THE PHYSIOLOGICAL ACTION OF β-IMINAZOLYL-ETHYLAMINE. By H. H. DALE and P. P. LAIDLAW.

(From the Wellcome Physiological Research Laboratories.)

β-IMINAZOLYLETHYLAMINE is the amine which is produced when carbon dioxide is split off from histidine. It was first prepared synthetically by Windaus and Vogt[1]. Recently Ackermann[2] obtained a large yield of the base by submitting histidine to the action of putrefactive organisms. It has been shown that several of the amines thus related to amino-acids possess marked physiological activity. The activity of β-iminazolylethylamine was discovered in the course of the investigation of ergot and its extracts by G. Barger and one of us[3], who attributed this structure to a base which they obtained, and which in minute doses produced tonic contraction of the uterus. The synthetic substance, and the base produced by splitting off carbon dioxide from histidine by bacterial action or by chemical means, were found to have an identical action. Meanwhile Kutscher[4] had simultaneously and independently described the isolation from ergot of a base having this action and presumably identical with that obtained by Barger and Dale. By its chemical properties this first ergot base of Kutscher was not distinguishable from β-iminazolylethylamine; but certain apparent differences in the physiological action of the two bases, observed by Ackermann and Kutscher[5], led them to the conclusion that the ergot base, though closely related to β-iminazolylethylamine, is not identical with it. The alleged difference in action, on the existence and cause of which our experiments throw light, was as follows: the

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[1] *Ber. d. deutsch. chem. Gesell.* XL. p. 3691. 1907.

[2] *Zeit. f. physiol. Chem.* LXV. p. 504. 1910.

[3] *Proc. Chem. Soc.* XXVI. p. 128. 1910. This *Journal*, XL. Proc. Phys. Soc. p. xxxviii. 1910.

[4] *Zentralbl. f. Physiol.* XXIV. p. 163. 1910.

[5] *Zeit. f. Biol.* LIV. p. 387. 1910.

ergot base, injected intravenously into a rabbit in a dose of a few milligrammes, caused stoppage of respiration and fall of blood-pressure terminating in fatal heart failure; whereas iminazolylethylamine, under the same conditions, caused always a rise of blood-pressure, an injection of even 200 mgms. not being fatal.

In the present paper we are not directly concerned with this question of the identity of the ergot base, and shall refer to it only in so far as our own experiments have a bearing on the alleged difference. We may note, however, in passing, that the case for identity of the two substances receives some slight support from the more recent isolation from ergot extract, by Engeland and Kutscher[1], of a "second active base," having an action in some points similar to the first. This second base they have identified as the analogous amine from arginine, previously prepared by Kossel[2], who named it "Agmatine." All the experiments here described were made with β-iminazolylethylamine prepared from histidine by a chemical process, which will be described elsewhere by Mr Ewins, to whom we are indebted for our supply. A few confirmatory experiments were made with the synthetic base, which Mr Ewins also prepared by Windaus and Vogt's method, and with the base prepared from histidine by putrefaction, for which we are indebted to the kindness of Dr Ackermann.

No conveniently short name being yet available we shall refer to the base in this paper as β-I. The hydrochloride was used in all our physiological experiments, and weighed without allowance for the difference in molecular weight. "One mgm. β-I." is, therefore, to be taken to mean one mgm. of the hydrochloride.

Action on the intact animal.

The Frog The frog is but slightly affected by β-I. Injections of one to ten mgms. into the dorsal lymph-sac caused gaping movements of the lower jaw, succeeded by depression of the central nervous system for periods increasing with the dose, the effect lasting for about 30 mins. after ten mgms. During this period the animal sprawls in a relaxed attitude and the legs are not withdrawn when passively extended. Recovery is rapid and complete and the effect is in no way peculiar to or characteristic of β-I.

[1] *Zentralbl. f. Physiol.* xxiv. pp. 479 and 589. 1910.
[2] *Zeitsch. f. physiol. Chem.* lxvi. p. 257. 1910.

Mammalia. In rodents the effects are very different in the case of intravenous and of subcutaneous injection. In a rabbit of medium size an injection of two mgms. intravenously (ear-vein) caused marked prostration, the respiration becoming irregular and laboured and the heart-beat intermittent and feeble. These effects passed off gradually and recovery took place if no further injection were given. A second dose of two mgms., injected intravenously before the effects of the first had wholly subsided, caused a renewal of the symptoms in an accentuated form, death ensuing in a few seconds. Spasmodic inspiratory efforts continued for some time after cessation of the heart-beat. *Post-mortem* the right side of the heart was found greatly engorged : the lungs were slightly distended, but not otherwise abnormal. Death was apparently due, therefore, to right-sided heart-failure, associated with, but apparently not wholly dependent on, respiratory disturbance. Larger doses of five to ten mgms., injected intravenously, caused rapid death with similar symptoms, convulsive and obstructed respiration being a prominent feature of the effect.

In large guinea-pigs, weighing 800—1000 grams, injection of 0·5 mgm. into the external saphena vein caused death in a few minutes. The immediate effect was a marked respiratory impediment, resulting in violent but largely ineffective inspiratory efforts, during which the lower ribs were drawn in. After a time the respiratory convulsions ceased, and the animal lay comatose, though the heart continued beating for some time longer. *Post-mortem* the lungs were found permanently distended. If the fatal amount were given more slowly, as in two doses of 0·25 mgm. after the second of which death ensued rapidly, the final condition of pulmonary distension was extreme. Death was clearly due to asphyxia, evidently resulting from progressive obstruction to the respiration, sufficient in its early stages to prevent the exit of the air sucked into the lungs by the violent inspiratory spasms, and later becoming complete. The larger the initial dose, and, therefore, the earlier the obstruction became complete, the less pronounced the distension of the lungs. Such an effect could only be due to constriction of the bronchioles by spasm of their muscular coats, though the effect would be aided by increased bronchial secretion. Preliminary injection of atropine, though it did not abolish the action, had decided protective value. After five mgms. of atropine a dose of one mgm. of β-I. intravenously had the normal fatal effect : but another guinea-pig, which received a preliminary injection of five mgms. of atropine, recovered from subsequent intravenous injections of 0·5 mgm.,

0·25 mgm., and again 0·5 mgm. of β-I., given in fairly rapid succession ; whereas one dose of 0·5 mgm. was, in our experience, invariably fatal when given intravenously to a guinea-pig untreated with atropine. Whether atropine actually weakens the bronchial spasm, or merely modifies the effect by preventing secretion, must remain uncertain. We were unable to remove the obstruction, when once developed, by a subsequent injection of atropine.

It may be noted, at this point, that the symptoms and *post-mortem* condition in the guinea-pig correspond in a suggestive manner with those described by several observers[1] as the effects of poisoning in that animal by Witte's peptone, or by serum or other protein in the sensitised guinea-pig ("anaphylactic shock"). Also that the dose of iminazolylethylamine which proved fatal in our experiments to the unanæsthetised rabbit, when given intravenously, is practically identical with that given by Ackermann and Kutscher[2] as the fatal dose of Kutscher's first ergot base for the rabbit. To both these points we shall return later.

When the injection is made subcutaneously much larger doses are easily tolerated, both by the rabbit and the guinea-pig. 25 mgms. thus administered to a rabbit caused a gradual increase in rate of both heart-beat and respiration, the effect first becoming marked about 15 minutes after the injection. Defæcation, with semi-fluid fæces, and micturition occurred, and during the hour succeeding the onset of the symptoms the animal showed signs of prostration, with moderately deep narcosis. The attitude was sprawling, the head sunk on the table, the ears pale and cold. Recovery then set in, and in a few hours the animal was apparently normal.

In the cat the discrepancy between the effects of intravenous and subcutaneous injections was not so marked. Intravenous injections (long saphena vein) of two, four, eight and ten mgms. caused immediate vomiting and purging, profuse salivation, and laboured respiration, with a subsequent period of collapse and light narcosis, increasing with the dose. During this narcotic stage the pupils were markedly constricted. The cat which received ten mgms. intravenously, and which at the end of an hour had partially recovered, was then given a second intravenous injection of 20 mgms. This caused renewed vomiting and collapse, but the symptoms were rather less marked than those produced by the

[1] Cf. Biedl and Kraus. *Zentralbl. f. Physiol.* xxiv. p. 258. 1910; and Auer and Lewis, *Journ. exper. Med.* xii. p. 151. 1910.

[2] *loc. cit.*

first injection of ten mgms. The animal, which had thus received 30 mgms. in all intravenously, recovered completely during the night. The effects of subcutaneous injections in the cat were similar, though naturally somewhat slower in onset. 50 mgms. injected into a cat subcutaneously produced vomiting in six minutes, followed by purgation, and subsequently collapse and mild narcosis very similar to the condition following smaller intravenous injections. The constriction of the pupils in the narcotic stage was strongly marked even in the shade, but dilatation could be produced by rousing the animal. Complete recovery followed.

Another cat, a female in late pregnancy, received a subcutaneous injection of 50 mgms. of β-I., the general symptoms which resulted being very similar to those above described. Periodical strong contractions of the uterus, alternating with periods of relaxation, could be observed by palpation of the abdomen. During the night one of the two fœtuses was born dead. On the following day a second injection of 100 mgms. was given, which produced a repetition of the symptoms. The second fœtus was born, also dead, $5\frac{1}{2}$ hours after this second injection. The mother recovered completely and was quite normal on the following day. It seems probable that the powerful incoordinate contractions of the uterus, though they had no expulsive value, caused separation of the placentæ and asphyxiation of the fœtuses, which were expelled by the normal action of the uterus when the direct effect of the drug on that organ had passed off.

The vascular system.

The effect of iminazolylethylamine on the arterial blood-pressure is complex and not easily interpreted. It not only varies in different species, but shows very wide variations in individuals of the same species, especially in rabbits. These variations appear altogether out of proportion to the small differences of experimental conditions, and it is probable that individual differences of sensitiveness are also concerned.

The Cat and Dog. Dealing first with the cat and dog, in which the effects are relatively constant, we find that in these animals, anæsthetised with morphia and A.C.E. mixture, with paraldehyde or urethane, or by pithing the brain, the effect of injecting a small dose of β-I. intravenously is almost always a considerable fall of systemic arterial pressure. This was also described by Ackermann and

Kutscher[1]. If the dose is small and the arterial pressure low, as in a pithed animal towards the end of a long experiment, the fall may be very slight and succeeded by a small rise of pressure, which is then the main effect (cf. Fig. 14). The normal and characteristic effect in these species, however, is a fall of pressure, which can sometimes be observed to occur in two stages, a preliminary fall, lasting about ten seconds, being succeeded by a more marked secondary fall, the duration of which varies with the dose (cf. Fig. 1). With doses of 1 mgm. or more the secondary fall is much prolonged, the pressure only returning very gradually to the original level.
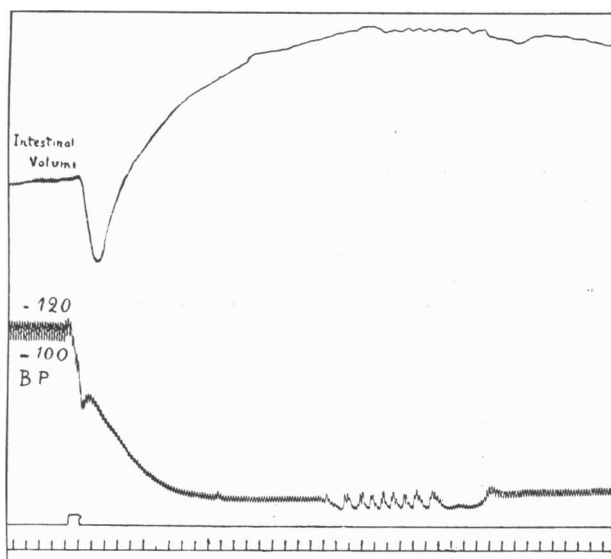
Fig. 1. Cat. Decerebrate. Effect of 1 mgm. β-I. on intestinal volume and blood-pressure. In this tracing, and following ones unless specially mentioned, the time marker intervals of 10″.

The significance of the different phases of this effect was investigated by examining separately the action on (*a*) the heart, (*b*) the pulmonary vessels, (*c*) the systemic vessels.

(*a*) The fall of systemic arterial pressure is not due to direct depression of the heart's activity. The action of iminazolylethylamine on the isolated, artificially perfused heart of the rabbit or cat is, indeed, to produce increase in both the rate and the force of the beat.

[1] *loc. cit.*

Fig. 2 shows the effect of injecting 0·25 mgm. of the hydrochloride into the cannula from which a rabbit's heart is perfused with warm oxygenated Ringer's solution, the substance being dissolved for injection in the same solution. The drop-record of the coronary flow, obtained by collecting the irregular spurts and drippings from the heart into a regular series of large drops, as previously described by one of us,
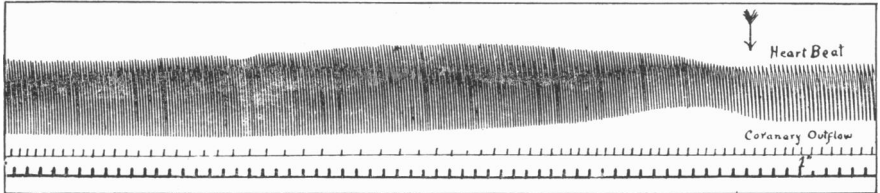

Fig. 2.   Isolated rabbit's heart.   Locke-Langendorff method.   Effect of 0·25 mgm. β-I. on heart beat and coronary outflow.   Time in secs.   Read from right to left.

shows that the increased activity of the heart is attended by distinct retardation of the outflow, presumably due to constriction of the arterioles of the coronary system. The effect on the cat's heart was very similar.

Cardiometer records from the heart *in situ* in the anæsthetised animal show a similar effect. Fig. 3 shows a cardiometer record from a cat anæsthetised with paraldehyde and ether, the vagi being cut. The rate of the heart-beat is slightly less after the injection, but the output per beat is more than proportionately increased, so that the output per unit time is greater, though the blood-pressure falls. The slowing of the beat in this case is probably explicable as a weak pilocarpine-like action, which β-I. also shows in other directions. As we have seen, this effect is absent in the case of the isolated organ, the
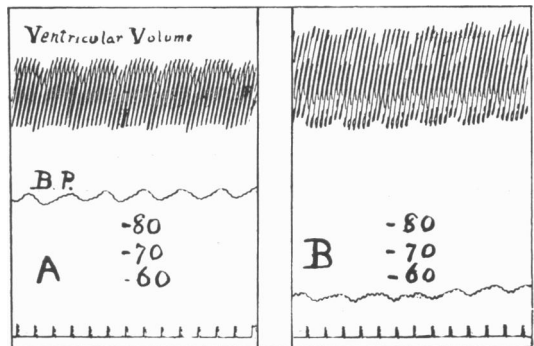

Fig. 3.   Cat.   Paraldehyde and ether.   Time in secs. *A* normal: *B* maximal effect of 0·25 mgm. β-I. cardiac output and blood-pressure.

directly stimulating effect of the base on the heart-muscle having free play. In any case, since the beat of the heart, even when slowed, is augmented sufficiently to increase the rate of output, the fall of blood-pressure must be due to something other than an action of the drug on either the muscle or the peripheral nervous mechanism of the heart. When large doses are given the large fall of pressure causes secondary weakening of the heart-beat, presumably due to anæmia of the muscle, resulting from the association of coronary constriction with falling arterial tension.· This secondary weakening then doubtless becomes a factor tending to accentuate and prolong the depressor effect of such doses.

(b) *The pulmonary vessels.* The effect on these was examined by recording the pulmonary blood-pressure, and by artificial perfusion of the surviving lung. The pressure was recorded from a branch of the pulmonary artery of a cat anæsthetised with paraldehyde and ether,
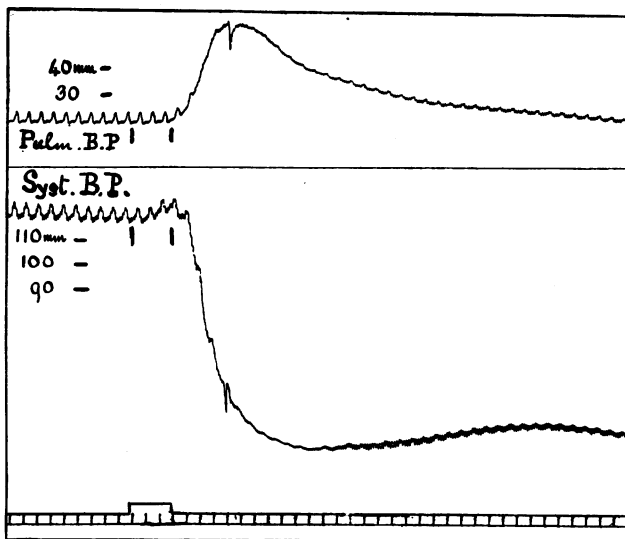

Fig. 4. Cat. Paraldehyde and ether. Time in 2″. Effect of 0·5 mgm. *β*-I. on pulmonary and systemic blood-pressures.

a mercury manometer being used. The method of operation was that described by Bradford and Dean[1]. The carotid blood-pressure was recorded simultaneously by a second manometer. Fig. 4 shows the effect of injecting 0·5 mgm. *β*-I. intravenously in this experiment. It

[1] This *Journal,* XVI. p. 34. 1894.

will be seen that a rise of pulmonary pressure, amounting to about
40 mm. at its maximum, follows closely on the injection, its commence-
ment preceding that of the systemic fall by about two seconds. Since the
action on the heart is but slight, this large rise of pulmonary pressure
can only be attributed to constriction of the pulmonary arterioles.
The perfusion with recorded rate of outflow was performed by Brodie
and Dixon's[1] method, the lung used being taken from a cat killed by
pithing. The perfusion fluid was the animal's own defibrinated blood
diluted with an equal volume of Ringer's solution. Injection of 0·25—
0·5 mgm. β-I. into the inflowing perfusion fluid, at a point near the
arterial cannula, regularly produced a pronounced diminution in the
rate of outflow from the venous side (Fig. 5). This, again, can only be
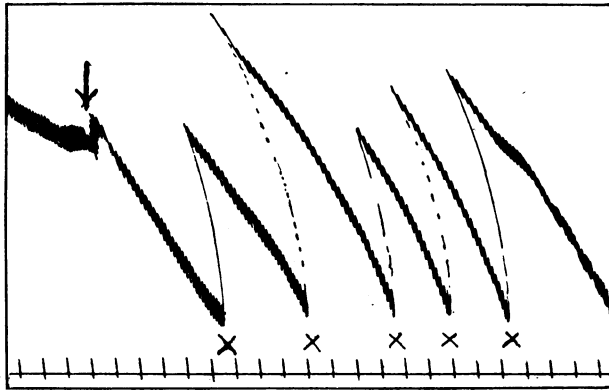attributed to constriction of the pulmonary arterioles.

Fig. 5. Perfusion of lung. Brodie-Dixon method. Venous outflow recorded by bellows
recorder. Effect of 0·5 mgm. β-I. injected into perfusion cannula: at points marked
× the bellows was readjusted. Read from left to right.

(c) *The systemic vessels.* We have shown that the fall of systemic
arterial pressure is not of cardiac origin, the output of the ventricles
being actually increased during the fall. The effect of the pulmonary
constriction, therefore, in diminishing the output of the left ventricle,
when its effect is perceptible at all, must be limited to the initial stage
of the systemic fall. This is clear also from the time relations of the two
effects, the pulmonary rise of blood-pressure having already passed its
maximum when the systemic fall is but beginning. In one experiment the
drug was injected into the central end of one carotid artery, the other

[1] This *Journal*, xxx. p. 476. 1904.

being used for recording the blood-pressure; and it was found that, when the injection was thus made into the main arterial stream, the fall of pressure began earlier than when the injection was made as usual into a systemic vein. In this case, then, the effect of the pulmonary constriction on the systemic pressure was negligible, and the fall must be regarded as wholly due to dilatation of the systemic arterioles. The time relations of the effects suggest, however, that, when the fall of pressure occurs in two phases, the preliminary phase is due to pulmonary constriction reducing the output from the left side of the heart. This is confirmed by plethysmographic observations. In Fig. 1 the first phase of the fall is seen to be associated with a distinct
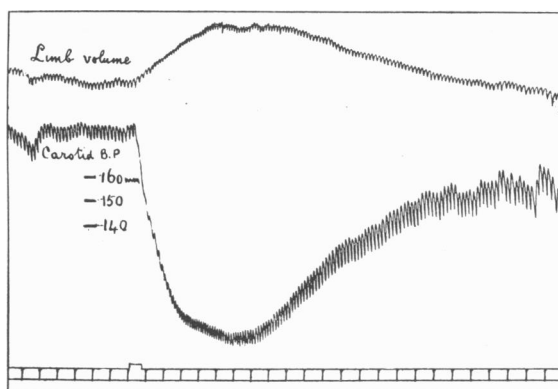

Fig. 6. Cat. Ether. Effect of 0·5 mgm. β-I. on limb-volume and systemic blood-
. pressure.

decrease in the volume of a loop of intestine enclosed in an air plethysmograph: as the second and main phase of the fall develops the intestinal volume undergoes a large expansion. When the first phase of the fall is not present the increase of intestinal volume either begins with the fall, or is preceded only by such a small preliminary diminution as is explicable by the less ready filling of the vessels of the loop, which is raised in the plethysmograph somewhat above the general level of the abdominal viscera. (Cf. Fig. 7.) The main effect, in any case, is an increase of intestinal volume corresponding to the fall of pressure, both returning to the normal *pari passu*.

Vaso-dilatation, corresponding to the fall of arterial pressure, also occurs in the limbs. The plethysmographic demonstration of this is not quite so simple, since the circulation in the limbs of an anæsthetised animal is apt to become sluggish, and the great fall of arterial pressure,

due mainly to vaso-dilatation in the splanchnic area, may mask the effect of the local vaso-dilatation in the limb. The normal effect, however, is that illustrated in Fig. 6, which is quite decisive.

The case of the kidney is different. Injection of β-I. regularly causes a large decrease of volume in this organ (Fig. 7): this is the case
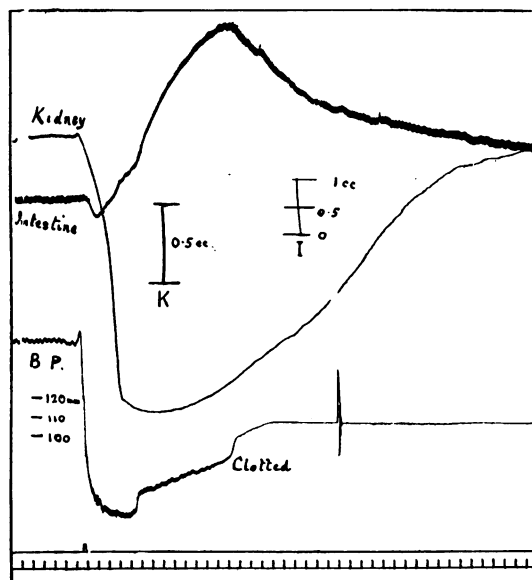

Fig. 7. Cat. Paraldehyde and ether. Effect of 0·5 mgm. β-I. on kidney volume, intestinal volume and blood-pressure. K and I are calibrations of recorders used to estimate changes in kidney volume and intestinal volume respectively.

even when the limbs show a good expansion. This decrease in the volume of the kidney appears too great to be wholly a passive effect of the fall of arterial pressure, and suggests an active constriction of the arterioles of the kidney: but this cannot be regarded as demonstrated.

The plethysmographic results thus show clearly that the fall of arterial pressure is mainly due to a general vaso-dilatation, in which the arterioles of the kidney do not participate: but the mechanism of this dilatation is not perfectly clear. When the vessels of the small intestine of a cat or dog, or of the hind limbs of a cat, were artificially perfused by Brodie and Dixon's method, the rate of venous outflow being recorded, an entirely different result was obtained. The perfusion-fluid used was the animal's own blood, defibrinated by whipping and diluted with an equal volume of Locke-Ringer solution. Injection of β-I. into the

arterial side of the system, close to the arterial cannula, in doses varying of 0·1—0·5 mgm., caused regularly a pronounced retardation of the venous outflow. (Fig. 8.) The hydrochloride was dissolved in a small quantity of the perfusion fluid, and injected at the temperature of that in the arterial tube, so that viscosity and temperature effects were excluded. The muscular coats of the intestinal wall appear to be rather more sensitive to β-I. when isolated from the body; but this difference would be quite inadequate to explain the actual reversal of the effect, and in any case could not account for the similar discrepancy between the effects during life and during artificial perfusion seen in the case of the limb-vessels. There is, therefore, no escape from the conclusion that β-I. has a vaso-dilator effect when injected into the animal, a vaso-constrictor effect when perfused through isolated organs.
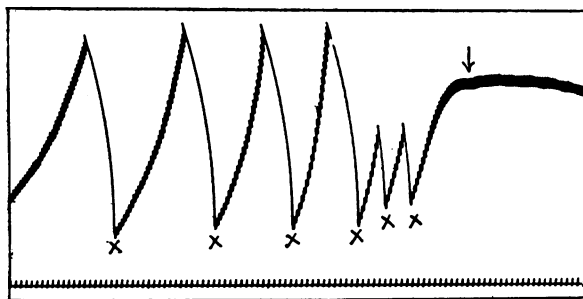

Fig. 8. Perfusion of small int:stine. As in Fig. 5 at ↓ 0·1 mgm. β-I. Read from right to left.

In other words the systemic arterioles respond to the drug, like most other plain muscle, by increase of tonus when isolated from the body. Their dilatation in the body must, therefore, be attributed to some intermediate mechanism which does not survive excision and artificial perfusion.

Concerning this vaso-dilator mechanism we know definitely only that it is localised at the periphery. After section of the splanchnics, or injection of nicotine in doses sufficient to block impulses through autonomic ganglia (30 mgms. for a cat), vaso-dilatation was still produced by β-I. in the intestinal vessels. In a cat under ether the right stellate ganglion was removed by Anderson's method. The animal was then turned on its back, and records taken of the carotid blood-pressure and volume of the right fore-limb. Injection of 0·5 mgm. β-I. caused the usual fall of blood-pressure and quite normal expansion of the limb.

We have previously referred to the analogy between the effect of
β-I. and that of Witte's peptone, as described by various observers.
Thompson[1] attributed the fall of pressure caused by "peptone" to loss
of "vasomobility," shown by loss of the normal constrictor response to
stimulation of the splanchnic nerves. It is of interest to note, in-
cidentally, that he found the kidney vessels immune to this vaso-dilator
action of peptone, as we found them to that of β-I. More recently
Popielski[2] has attributed the vaso-dilator action of peptone, and
of other preparations containing his hypothetical "vaso-dilatin," to
blocking of tonic sympathetic impulses by paralysis of peripheral
nervous structures: since he found that adrenine caused a rise of
pressure after "vaso-dilatin" he regarded the former as acting more
peripherally. On the other hand, Biedl and Kraus[3] state the vaso-
dilatation caused by "peptone" does neutralise the pressor effect of
adrenine; but they agree with Thompson and Popielski in regarding
the vaso-dilator action as due to the blocking or rendering ineffective of
tonic vaso-constrictor impulses in the sympathetic. If it is legitimate
to transfer conclusions drawn from experiments with β-I. to the closely
similar action of "peptone" and similar substances, we have shown that
this blocking of tonic sympathetic impulses is not an adequate ex-
planation of the effect, unless we postulate the presence of a peripheral
nervous mechanism by which tonus is maintained. Removal of the
ganglia, as we have shown, whether actual or functional, does not
prevent further vaso-dilatation in response to β-I. Whether the dila-
tation is due to action on peripheral nerve-endings can only be settled
by degeneration experiments which we hope shortly to undertake.
Experiments by Hamburger[4] appear to show that post-ganglionic
degeneration of the sympathetic nerve-supply destroys the vaso-dilator
action of "peptone." However that may be, the facts available appear
to indicate that the depression of the adrenine effect, which is also seen
with β-I., is due to the antagonism of an active dilatation, not to the
paralysis of a receptive mechanism common to the two.

The Rabbit. The effect of β-I. on the blood-pressure of the rabbit
is greatly modified by the respiratory effects, which, as we have noticed
in describing the action on the intact animal, are much more marked in

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[1] This *Journal*, xx. p. 455. 1896: xxiv. p. 374. 1899: and xxv. p. 1. 1899.

[2] *Arch. f. exp. Path. u. Pharm. (Schmiedeberg Festschr.)* p. 437. 1908. *Pflüger's Arch.*
cxxvi. p. 483. 1908.

[3] *Wien. klin. Wochenschr.* xxii. 1909.

[4] *Amer. Journ. of Phys.* xi. 282. 1904.

rodents than in carnivora. For this reason the condition of anæsthesia, and the length of time during which the animal has already been under the anæsthetic when the injection is given, have a considerable influence on the result. It was pointed out by Brodie and Dixon[1] that the response of the bronchial muscles is depressed by various anæsthetics, especially by urethane, which can even obscure the bronchio-constrictor effect of muscarine. We have seen that bronchial spasm is a typical feature of the action of β-I. on the unanæsthetised rabbit or guinea-pig. We have also seen that, under these conditions, β-I. is as fatal to the rabbit as Ackermann and Kutscher found the ergot-base. It seemed

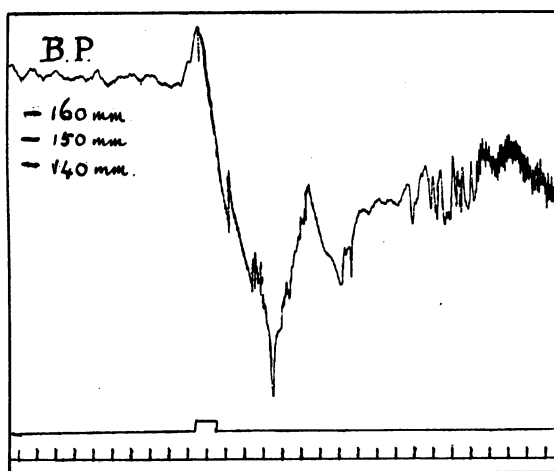Fig. 9. Rabbit. Urethane. Effect of 1 mgr. β-I. on blood-pressure.

possible, therefore, that the relatively harmless effect of β-I. in their experiments might be connected with their use of urethane as an anæsthetic. We therefore made observations on the blood-pressure of rabbits anæsthetised with urethane for varying periods, and a comparison of the results of the two following experiments is instructive. Each of two rabbits was anæsthetised by an injection of urethane solution, 1·5 grms. per kilo. being given in each case. In the first rabbit, as soon as complete anæsthesia was produced, the operation of inserting the necessary cannulæ was rapidly completed. The record was then started and an injection of 1 mgm. β-I. given intravenously. Fig. 9 shows the effect on the carotid blood-pressure. It will be seen

[1] This *Journal*, xxix. p. 97. 1903.

that the pressure begins to rise, but the rise soon gives way to a rapid fall. During this fall vigorous but largely ineffective inspiratory efforts occurred, the resistance to air entry being obviously very great. Heart-failure seemed imminent, but recovery soon set in and the blood-pressure again became steady at a rather lower level than that obtaining at the beginning of the experiment. A second injection of 2 mgms. was then given: violent and ineffective respiratory efforts immediately reappeared, during which the blood-pressure fell rapidly and permanently to zero, the force of the artificial respiration pump, which was applied, being insufficient to produce an effective expansion
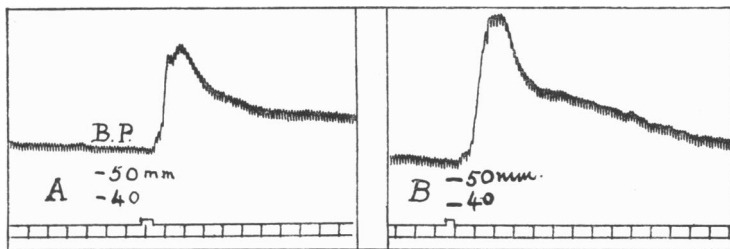

Fig. 10. Rabbit. Urethane. Effect of, *A* 0·1 c.c. extract of ergot; and *B* 1 mgr. β-I. on the blood-pressure.

of the lungs. The second rabbit was left for about half an hour under the full influence of urethane before the preparation was begun. Injection of the same doses of the same solution of β-I. caused, in this experiment, simple rises of blood-pressure. Some temporary increase of resistance to air-entry, with deepened respiration, was manifest, but not sufficient seriously to interfere with the circulation. Larger doses in this rabbit simply caused more prolonged rises of blood-pressure. Fig. 10 shows the effect on the blood-pressure of a rabbit, after pro-longed urethane anæsthesia of β-I. and of an ergot extract having a very powerful stimulant action on the isolated uterus. It seems clear that the uncomplicated effect of β-I. on the heart and vessels of the rabbit is to cause a rise of systemic pressure. This can be shown by the plethys-mograph to be due mostly to arterial constriction, in which, in this animal, the intestinal vessels share. (Fig. 11.) Unless, however, the effect on the bronchioles be depressed, as by prolonged urethane anæsthesia, this effect is overshadowed by the secondary effects. The sudden and even fatal fall of pressure, produced under such conditions by small doses of the drug, may probably be attributed to the combined

effects of the sudden reduction of intrathoracic pressure by obstructed inspiratory spasms and of constriction of the pulmonary arterioles, the two together causing acute distension of the right side of the heart, terminating in heart-failure.

We have not done sufficient experiments of this kind to be able to state positively that the difference is entirely due to difference in the duration of the anæsthesia prior to the injection. Not improbably the age of the animal, or idiosyncrasy for the drug may be an important factor.

Fig. 11. Rabbit. Urethane. Effect of 1 mgr. β-I. on blood-pressure and intestinal volume.

However that may be, our experiments show that it is possible with β-I. to obtain in different rabbits results differing from one

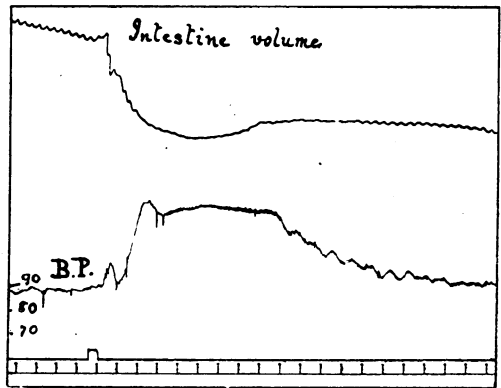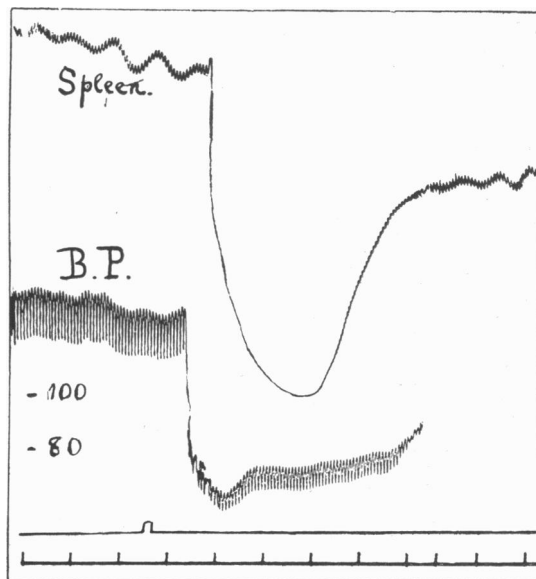Fig. 12. Cat. Decerebrate. Time in 30″. Effect of 0·5 mgr. β-I. on spleen volume and blood-pressure.

another as widely, and in the same manner, as the results obtained by Ackermann and Kutscher with the ergot base on the one hand, and β-I. on the other. Their results cannot, therefore, be properly used as evidence against the identity of the bases[1].

In the guinea-pig we found likewise that, when the bronchioles are paralysed by prolonged anæsthesia, intravenous injection of β-I. causes a rise of blood-pressure.

The Spleen. A marked diminution of volume of the cat's spleen, with abolition of the rhythm, is caused by an intravenous injection of β-I. This may be due partly to the fall of arterial pressure: but the rapid recovery of the spleen volume while the blood-pressure remains low, and the puckered appearance of the surface of the organ, show that active contraction of the muscular capsule must be the principal factor in the effect (cf. Fig. 12).

The respiratory system.

The most obvious of the respiratory effects has already been mentioned, namely, the acute obstruction of air-entry seen in rodents, and especially in the guinea-pig. This must be attributed primarily to bronchial spasm, though increased secretion of bronchial mucus would intensify the effect, especially in a small animal such as a guinea-pig. This bronchial constriction can be mechanically recorded by means of a lung-plethysmograph, as described by Brodie and Dixon[2]. Fig. 13 shows such a record from a pithed guinea-pig. It will be seen that the complete obstruction, once produced, was not relaxed by injecting atropine. Possibly with a smaller dose of β-I. atropine might be effective. If so the effect would be in all respects similar to that of "peptone" described by Biedl and Kraus[3].

In the cat the effect on the bronchioles is usually much less pronounced. Fig. 14 shows a typical plethysmographic record from the lung of a pithed cat. In one instance we observed in the cat a bronchial constriction approaching in severity that which occurs in rodents. Since all the cats were pithed the variation cannot be attributed to the anæsthetic, and the abnormally intense action must be

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[1] Recently the physiological identification has been completed by experiments which Barger and Dale are publishing elsewhere. It was found that in a rabbit, after an hour under urethane, the pure ergot base produced a simple rise of blood-pressure, indistinguishable from that produced by β-I.

[2] *loc. cit,*   [3] *loc. cit.*

attributed to idiosyncrasy. We could find no evidence that atropine, previously injected, in doses up to 5 mgms., prevented the constrictor effect of β-I. on the cat's bronchioles, or accelerated recovery from the effect when injected subsequently to its production.
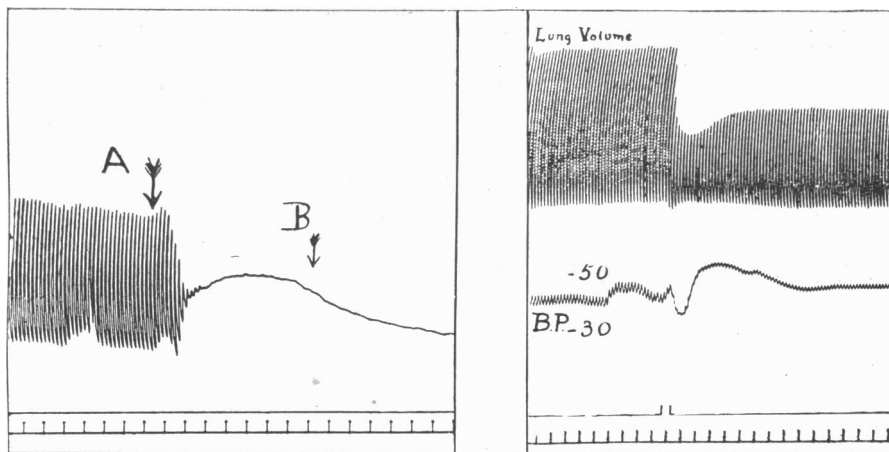

Fig. 13. Guinea-pig. Pithed. Effect of 0·5 mgr. β-I. on lung volume at *A*. At *B* 5 mgrs. of atropine.

Fig. 14. Cat. Pithed. Effect of 0·5 mgr. β-I. on lung volume and blood-pressure.

The local effect on the bronchioles produces such disturbance of the respiratory rhythm that it is not possible to state definitely whether β-I. has a direct effect on the respiratory centre. Large hypodermic injections, causing no serious impediment to the air-entry, are, indeed, followed by slowing and deepening of the respiration. This, however, may be secondary to the changes of blood-pressure.

The uterus.

The intense stimulating action of β-iminazolylethylamine on the muscle of the uterus is the characteristic which first drew attention to its physiological activity. The use of the isolated uterus, preferably of a non-pregnant cat, as a test-object for ergot preparations, was first suggested by Kehrer[1]. In our own experiments we have found the uterus of the virgin guinea-pig the most sensitive and convenient form of plain muscle for exhibiting the action of β-I. A horn of the uterus

[1] *Arch. f. exp. Path. u. Pharmakol.* LVIII. p. 366. 1908.

was suspended in a glass vessel holding 250 c.c. of Ringer's solution, the temperature of which was maintained steadily at 38°—39° C. by means of an outer copper vessel filled with water, the temperature of which was regulated by the method described by Locke. A tube leading from the lower end of the Ringer bath passed through a cork in the bottom of the copper jacket, and through this the Ringer's solution could be changed without disturbing the suspended organ, the fresh solution being run in from a reservoir kept at the same temperature as the bath. The Ringer's solution was kept saturated with oxygen by bubbling the gas through it in a gentle stream. The uterus was suspended vertically between two platinum hooks, the lower one attached to the lower end of the oxygen tube, the upper one to a thread which hung from one end of a light lever, of which the other end bore the writing-point.
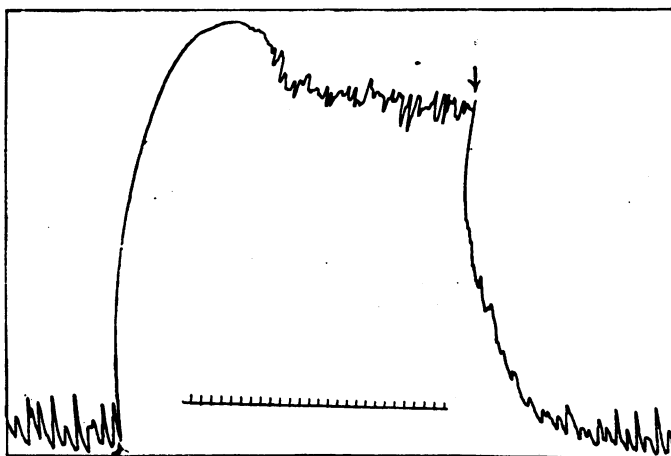

Fig. 15. Isolated uterus of virgin guinea-pig. Suspension method. Time 30″. At ↓ change to fresh Ringer. Upstroke = contraction.

Fig. 15 shows a record from the virgin uterus of a guinea-pig thus suspended. Left to itself in the warm Ringer's solution the organ quickly becomes completely relaxed, except for periodical small contractions. The figure shows the effect of adding to the bath 0·1 mgm. of β-I., of which the concentration in the bath was, therefore, 1 in 2,500,000. The uterus promptly contracts to its maximum tonus: after a time the originally smooth tonus becomes broken by a rhythm,

but the tonus remains high until the solution is changed, when relaxation quickly occurs.

Fig. 17 shows the effect in a similar experiment, of 0·01 mgm. of β-I., *i.e.* of a concentration of 1 : 25,000,000. The effect of 0·001 mgm., or 1 in 250,000,000, was still distinctly perceptible.

A quite similar tonic contraction of the uterus *in situ* was produced by the intravenous injection of somewhat larger doses. Fig. 16 shows the effect of one mgm. of β-I., injected in-
travenously, on the uterus of a pithed non-
pregnant cat. The sense of the response is
the same in all species and in all conditions
as regards pregnancy. Quantitative differ-
ences of responsiveness occur, and it is
somewhat remarkable that the most marked
and persistent contraction with β-I. is ob-
tained from the uterus of the virgin cat or
guinea-pig ; that is from an organ which
responds to stimulation of its nerve supply
or to adrenine by pure inhibition. The
effect is quite unaltered by atropine. Late
in pregnancy the sensitiveness of the uterus
to β-I. is markedly diminished, as Kehrer
observed with ergot extracts.

The action has no obvious relation to
innervation, and, as might be expected,
shows no coordination. The uterus contracts
as a whole and tonically, except with minute
doses. The tonic contractions thus directly produced by the drug can have no expulsive effect on the uterine contents, though it is probable that very small doses, by simply increasing the excitability of the muscle, would add power to the coordinate contractions produced by nerve-impulses or by the automatic rhythm of the organ.

Fig. 16. Uterus of pithed cat *in situ.* Attached by thread and pulley to lever. Effect of 1·0 mgr. β-I. Down-stroke = contraction.

Mention may be made at this point of the fact that preparations such as Witte's peptone, and various organ extracts, resemble β-I. in their action on the uterus as well as in other respects. Fig. 18 shows the effect on the isolated uterus of a virgin guinea-pig of adding to the bath 0·1 grm. of Witte's peptone, dissolved in warm Ringer's solution. The effect is indistinguishable from that of 0·1 mgm. of iminazolylethyl-amine. 0·5 c.c. of an extract of intestinal mucous membrane (containing also secretin) had a precisely similar effect.
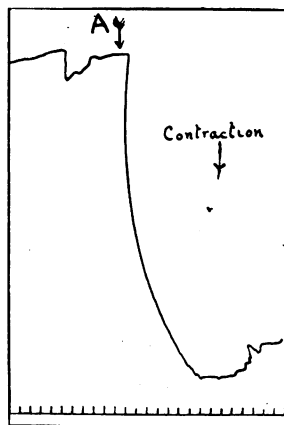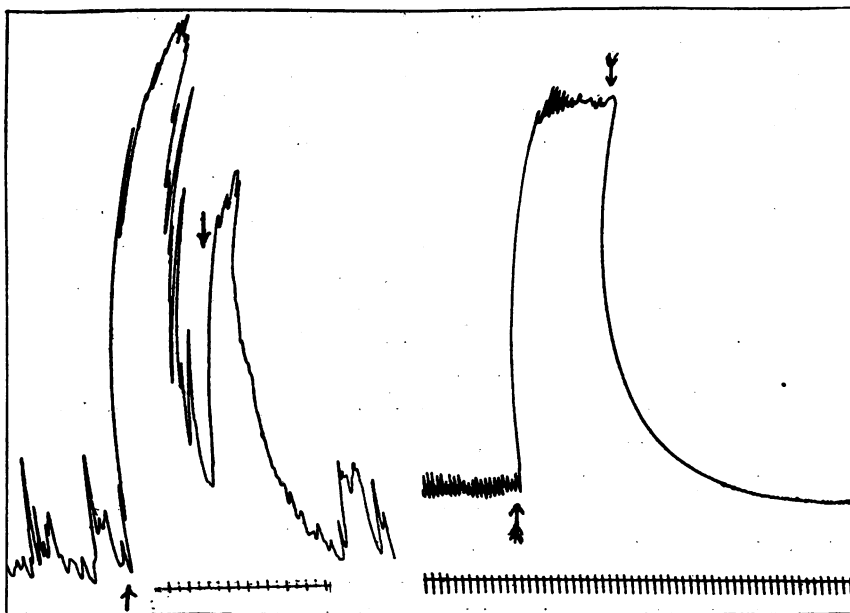
Fig. 17.   Fig. 19.

Fig. 17. Similar to Fig. 15. Effect of 0.01 mgr. β-I.

Fig. 19. Isolated intestine of cat. Suspension method. At ↑ 0·5 mgr. β-I. added to 250 c.c. Ringer bath; at ↓ change to fresh Ringer.
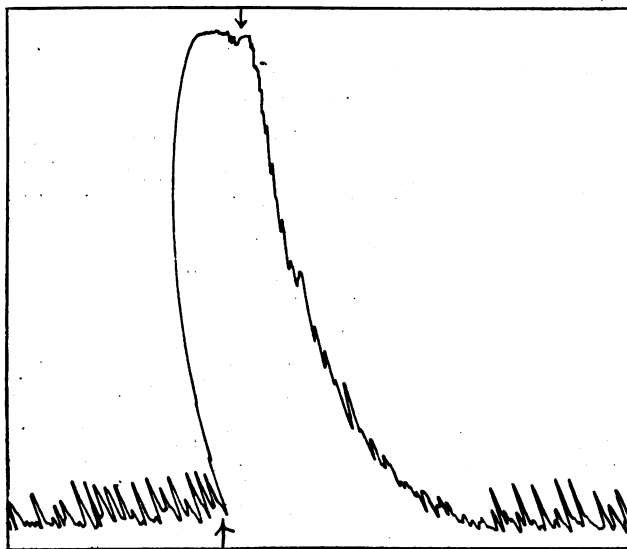

Fig. 18. As in Fig. 15. Effect of 0·1 grm. Witte's peptone.

The stomach and intestines.

The vomiting and purging produced in the unanæsthetised cat by intravenous injections of β-I. have already been mentioned. In the anæsthetised or pithed animal the effects on the exposed viscera of smaller injections (0·25—0·5 mgm.) are less striking, but still quite obvious. Both tone and rhythm appear to be augmented. An isolated loop of intestine, whether perfused artificially or simply suspended in warm oxygenated Ringer's solution, is more responsive to the stimulating action of the base than the undisturbed intestine with normal circulation. Fig. 19 (*supra*) shows the effect, on a short loop of cat's jejunum, suspended in the saline bath, of adding 0·5 mgm. β-I. to the bath, which had thus a concentration of 1 part of the base in 500,000. The effect is not abolished by atropine.

The urinary bladder.

In the intact animal the injection of β-I. frequently causes evacuation of the bladder. A record of the volume of the bladder contents in a pithed cat, by means of a catheter connected with a reservoir half filled with water, which again communicated with a bellows recorder, showed, as the result of a first injection of 0·25 mgm. β-I., a small relaxation of the bladder wall. Subsequent injections produced in every case a contraction of the bladder, the contractions becoming progressively larger with each injection, till the sixth injection produced a contraction leading to the expulsion of more than 40 c.c. of the contents. That this contraction was not due to direct effect on the musculature of the bladder was shown, however, by the fact that, after destruction of the sacral cord, a further injection caused practically no change of bladder volume.

We found little evidence, indeed, that the base has any marked direct effect on bladder muscle. All the effects which we observed can fairly be attributed to the stimulation of centres in the cord by the anæmia caused by fall of arterial pressure.

The plain muscle of other organs.

The retractor penis of the dog or goat is thrown into tonic contraction by small doses of β-I. Good responses were obtained, when the muscle was treated as an isolated organ, with dilutions of 1 in 250,000.

In the anæsthetised animal no effect was observed on the size of the pupil as the result of injecting intravenously 0·25 to 0·5 mgr. β-I.; but in unanæsthetised cats, receiving larger doses by intravenous or hypodermic injection, constriction of the pupil, even in the dusk, is a noticeable feature of the effect, as already mentioned. It may be doubted whether this is in any degree due to direct effect on the plain muscle of the sphincter. The fact that the pupil, though remaining small when the eyes are shaded, dilates when the animal is roused or excited in any way, seems rather to indicate that the constriction is of central origin and associated with the narcotic action of the base. We have seen no evidence of an effect of the base on the pilomotor muscles.

Gland cells.

Salivary gland. Salivation has been mentioned as one of the effects of the base on the unanæsthetised cat. Experiments on the anæsthetised cat and dog show that this effect is, in part at least, due to a direct peripheral action of the drug. In a dog anæsthetised with A.C.E. mixture a cannula was inserted into Wharton's duct and connected to a narrow horizontal glass tube attached to a millimetre scale. The chorda tympani was cut and stimulated with a weak tetanising current for a few seconds. When the flow of saliva resulting from the preliminary stimulation had ceased an intravenous injection of 0·25 mgm. β-I. was made. A flow of saliva began almost at once, rapidly reached its maximum rate and then quickly declined. The total movement of the column of fluid along the tube, resulting from the injection, was 8 cm., representing about 0·55 c.c. saliva. A second injection of 0·5 mgm. caused the secretion of about 0·7 c.c. saliva. 1 mgm. of atropine was administered intravenously. A further injection of 0·5 mgm. β-I. then produced no trace of salivary secretion. A very similar effect was produced in a cat anæsthetised with paraldehyde.

A secretion of tears can usually be observed as a result of an injection of β-I. in the anæsthetised cat.

The part probably played by increased bronchial secretion in the respiratory impediment produced by the base has already been mentioned.

The pancreas. β-I. has also a definite stimulant effect on the pancreatic secretion. In a dog anæsthetised with A.C.E. mixture a cannula was inserted into the pancreatic duct and the flow of pancreatic juice recorded by a drop recorder. 10 c.c. "secretin" (acid duodenal extract) were injected intravenously and 135 drops of juice were secreted in the

16 minutes following the injection, at the end of which time the flow had returned to its original rate of about four drops in 10 minutes. 1 mgm. β-I. was then given, the cannula being first carefully freed from secretin, and 25 drops of juice were secreted in the 10 minutes following the injection, the first 20 drops being secreted in the first five minutes of this period. 5 mgms. of atropine were then given and after a short interval 1 mgm. β-I. was administered intravenously. Four drops of juice were secreted in the 10 mins. following the injection: that is to say, the rate of secretion was not affected at all. 10 c.c. of secretin were then given and over 90 drops of pancreatic juice were secreted in the seven mins. following the injection, the experiment being discontinued while rapid secretion was still in progress. It is thus evident that β-I. evokes a small secretion of pancreatic juice, but that this action is completely abolished by atropine, which leaves the effect of secretin unchanged. In other directions the injection of 10 c.c. of the duodenal extract was roughly the physiological equivalent of that of 1 mgm. of β-I. Each produced a fall of blood-pressure from 110 mm. to about 25 mm., the recovery being rather slower after the 1 mgm. of β-I. We shall mention later certain considerations which suggest the possibility that the duodenal extract may contain β-I. or a closely related substance, which would account for some at least of its depressor action. However that may be, it is abundantly clear that the slight action of β-I. on pancreatic secretion is of a different type from, and of an altogether lower order of intensity than, that of secretin.

Kidney. We found no evidence that β-I. had any effect on renal secretion apart from that produced by vascular changes. The rate of urinary flow followed with tolerable accuracy the arterial blood-pressure.

Excretion. β-I. is not excreted as such in the urine. The urine of the cat to which 150 mgms. in all were administered hypodermically was collected during the 48 hours succeeding the first injection. It gave Pauly's reaction with diazobenzenesulphonic acid with great intensity, but had no perceptible effect on the isolated uterus of a guinea-pig in doses of 5 c.c. This seems to point to excretion as a compound devoid of the characteristic physiological activity, but with the iminazole ring intact. This compound has not as yet been identified.

Striped muscle.

The effect of β-I. on striped muscle is altogether insignificant as compared with its effect on the plain muscle of most viscera. The application of a 1 in 1000 solution of the hydrochloride in ·6 °/₀ saline to a muscle-nerve preparation, produced no contraction. The preparation was left overnight in the solution and the muscle then responded to the excitation of its nerve with a single induction shock by a twitch, which differed from that given by a control preparation (from the other leg) kept in saline for the same time, only in being slightly lower. The effect may be regarded as practically nil.

DISCUSSION AND SUMMARY.

The action of β-iminazolylethylamine, as described in detail in the preceding sections, appears a somewhat complicated one. It cannot be summarised with reference to any division of the autonomic system, like that of some other amines. The fundamental and characteristic feature of its action is its direct stimulant effect on plain muscle, in which it produces exaggeration of rhythm with increased tonus, or steady maximal tonus unbroken by rhythm, according to the concentration in which it is applied. The sensitiveness of plain muscle from different organs and in different species varies within wide limits. The most sensitive of all appears to be the plain muscle of the uterus: the non-pregnant uterus of some species responds to the drug in extreme dilution. The muscular coats of the bronchioles are also highly sensitive to the action, especially in rodents. The plain muscle of the intestinal wall, of the arterioles and of the spleen appears to occupy an intermediate position as regards responsiveness: that of the bladder and the iris was not perceptibly affected by the direct action of such doses as we employed. Cardiac muscle is mildly stimulated by the drug: skeletal muscle not perceptibly affected in any way.

In rodents the main features of the effect are manifestations of this action on plain muscle. A rise of blood-pressure is produced in these animals by constriction of the arterioles, unless this is masked by embarrassed respiration due to bronchial constriction, which in its severest form causes death by asphyxia. The only additional effect to be noted in the rodents is a narcotic action, especially manifest with large doses given hypodermically.

In carnivora the direct action on plain muscle is overcome, in the case of the systemic arterioles, by an antagonistic peripheral action, the mechanism of which is not clear. This result is general vaso-dilatation, in which the kidney vessels, however, do not participate, causing a fall of systemic blood-pressure. The pulmonary arterioles on the other hand constrict in response to the drug whether in the body or isolated. Thus β-I. produces in carnivora the association of a rise in pulmonary with a fall of systemic pressure, described by Bradford and Dean[1] as characteristic of ergot alone among the drugs with which they experimented. Narcosis is also observed in carnivora, and the constricted pupil may be regarded as a feature of this narcotic effect, since it is not produced by β-I. in animals otherwise anæsthetised. In addition the base has a mild direct stimulant action on the activity of the salivary glands and the pancreas. This secretory effect, being paralysed by atropine, may be regarded as a weak action of the pilocarpine type: the association has some interest in that pilocarpine also contains an iminazole ring. The action on the pancreas is not at all like that of secretin.

In the case of several features of the action of β-I. we have drawn attention to the similarity of its effect to that of Witte's peptone and of certain organ extracts. It has been recognised that a certain symptom-complex is common to the action of extracts from a number of organs, and Popielski has suggested the name "vasodilatin" for a hypothetical depressor active principle, present in such extracts and in preparations such as some commercial "peptones," and responsible for the effects which they have in common. It is of interest to note that this common group of effects, in almost all essential particulars, is produced by β-I. We would add to the common actions, described by Popielski and others, the direct stimulant action on plain muscle, as exemplified by the action on the isolated uterus. In one respect the parallelism appears to break down. In the few experiments as yet made for the purpose, we have been unable to detect any action of injections of iminazolylethylamine on the coagulability of the blood. In other respects, however, the correspondence in action is so close as to suggest the presence in "peptone" and in various organ extracts of some substance at least related to iminazolylethylamine. The matter is at present the subject of chemical investigation by Dr Barger[2].

[1] loc. cit.

[2] Since the above was written β-iminazolylethylamine has been isolated from intestinal extract. A forthcoming paper by Barger and Dale will give the details.

This symptom-complex has recently acquired interest in another direction. Biedl and Kraus[1] drew attention to the identity of the symptoms of anaphylactic shock with those produced by intravenous injection of "peptone," which, as we have seen, are again very largely identical with those of β-I. The correspondence cannot yet be regarded as sufficient basis for theoretical speculation, and we content ourselves with recording, as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to a large extent those of poisoning by β-iminazolylethyl-amine.

[1] *loc. cit.*