aromatic amine for the production of the sympathomimetic action is, therefore, that which is found in adrenine itself, viz. a benzene ring with a side-chain of two carbon atoms, of which the second bears the amino group.

The modifications necessary to produce adrenine from phenylethylamine are:

(i) The introduction of two phenolic hydroxyls in the 3 : 4 position.

(ii) The introduction of a secondary alcoholic hydroxyl on the first carbon atom of the side-chain.

(iii) Methylation of the amino group.

The effect of introducing phenolic hydroxyls will be dealt with in later sections. Modifications (ii) and (iii), separately and together, produce Nos. (5), (6) and (7) of this series. All these bases are active, but none of them differs noticeably in activity from β-phenylethylamine itself. These modifications, therefore, which, as we shall show later, profoundly alter the activity of the bases possessing phenolic hydroxyls, are practically without effect in the absence of the latter.

The action of β-tetrahydronaphthylamine, which may be regarded as cyclo-hexylamine condensed with a benzene nucleus, has been investigated by Jonescu[1], who showed that in most respects it was sympathomimetic. We have, therefore, been content to compare its

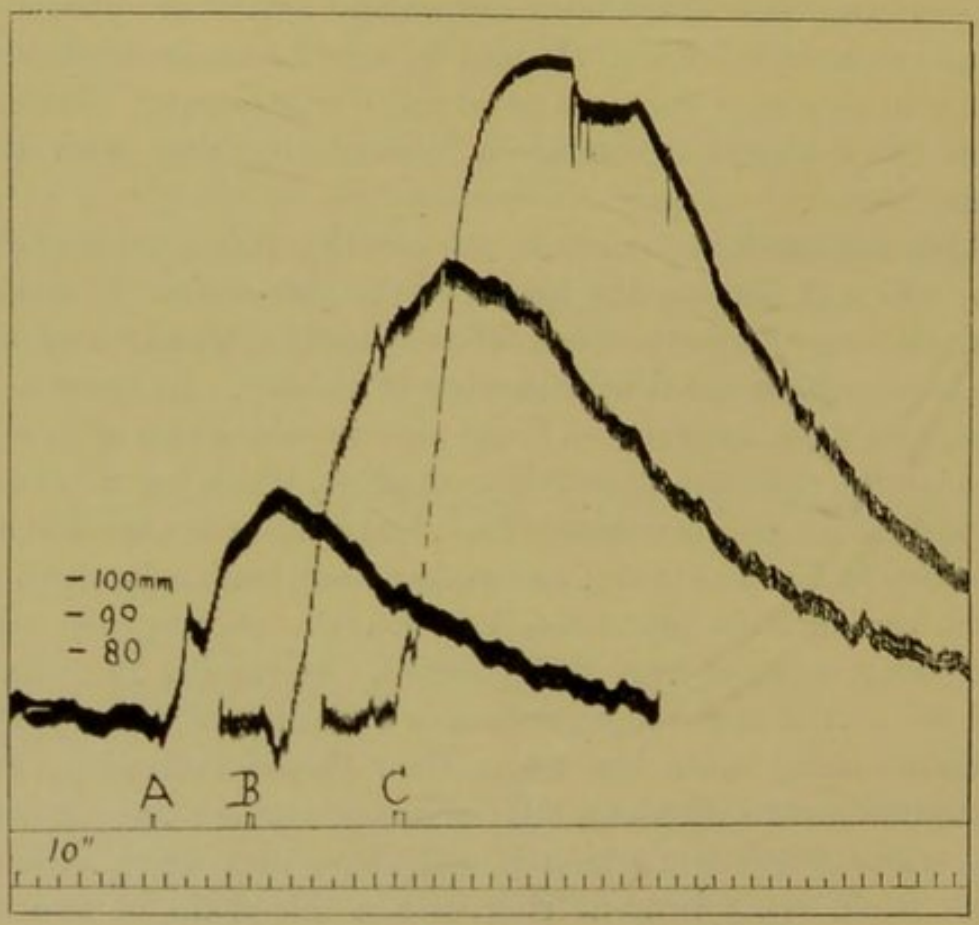


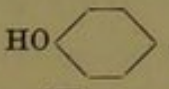
Fig. 4. At *A*, 2 c.c. $\frac{N}{100}$ phenylpropylamine.
B, ,, ,, phenylethylamine.
C, ,, ,, *p.* hydroxyphenylethylamine.

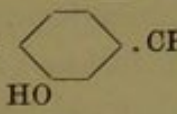
action on the blood-pressure with that of β-phenylethylamine. We found it to be considerably more active than the latter. On the other hand it is distinctly less active than the phenolic base *p.* hydroxyphenylethylamine, which forms our starting-point for the next series.

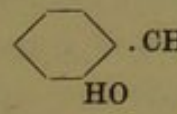
[1] *Arch. f. exp. Path. u. Pharmakol.* LX. p. 345. 1909.

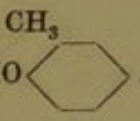
C. Amines with one phenolic hydroxyl.

The following were tested :—

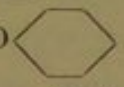
(1) *p.* hydroxyphenylethylamine  $.CH_2.CH_2.NH_2$.

(2) *m.* hydroxyphenylethylamine  $.CH_2.CH_2.NH_2$.

(3) *o.* hydroxyphenylethylamine  $.CH_2.CH_2.NH_2$.

(4) *m.* methyl *p.* hydroxyphenylethylamine  $.CH_2.CH_2.NH_2$.
(*o.* cresylethylamine)

(5) *p.* hydroxyphenylethanolamine  $.CHOH.CH_2.NH_2$.

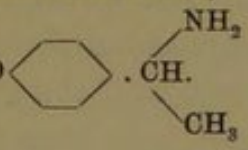
(6) *p.* hydroxy *ω.* amino acetophenone  $.CO.CH_2.NH_2$.

(7) *p.* hydroxyphenylethylmethylamine  $.CH_2.CH_2.NH.CH_3$.

(8) *p.* hydroxyphenylethyl-ethylamine  $.CH_2.CH_2.NH.C_2H_5$.

(9) *p.* hydroxyphenylethyldimethylamine  $.CH_2.CH_2.NH(CH_3)_2$.
(hordenine)

(10) *p.* hydroxyphenylethyltrimethyl ammonium iodide  $CH_2.CH_2.N(CH_3)_3I$.
(hordenine methiodide)

(11) *iso p.* hydroxyphenylethylamine 

(1) was our starting-point in this series, having been identified as a pressor constituent of putrid meat by Barger and Walpole: its action has been described in detail by Dale and Dixon. The base employed for the present investigation was prepared synthetically (cf. Barger, *Journ. Chem. Soc.* xcv. p. 1123. 1909). Nos. (2), (4), (5), (6), (7), (8) and (11) are new substances, and their methods of preparation have been described elsewhere. For Nos. (5) and (6) we are indebted to Mr F. Tutin[1]: for (7) and (8) to Mr G. S. Walpole[2]. A specimen of No. (2) was very kindly sent to us, at our request, by Prof. R. Pschorr

[1] *Journ. Chem. Soc.* xcv. p. 2113. 1909. [2] *Journ. Chem. Soc.* xcvii. p. 941. 1910.

of Berlin. For No. (9), extracted from malt-germs, we are indebted to Mr F. H. Carr. (10) was prepared from (9), and also from (1), by methylation.

Dale and Dixon showed that *β-p.* hydroxyphenylethylamine, No. (1), is at once more powerful (roughly 10 times) and more strictly sympathomimetic in its action than *iso.* amylamine. We have already stated that it is more active than phenylethylamine (cf. Fig. 4). The ratio of the activities of the two seems to vary with the condition of the animal, being in some cases about 1 : 3, in others about 1 : 5. Conditions affecting the sensitiveness of response act unequally in the two cases. The action of the phenolic base appears to be more strictly peripheral, so that the degree of shock to the spinal centres has more influence on the action of phenylethylamine. For our present purpose, however, it is enough to emphasise the fact that the introduction of a phenolic hydroxyl, in the para position, has further increased the activity, already increased, as has been shown, by the presence of the aromatic ring. A phenolic hydroxyl in the meta position is equally effective, the activity of (2) being practically equal to that of (1). In the ortho position it has not this effect, (2) being no more active than phenylethylamine. It should be noted, in this connexion, that the two phenolic hydroxyls of adrenine, and of the allied bases dealt with in the next section, occupy the meta and para positions relatively to the side-chain. The base numbered (11) in this series bears the same relation to (1) as does α-phenylethylamine to β-phenylethylamine. Like the former it proved very slightly active. The view was already expressed, in discussing the last series, that the optimum arrangement for the production of sympathomimetic activity in an amine, is the attachment of a benzene ring and the amino-group each to a different carbon atom of a two-linked fatty chain. The presence of a phenolic hydroxyl clearly does not affect the validity of this statement.

Methylation of the ring is known to increase the activity of phenolic compounds in certain directions. For example, cresol is a more powerful germicide than phenol. Methylation of the ring has no such intensifying effect on the sympathomimetic action of phenolic amines. No. (4), which was examined to test this point, was found to be considerably less active than No. (1), being roughly one half as active.

The introduction of a phenolic hydroxyl, forming *p.* hydroxyphenylethylamine from phenylethylamine, which has been shown to cause a notable increase of activity, brings the structure one stage nearer that of adrenine. It might be expected that the association with this

change of substitutions in the side-chain, which assimilate the latter to the adrenine side-chain, would result in a further increase of activity. Such is not the case, however. The necessary modifications are the introduction of the secondary alcoholic hydroxyl, producing No. (5) and the methylation of the amino-group, producing No. (7). No. (5) was prepared for us by Mr Tutin by reduction of No. (6), which was also tested, in view of the known activity of the ketone which yields adrenine on reduction. No. (6) was but feebly active, the activity being of the order of one tenth that of No. (1). Contrary to expectation No. (5) also proved itself less active than No. (1), though considerably more active than No. (6). Qualitatively the activity of (5) does, indeed, make an approach to that of adrenine in so far that the rise of pressure produced is much more rapid and correspondingly more evanescent than that produced by an equipotent injection of (1). This may, with great probability, be attributed to the greatly decreased resistance to oxidation, which the introduction of the alcoholic hydroxyl entails. Quantitatively, however, (5) is greatly inferior to (1) in activity, about 5 mgms. of the former being required to produce a rise of pressure to the same height as that caused by 1 mgm. of the latter.

Methylation of the amino-group of No. (1), which brings its structure nearer to that of adrenine in another direction, failed again to produce the expected increase of activity. The effect of the change is, indeed, surprisingly small. Of three cats, on which the base (1) and (7) were compared in equimolecular solutions, two gave regularly a larger rise of blood-pressure with (1), the other giving, equally regularly, a larger rise with the equivalent dose of (7). In connexion with the catechol bases we shall refer again to these individual differences of reaction. The point which chiefly concerns us now is that the methylation causes no definite increase of activity in this instance. This is true not only of the pressor action, but of the inhibitor action on the non-pregnant cat's uterus, on which (1) and (7) produce closely similar effects. This is the more remarkable in view of the very marked difference produced on the activity of the catechol bases, in this direction, by methylating the amino-group.

No. (8), the corresponding ethylamino-base, was made for us by Mr Walpole, and tested in comparison with (1) and (7) on account of the interesting results obtained with the ethylamino-bases in the catechol series. It proved considerably less active than (1) and (7).

The inhibitor action of these three bases, (1), (7) and (8) was also tested on a virgin cat's uterus. The same order of activity was obtained,

(1) and (7) being practically identical in action, (8) considerably less active (Fig. 5). The dimethylamino-base, No. (9), occurs in nature as the alkaloid hordenine, isolated from malt-germs by Leger[1]. It has been examined physiologically by Camus[2], who found that it produced a rise of blood-pressure, due to peripheral vaso-constriction, accompanied by cardiac inhibition or acceleration, according as the vagi were intact

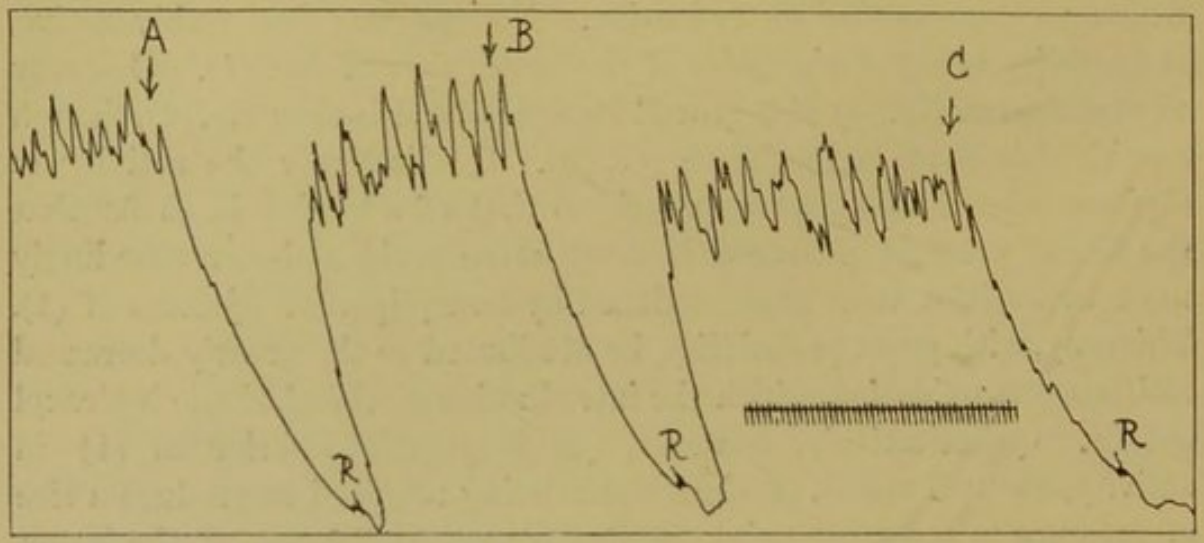


Fig. 5. Isolated uterus of virgin cat in 250 c.c. Ringer's solution. Lever rises with contraction.

At *A*, 2 c.c. $\frac{N}{100}$ *p.* hydroxyphenylethylamine.

B, ,, ,, *p.* hydroxyphenylethylmethylamine.

C, ,, ,, *p.* hydroxyphenylethylethylamine.

At *R*, *R*, *R* the Ringer's solution was changed.

or cut. He observed secretion of saliva, tears, gastric juice and bile, followed by diminished secretion if larger doses were used. Such large doses produced an evanescent paralysis of the vagus and the chorda tympani. We have not investigated the action of these large doses. The pressor action of injections of 2—5 mgms. of hordenine into the pithed cat is slight, but distinct. In this respect hordenine is very much less active than (1) or (7) (Fig. 6). The different effects described by Camus, are not inconsistent with an action mainly sympathomimetic, but more evidence is needed before it could be referred definitely to that type. On account of the relative weakness of the action we have not analysed it further. The relatively very weak action of dimethylaminoacetocatechol, as compared with the corresponding primary and secondary amines, was observed by Loewi and

[1] *Comptes Rendus*, CXLII. p. 108. 1906.

[2] *Arch. intern. de Pharm. et de Thér.* XVI. p. 43. 1906.

Meyer, and presents an interesting analogy. The question whether these tertiary amines really have an action of the same type deserves further investigation.

The action of the quarternary ammonium salt, hordenine methiodide, is of great interest. A large number of such quarternary bases from alkaloids have been examined by various observers, beginning with Fraser and Crum-Brown, and the generalisation that they have a curare action has been weakened by comparatively few exceptions.

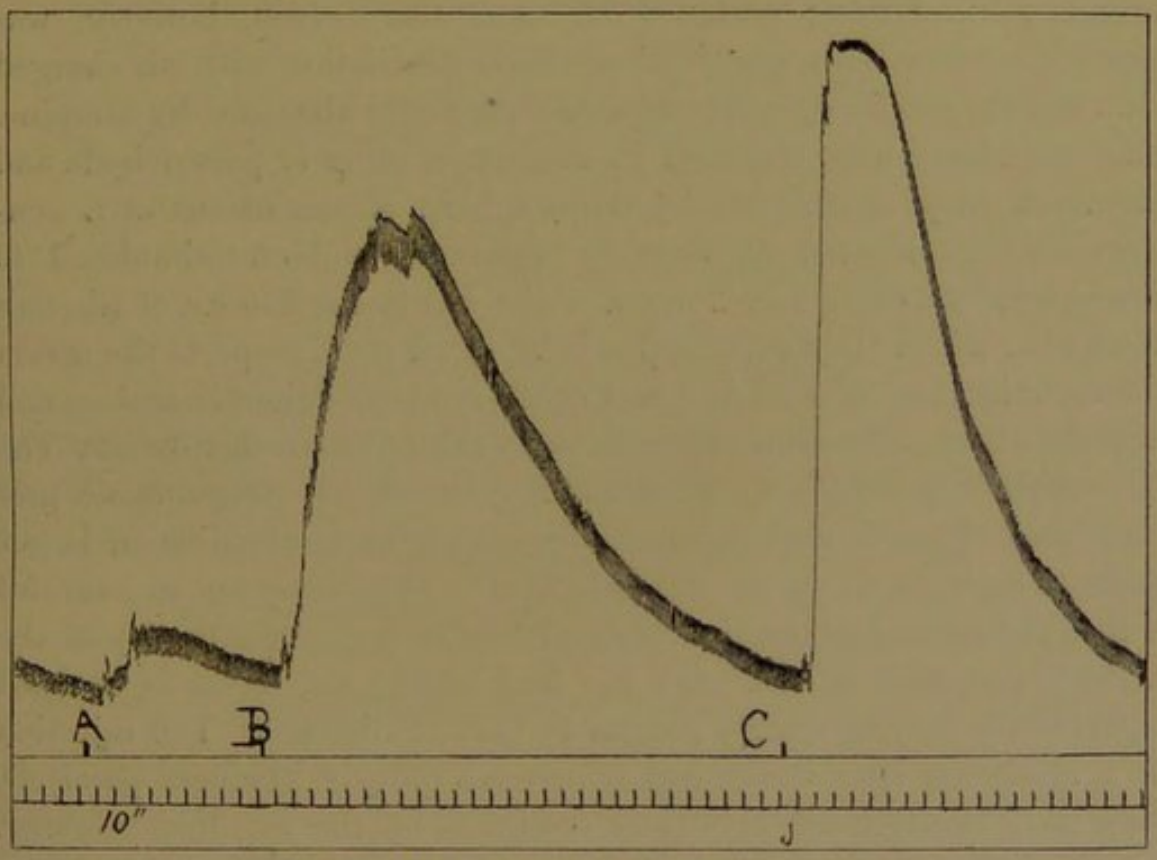


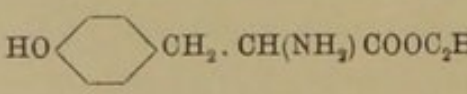
Fig. 6. At *A*, 2 mgms. hordenine.
B, ,, *p*. hydroxyphenylethylamine.
C, ,, hordenine methiodide.

In view of the recent evidence of the physiological antagonism between nicotine and curare (Langley[1]) it was of particular interest, therefore, to find in hordenine methiodide a quarternary ammonium salt of which the action resembles that of nicotine in almost every particular. 1 milligramme of this salt, injected intravenously, causes inhibition of the heart for a few beats, followed by the characteristic rapid rise of blood-pressure and rapid fall (Fig. 6). The effect is indistinguishable from that caused by 0·5 mgm. of nicotine. The effect

[1] *Proc. Roy. Soc.* B. LXXVIII. p. 170. 1906.

on the involuntary eye-musculature varied with the anæsthetic; the typical effect, however, of injecting 1—2 mgms. intravenously into a cat under ether was brief dilatation, followed by constriction of the pupil, narrowing of the palpebral fissure, and forward movement of the nictitating membrane. Painting 0·2 % hordenine methiodide on the superior cervical ganglion caused dilatation of the pupil: injection of a few drops into the orbit through the conjunctiva caused constriction of the pupil. Other effects of intravenous injection were rapid and large contraction of the urinary bladder, quickly giving way to secondary inhibition; paralysis of respiration, which, however, was resumed after a short period of artificial ventilation with air charged with ether; profuse secretion of saliva, promptly abolished by atropine. All these effects were observed in cats under ether or paraldehyde and ether. A loop of rabbit's jejunum, a horn of the uterus of a non-pregnant cat, treated as isolated organs, were both stimulated to contraction by adding 1 or 2 mgm. of the salt to the 250 c.c. of Ringer's solution in which they were suspended. In all these respects the action differs from that of adrenine and other sympathomimetic amines and resembles that of nicotine. The similarity extends to further details. The characteristic paralysis by nicotine of the effects of autonomic pre-ganglionic fibres is also produced by hordenine methiodide in larger doses, though its effect in this direction is apparently not so powerful as that of nicotine either absolutely or relatively to the intensity of the primary stimulant effects. On the frog, again, the action is, at least superficially, very strikingly similar to that of nicotine. The injection of 1 milligram into the dorsal lymph-sac quickly produces paralysis, with the characteristic cataleptic condition of the fore-limb muscles. It will be seen, in the next section, that quarternary bases produced by complete methylation of other sympathomimetic amines have a similar nicotine-like action.

One other observation may be conveniently mentioned here. It will have been noticed that all the substances hitherto dealt with are organic amines. Any modification which destroys the basic properties immediately annuls the activity. Thus the acetyl derivative of *p.* hydroxyphenylethylamine, is devoid of activity. So also is the closely related tyrosine ethyl ester,



in spite of its basic properties.

D. Amines with two phenolic hydroxyls.

Of the amines which we have examined in this group all except one have the phenolic hydroxyls in the ortho-relation to one another (*i.e.* they are catechol derivatives) and in the 3 : 4 position relatively to the side-chain. Among these is, of course, adrenine itself. The catechol bases which we have tested may be classified as follows :—

(*a*) *Derivatives of aceto-catechol* (*ketones*).

(1) Amino-aceto-catechol $(OH)_2C_6H_3 . CO . CH_2NH_2$.
(2) Methylamino-aceto-catechol $(OH)_2C_6H_3 . CO . CH_2NHCH_3$.
(3) Ethylamino-aceto-catechol $(OH)_2C_6H_3 . CO . CH_2NHC_2H_5$.
(4) Propylamino-aceto-catechol $(OH)_2C_6H_3 . CO . CH_2NHC_3H_7$.
(5) Trimethylamino-aceto-catechol chloride $(OH)_2C_6H_3 . CO . CH_2 . N(CH_3)_3Cl$.

(*b*) *Derivatives of ethyl-catechol.*

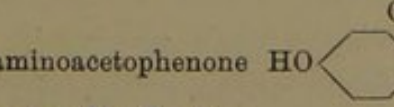
(6) Amino-ethyl-catechol $(OH)_2C_6H_3CH_2CH_2NH_2$.
(7) Methylamino-ethyl-catechol $(OH)_2C_6H_3CH_2CH_2NHCH_3$.
(8) Ethylamino-ethyl-catechol $(OH)_2C_6H_3CH_2CH_2NHC_2H_5$.
(9) Propylamino-ethyl-catechol $(OH)_2C_6H_3CH_2CH_2NHC_3H_7$.
(10) Trimethylamino-ethyl-catechol chloride $(OH)_2C_6H_3CH_2CH_2N(CH_3)_3Cl$.

(*c*) *Derivatives of ethanol-catechol* (*secondary alcohols*).

(11) Amino-ethanol-catechol $(OH)_2C_6H_3CH(OH)CH_2NH_2$.
(12) Methylamino-ethanol-catechol (adrenine) $(OH)_2C_6H_3CH(OH)CH_2NHCH_3$.

Of these catechol bases, those of classes (*a*) and (*c*) have been examined previously by Loewi and Meyer[1], in connexion with the synthetic work of Stolz[1], and by Dakin[1]. Nos. (3), (11), and (12), which are obtainable commercially, have recently been the subject of elaborate physiological comparison by Schultz[1]. Those in class (*b*) are all new. For (7), (8), and (9) we are indebted to Dr F. L. Pyman[2], who has elsewhere described their preparation.

In addition to these catechol bases we have had the opportunity of examining one in which the phenolic hydroxyls are in the 2 : 4 position relatively to the side-chain and therefore in the meta-relation to one another. This substance

(13) 2 : 4 dihydroxy ω aminoacetophenone 

was kindly supplied to us by Mr Tutin.

It will be convenient to begin the consideration of this series by

[1] *loc. cit.* [2] *Journ. Chem. Soc.* xcvii. p. 264. 1910.

examining Dakin's statement that even catechol itself possesses the adrenine action in some degree. His deduction that the catechol nucleus is essential to such action has been sufficiently disproved by the results recorded in the foregoing sections. But since all the substances in which we have been able hitherto to trace the sympathomimetic action are amines, the possession of such an action by a non-basic substance such as catechol would be interesting if substantiated. We confirmed the observation that 5—10 mgms. of catechol, injected intravenously, cause a very distinct rise of blood-pressure. This is true of the pithed cat, as well as of the anæsthetised rabbit, as used by Dakin. The action is, therefore, not wholly dependent on the integrity of the vasomotor centre. When, however, we looked for the other characteristic features of sympathomimetic action we could observe none of them. No action on the pupil or the urinary bladder of the cat could be observed with intravenous injections. When catechol was added to a bath of Ringer's solution containing an isolated horn of the virgin cat's uterus it caused merely a slight increase in the tone of the organ. Fig. (7) contrasts the effects on such a uterus of catechol and *p.* hydroxyphenylethylamine, showing that the amine without a catechol nucleus reproduces the characteristic sympathetic effect, while catechol itself merely causes increase of tone,

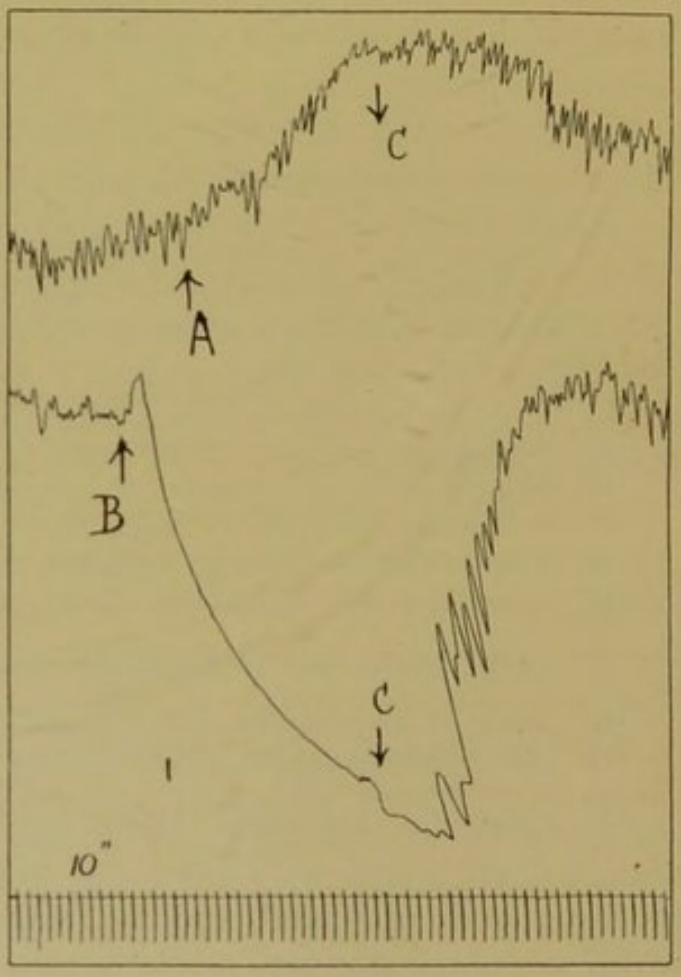


Fig. 7. Isolated uterus of virgin cat.
Upper tracing. Effect of 5 mgms. of catechol at *A*.
Lower tracing. Effect of 2 mgms. of *p.* hydroxyphenylethylamine.
Fresh Ringer at *C*, *C*.

due presumably to direct tonic action on the muscle-fibres. Catechol, so far as our observations go, appears to be a general, not powerful stimulant of plain muscle. When the centres are intact a central action probably contributes to the pressor effect obtained. Its action has no relation to the specific one with which we are concerned, and the description of its action as adrenine-like has no proper justification.

Though catechol itself has not the sympathomimetic action, the bases of this series, which contain a catechol nucleus, possess that action in a much higher degree than those of the series previously examined. By this we do not mean that any one member of this series will be found much more active than any one member, or even always than the corresponding member of the previous series. We shall show that this is not always the case: but the optimum activity in the series of catechol bases is very much greater than the optimum in any of the previous series.

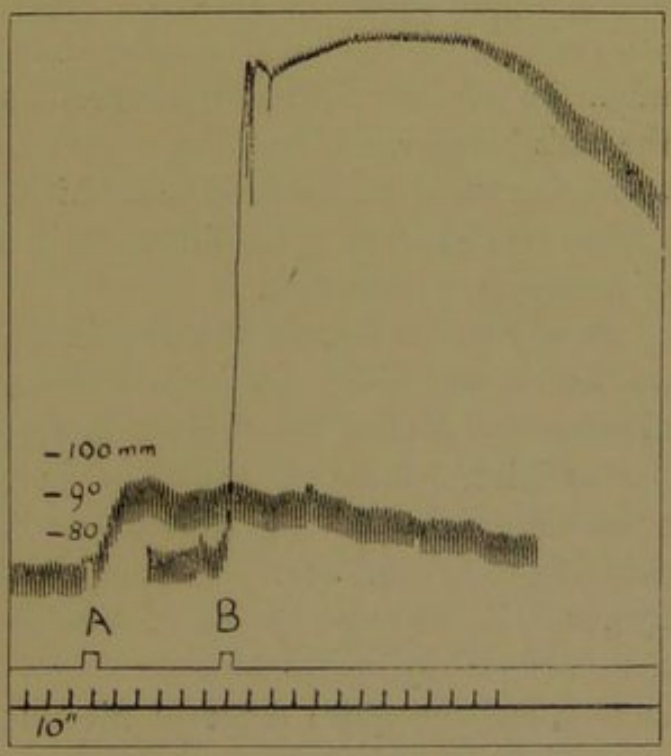


Fig. 8. At *A*, 2 c.c. $\frac{N}{100}$ amino-aceto-resorcinol.
B, ,, ,, amino-aceto-catechol.

Dakin's experiments showed the importance of the presence of the two phenolic hydroxyls. He found that dimethoxyphenyl bases were inactive, so that the hydroxyl groups must be free. Examination of the base numbered (13) in this series adds another point to our information. This base, which contains a resorcinol instead of a catechol nucleus, is no more active than the corresponding *p.* hydroxyphenyl base, No. (6) of the previous series. The introduction of a second hydroxyl in the 2nd position relatively to the side-chain has, therefore, not increased the activity, whereas if the second hydroxyl occupies the 3rd position, so that a 3 : 4 dihydroxyphenyl base is produced, the activity is, in this instance, immensely increased (Fig. 8).

Of the catechol bases, those in class (*a*) were examined by Loewi

and Meyer who tested (1), (2) and (3) and by Dakin, who tested (1), (2), (3) and (5). According to Loewi and Meyer the amino-ketone (1) is more active than the methylamino- (2) or ethylamino- (3). Dakin appears to have regarded them as equally active, but found (5) more active than any of them, though he noticed a peculiarity in its action, in that the effect of a large dose lasted no longer than that of a smaller dose. This peculiarity is probably explained by the fact that this base (5), like the other quarternary ammonium bases of this and the previous series, has an action of the nicotine type. This difference was not perceptible in Dakin's experiments, which were limited to observations on the blood-pressure, but immediately becomes apparent when the effects on other organs are studied. The actions on the pupil, the cat's bladder, and the virgin cat's isolated uterus, are all similar to those described for hordenine methiodide and clearly characterise the action. The action in all directions is, however, less powerful than that of hordenine methiodide.

It will be convenient at this point to mention the action of No. (10), another quarternary ammonium base, which again has a typical nicotine-like action, but is more powerful than hordenine methiodide, the activity, as far as could be judged with the small specimen available, approximating closely to that of nicotine itself. It is a point of some interest that the introduction of a second phenolic hydroxyl in the 3rd position, relative to the side-chain, intensifies not only the sympathomimetic action of the primary and secondary amines, but the quite different nicotine-like action of the quarternary ammonium base.

All the other amines of this series have the typical sympathomimetic action in different degrees. In comparing their activities we find it necessary for the first time to give separately the results obtained by different methods. In the case of the bases in previous series the inhibitor activities, when these have been the subject of quantitative comparison, have been found to run parallel to the activities as measured by the blood-pressure. In the case of the catechol bases there is no such parallelism. Nor is the divergence merely due to small differences in the ratios obtained: the accuracy with which the inhibitor effects can be compared is, indeed, not sufficient to permit the assignment of exact ratios. If, however, the bases in one class—*e.g.* the ketones—be arranged in order according to their activity in producing a rise of blood-pressure, or in inhibiting the non-pregnant uterus, the order will not be the same in the two cases.

It will be convenient to describe first the results obtained by the conventional blood-pressure method, and to discuss afterwards the light thrown on these by experiments on other organs.

Effects on the blood-pressure.

Of the bases in class (*a*), Nos. (1), (2), (3) and (4), the most active in nearly all our blood-pressure experiments has been No. (3). No. (1), however, is but little less active, the ratios of activities of (1) to (3), given by the reciprocals of the volumes of $\frac{N}{100}$ solutions necessary to produce equal submaximal rises of pressure, being, in several experiments, 1 : 1·5. In the case of one cat, however, the relation was reversed, the ratio being 1·5 : 1. This exception was so unexpected that we were inclined to attribute it to mere error in labelling the solutions, until we confirmed the result with new solutions, and subsequently found the same reversal of the usual relation of activities of the amino- and ethylamino-bases of class (*b*). There is no room for doubt, therefore, that the result was due to an abnormal sensitiveness of this cat to the amino-bases as compared with its sensitiveness to the ethylamino-bases.

Although the ratio given above, 1 : 1·5, was found to hold generally in our experiments when the comparison was made on the freshly prepared animal, it does not hold good indefinitely even for the same animal. The phenomenon of decline of activity at unequal rates for the different bases is better marked in the case of the bases of classes (*b*) and (*c*), and will be discussed more fully in dealing with them. It is, however, observable with the bases (1) and (3), more of (1) as a rule being necessary to match a given dose of (3) in activity, the longer the animal has been prepared.

The effects of bases (1) and (3), while thus differing quantitatively, are qualitatively very similar. Both cause a rapid rise of blood-pressure succeeded by a fairly prompt fall. When, however, an equal dose of $\frac{N}{100}$ solution of (2) is injected the form of curve obtained is very different. The pressure begins to rise fairly rapidly, but the rise soon becomes slower, and the pressure may remain practically level for a time, or may even fall slightly: then follows a long, slow, secondary rise and fall.

The contrast between the two types of action is illustrated in Fig. (9) and in Fig. (14). It is clearly impossible to make an accurate numerical comparison between actions of such different time-relations

and the statement that the pressor action of (2) is considerably weaker than that of (1) must in this case suffice. The action of (4) is still much weaker. As regards their action on the blood-pressure, then, the order of activity of these four bases is normally (3), (1), (2), (4): exceptionally (1), (3), (2), (4).

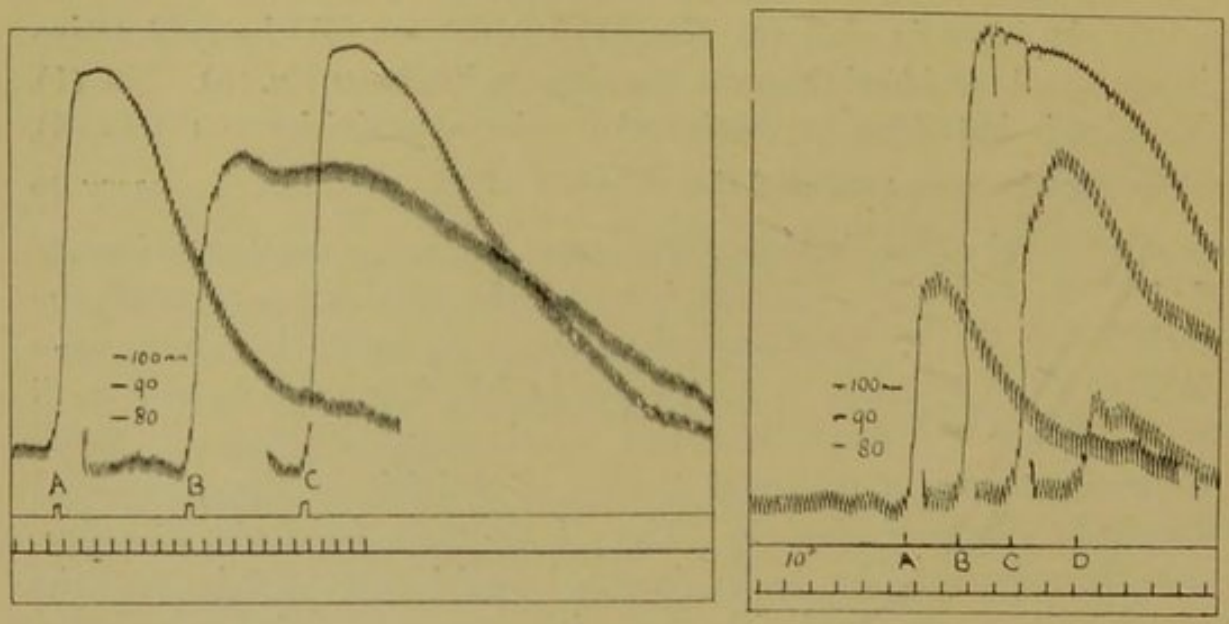


Fig. 9. At *A*, 0·5 c.c. $\frac{N}{100}$ amino-aceto-catechol.
B, ,, ,, methylamino-aceto-catechol.
C, ,, ,, ethylamino-aceto-catechol.

Fig. 10. At *A*, 1 c.c. $\frac{N}{200}$ amino-ethyl-catechol.
B, ,, ,, methylamino-ethyl-catechol.
C, ,, ,, ethylamino-ethyl-catechol.
D, ,, ,, propylamino-ethyl-catechol.

In group (*b*) the nicotine-like action of No. (10) has already been described. The other four have the typical sympathomimetic activity in varying degrees. The amino-base of this class (No. 6) is distinctly less active than the amino-ketone, No. (1), the ratio of the activities of (1) to (6), as measured by the blood-pressure effects, being about 1·5 : 1. The methylamino-base of the ethyl-catechol class, No. (7), on the other hand, is not only many times as active as the corresponding ketone, No. (2), but is the most active of all the compounds yet examined, with the exception of those in class (*c*), which includes adrenine itself. The ratio of activities of (6) and (7) is found to vary somewhat widely not only in different animals, but in the same animal at different stages of the experiment. Thus we have determined the ratio as 1 : 5 at the beginning of a long experiment; redetermined

later in the same experiment it has been found 1 : 10. The activity of the ethylamino-base, No. (8), seems to bear a more constant relation to that of the amino-base, the ratio being about 1·5 : 1, as in the corresponding bases of the ketone class (*a*). Here again, however, the ratio increases somewhat as the sensitiveness of the animal declines. The propylamino-base of class (*b*), No. (9), is again much the least active of those examined (Fig. 10).

In class (*c*) only two amines have been available for examination the amino- and methylamino-bases, the lævo-rotary naturally occurring form of the latter being adrenine. Of the amino-base we have had only the *dl.* form, and for purposes of comparison the synthetic *dl.* adrenine has therefore been employed as well as the natural *l.* base. It was first pointed out by Cushny[1] and confirmed by Abderhalden and Müller[2] that the *dl.* is considerably less active than the *l.* form, the ratio according to Cushny's determinations being 1 : 2. At the time of his publication we had already made a similar comparison and had obtained a somewhat different ratio, viz. 6·5 : 10. Recently Schultz[3] has published the results of a very careful comparison, made with a very carefully purified sample of the natural base and gives the ratio as 1 : 1·5. This agrees more closely with our own result, but we do not regard the small discrepancy between his results and our own, on the one hand, and Cushny's on the other, as having any significance. A study of Schultz's protocols shows that he observed, as we also did, some variation in the ratio in different experiments, and the differences in the methods of anæsthesia used by the different observers would be quite sufficient to account for some numerical difference in their results. On the other hand Biberfeld's[4] clearly erroneous statement that the *dl.* is as active as the *l.* base is attributable to his use of the minimal-effective-dose method, with which accurate results are impossible.

The relative activities of the *dl.* adrenine and *l.* adrenine being thus somewhat variable, it was thought better to eliminate one source of uncertainty in making comparison with the amino-base, and for this purpose the synthetic *dl.* adrenine was therefore used. We agree with Schultz that the *dl.* amino-base (No. 11) is usually distinctly more active than the *dl.* methylamino-base (No. 12) on the blood-pressure. Schultz gives the ratio as 1·5 : 1. We determined it, in different

[1] *loc. cit.* [2] *loc. cit.*

[3] *Med. Klinik.* 1906. No. 45.

[4] *Zeitsch. f. physiol. Chem.* LVIII. p. 185. 1908.

experiments, as 1·5 : 1, and 1·25 : 1. Not only, however, did we find that it varied somewhat in different experiments, but even in the same experiment the relation of the activities became altered or even reversed. In a freshly prepared pithed animal the amino-base was always slightly the more active: but if the animal were left for some hours, under artificial respiration with warmed air, and the comparison again made, it was usually found that the methylamino-base was now as distinctly the more active as it had initially been the less active of the two.

We have mentioned now in several instances this variation in the relative responsiveness of the animal to different bases with varying condition. The varying ratios obtained with the *dl.* and *l.* adrenines are probably due to the same cause, depression of the excitability of the heart and arteries by the anæsthetic, or by other conditions, affecting the weaker response to *dl.* adrenine in greater degree than the more active response to *l.* adrenine. Similarly, in the other cases, the response to that one of two bases, which the more nearly approaches adrenine in structure and activity, is more resistant to depressing influences of various kinds than the response to the other. In classes (*b*) and (*c*) the response to the amino-base falls off more rapidly than that to the methylamino-base, even when the former is initially the more potent stimulus. To use a metaphor, which, however, must not be interpreted too literally, the discrimination of the excitable tissue in favour of the configuration of its natural stimulant (adrenine) appears to become more severe as its avidity diminishes.

It will be clear that under such conditions an accurate estimate of the relative activities even of corresponding members of groups (*a*), (*b*) and (*c*) is not possible. Methylamino-ethyl-catechol, the most active of those outside group (*c*), was compared with *dl.* adrenine and with the natural *l.* base, ratios of 1 : 7 and 1 : 10 being obtained by finding, as usual, doses causing rises of pressure to equal submaximal summits. Equal summits do not, however, indicate equal total effects, since the effect of the ethyl-catechol-base lasts considerably longer than that of adrenine, with doses producing equal pressure maxima. The same criticism applies to most of the comparisons between members of different groups and different series. Bearing in mind the rather arbitrary nature of the method, the approximate average activity-values by the blood-pressure method in the catechol series of bases may be tabulated as follows:—

$(OH)_2C_6H_3.CH_2.CH_2NH_2$ 1.
$(OH)_2C_6H_3.CH_2.CH_2NHCH_3$ 5.
$(OH)_2C_6H_3.CH_2.CH_2NHC_2H_5$ 1·5.
$(OH)_2C_6H_3.CH_2.CH_2NHC_3H_7$ 0·25.
$(OH)_2C_6H_3.CO.CH_2NH_2$ 1·5.
$(OH)_2C_6H_3.CO.CH_2NHCH_3$?
$(OH)_2C_6H_3.CO.CH_2NHC_2H_5$ 2·25.
$(OH)_2C_6H_3.CO.CH_2NHC_3H_7$ 0·25.
dl. $(OH)_2C_6H_3.CHOH.CH_2NH_2$ 50.
dl. $(OH)_2C_6H_3.CHOH.CH_2NHCH_3$ 35.

As mentioned above, these ratios are subject to somewhat wide variation with the sensitiveness of the animal, even when a uniform method of preparation, such as decerebration, is employed. It is not surprising, therefore, to find Schultz assigning the ratio 1 : 80 for the activities of ethylamino-aceto-catechol to adrenine, whereas our table shows a much smaller ratio.

Effects on other organs than the circulatory system.

Apart from the effects on the blood-pressure the sympathomimetic action which has been most fully studied is that on the uterus of the non-pregnant cat. For the purpose of comparing the effects of a number of the bases this is most conveniently treated as an isolated organ by Kehrer's[1] method, provision being made for repeatedly changing the Ringer's solution without disturbance of the preparation. An exact numerical comparison of activities in producing inhibition of this organ has not been possible. The differences to which we refer are, however, so marked that precise measurement is unnecessary. The factors to be taken into account in forming an estimate of the relative activities of two bases, on such a preparation, are the rapidity with which relaxation takes place, and the extent to which the normal rhythm is abolished, as well as the completeness with which the tone is ultimately inhibited.

A very wide range of sensitiveness in response is presented by different specimens of the uterus. This is to be expected from the known variety of response presented by the non-pregnant but not virgin organ to stimulation of the hypogastric nerves, a variety which, for convenience of conception, may be pictured as dependent on the presence of varying mixtures of motor and inhibitor elements in the peripheral excitable mechanism.

On testing the action of the various catechol bases on any non-pregnant cat's uterus, however, one fact at once becomes distinct, namely that the methylamino-bases have a far more pronounced inhibitor action than any of the others (Figs. 11, 12, 13). The

[1] *Arch. f. Gynäkol.* LXXXI. p. 160. 1906.

ethylamino-bases in each of the two classes, (*a*) and (*b*), in which they have been examined generally, come next in order of activity; but the order of the bases other than the methylamino-bases varies with the uterus employed. With the virgin organ, which gives a purely inhibitor response to stimulation of the hypogastric nerves, the order is, almost invariably, methylamino, ethylamino, amino, propylamino. In class (*b*) this, it will be remembered, is also the order of the pressor activities; but the superiority of the methylamino-base of class (*a*) in inhibitor action is especially noteworthy in view of its markedly inferior

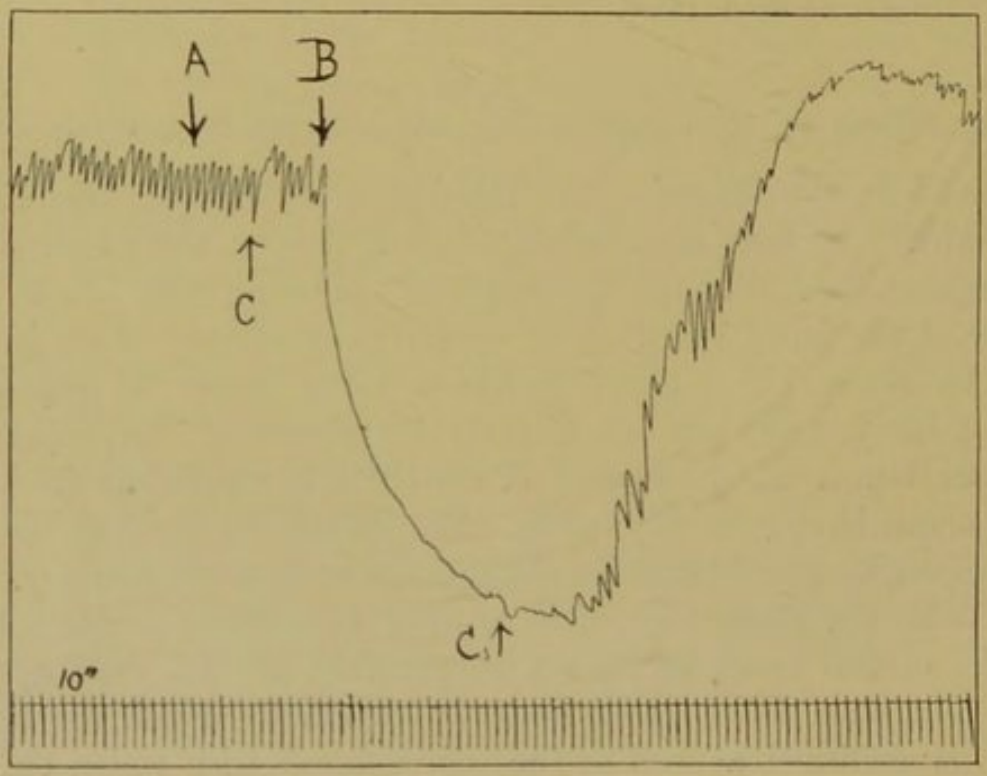


Fig. 11. Isolated uterus of non-pregnant cat.

At *A*, 0·25 c.c. $\frac{N}{100}$ amino-aceto-catechol.

B, ,, ,, methylamino-aceto-catechol.

Fresh Ringer at *C*, *C*.

pressor activity as compared with the ethylamino- and amino-bases of that class. With the non-pregnant but multiparous organ a different order is frequently observed. On such an organ the inhibitor action of the amino-bases is usually very slight, and it may even be replaced by a very weak augmentor effect on the tonus, the methylamino-bases still causing profound inhibition. In such a case as the last-mentioned it is usually found that the inhibitor action of the ethylamino-bases is also comparatively weak, and, in one such case, that of the ethylamino-ketone was distinctly inferior to that of the propylamino-ketone.

In class (*c*) only the amino- and methylamino-members were available, but here the comparatively weak inhibitor action of the powerfully pressor amino-base and the intense inhibitor action of the slightly less powerfully pressor methylamino-base were again clearly marked (Fig. 13).

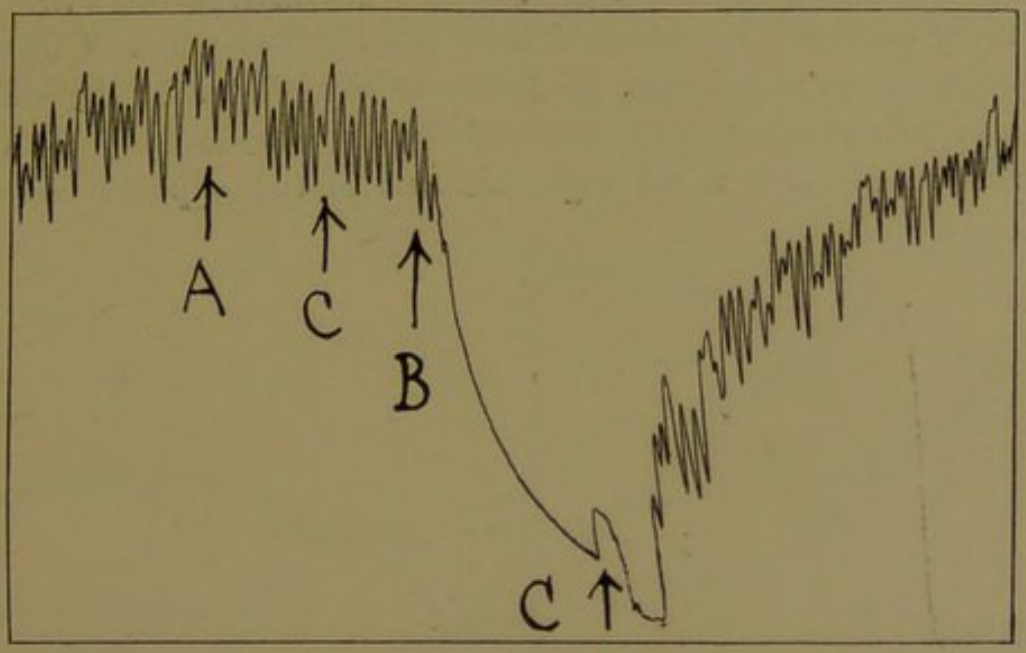


Fig. 12. Same as Fig. 11. Ethyl-catechol bases. Amino-base at *A*: methylamino-base at *B*.

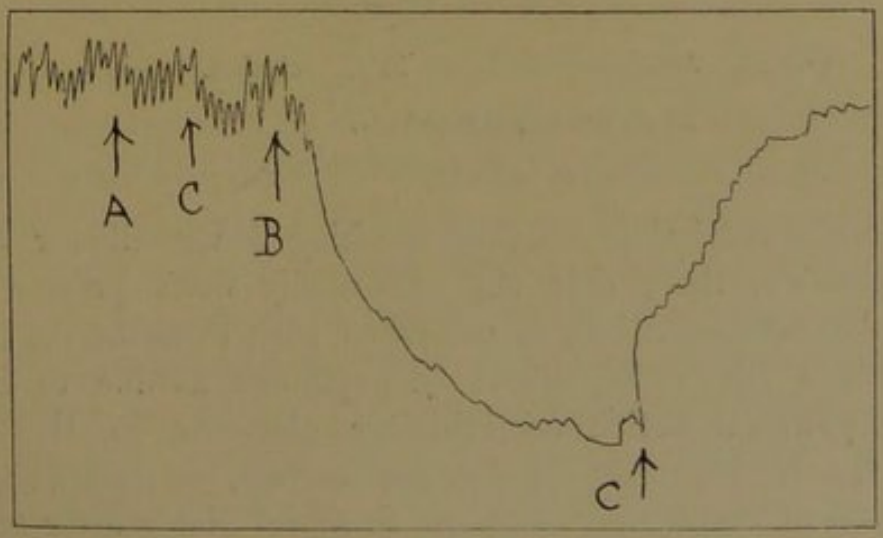


Fig. 13. Same as Figs. 11 and 12. Ethanol-catechol-bases in 0·1 % solutions. One drop amino-base at *A*: 1 drop methylamino-base (*dl.* adrenine) at *B*.

In terms of the conception of the excitable mechanism as containing a mixture of motor and inhibitor elements these irregular results admit of interpretation, since we must suppose that in each case the effect produced is the algebraic sum of the two opposed effects. If we

assume that the virgin uterus gives a purely inhibitor response to all the bases, the results obtained with it represent the true order of inhibitor activity of the bases. We shall return to this point after considering the reactions of some other organs. It was evident that the exceptional position of the methylamino-bases as regards inhibitor activity must be taken into account in interpreting the order of activity obtained by observation of the blood-pressure. One of us[1] has produced some evidence in favour of the view that the effect of sympathetic nerves and of sympathomimetic substances on the arterioles, of carnivora at least, is the algebraic sum of two opposed effects—a

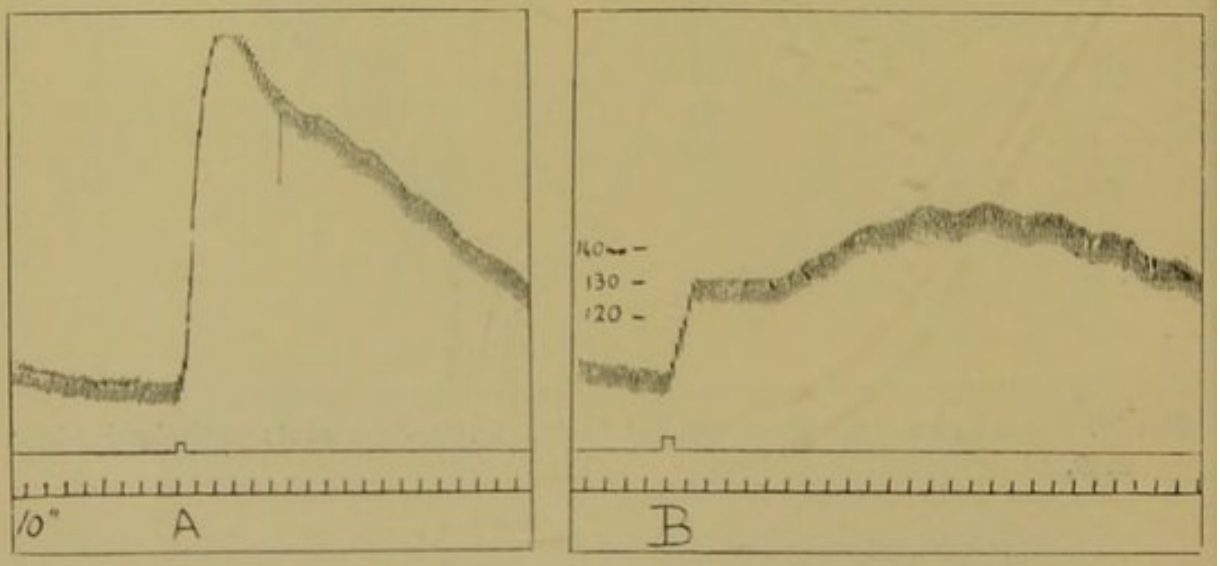


Fig. 14. Aceto-catechol bases in $\frac{N}{100}$ solution.

At *A*, 0·5 c.c. amino-base.

B, ,, methylamino-base.

predominant constriction normally masking a vaso-dilator effect. It seemed possible, then, that the abnormally weak pressor effect of methylamino-aceto-catechol, as compared with those of its immediate neighbours in the series, might be explained as due to its proved relatively powerful action on inhibitor elements in the excitable mechanism. If this interpretation were correct, we should expect that, after a dose of ergotoxine sufficient to annul the pressor action, the methyl-amino-ketone would produce a larger fall of blood-pressure, due to vaso-dilatation, than either the amino- or ethylamino-ketone. As a matter of fact we found it quite easy to give such a dose of ergotoxine that, while the amino-ketone still caused a small rise of pressure, an equivalent dose of the methylamino-ketone produced a large purely

[1] Dale. This *Journal*, xxxiv. p. 163. 1906.

depressor effect (see Figs. 14 and 15). On the same lines it might be suspected that the apparently weaker pressor action of *dl.* adrenine, as compared with *dl.* amino-ethanol-catechol, was attributable to the greater relative affinity of the former for the inhibitor element in the excitable mechanism. This can again be verified with the aid of ergotoxine, moderate doses of which leave the amino-base with a remnant of pressor action, while that of the methylamino-base (adrenine) is replaced by depressor action.

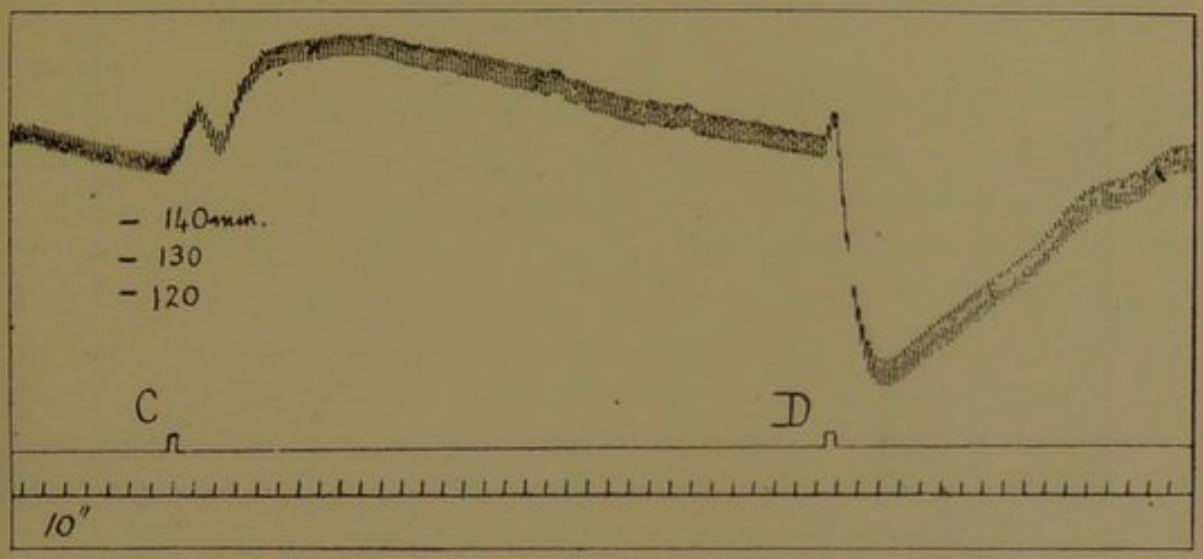


Fig. 15. Same experiment at 14, after 2 mgms. of ergotoxine phosphate.
At *C*, 0·5 c.c. amino-base.
D, ,, methylamino-base.

It will be clear that, if we are right in the supposition that the receptive mechanism of the arterioles contains inhibitor as well as motor elements, an organ which gives a purely motor response to these bases should give us yet another order of activity for the ketones. There is reason to expect such a purely motor response from the retractor penis muscle of the dog[1]. The motor effect of stimulating the sympathetic nerve-supply, or of adrenine, on this muscle is gradually extinguished by ergotoxine, but never, in our experience, replaced by relaxation. For comparison of the actions of the bases we treated it as an isolated organ.

The effects on it of the amino-, methylamino-, and ethylamino-ketones, are closely similar to one another, but the methylamino- is almost identical in activity with the amino-ketone (Fig. 16), the

[1] We obtained closely similar results in one experiment on the retractor penis of the goat.

ethylamino- rather more active than either. The propylamino-ketone is far less active than the other three.

Of the bases in group (*b*), derivatives of ethyl-catechol, the methylamino-base has by far the most powerful action on the retractor penis, the ethylamino-, amino-, and propylamino-bases following in that order of activity. This order, it will be seen, is identical with that obtained with the blood-pressure, and the non-pregnant uterus.

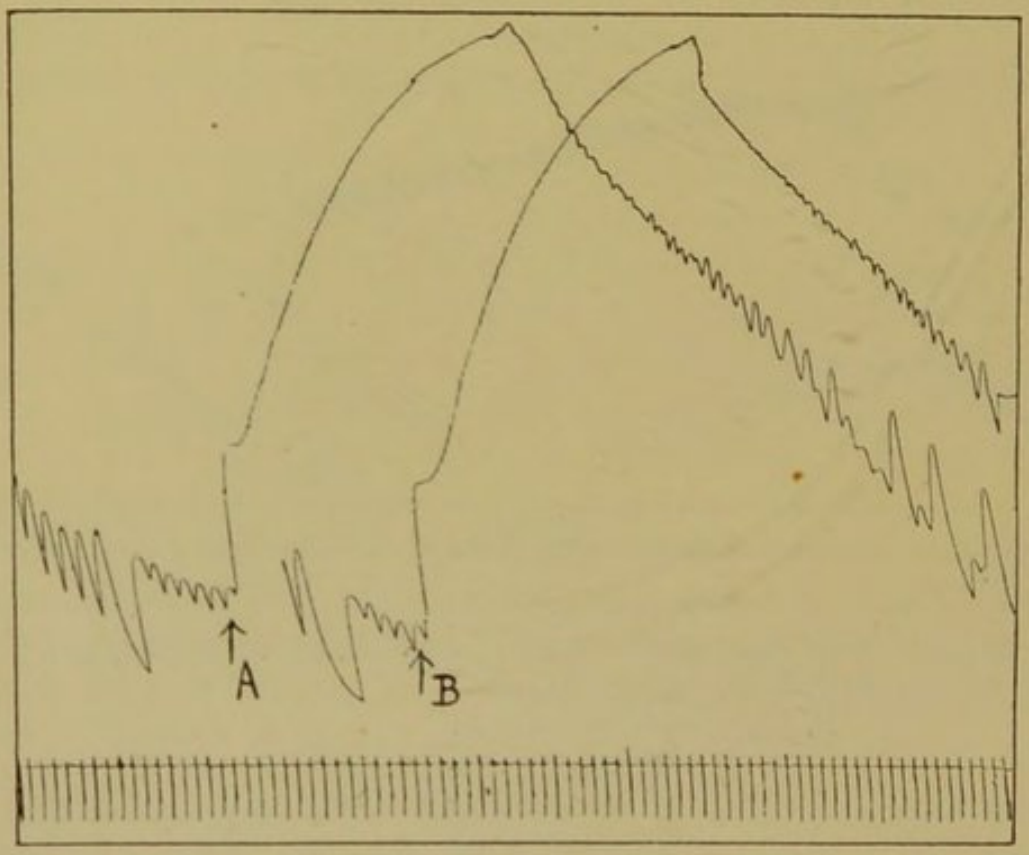


Fig. 16. Isolated retractor penis of dog in 250 c.c. Ringer's solution.
At *A*, 0·5 c.c. amino-aceto-catechol.
B, ,, methylamino-aceto-catechol.

In group (*c*) it is interesting to find that the methylamino-base (adrenine) is markedly more active on the retractor penis than the amino-base, the *dl.* form being used in both cases.

It is quite possible that yet different orders of activity might be obtained by experiments on other organs innervated by sympathetic nerves. We have confined our attention to these for this purpose since they provide instances of what we regard as purely motor, purely inhibitor, and mixed responses. It will be clear that, in the last case, the order of activity in a particular direction may be expected to show variations if the proportion of the motor to the inhibitor factor in the response varies. This is known to be the case with the non-pregnant

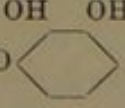
but not virgin cat's uterus. Such variations of order would be particularly probable in the case of the ketones, in which the orders of activity on organs with purely motor and purely inhibitor responses are not identical. It is, indeed, in the ketone group that the variations of order with different examples of the non-pregnant uterus are observed.

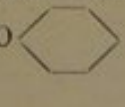
It may be said, then, that the view which regards the effect of these bases on most organs as the algebraic sum of two opposed effects is in accordance with the known facts, the apparent irregularities and variations in the order of activity being to some extent explicable on this view.

It has been mentioned that the ratios between the activities of the bases on the blood-pressure vary not only with different animals, but with the same individual at different stages of an experiment. This unequal rapidity of decline in the activity of different bases can be observed very readily in the case of isolated organs. As already stated the exact determination of ratios of activity is not easy in such circumstances: but, on the other hand, the experiment can easily be extended over several days, in which time differences initially slight become greatly accentuated. One striking instance will suffice. A virgin cat's uterus, isolated on April 15th, gave a marked inhibitor response on that day to *p.* hydroxyphenylethylamine and its alkylamine homologues, as shown in Fig. 5. It was kept in cold oxygenated Ringer's solution till April 18th, when, on warming again to 38°, it resumed an active rhythm. It had now, however, completely lost its sensitiveness to the bases with one phenolic hydroxyl, 5 c.c. of $\frac{N}{100}$ solutions producing no trace of inhibitor action. On the other hand its inhibitor response to methylamino-aceto-catechol was retained without perceptible impairment. Similar, though smaller differences in rate of activity-decline are observable within the limits of the catechol series of bases, and with the motor response of the retractor penis muscle.

E. Amines with three phenolic hydroxyls.

Only two of these have been available, both of them being amino-bases.

(1) Amino-aceto-pyrogallol 

(2) Amino-ethyl-pyrogallol 

They were tested on the blood-pressure and the isolated uterus of the non-pregnant cat. Both show sympathomimetic activity, but their pressor action is in each case somewhat weaker than that of the corresponding catechol base, their inhibitor action not greater. The introduction of the third hydroxyl group, therefore, in the first position relatively to the side-chain, while greatly lessening the resistance to oxidation, has not increased the sympathomimetic activity in any direction.

Some theoretical considerations.

We have already pointed out that most of the few provisional generalisations, based by previous observers on the examination of a small number of substances, for the most part closely related to adrenine, break down when the enquiry is extended over a wider field. A catechol nucleus is not an essential constituent of the molecule of a sympathomimetic substance, nor has catechol itself an action of the sympathomimetic type. It is true, however, that among the catechol bases are the most active in this direction of those which have hitherto been prepared. The fact, moreover, that the two pyrogallol bases examined were not more active than their catechol analogues suggests that one optimum condition for this type of activity is the presence of the catechol nucleus.

The suggestion that activity increases with diminishing resistance to oxidation needs more careful consideration. Broadly it is true, but it needs much qualification when applied to the individual members of an homologous series. If the pressor activity be accepted as the index the generalisation at once breaks down when so applied. We have shown, indeed, that the activity in producing motor effects, within the limits of such a series as that of the aceto-catechol bases, by no means runs parallel to the activity in producing inhibitor effects. A parallelism with instability or reducing action cannot, therefore, hold good for both types of activity. At first sight there seems some correspondence between instability and inhibitor potency in each group of catechol bases examined. Ewins[1] recently compared these bases with regard to reducing action, and found that the methylamino-base in each group was the most unstable, the amino-base the most stable. In both groups in which they were available the ethylamino- and propylamino-bases occupied an intermediate position as regards insta-

[1] This *Journal*, xl. p. 317. 1910.

bility. If the propylamino-bases be left out of consideration the same order holds for the inhibitor activity of the bases, as long as comparison is confined within the limits of an homologous series. But the necessity for the omission of the propylamino-bases weakens the significance of the comparison, which further breaks down completely when comparison is made between members of different series. Thus the comparatively stable methylamino-aceto-catechol has a more powerful inhibitor action than the much more easily oxidised methylamino-ethyl-catechol: on the other hand the amino-bases of the pyrogallol series, which are very readily oxidised, have no more inhibitor activity than the comparatively stable amino-bases of the catechol series. It must be concluded, therefore, that instability to oxidising agents is at most a subsidiary factor in determining sympathomimetic activity.

The generalisations which can be made from our results are, indeed, but few. All the substances in which we have traced the sympathomimetic action are bases. All those which show it characteristically and certainly are, moreover, primary and secondary amines. The quarternary ammonium bases, corresponding to the sympathomimetic amines of the phenolic and catechol series, have a marked activity of a quite different type, closely resembling that of nicotine. In a general way it can be stated, that approximation to adrenine in structure is attended by increase of sympathomimetic activity. The optimum carbon-skeleton, of a primary or secondary amine, for the production of this type of activity, appears to consist of a benzene ring with a side-chain of two carbon atoms, the amino-group and the benzene nucleus being attached each to a different carbon atom of this side-chain. The activity is increased by phenolic hydroxyls in the 3 : 4 position relative to the side-chain. When these are both present, but only then, the introduction of an alcoholic hydroxyl, attached to that carbon atom which is linked to the ring, further increases the activity. Inhibitor and motor activity vary to some extent independently when a hydrogen atom of the amino-group is replaced by various alkyl radicles.

Taking the last point first, it is clear that our results are compatible with such a proximate conception as that of Elliott[1], which, without involving any theory of the intimate nature of the action, postulates the existence of a myoneural junction, the function of which is to receive the nerve-stimulus or chemical stimulant substance, and to which must be ascribed the determination of the response in the

[1] *loc. cit.* and This *Journal*, xxxv. p. 367. 1907.

direction of augmentation or inhibition. If such a conception be regarded as adequate, our results merely emphasise the necessity for supposing that the myoneural junctions, or parts of myoneural junctions concerned with inhibition are not identical, in their affinities for chemical substances, with those which are concerned with motor effects. Evidence in the same direction had been previously furnished by the selective paralysis of motor sympathetic effects by ergotoxine.

Another suggestion, for which Elliott[1] was originally responsible, may be considered here, namely, that the parallelism between the actions of adrenine and of sympathetic nerves may be due to the fact that the latter produce their effects by liberating adrenine at their endings. This has more recently been adopted and propounded in greater detail by Dixon and Hamill[2], who suppose that the immediate effect, not only of nervous impulses, but also of drugs, is to liberate the appropriate hormone, which, in the case of sympathetic nerve-impulses, and of drugs reproducing their effects, is adrenine. The difficulty of applying this conception to the action of the amines which we have examined will be obvious. It would be fanciful to assume that the base, differing from adrenine merely in the fact that its amino-group is not methylated, acts not directly, but by liberating its homologous and not more active neighbour. If, however, we concede to amino-ethanol-catechol the power of acting directly, we cannot reasonably invoke the liberation of adrenine to explain the action of bases one stage further removed from it in structure, and, continuing the argument, we are ultimately bound to admit even the primary fatty amines to the list of substances acting directly, like the hormone adrenine. If these be admitted, it becomes difficult to conceive why the mediatory action of adrenine should be called in for any substance whatever. The distinction drawn between the action of a hormone and that of a compound foreign to the body, but producing similar effects, breaks down inevitably when a continuous series is available.

The conception of sympathetic nerve-impulses as acting by the liberation of adrenine seems to us unsatisfactory for another reason. It involves the assumption of a stricter parallelism between the two actions than actually exists. Adrenine has, in common with the other methylamino-bases of the catechol group, the property of exaggerating inhibitor as compared with motor effects. The inhibitor effects of these

[1] This *Journal*, xxxi. p. 20 (*Proc. Phys. Soc.*). 1904. [2] xxxviii. p. 314. 1909.

methylamino-bases are relatively prominent not only as compared with those of homologous bases, in particular the amino-bases, but also in comparison with those of sympathetic nerves. All the sympathetic effects which are weakly or doubtfully reproduced by adrenine are motor effects—*e.g.* pilo-motor action, or contraction of the trigone of the cat's bladder. On the other hand certain inhibitor effects, such as inhibition of the fundus of the cat's bladder, or of the non-pregnant uterus of the same animal, are more easily and completely produced by adrenine than by nerve-stimulation. Similarly certain normally motor effects of adrenine are reversed by smaller doses of ergotoxine than are needed for the reversal of the corresponding motor effects of stimulating sympathetic nerves. In these respects the action of some of the other bases, particularly of the amino- and ethylamino-bases of the catechol group, corresponds more closely with that of sympathetic nerves than does that of adrenine. To suppose that such bases and sympathetic nerve-impulses alike owe their action to the liberation of adrenine seems to us to create additional difficulties of conception.

Apart from such proximate conceptions our results have some interest in relation to the current controversy as to whether the activity of these and other bases depends ultimately on a physical or chemical process. It is, perhaps, desirable to point out, in the first place, that there is no reason why the whole of the facts should necessarily be interpreted in terms of the one class of action or the other. The most striking feature in the action of the bases under consideration is the more or less strict localisation of their action to cells innervated by a certain morphological system, on which cells they act when present in very high dilutions. There must evidently be something in those cells, or connected with them and them only, which has a strong affinity for these amines. But the property on which this affinity depends is by no means necessarily or even probably that which confers stimulant activity on the amines. In brief, the stimulant activity may depend on one property, the distribution of the action on quite a different property. The existence of pairs of bases, such as atropine and pilocarpine, the action of which has a practically identical distribution, though one paralyses where the other stimulates, makes it, indeed, impossible to regard the localisation of the activity and the existence of the activity as due to the same property. Langley[1] suggests that "it is conceivable that combinations should be formed by poisons which have no effect observable by our present methods." If

[1] *Journ. of Physiol.* xxxiii. p. 409. 1905.

we are right, however, in suggesting that distribution in the body and activity depend on distinct properties, the wider possibility is open that physiologically inert substances may exist, which have a similar affinity for the structures on which, for example, atropine and pilocarpine act, but that this affinity and the resultant localisation escape recognition for lack of the property conferring physiological activity. In the case of the sympathomimetic bases, the fact that these possess stimulant properties may depend on some quite simple chemical attribute. This would be the sole factor in their action on a tissue for which they have no specific affinity. If the bases were tested, for example, on frog's skeletal muscle, in the comparatively concentrated solutions in which they affect it, it is not improbable that their activities would be found proportional to some such property as their strengths as bases. Again the action of one base, even on a sympathetically innervated tissue, would very probably be found to vary with conditions, such as temperature, in such a manner as to show that the act of stimulation depends on a chemical reaction. Hill's[1] recent mathematical investigation of the contraction-curve of frog's muscle in response to nicotine under varying conditions leads him to such a conclusion. But it by no means follows that the peculiar distribution of the action of nicotine or of the sympathomimetic amines depends on the existence of specific chemical receptors in the cells peculiarly sensitive to them, as supposed by Langley[2]. Stimulation may be a chemical process: but the fact that certain cells are preferentially stimulated by a certain group of substances, such as our amines, may mean that in those cells these substances easily reach the site of action; a supposition which is in accordance with the view advanced by Straub[3].

Our results provide no decisive evidence in one direction or the other. The theory of receptive side-chains is, indeed, very difficult to apply to our results with such precision as ought to be possible in the case of simple substances of known constitution. If the relation between the receptive substance and the active base is to be regarded as one of ordinary chemical union, such points of constitution as are common to all the bases should give some indication as to the chemical nature of the side-chain which affords them anchorage. But the only complex common to all the bases is the group $\begin{smallmatrix} | & | & | \\ C & - & C & - & N \\ | & | & | \end{smallmatrix}$, which exists in innumerable bases having no sympathomimetic activity. The theory

[1] This *Journal*, xxxix. p. 361. 1910.

[2] This *Journal*, xxxix. p. 235. 1910.

[3] *Pflüger's Archiv*, cxix. p. 127. 1907.

further affords no means of interpreting the somewhat irregular variations of activity in the series, in many cases corresponding to variations of no known chemical characteristic.

From this point of view the alternative conception, which makes the activity primarily dependent on physical properties, in virtue of which these bases rapidly enter certain cells even from very high dilutions, has the advantage of making activity dependent on properties such as solubility, the laws connecting which with chemical structure are so complex and imperfectly known as to give scope for irregularity. The advantage is obviously one which further knowledge may destroy. One theory of this kind would make the affinity of certain cells for these bases depend on the presence in their limiting membranes of a highly specific solvent, which leads to the extraction of the bases from dilute watery solutions and brings them into relation with the responsive constituents of the cell, corresponding to the chief substance of Langley. On such a view the degree of activity of a sympathomimetic amine, that is, the dilution in which it produces an effect of a given intensity, would clearly depend on its partition coefficient between the specific solvent, on the one hand, and the body fluids, or other solution in which it is presented to the tissue, on the other. On the lines of the suggestion made above, however, it would also be dependent on the degree in which it possesses the other, probably chemical characteristic, in virtue of which it has a stimulant action. The existence of two independent variables would give further scope for apparent irregularities.

A further advantage of a mainly physical hypothesis is that it admits more readily of individual differences, and of differences in the one individual under different conditions. It is difficult, on the theory of chemical combination with receptive side-chains, to imagine why in one cat amino aceto-catechol should be more active than its ethylamino-homologue, while in most cats the reversed relation holds: or why at one stage of an experiment *dl.* adrenine should appear less active, at a later more active than its amino-homologue. The only possibility seems to be the assumption that receptors of different types, corresponding to the different bases, exist in different proportions and differ in their stability. But since the number of possible sympathomimetic amines is indefinitely large, it is impossible to postulate a new kind of receptive side-chain for each new base in which this type of activity is demonstrated. On the other hand a relatively small change in the composition of the solvent mixture required by the other hypothesis might easily account for such variations.

Similarly the fact that, with approximation to adrenine in structure, the activity not only increases in intensity but becomes gradually more strictly limited to structures innervated by sympathetic nerves, is more easily explicable on the physical hypothesis. On the other hand there is no positive evidence of any weight in favour of solubility in the ordinary sense as the important factor. The relation of the receptive mechanism to the base may well be one of solid solution or adsorption, and therefore more analogous to that of an enzyme to its substrate, as the widely different activities of optical isomers suggests.

On the whole, then, the least unsatisfactory view in the present state of knowledge seems to us to be that which regards the existence of stimulant activity as dependent on the possession of some chemical property, the distribution and, in the main, the intensity of the activity as due to a physical property.

Neither the purely chemical nor the mainly physical view satisfactorily accounts for the production of inhibition and motor action in different tissues by the same, or in the same tissue by different bases. It seems impossible at present to summarise the known facts in this direction, without having recourse to a more complicated and morphological conception such as that of Elliott, and further regarding his myoneural junction as multiple or composite, the receptive substances or solvents, in the portions concerned with inhibition and motor action respectively, not being identical.

Summary.

The following are some of the principal conclusions from the foregoing results:

(1) An action simulating that of the true sympathetic nervous system is not peculiar to adrenine, but is possessed by a large series of amines, the simplest being primary fatty amines. We describe all such amines and their action as "sympathomimetic."

(2) Approximation to adrenine in structure is, on the whole, attended with increasing intensity of sympathomimetic activity, and with increasing specificity of the action.

(3) All the substances producing this action in characteristic manner are primary and secondary amines. The quarternary amines corresponding to the aromatic members of the series have an action closely similar to that of nicotine.

(4) The optimum carbon-skeleton for sympathomimetic activity consists of a benzene ring with a side-chain of two carbon-atoms, the terminal one bearing the amino-group. Another optimum condition is the presence of two phenolic hydroxyls in the 3:4 position relative to the side-chain: when these are present, an alcoholic hydroxyl still further intensifies the activity. A phenolic hydroxyl in the 1 position does not increase the activity.

(5) Catechol has no sympathomimetic action.

(6) Motor and inhibitor sympathomimetic activity vary to some extent independently. Of the catechol bases those with a methylamino-group, including adrenine, reproduce inhibitor sympathetic effects more powerfully than motor effects: the opposite is true of the primary amines of the same series.

(7) Instability and activity show no parallelism in the series.